Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Patients with Gastric or Gastroesophageal Junction Carcinoma (MORPHEUS C-Gastric and Gastroesophageal Junction Carcinoma)

NCT Number: NCT05251948

Document Date: Protocol Amendment Version 5: 01-Dec-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH GASTRIC OR GASTROESOPHAGEAL JUNCTION CARCINOMA (MORPHEUS C–GASTRIC AND GASTROESOPHAGEAL JUNCTION CARCINOMA)**
PROTOCOL NUMBER:	YO43408
VERSION NUMBER:	5
TEST COMPOUNDS:	Atezolizumab (RO5541267) Tiragolumab (RO7092284)
STUDY PHASE:	Phase Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS:	NCT Number: NCT05251948
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on the final page of this document.
4	2 June 2023
3	20 December 2022
2	10 January 2022
1	10 June 2021

PROTOCOL AMENDMENT, VERSION 5
RATIONALE

Protocol YO43408 has been amended to remove two treatment arms. In addition, risks and management guidelines for atezolizumab have been updated to align with the latest Atezolizumab Investigator's Brochure (Version 20). Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The following stage 1 treatment arms have been removed: atezolizumab and CAPOX in combination with AB011 (Atezo+CAPOX+AB011), or CAPOX in combination with AB011 (CAPOX+AB011). No patient had been enrolled in any of these arms (Section 3.1.2, Table 4, Figure 2, Section 3.1.3, Section 4.1.2, Section 4.1.2.4, Section 4.3.1, Section 4.5.7, Section 5.3.5.12, Section 5.7, Appendix 6, Appendix 9 and Appendix 10).
- As a result of the removal of these arms, other changes have been made as follows:
    - Information about AB011 has been removed (Section 1.3)
    - Number of participants to be enrolled during Stage 1 has been reduced to approximately 40–90 patients due to the removal of two arms (Section 3.1.2, Section 6.1)
    - Specific biomarker assessment for claudin-18 isoform 2 [CLDN18.2] is no longer required (Section 3.3.3, Section 4.5.7, Appendix 6)
    - Treponema pallidum antibody test and fecal occult blood test have been removed as these were only applicable to AB011 arms. Stool samples have been made optional (Section 3.3.3, Section 4.5.7, Section 4.5.9, Appendix 6, Appendix 7, Appendix 8)
    - Number of FFPE tumor specimen slides has been reduced (Section 3.3.3, Section 4.5.7)
    - Optional tumor biopsy frequency has been reduced to every 8 weeks (±7 days) (Section 4.5.8).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse events management guidelines have been updated to align with the Atezolizumab IB, Version 20 (Appendix 5).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Appendix 7 and Appendix 8).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH GASTRIC OR GASTROESOPHAGEAL JUNCTION CARCINOMA (MORPHEUS C–GASTRIC AND GASTROESOPHAGEAL JUNCTION CARCINOMA)**
PROTOCOL NUMBER:	YO43408
VERSION NUMBER:	4
TEST COMPOUNDS:	Atezolizumab (RO5541267) Tiragolumab (RO7092284)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by Fortrea.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH GASTRIC OR GASTROESOPHAGEAL JUNCTION CARCINOMA (MORPHEUS C–GASTRIC AND GASTROESOPHAGEAL JUNCTION CARCINOMA)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	NCT Number: NCT05251948

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy and safety of multiple treatment combinations in patients with inoperable locally advanced, metastatic, or advanced gastric carcinoma (GC) or gastroesophageal junction carcinoma (GEJC), with adenocarcinoma confirmed as the predominant histology, who have not received prior systemic therapy for advanced or metastatic disease. The current standard-of-care treatment options for patients with GC and GEJC are primarily limited to cytotoxic chemotherapy in combination with checkpoint inhibitors and targeted therapy (if applicable). Cytotoxic agents given as backbone treatment are associated with significant toxicities and the majority of patients who received standard-of-care treatments will still experience disease progression within 1 year. Therefore, there is a high unmet need for improved medical intervention for patients with inoperable locally advanced, metastatic, or advanced GC or GEJC.

OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are summarized in Table 1.

Table 1 Objectives and Corresponding Endpoints for Stage 1

Primary Objective	
Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment combinations during Stage 1	• ORR, defined as the proportion of patients with a complete response or a partial response on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Objectives	
Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of treatment combinations during Stage 1	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization, defined as the time from randomization to death from any cause, regardless of stage • OS at specific timepoints (e.g., 6 and 12 months) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • Disease control rate, defined as the proportion of patients with stable disease for ≥12 weeks or a complete or a partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	Corresponding Endpoint
• To evaluate the safety of treatment combinations during Stage 1	• Incidence and severity of adverse events, with severity of all events graded according to NCI CTCAE v5.0 and severity for CRS also graded according to the ASTCT CRS Consensus Grading Scale

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; DOR = duration of response; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

OVERALL DESIGN AND STUDY POPULATION

This Phase Ib/II, open-label, multicenter, randomized umbrella study will evaluate the efficacy and safety of multiple treatment combinations in patients with advanced GC or GEJC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or

unacceptable toxicity, and modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status).

Several key aspects of the study design and study population are summarized in Table 2.

Table 2 Study Design and Population

Phase:	Phase Ib/II	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Inoperable locally advanced, metastatic, or advanced GC or GEJC
Interventional Model:	Parallel group	**Population Age:**	Age $\geq$ 18 years
Test Compounds:	Atezolizumab, tiragolumab	**Site Distribution:**	Multi-site
Active Comparator:	Atezolizumab in combination with capecitabine plus oxaliplatin	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 40–90 patients

GC = gastric carcinoma; GEJC = gastroesophageal junction carcinoma.

STUDY TREATMENT

The study treatment is summarized in Table 3.

Table 3 Study Treatment

Stage 1 Study Treatments	
Treatment Group	Dose, Route, and Regimen (drugs listed in order of administration)
Atezo + CAPOX (control group treatment combination) (21-day cycles)	• Atezolizumab 1200 mg by IV infusion on Day 1 • Capecitabine 1000 mg/m^2 orally twice daily on Days 1–14 [a] • Oxaliplatin 130 mg/m^2 by IV infusion on Day 1 [a]
Atezo + CAPOX + Tira (treatment combination) (21-day cycles)	• Atezolizumab 1200 mg by IV infusion on Day 1 • Tiragolumab 600 mg by IV infusion on Day 1 • Capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 [a] • Oxaliplatin 130 mg/m^2 by IV infusion on Day 1 [a]

Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin; Tira = tiragolumab.

[a] Treatment for up to six cycles.

There will be no dose modifications for atezolizumab *or* tiragolumab in this study.

Capecitabine Dose Modification

The capecitabine dose can be modified as presented in Table 4 for the management of drug-related toxicities. Once the dose has been reduced, it cannot be increased later. Omitted doses of capecitabine because of toxicity will not be replaced.

Table 4 Dose Modification for Capecitabine for Drug-Related Toxicities

Toxicity [a]	Action to Be Taken for Current Treatment	Dose Modification for the Next Treatment (% of Starting Dose)
Grade 1	Maintain dose level.	Maintain dose level.
Grade 2		
First occurrence	Withhold until resolved to Grade 1 or better.	100% (1000 mg/m^2)
Second occurrence		75% (750 mg/m^2)
Third occurrence		50% (500 mg/m^2)
Fourth occurrence	Discontinue permanently.	—
Grade 3		
First occurrence	Withhold until resolved to Grade 1 or better.	75% (750 mg/m^2)
Second occurrence		50% (500 mg/m^2)
Third occurrence	Discontinue permanently.	—
Grade 4		
First occurrence	Discontinue permanently or continue at the discretion of the investigator once the event has resolved to Grade 1 or better.	50% (500 mg/m^2)

[a] Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Oxaliplatin Dose Modification

Dose Modifications for Patients with Neurotoxicity

- For Grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia) or limiting instrumental activities of daily living, omit oxaliplatin. When toxicity resolves to Grade 1 or better, resume oxaliplatin to 75% of the initial dose. If oxaliplatin is omitted for 6 weeks (two consecutive cycles) for neurologic toxicity, discontinue oxaliplatin.
- For Grade 3 and 4 peripheral sensory neuropathy (severe paresthesia or dysesthesia) or limiting self-care activities of daily living), discontinue oxaliplatin.

Dose Modifications for Patients with Renal Impairment

- For normal renal function or mild to moderate renal impairment (creatinine clearance $>$ 50 mL/min), the full dose of oxaliplatin can be administered.
- For severe renal impairment, the oxaliplatin dose should be reduced to 75% of the initial dose.

Dose Modifications for Patients with Hematologic Toxicity

- For Grade 2 and 3 thrombocytopenia, the oxaliplatin dose should be reduced to 75% of the initial dose. For Grade 4 thrombocytopenia, the dose should be reduced to 50% of the initial dose.
- For Grade 3 and 4 neutropenia or febrile neutropenia, the oxaliplatin dose should be reduced to 75% of the initial dose.

DURATION OF PARTICIPATION

Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody
ASTCT	American Society for Transplantation and Cellular Therapy
Atezo	atezolizumab
Atezo + CAPOX	atezolizumab in combination with capecitabine and oxaliplatin
Atezo + CAPOX + Tira	atezolizumab in combination with capecitabine, oxaliplatin, and tiragolumab
CAPOX	capecitabine in combination with oxaliplatin
CIT	cancer immunotherapy
COVID-19	coronavirus disease 2019
CPS	combined positive score
CRS	cytokine release syndrome
CT	computed tomography
DOR	duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FFPE	formalin-fixed, paraffin-embedded
GC	gastric carcinoma
GEJ	gastroesophageal junction
GEJC	gastroesophageal junction carcinoma
HBcAb	hepatitis B core antibody

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (cont.)

Abbreviation	Definition
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HR	hazard ratio
ICH	International Council for Harmonisation
IFN (-γ)	interferon (-γ)
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (cont.)

Abbreviation	Definition
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
Tira	tiragolumab
TNF-α	tumor necrosis factor–α
ULN	upper limit of normal
VCA	viral capsid antigen
WES	whole exome sequencing

1. BACKGROUND

1.1 BACKGROUND ON GASTRIC CANCER AND GASTROESOPHAGEAL JUNCTION CANCER

Gastric carcinoma (GC) is the fifth leading cancer and the fourth leading cause of cancer-related deaths globally. The incidence of GC varies with different geographic regions, with more than 70% of GCs occurring in developing countries (Global Cancer Observatory 2020), and about 50% of these cases are in East Asia, with China the most affected country as it accounts for 42.6% of the global incidence and 45% of all GC-related deaths (Torre et al. 2015; Wang et al. 2018). In China, GC remains the second in terms of incidence among all malignancies, just below lung cancer (Zheng et al. 2017; Chen et al. 2018). In terms of incidence, GC is ranked second and fifth among males and females, respectively. With respect to mortality, GC is ranked third, preceded by lung cancer and liver cancer, whereas the mortality among males and females is ranked third and second, respectively (Chen et al. 2018).

The incidence of proximal GC is rising in the West, and that of non-proximal locations is rising in the East, especially in Japan and China. At diagnosis, GC often presents as advanced disease, comprising approximately 40% of newly diagnosed cases in the United States and Europe and approximately 20% in Japan and Korea, where early detection is common. However, in China more than 80% of patients with GC are already in advanced stages of the disease at the time of diagnosis, and many patients may miss the opportunity of radical resection or are at high risk of postoperative metastasis and relapse.

GC, including gastroesophageal junction (GEJ) carcinoma (GEJC), is a heterogeneous cancer type with multiple identified risk factors, including environmental, genetic, and behavioral risks. There has been a decline in GC mortality attributable to lifestyle and dietary changes globally (Global Burden of Disease 2017 Stomach Cancer Collaborators 2020) as well as to decreased infection with *Helicobacter pylori*, which is considered the main cause of mortality in Asian countries (Lichtenstein et al. 2000). However, the incidence of GEJ tumors has increased considerably because of increases in risk factors, such as smoking, obesity, and gastroesophageal reflux disease (Buas and Vaughan 2013; Coleman et al. 2018).

1.2 FIRST-LINE TREATMENT OF GC AND GEJC

GEJ tumors are frequently grouped together with GC and treated in a similar fashion as GC due to its anatomical location straddling the distal esophagus and proximal stomach and given that the majority of GEJ tumors are adenocarcinomas (Hasegawa and Yoshikawa 2010). Moreover, advanced and metastatic GEJ cancers are treated in a similar manner as GC according to oncology guidelines (National Comprehensive Cancer Network [NCCN] 2021a).

Platinum (cisplatin and oxaliplatin) and fluoropyrimidines (5-fluorouracil [5-FU], capecitabine, and S-1) doublets are generally considered as standard-of-care treatment in the first-line setting of metastatic GC and GEJC across different regions (Japanese Gastric Cancer Association 2021; NCCN 2021a, 2021b; Wang et al. 2021). In patients with good performance status who are willing to sacrifice toxicity for higher response rates and potentially longer progression-free survival (PFS), triplet regimens consisting of fluoropyrimidine, oxaliplatin, and docetaxel can be considered (Lyons 2017). Overexpression or amplification of human epidermal growth factor 2 (*HER2;* also known as *ERBB2*) is present in approximately 15%–20% of patients with advanced GC. The pivotal Phase III ToGA trial established the addition of trastuzumab to cytotoxic chemotherapy as the standard of care in the first-line treatment of patients with HER2-positive GC and GEJC (Bang et al. 2010; Lyons 2017).

Immunotherapeutic approaches have demonstrated clinical efficacy in several advanced cancer types, including GC and GEJC. Two anti-programmed death–1 (PD-1) monoclonal antibodies, pembrolizumab and nivolumab, have demonstrated improved overall survival (OS) in patients with refractory GC that has progressed after two or more lines of chemotherapy, and both received regulatory approval for corresponding indications in 2017 (Kang et al. 2017; Fuchs et al. 2018). Recently, CheckMate-649 (NCT02872116), a Phase III trial investigating nivolumab plus chemotherapy or nivolumab plus ipilimumab compared with chemotherapy alone in the first-line treatment of metastatic HER2-negative GC and GEJC, showed improved OS (14.4 vs. 11.1 months; hazard ratio [HR]: 0.71) and improved PFS (7.7 vs. 6.1 months; HR: 0.74) in patients with a programmed death–ligand 1 (PD-L1) combined positive score (CPS) ≥ 5 receiving nivolumab plus chemotherapy compared with chemotherapy alone (Moehler et al. 2020). An OS benefit (13.8 vs. 11.6 months; HR: 0.80) was also seen in an all-randomized population. With the recent regulatory approval by the U.S. Food and Drug Administration, this practice-changing study has established chemotherapy plus nivolumab as a new standard of care for the first-line treatment of patients with HER2-negative GC and GEJC.

1.3 STUDY RATIONALE

The current standard-of-care treatment for the first-line treatment of patients with HER2-negative GC and GEJC with cytotoxic chemotherapy is typically palliative in intent and results in poor prognosis, with the duration of median OS ranging from 8 to 14 months across Asia, the United States, and Europe (Moehler et al. 2020). In patients with GC and GJEC with a PD-L1 CPS ≥ 5, nivolumab in combination with chemotherapy conferred an additional survival benefit compared with chemotherapy alone. However, the survival benefit in an all-randomized population was marginal and the treatment effect in the CPS < 5 population remained unclear (Moehler et al. 2020). In addition, cytotoxic agents used as treatment backbone are accompanied by high toxicity, with Grade 3 and 4 toxicities reported in up to 77% of patients treated with platinum-doublet regimens and in > 80% of patients treated with triplet regimens (Van Cutsem et al. 2006;

Cunningham et al. 2008; Ohtsu et al. 2011; Lordick et al. 2013). Therefore, new treatment options are needed to improve survival and response as well as decrease toxicity in the first-line treatment setting of GC and GEJC.

This Phase Ib/II umbrella study is designed to accelerate the development of treatment combinations by identifying early signals and establishing proof-of-concept clinical data in patients with GC or GEJC. The study is designed with the flexibility to open new treatment arms as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms in a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving control arm treatment. More importantly, this study will assess the importance of simultaneously targeting multiple pathways, including immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination. To improve the confidence of clinical signal detection in the experimental arms, this study will include a control arm. In addition, patients who experience disease progression with the initial treatment regimen (Stage 1) may be eligible to continue treatment with a different treatment regimen (Stage 2), which may advance the scientific understanding of treatment resistance mechanisms in patients who do not respond to or experience disease progression during treatment.

This study will enroll patients with inoperable locally advanced, metastatic, or advanced GC or GEJC, with adenocarcinoma confirmed as the predominant histology, who have not received prior systemic therapy for their disease. Despite the recently demonstrated clinical benefit of nivolumab plus chemotherapy in patients with a PD-L1 CPS $\geq$5, there remains a high unmet medical need for treatment-naive patients with inoperable locally advanced, metastatic, or advanced GC or GEJC, requiring further evaluation of novel, more efficacious treatment combinations.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) are presented in Table 1. The control and experimental treatment regimens are described in Sections 3.1.1 and 3.1.2 (see Table 4 and Table 5). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agent, are provided in the respective appendix for that treatment arm, as outlined in Table 4 and Table 5.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Checkpoint inhibitor
Tiragolumab	TIGIT	Checkpoint inhibitor; improves activation and effectiveness of T-cell and NK-cell tumor-killing activity [a]

IMP = investigational medicinal product; NK = natural killer; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

[a] Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014.

1.4 COVID-19 BENEFIT–RISK ASSESSMENT

In the setting of the coronavirus disease 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 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Wykes and Lewin 2018; Schorer et al. 2020). 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) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy (CIT).

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 (Merad and Martin 2020). Although it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving immune checkpoint inhibitor therapies (e.g., atezolizumab and/or tiragolumab). At this time, there is insufficient evidence for causal association between atezolizumab or tiragolumab 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 immune checkpoint inhibitor therapies and clinical and radiologic features for SARS-CoV-2–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 CIT 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 of Cancer [SITC] 2020).

Per recommendations of the 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 (NCCN 2021c). 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 CIT (SITC 2020). For patients enrolling in this study and receiving CIT, 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 CIT 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, COVID-19 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 (see Section 4.4).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of multiple treatment combinations in patients with advanced GC or GEJC. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 2) and Stage 2 (see Table 3).

Table 2 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment combinations during Stage 1	• ORR, defined as the proportion of patients with a complete response or a partial response on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment combinations during Stage 1	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization, defined as the time from randomization to death from any cause, regardless of stage • OS at specific timepoints (e.g., 6 and 12 months) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • Disease control rate, defined as the proportion of patients with stable disease for ≥12 weeks or a complete or a partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety of treatment combinations during Stage 1	• Incidence and severity of adverse events, with severity of all events graded according to NCI CTCAE v5.0 and severity for CRS also graded according to the ASTCT CRS Consensus Grading Scale

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; DOR = duration of response; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To characterize the PK profile of drugs that are administered as part of a treatment combination during Stage 1	• Plasma or serum concentrations of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of treatment combinations	• Relationship between plasma or serum concentrations or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentrations or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of a treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; DOR = duration of response; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of treatment combinations during Stage 2	• ORR, defined as the proportion of patients with a complete response or a partial response on two consecutive occasions ≥ 4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • OS after initiation of Stage 2, defined as the time from initiation of Stage 2 to death from any cause, regardless of stage • DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Disease control rate, defined as the proportion of patients with stable disease for ≥ 12 weeks or a complete or a partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety of treatment combinations during Stage 2	• Incidence and severity of adverse events, with severity of all events graded according to NCI CTCAE v5.0 and severity for CRS also graded according to the ASTCT CRS Consensus Grading Scale

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; DOR = duration of response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To characterize the PK profile of drugs that are administered as part of a treatment combination during Stage 2	• Plasma or serum concentrations of each (as appropriate) drug at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentrations or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentrations or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of a treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; DOR = duration of response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Biomarker Objective	Corresponding Endpoint
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; DOR = duration of response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

3. STUDY DESIGN

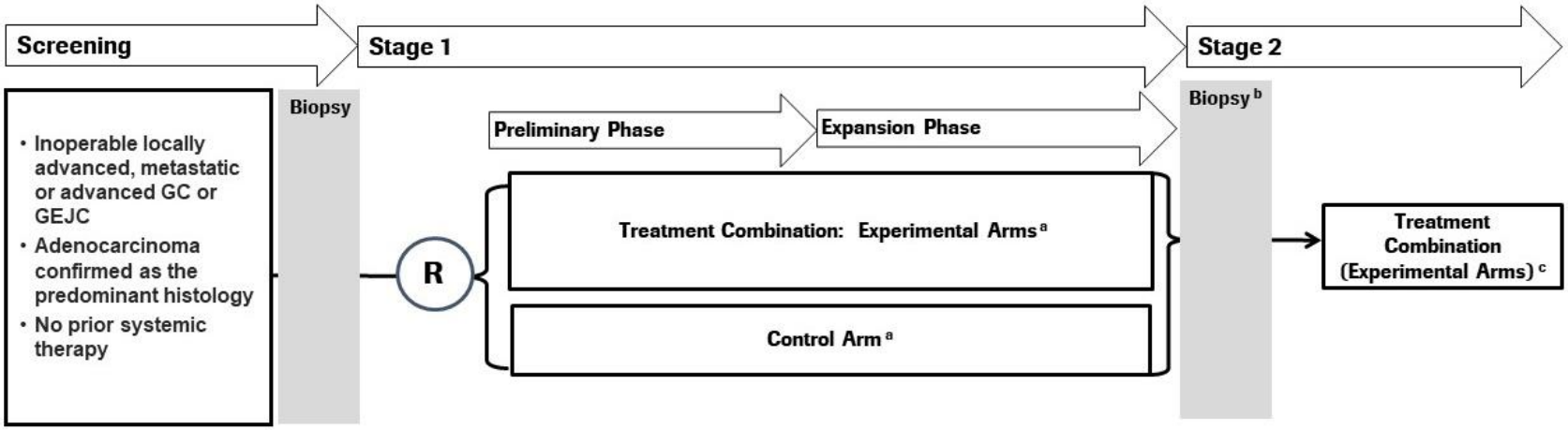
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in patients with advanced GC or GEJC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, and modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status).

Cohort 1 will enroll patients with inoperable locally advanced, metastatic, or advanced GC or GEJC, with adenocarcinoma confirmed as the predominant histology, who have not received prior systemic therapy for advanced or metastatic disease (see Figure 1). Eligible patients will initially be randomly assigned to one of the treatment arms (Stage 1; see Section 3.1.2). Patients who experience loss of clinical benefit or unacceptable toxicity during Stage 1 may be eligible to receive treatment with a different treatment combination (Stage 2; see Section 3.1.3). When a Stage 2 treatment combination is available, this will be introduced by amending the protocol.

Figure 1 Study Schema



GC = gastric carcinoma; GEJC = gastroesophageal junction carcinoma; R = randomization.

[a] See Table 4 for a summary of available Stage 1 treatment regimens.

[b] If deemed clinically feasible by the investigator, a biopsy will be performed for patients who discontinue Stage 1 because of unacceptable toxicity or loss of clinical benefit, as determined by the investigator (see details on tissue sample collection in Section 4.5.7).

[c] See Table 5 for a summary of available Stage 2 treatment regimens.

3.1.2 Stage 1

During Stage 1, patients will be randomly assigned to a control arm (atezolizumab in combination with capecitabine and oxaliplatin [CAPOX] [Atezo + CAPOX]) or an experimental arm consisting of atezolizumab and CAPOX in combination with tiragolumab (Atezo + CAPOX + Tira). Details on the treatment regimens for Stage 1 are provided in Appendix 7 *and* Appendix 8, as specified in Table 4.

Approximately *40-90* patients will be enrolled during Stage 1. Enrollment in the experimental arm will take place in two phases: a preliminary phase, followed by an expansion phase. For most arms, approximately 20 patients will be enrolled during the preliminary phase. If clinical activity is observed in the experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. If the experimental arm shows minimal clinical activity or unacceptable toxicity, then it will not undergo expansion. Additional patients may be enrolled to ensure balance across treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Patients in Stage 1 will be randomly assigned to experimental arms or the control arm, and the randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 50%. The treatment regimen in the control arm may change with emerging data to reflect the evolving standard-of-care treatments; new control arm treatment will be updated by amending the protocol. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 4 Stage 1 Treatment Regimens

Arm Name	Study Treatment [a]	Number of Patients		Appendix
		Preliminary Phase	Expansion Phase [b]	
Control (Atezo + CAPOX) [c]	Atezolizumab plus capecitabine plus oxaliplatin	Variable [d]		Appendix 7
Atezo + CAPOX + Tira	Atezolizumab plus capecitabine plus oxaliplatin plus tiragolumab	20	25	Appendix 8

Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin; Tira = tiragolumab.

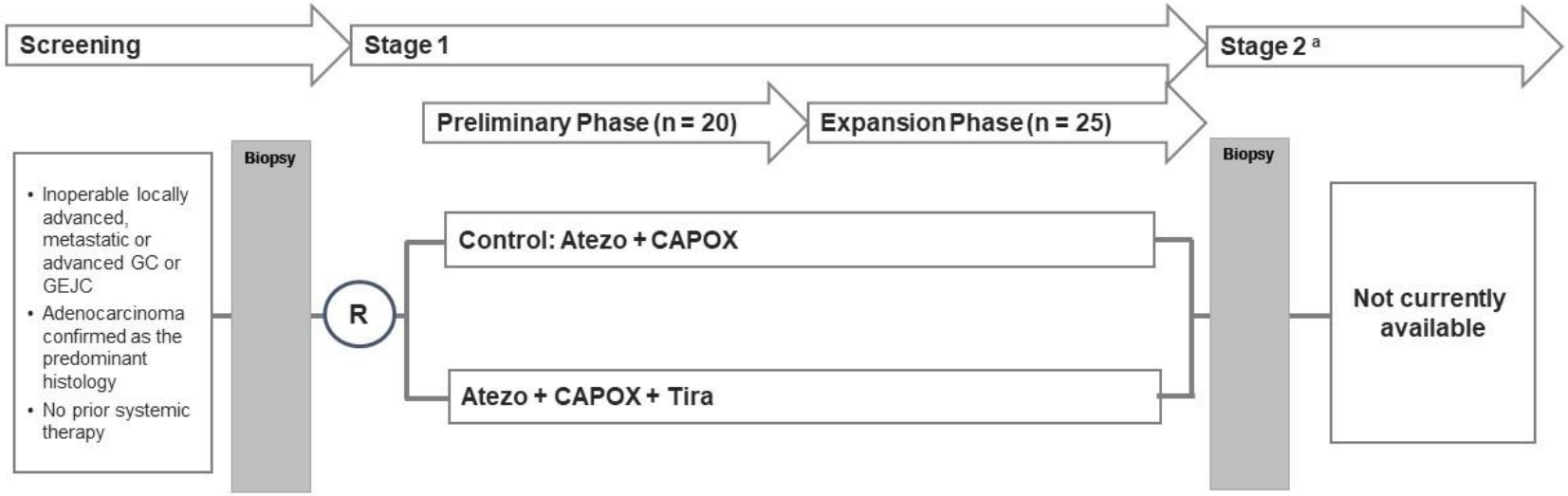
[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.

[b] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

[c] The treatment regimen in the control arm may change with emerging data to reflect the evolving standard-of-care treatments, and new control arm treatment will be updated by amending the protocol.

[d] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 50% (see Section 3.1.2 for details).

Figure 2 Detailed Study Design



Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin; GC = gastric carcinoma; GEJC = gastroesophageal junction carcinoma; R = randomization; Tira = tiragolumab.

[a] Patients who experience loss of clinical benefit as determined by the investigator (details provided below) or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment combination during Stage 2, provided they meet the eligibility criteria and a Stage 2 arm is open for enrollment. Details are provided in the respective appendix for each treatment arm (see Appendix 7 and Appendix 8.

Patients in the control and experimental arms will continue to receive treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab and other CITs, radiographic progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT-based combination will be permitted to continue treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.3 Stage 2

Patients in a control or experimental arm who experience loss of clinical benefit as determined by the investigator (as described above) during Stage 1 will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 5, provided they meet eligibility criteria (see Section 3.1.2) and a Stage 2 arm is open for enrollment. Patients who experience unacceptable toxicity during Stage 1 may be eligible to receive treatment during Stage 2.

Stage 2 treatment must begin within 3 months after a patient has experienced loss of clinical benefit or unacceptable toxicity in Stage 1 and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. However, it is recommended that patients begin Stage 2 treatment as soon as possible.

Table 5 Stage 2 Treatment Regimens

Study Treatment	Appendix
No Stage 2 treatment currently available	—

The Sponsor may also decide to discontinue enrollment in the Stage 2 treatment arms on the basis of a review of all available safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

3.1.4 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). Severity for CRS will also be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading Scale.

Patients will undergo tumor assessments every 6 weeks (±1 week) during the first 48 weeks (from Day 1 of Cycle 1) and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays until confirmed radiographic disease progression, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 4.5.6). Response will be assessed by the investigator according to RECIST v1.1 (see Appendix 1). If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm and the corresponding control arm be submitted for evaluation by an independent review facility.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided the tissue was obtained within 6 months prior to enrollment and the patient has not received any systemic anti-cancer therapy since the time of the procedure. If deemed clinically feasible by the investigator, tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity or loss of clinical benefit as determined by the investigator.

These samples will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.3.3 and details on tissue sample collection in Section 4.5.7).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be taken at various timepoints before and during study treatment administration.

Based on a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

The schedule of activities for each treatment arm is presented in Appendix 7 *and* Appendix 8.

3.1.5 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from Clinical Science, Clinical Safety, and Biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit (last patient, last visit [LPLV]), including survival follow-up visits conducted by telephone or in the clinic.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

This study will enroll patients with inoperable locally advanced, metastatic, or advanced GC or GEJC, with adenocarcinoma confirmed as the predominant histology, who have not received prior systemic therapy for their advanced or metastatic disease.

The current standard-of-care treatment for the first-line treatment of patients with HER2-negative GC and GEJC with cytotoxic chemotherapy is typically palliative in intent and results in poor prognosis, with median OS duration of 8 to 14 months across Asia, the United States, and Europe (Cunningham et al. 2008; Ohtsu et al. 2011; Yamada et al. 2015). In patients with GC and GEJC with a PD-L1 CPS ≥ 5, nivolumab in combination with chemotherapy resulted in additional survival benefit compared with chemotherapy alone. However, the survival benefit in the all-randomized population was marginal and the treatment effect in the PD-L1 CPS < 5 population remained unclear (Moehler et al. 2020). Moreover, cytotoxic agents given as treatment backbone are accompanied by high toxicity, with Grade 3 and 4 toxicities reported in up to 77% of

patients treated with platinum-doublet regimens and >80% of patients with triplet regimens (Van Cutsem et al. 2006; Cunningham et al. 2008; Ohtsu et al. 2011; Lordick et al. 2013). Therefore, despite the recently demonstrated clinical benefit of nivolumab plus chemotherapy in patients with a PD-L1 CPS ≥5, there remains a high unmet medical need for treatment-naive patients with inoperable locally advanced, metastatic, or advanced GC and GEJC, requiring further evaluation of novel, more efficacious treatment combinations to improve survival and response as well as decreased toxicity in the first-line setting.

Patients affected by signet ring cell dominant carcinoma (>50% of the tumor) will be excluded. This specific histotype differs significantly from the other gastric adenocarcinomas with regard to epidemiology (Lauren 1965; Henson et al. 2004), oncogenesis (Fukui 2014), and clinical presentation (Taghavi et al. 2012). In addition, signet ring cell carcinoma seems to have a different chemosensitivity profile (Henson et al. 2004), and in particular, recent data suggest that a taxane-based therapy could be more effective in this histotype (Pernot et al. 2015a, 2015b). Advanced-stage signet ring cell adenocarcinoma is commonly thought to be associated with poor prognosis.

Patients with HER2-positive carcinoma will be excluded on the basis of the pivotal Phase III ToGA trial that established the addition of trastuzumab to cytotoxic chemotherapy as the standard-of care treatment in the first-line setting of HER2-positive GC and GEJC.

3.3.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients randomly allocated to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged by the investigator to be favorable (see Section 3.1.2 for the criteria). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.2 for details).

3.3.3 Rationale for Biomarker Assessments

Blood samples for biomarker assessments will be collected at baseline and during the study. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell subpopulations, gene expression, and circulating tumor DNA) and drug dose, efficacy, or safety endpoints may allow for the development of a blood-based biomarker to help define future treatments and predict which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be obtained from all patients, preferably by means of a biopsy performed at study entry. If deemed clinically feasible by the investigator, tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details) to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of study treatments.

Tumor samples will be evaluated for biomarkers, such as tumor-infiltrating immune cells, PD-L1, CD8, Epstein-Barr virus (EBV) infection, and expression of targets specific to each drug combination (e.g., T-cell immunoreceptor with Ig and ITIM domains [TIGIT]). Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number and functional status of tumor-infiltrating immune cells, may provide validation of the postulated mechanism of action and confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved.

Tumor tissue and blood samples may be analyzed through use of next-generation sequencing (NGS), including whole exome sequencing (WES), to identify somatic mutations that are predictive of response to study drugs, are associated with progression to a more severe disease state, are associated with acquired resistance to study drugs, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

*Optional s*tool samples will be collected to assess the gut microbiota diversity at baseline and during the study. The gut microbiome has been shown to be a key determinant in immune regulation in cancer, in part by influencing T cell–driven anti-tumor responses (Routy et al. 2018). For example, antibiotic treatment is associated with poor survival outcomes to anti–PD-1 therapy in non–small cell lung cancer, renal cell carcinoma, and urothelial carcinoma (Elkrief et al. 2019). Conversely, the risk of colitis with CITs may be predictive based on a patient's pretreatment microbiome (Dubin et al. 2016; Chaput et al. 2017). Thus, heterogeneity in microbiome composition across patients may be a key driver of safety events in addition to efficacy. In addition, dysbiosis, or altered microbial communities, has been observed in patients with GC

(Ferreira et al. 2018). This study will examine whether a patient's microbiome may be used to assess response to a CIT combination, and conversely, whether a CIT combination can alter the microbiome to such an extent that changes during treatment to the microbiome may be early predictors of adverse events, including colitis.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria outlined in Sections 4.1.1.1 and 4.1.1.2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 4.1.1.2 and 4.1.1.3 to qualify for Stage 2.

4.1.1.1 Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age ≥ 18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1 (see Appendix 2)
- Inoperable locally advanced, metastatic, or advanced GC or GEJC, with adenocarcinoma confirmed as the predominant histology
- No prior systemic treatment (including systemic investigational agents or HER2 inhibitors) for advanced or metastatic disease

  Prior adjuvant or neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy for GC and GEJC are permitted as long as the last administration of the last dose (whichever was given last) occurred at least 6 months prior to randomization. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.

  Prior treatment with herbal therapies, including traditional Chinese medicines, with anti-cancer activity noted in the label are allowed, provided that the medications are discontinued prior to randomization.
- Life expectancy ≥ 3 months, as determined by the investigator
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by central testing

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a previous surgery or biopsy within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the procedure.

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen *7-18* slides *(18* slides highly preferred) containing unstained, freshly cut serial sections must be submitted along with an associated pathology report. The number of slides

provided may also be governed by local regulation. See Section 4.5.7 for additional information on tumor specimens collected at screening.

- Patients whose tumors are without *HER2* amplification documented by fluorescence in situ hybridization or in situ hybridization or are negative by immunohistochemistry (IHC) 0 or +1 on previously collected and assessed tumor tissue at initial diagnosis of disease by local laboratory testing

  If more than one test result from local testing is available and not all results meet the inclusion criterion definition, all the results should be analyzed and the assessment needs to be documented to establish eligibility of the patient. The Medical Monitor is available to advise as needed.

4.1.1.2 Inclusion Criteria for Stage 1 and Stage 2

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - [redacted]
- Patients without hepatitis B virus (HBV) infection at screening
  - [redacted]

[redacted]

  - 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.

- Negative HIV test at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as outlined for each specific treatment arm in Appendix 7 *and* Appendix 8
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 7 *and* Appendix 8

4.1.1.3 Inclusion Criteria for Stage 2

Patients must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0 or 1 (see Appendix 7)
- Ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details) while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible by the investigator) because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment in specific arms during Stage 1 or enrollment during Stage 2 if they meet any of the criteria outlined in subsequent sections, as specified by treatment arm below:

Table 6 Arm-Specific Exclusion Criteria

Stage	Treatment Arm	Applicable Exclusion Criteria
1	Control (Atezo+CAPOX)	Sections 4.1.2.1 and 4.1.2.2
	Atezo+CAPOX+Tira	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
2	Not currently available	—

Atezo=atezolizumab; CAPOX=capecitabine plus oxaliplatin; Tira=tiragolumab.

4.1.2.1 Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including, but not limited to, anti-CTLA-4, anti−PD-1, anti−PD-L1, and anti-TIGIT therapeutic antibodies
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Any contraindications to any of the study drugs of the chemotherapy regimen

  Investigators should refer to local package insert of the chemotherapy drugs.
- Eligible only for the control arm

4.1.2.2 Exclusion Criteria for Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Patients with a signet ring cells dominant carcinoma (>50% of the tumor)
- Symptomatic, untreated, or actively progressing 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 the CNS.

  The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

  The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 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.

  Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

  There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

  Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
- History of leptomeningeal disease
- 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. Patients should be recovered from the side effects of radiation. There is no required minimum recovery period.

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 locoregional therapy if appropriate prior to enrollment.

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium greater than ULN)

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 3 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  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.
  - 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.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on the screening chest computed tomography (CT) scan

- History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Active tuberculosis

- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than GC or GEJC within 2 years prior to initiation of study treatment, 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, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- 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, in the opinion of the investigator, could impact patient safety
- 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.
- Prior allogeneic stem cell or solid organ transplantation
- 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
- Pregnancy or breastfeeding, or intending to become pregnant during the study

    Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab or tiragolumab treatment, within 5 months after the final dose of atezolizumab, or 90 days after the final dose of tiragolumab, whichever is later
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients

- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [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 or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- For patients entering Stage 2: immunotherapy-related adverse events that have not resolved to Grade 1 or better or to baseline at the time of consent with the following exception:

  Patients with ongoing endocrine events that are adequately managed with supplemental therapy are eligible.

4.1.2.3 Exclusion Criteria for Tiragolumab-Containing Arm

Patients who meet any of the following criteria will be excluded from the tiragolumab-containing arm during Stage 1:

- Prior treatment with an anti-TIGIT agent
- Active EBV infection or known or suspected chronic active EBV infection at screening

  Patients with a positive EBV viral capsid antigen (VCA) IgM test at screening are excluded from this arm. An EBV PCR test should be performed as clinically indicated to screen for active infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded from this arm.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment through use of the IxRS and will retain the same patient identification number that is assigned in Stage 1.

For Stage 1, this study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment during the study. The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 50%. The randomization ratios may be altered to increase enrollment in a particular experimental arm that has demonstrated promising clinical activity.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Section 4.1.2. If a patient is eligible only for the control arm, the patient will not be enrolled in the study.

Patients who do not receive at least one dose of each drug for their assigned treatment regimen will not be included in the efficacy analyses. Additional patients may be enrolled in Stage 1 to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4 for Stage 1 and Table 5 for Stage 2.

4.3.1 Investigational Medicinal Product Handling and Accountability

The IMPs for this study are atezolizumab *and* tiragolumab. All IMPs required for completion of this study will be provided by the Sponsor where required by local practices. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

All IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on a drug accountability log.

Refer to the pharmacy manual and/or the applicable Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing study treatments in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4 for Stage 1 and Table 5 for Stage 2.

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm (see Appendix 7 *and* Appendix 8). All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Written informed consent must also be obtained before performing screening evaluations for Stage 2.

Screening evaluations for Stage 1 and Stage 2 are to be performed within 28 days prior to initiation of study treatment (Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment (see Appendix 6 for the schedule of activities for Stage 1 screening).

Patients who fail their first screening for study eligibility (Stage 1 or Stage 2) may qualify for two re-screening opportunities (for a total of three screening opportunities per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to Day 1 (see the schedule of activities for each arm in Appendix 7 *and* Appendix 8) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. A patient's molecular profile for GC and GEJC, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time prior to initiation of study treatment will be recorded (as outlined for each arm in Appendix 7 *and* Appendix 8). At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits 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 on the Adverse Event eCRF.

During visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Weight will be recorded at specified timepoints during the study.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured at other specified timepoints as outlined for each arm in the schedule of activities in Appendix 7 *and* Appendix 8.

4.5.5 Electrocardiograms

An ECG is required at screening and as outlined in the schedule of activities. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

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

4.5.6 Tumor and Response Evaluations

Patients will undergo tumor assessments every 6 weeks (±1 week) during the first 48 weeks (from Day 1 of Cycle 1) and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays until confirmed radiographic disease progression, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start a new non–protocol-specified anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of unacceptable toxicity or loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

All measurable and/or evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable but will be documented at screening as a site of metastatic disease. Tumor assessments performed as standard of care 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 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 spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., 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. Bone scans, CT or MRI scans of the neck, and CT or MRI scans of the brain 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 be used.

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.

All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. 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 (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. 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). Tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable) at all subsequent assessments.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator prior to treatment administration.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if available), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate (or phosphorus), calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase (if available)
- Coagulation: INR and aPTT
- Thyroid-function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4
- C-reactive protein
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  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), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes,

and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

- Urinalysis includes pH, specific gravity, glucose, protein (or albumin), ketones, and blood; dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for PK analysis through use of validated assays (see Appendix 7 *and* Appendix 8)
- Serum samples for immunogenicity analysis through use of validated assays (see Appendix 7 *and* Appendix 8)
- *Blood*, serum, plasma, and WBC samples for biomarker analysis and biomarker assay development (see Appendix 7 *and* Appendix 8)

  Plasma and WBC will be isolated from blood at central laboratory.
- Archival or newly collected tumor tissue sample collected at baseline for determination of PD-L1 *and* TIGIT expression, tumor-infiltrating lymphocytes, microsatellite instability (MSI) status, EBV infection, gene expression profiling, and other biomarkers

  Baseline tumor tissue samples from the primary lesion or a metastatic lesion will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the patient has not received any systemic anti-cancer therapy and that the tissue was obtained from a previous surgery or biopsy performed within 6 months prior to enrollment.

  A representative FFPE tumor specimen *7-18* slides (*18* slides highly preferred) containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (16–18 gauge preferred, at least three cores and embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.
- Tumor tissue sample collected during Stage 1 at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details), if deemed clinically feasible by the investigator, for biomarkers analysis

Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor molecular subtype and tumor immunobiology, PD-L1, expression of targets specific to each drug combination (e.g., TIGIT), EBV, tumor mutation load, MSI status, lymphocyte subpopulations, T cell–receptor repertoire, or cytokines. Research may involve DNA or RNA extraction, analysis of somatic mutations, and use of NGS (including WES). Biomarker sample collections and research are applicable only after approval from the local regulatory authorities.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma, serum, blood, tumor tissue, and stool samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For patients who are not enrolled, remaining archival tissue specimens will be returned to the site no later than 6 months after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Optional Tumor Biopsies

Patients will be given the option of consenting to additional tumor biopsies. Patients who consent to optional biopsies will undergo tumor biopsy sample collection *8* weeks (±7 days) after treatment initiation, if deemed clinically feasible by the investigator. In addition, patients who consent to optional biopsies may undergo additional biopsies during treatment at any other time at the investigator's discretion.

Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.
For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for biomarker analysis as described in Section 4.5.7.
See Section 4.5.7 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.9 *Optional Stool Samples*

Patients will be given the option of consenting to provide stool samples. Patients who consent to providing optional stool samples will receive the collection device prior to baseline and the Day 1, Cycle 3 visit. For sampling procedures, storage conditions,

and shipment instructions, see the laboratory manual. The Informed Consent Form will contain a separate section that addresses optional stool samples. A separate, specific signature will be required to document a patient's agreement to provide optional stool samples.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Stool Sample Informed Consent eCRF. Samples may be used for biomarker research as described in Section 4.5.7. Refer to Section 4.5.7 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment, including 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
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.2 for details)

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each arm in Appendix 7 *and* Appendix 8.

After treatment discontinuation, information on survival follow-up and initiation of a new anti-cancer therapy will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±2 weeks) or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm, in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining approximately 20% of patients will be discontinued from the study).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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. Patients who withdraw from the study 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.

4.6.3 Study Discontinuation

The Sponsor 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 will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm, as outlined in Appendix 5, Appendix 7 *and* Appendix 8.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 5 through Appendix 8. See Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection will be excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines 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 COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for each treatment arm are listed in the respective appendix for that treatment arm, as outlined in Appendix 7 *and* Appendix 8.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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 (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

The ASTCT CRS Consensus Grading Scale (see Table 8) should be used in addition to NCI CTCAE when reporting severity of CRS (see Section 5.3.5.1 for details on CRS reporting).

Table 8 ASTCT CRS Consensus Grading Scale

Grade	Symptom(s)
1	• Fever [a], with or without constitutional symptoms • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by
3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor, with or without vasopressin – Hypoxia requiring high-flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring multiple vasopressors (excluding vasopressin) – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)
5	• Death due to CRS for which the cause is not the principal factor leading to this outcome

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

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

[b] Low flow is defined as oxygen delivered at ≤ 6 mL/min, and high flow is defined as > 6 L/min.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 9 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome"). Avoid ambiguous terms such as "systemic reaction."

Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF, as appropriate.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 5.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF 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, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range

(e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 x ULN for patients with normal baseline liver function test or $>3\times$ baseline value for patients with abnormal baseline liver function tests) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN or baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ ULN or baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of GC or GEJC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Gastric Cancer or Gastroesophageal Junction Carcinoma

Medical occurrences or symptoms of deterioration that are anticipated as part of gastric cancer or gastroesophageal carcinoma should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened

in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of gastric cancer or gastroesophageal carcinoma on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of gastric carcinoma or gastroesophageal carcinoma").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose

- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab *and* tiragolumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab *and* tiragolumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take

place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see arm-specific appendices for details on pregnancy reporting requirements for each treatment arm)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board or Ethics Committee (IRB/EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until [redacted] days after the final dose of study treatment or until

initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 7 *and* Appendix 8.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as [redacted] days after the final dose of study treatment or until

initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Tiragolumab	Tiragolumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. Adverse events of special interest for each treatment arm are listed in the respective appendix for that treatment arm, as outlined in Appendix 7 *and* Appendix 8.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen, and safety analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment regimen that patients actually receive, as well as by stage (Stage 1 or Stage 2). Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and ranges. Categorical variables will be summarized through use of counts and percentages. Listings will be used in lieu of tables in the event of small sample sizes.

New baseline values will be established for the Stage 2 efficacy and safety analyses. For evaluation of tumor response, new baseline tumor assessments will be established as described in Section 4.5.6. For other endpoints (e.g., change from baseline in vital signs or laboratory test results), the last non-missing value prior to a patient's first dose during Stage 2 will serve as the new baseline.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with GC or GEJC. Cohort 1 will enroll patients with inoperable locally advanced, metastatic, or advanced GC or GEJC with adenocarcinoma confirmed as the predominant histology who have not received prior systemic therapy for advanced or metastatic disease.

Approximately $40\text{-}90$ patients will be randomly allocated to the control and experimental arms during the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm in the two stages. Patient disposition will be summarized by treatment arm in each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm in each stage.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm in each stage, and any dose modifications will be flagged. Means and

standard deviations will be used to summarize the total dose and dose intensity for each study drug. The reasons for discontinuation of study treatment will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site, and baseline ECOG Performance Status) will be summarized overall and by treatment arm in each stage.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is objective response rate (ORR) (defined as the proportion of patients with an objective response [a complete or a partial response]) during Stage 1 based on RECIST v1.1, as defined in Section 2 (see Table 2). Patients with missing or no response assessments will be classified as non-responders.

ORR, the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% CIs ([redacted]). The difference in ORR between the experimental arms and the control arm will also be calculated, along with 95% CIs using the [redacted] with continuity correction.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, OS, OS at specific timepoints (e.g., 6 and 12 months), duration of response (DOR), and disease control during Stage 1, as defined in Section 2 (see Table 2). PFS, DOR, and disease control will be determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a complete response or a partial response.

For patients who do not have documented disease progression or die, PFS and DOR will be censored at the day of the last tumor assessment.

Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The [redacted] method will be used to estimate the median for PFS, OS, and DOR, with 95% CIs constructed through use of the [redacted] method. The OS rate at specific timepoints will also be estimated using the [redacted] method, with 95% CIs calculated based on [redacted] for variance.

Disease control rate (the proportion of patients with stable disease for ≥12 weeks, a partial response, or a complete response) will be calculated for each treatment arm, with 95% CIs estimated using the [redacted].

6.5 SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm within each stage.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0, and severity of CRS will also be graded by the investigator according to the ASTCT Consensus Grading (Lee et al. 2019). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and causes of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for potential PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and specified drugs given in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs may be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm, and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs may be plotted by treatment arm, cycle, and day when appropriate and as data allow. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab or other study drug concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the concentration–time curve.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity may be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or are missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or are missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

For other study treatments for which ADAs are tested, positivity will be determined according to standard methods established for previous studies of these drugs.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported using descriptive statistics.

6.8 BIOMARKER ANALYSES

Biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy and safety endpoints (see Section 4.5.7 for more details).

6.9 INTERIM ANALYSES

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered on the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions

that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly on the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Forms (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, they will be provided in a certified translation into the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of biomarker analyses, data derived from these analyses will generally not be provided to patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details). In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of any changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to patients.

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Appendix 1
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.[1]

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.

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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, 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").

[1] 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 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) because 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 locoregional 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, because 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 prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, because 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 utilized 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 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 because 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 $\times$ 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 non-pathological 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 non-target 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, because 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 because 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 schedules 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 non-target 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.

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

having "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 non-target 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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Appendix 2
ECOG Performance Status Scale

Grade	Description
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 any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Appendix 3
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 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 for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty about any autoimmune exclusions.

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 • 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

Appendix 4
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for SC, IV, and/or endotracheal use in accordance with standard practice
- 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:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 5
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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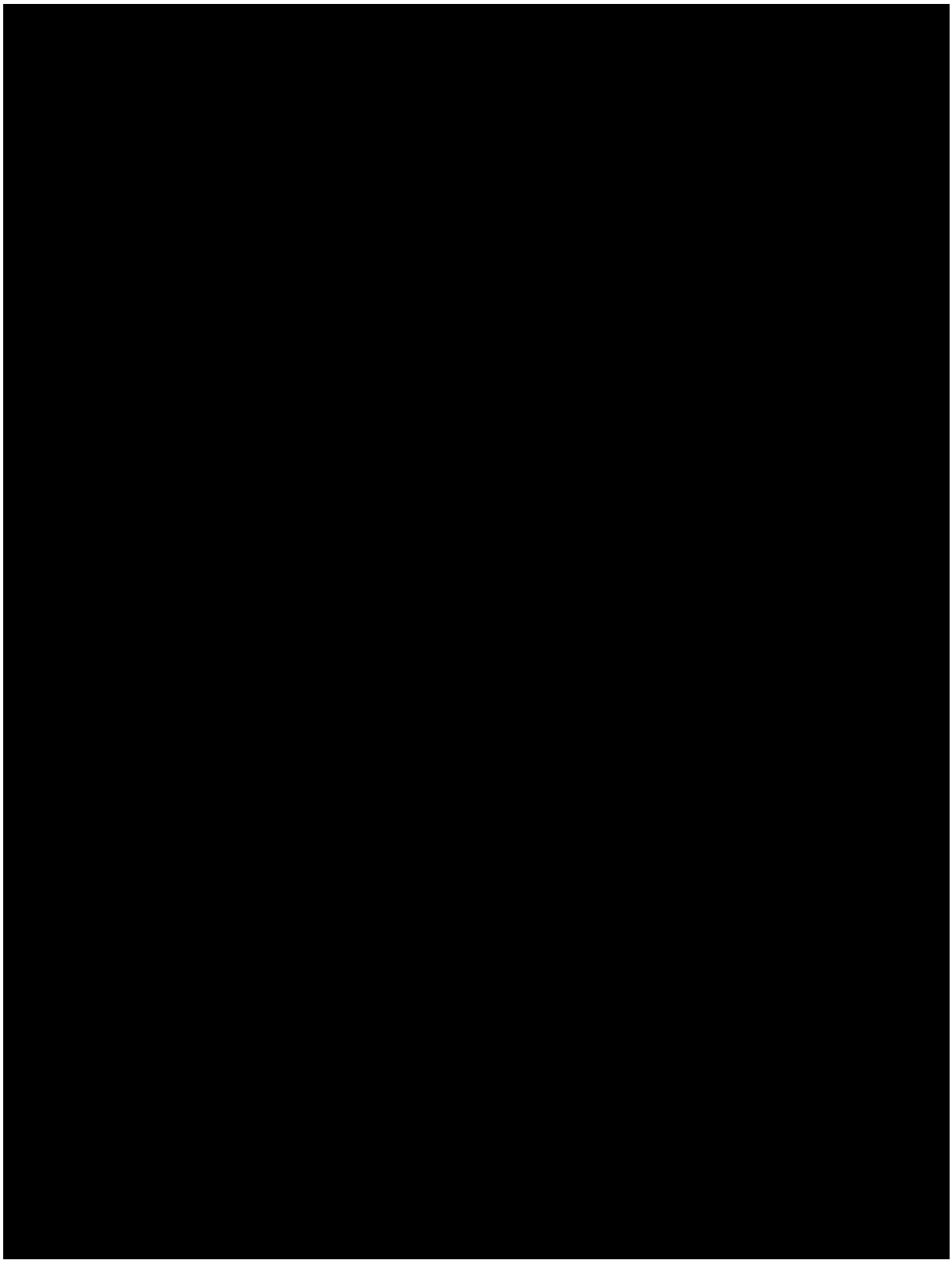

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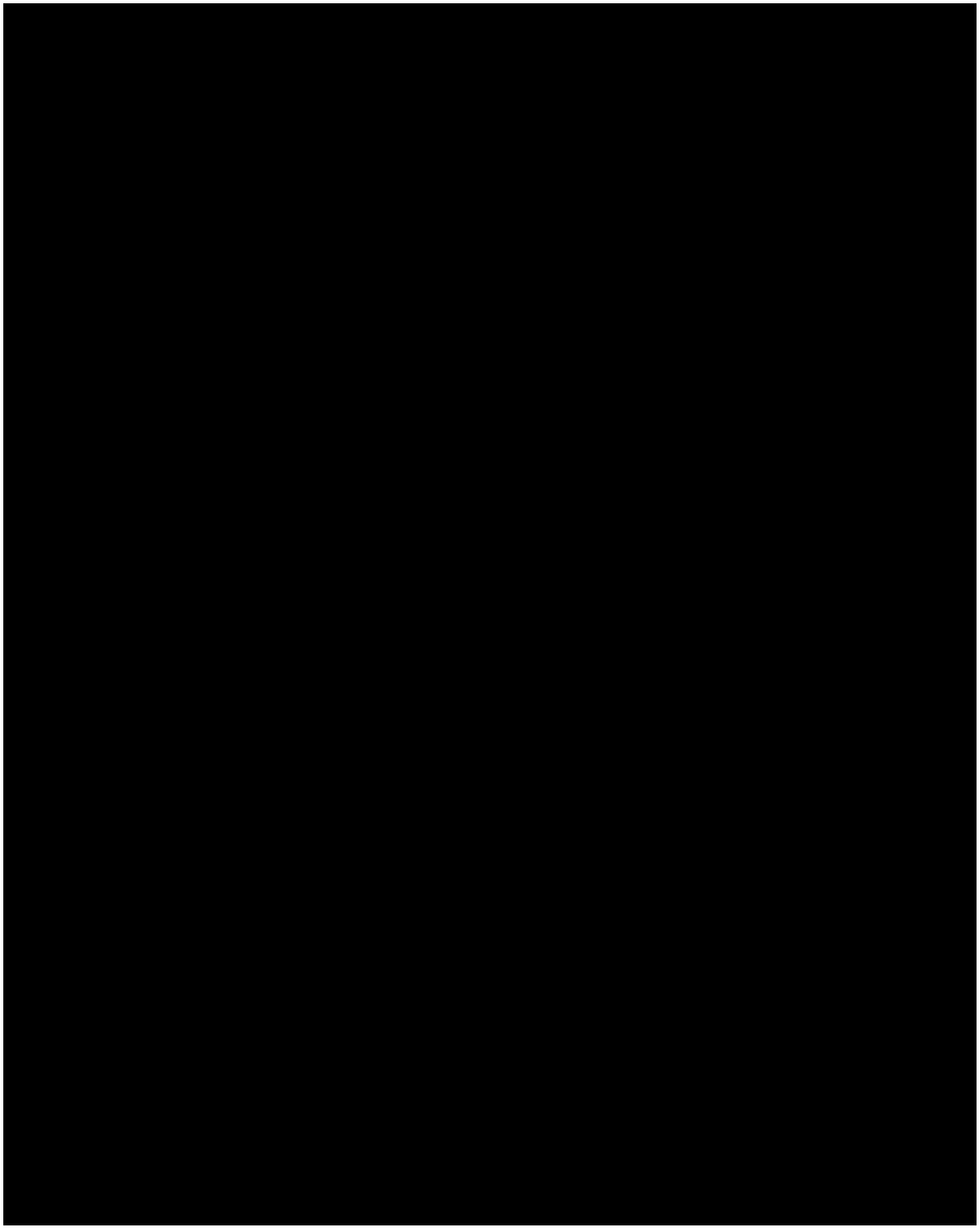

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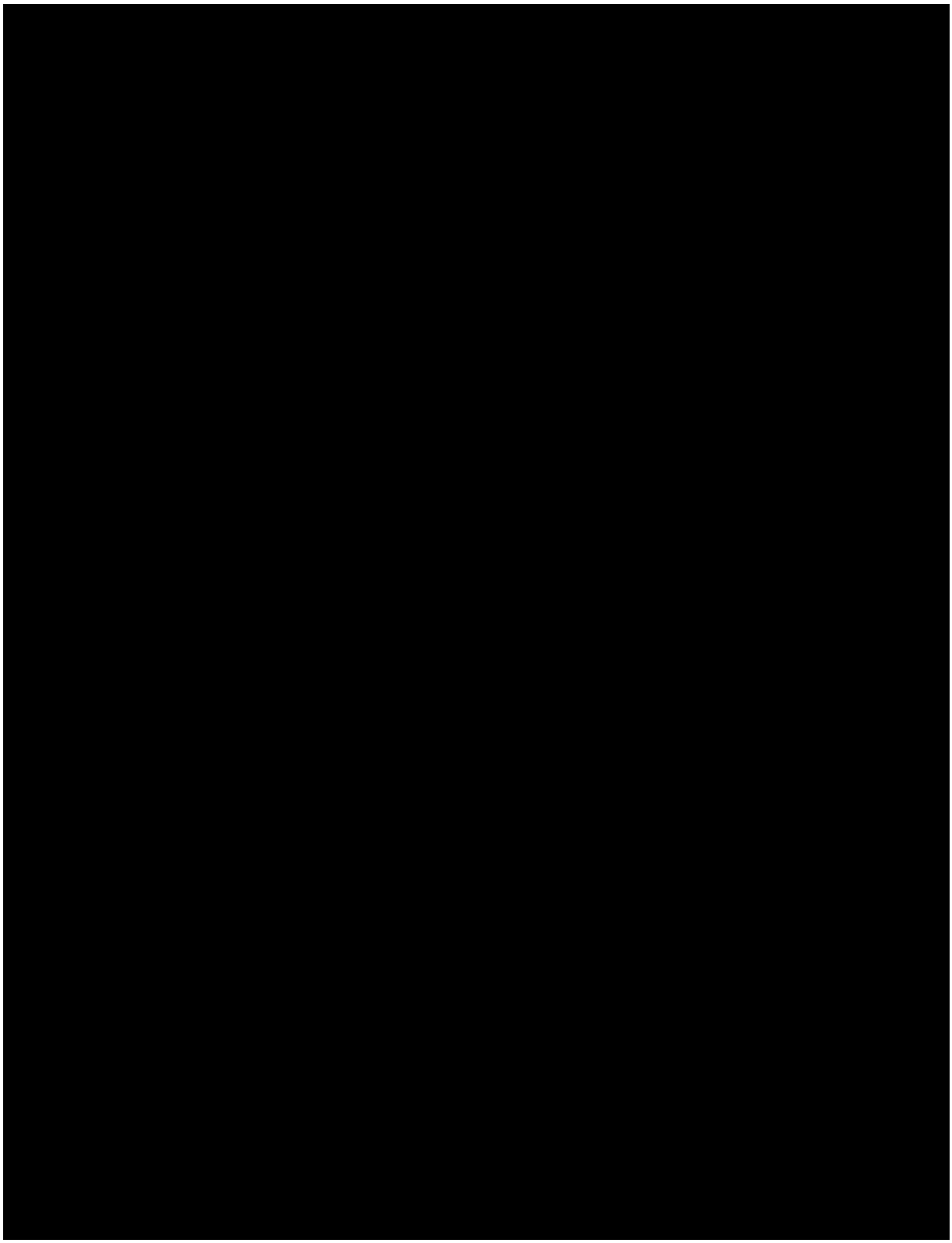

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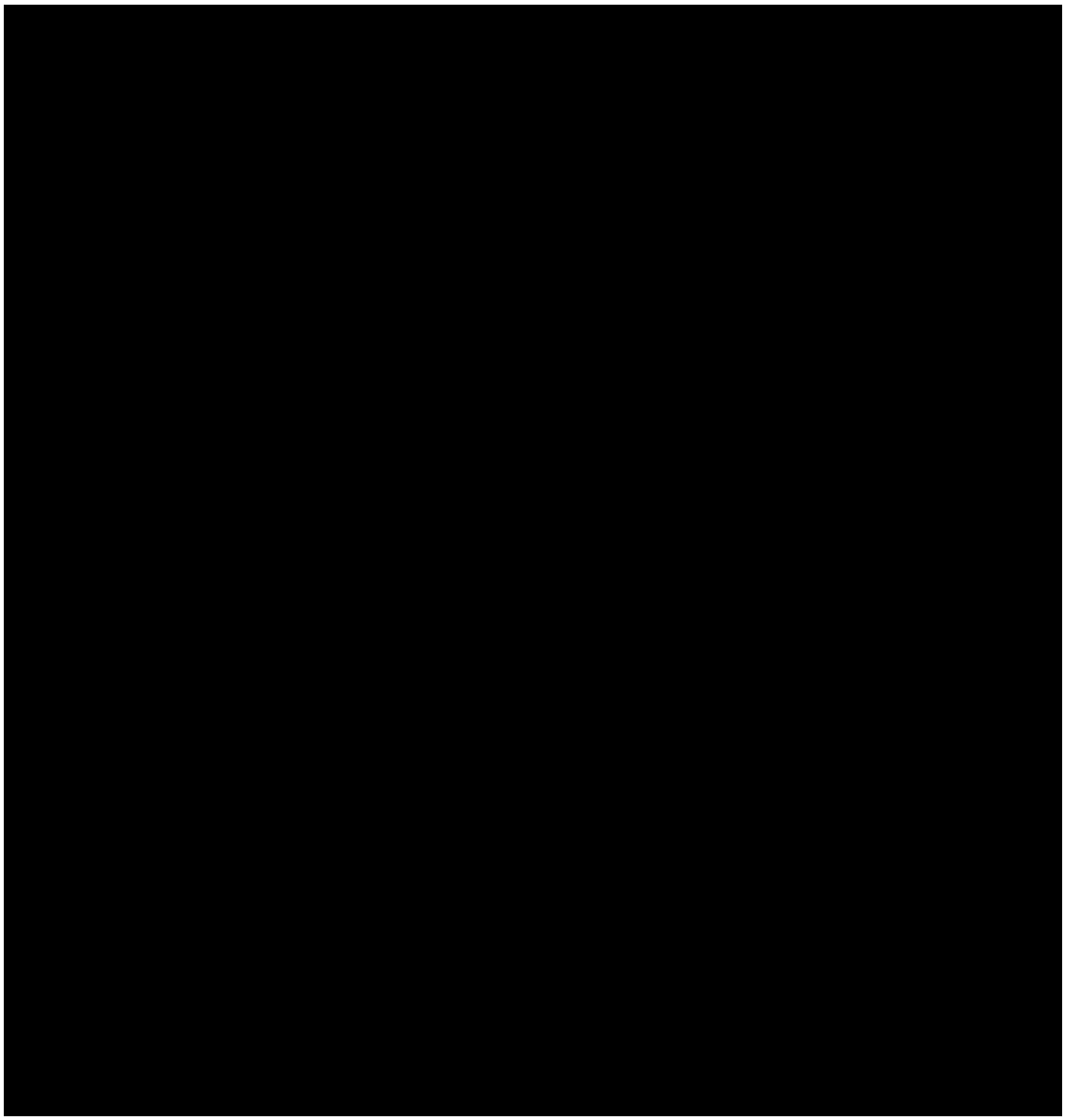

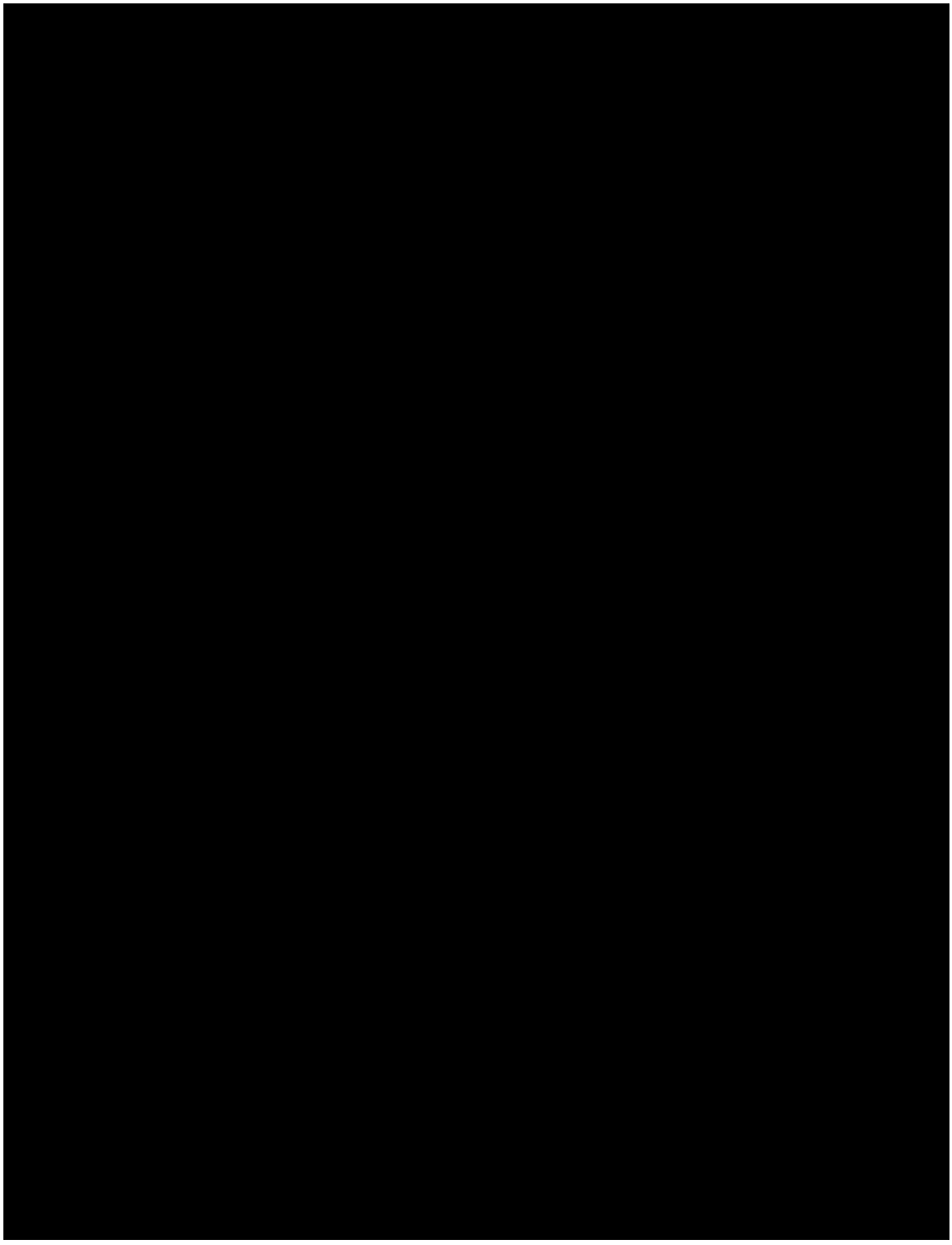

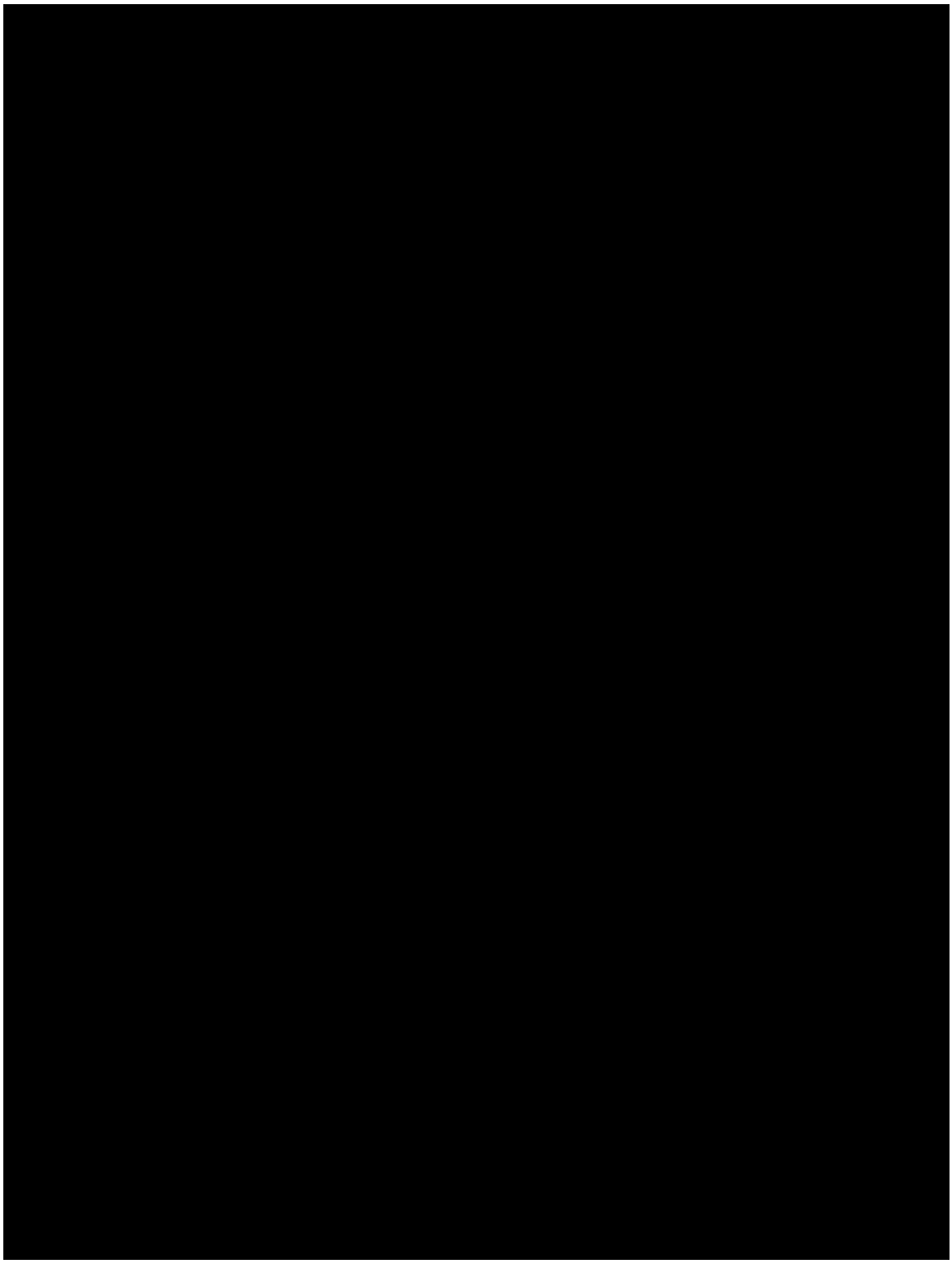

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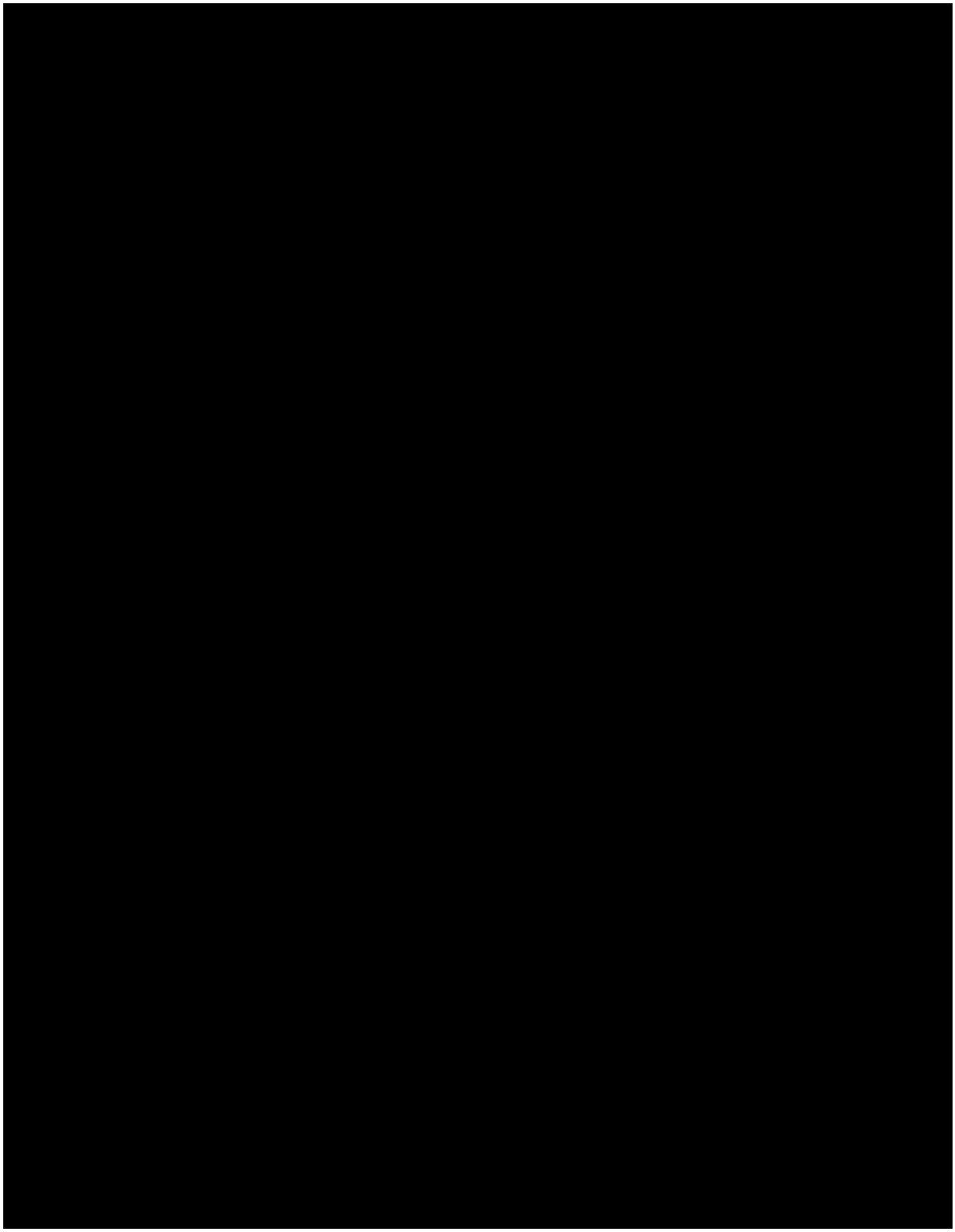

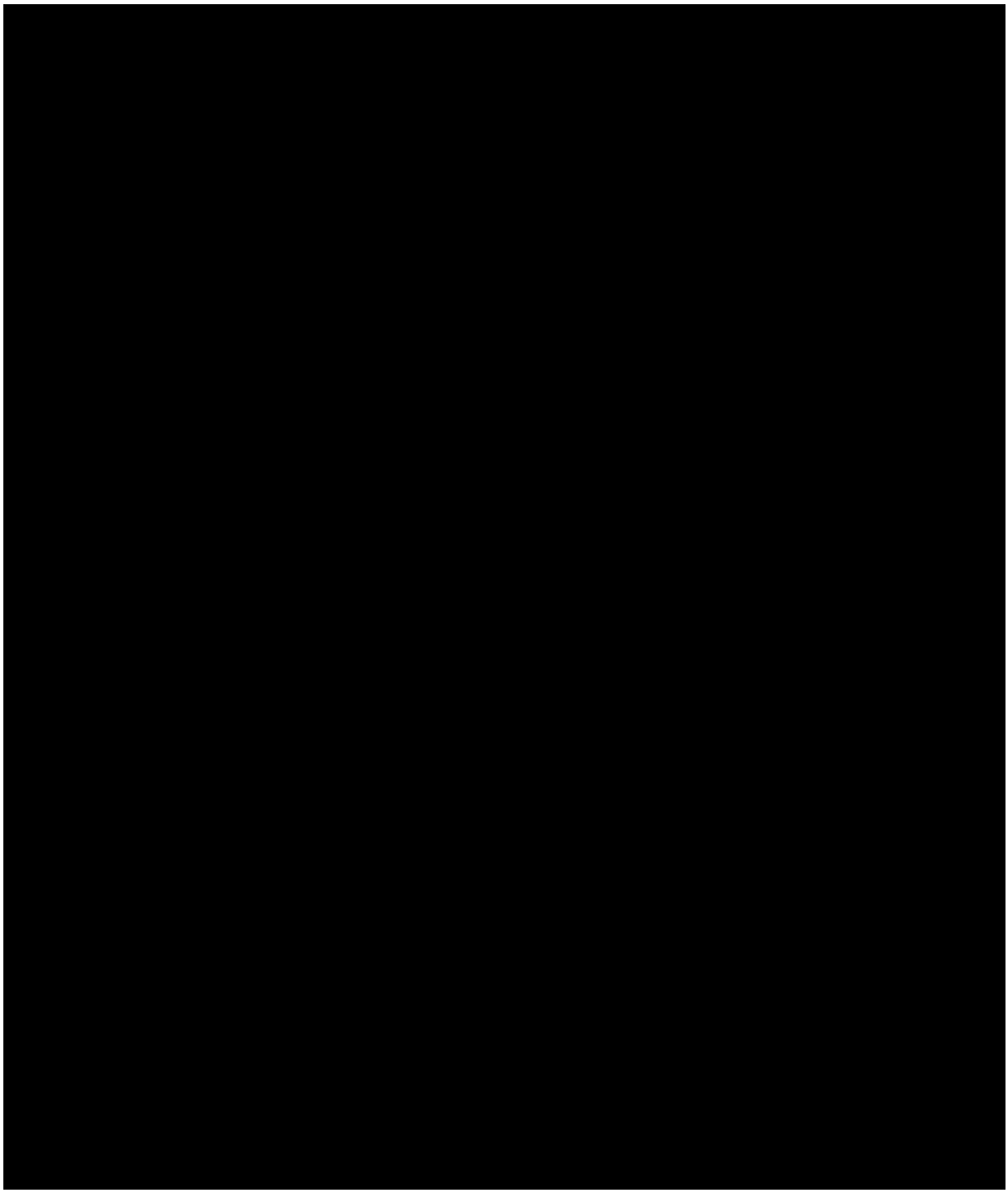

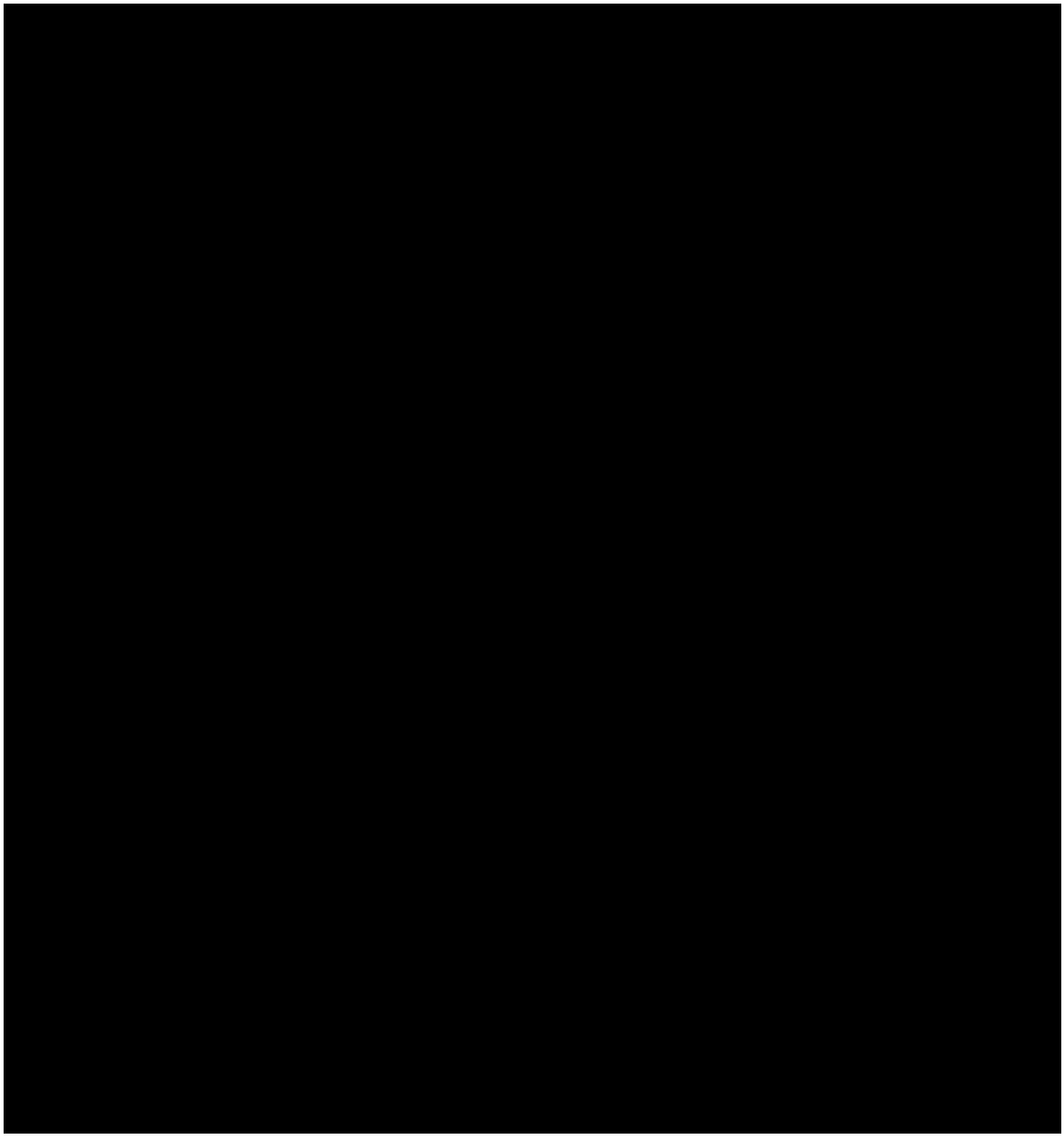

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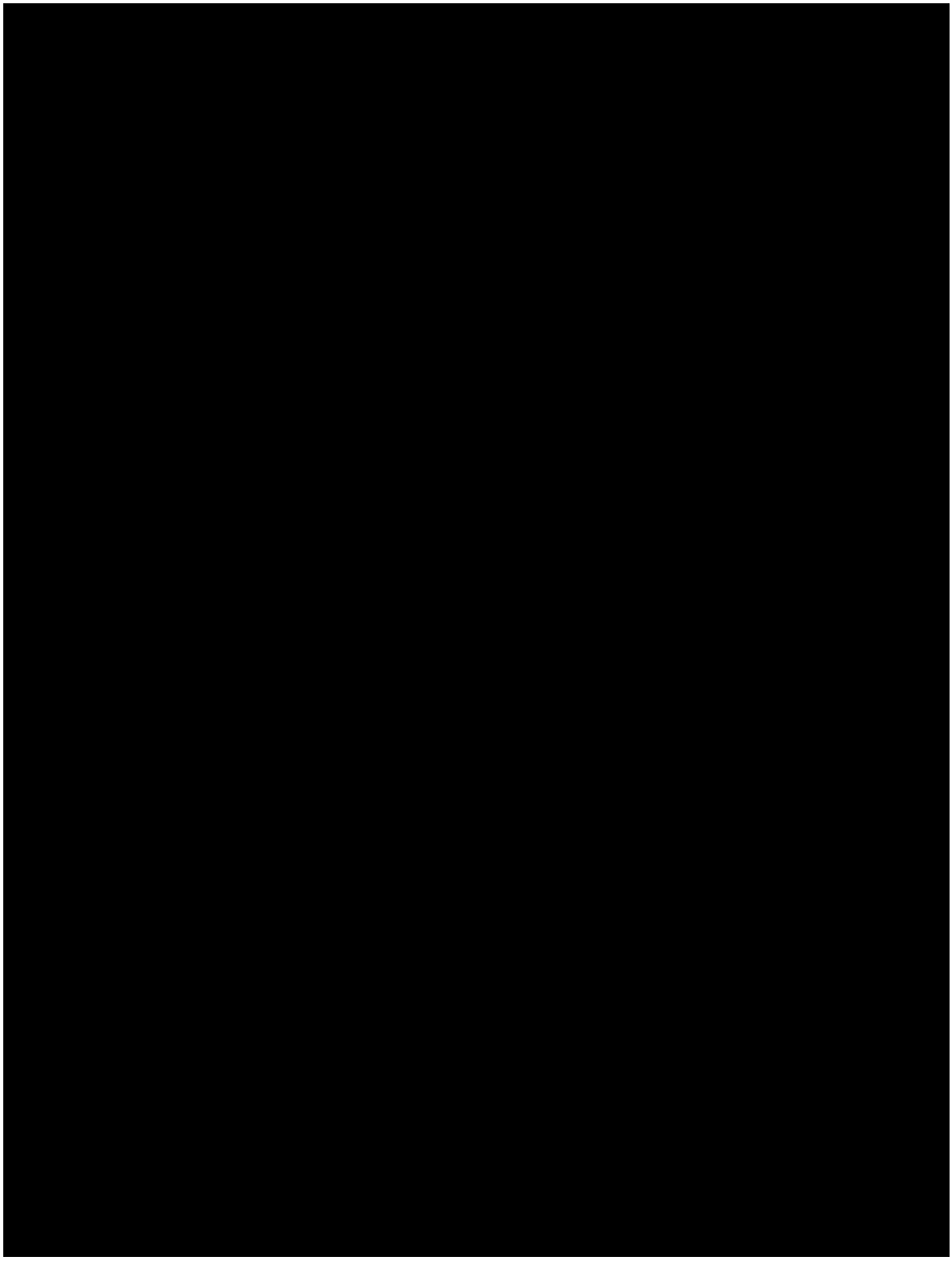

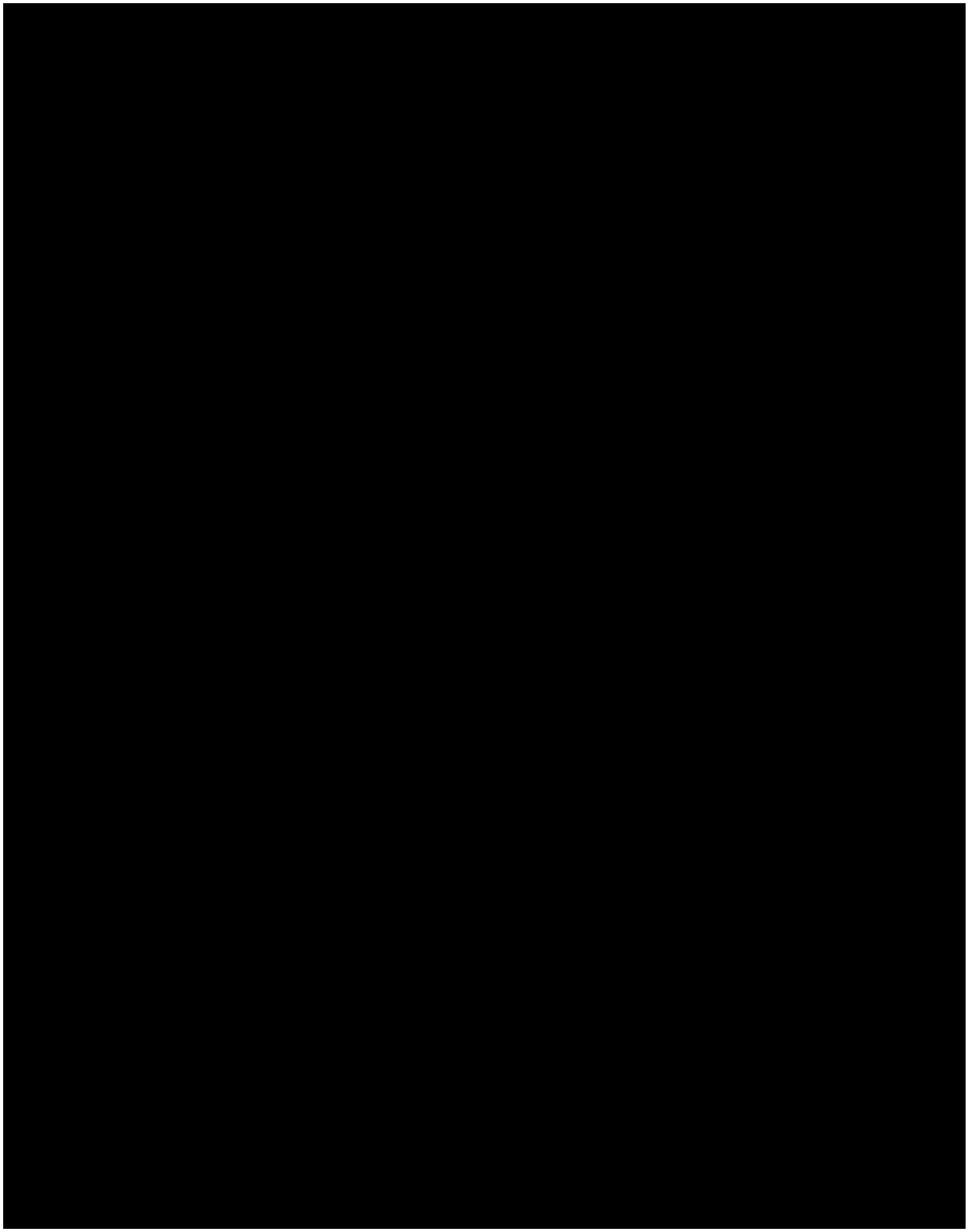

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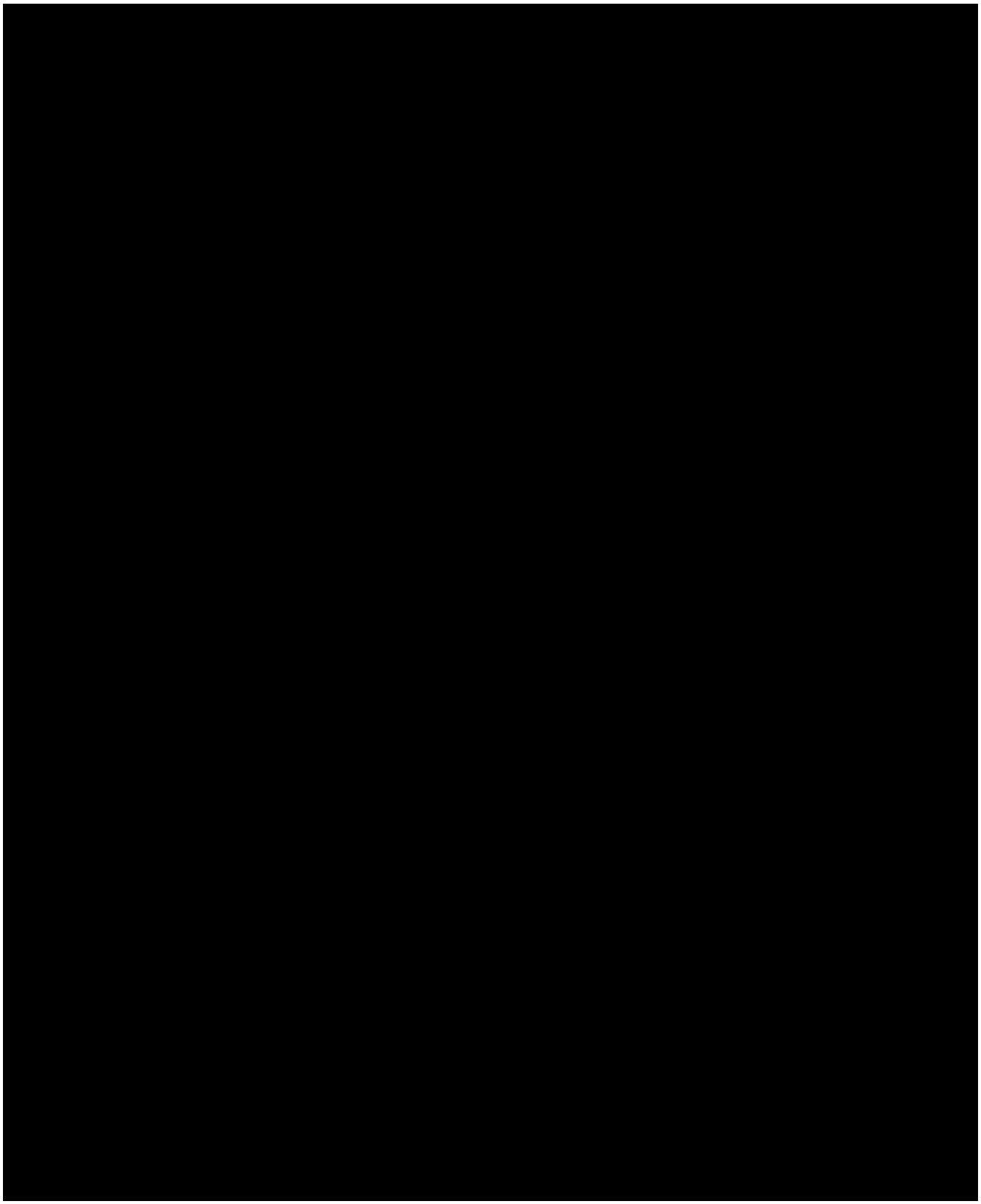

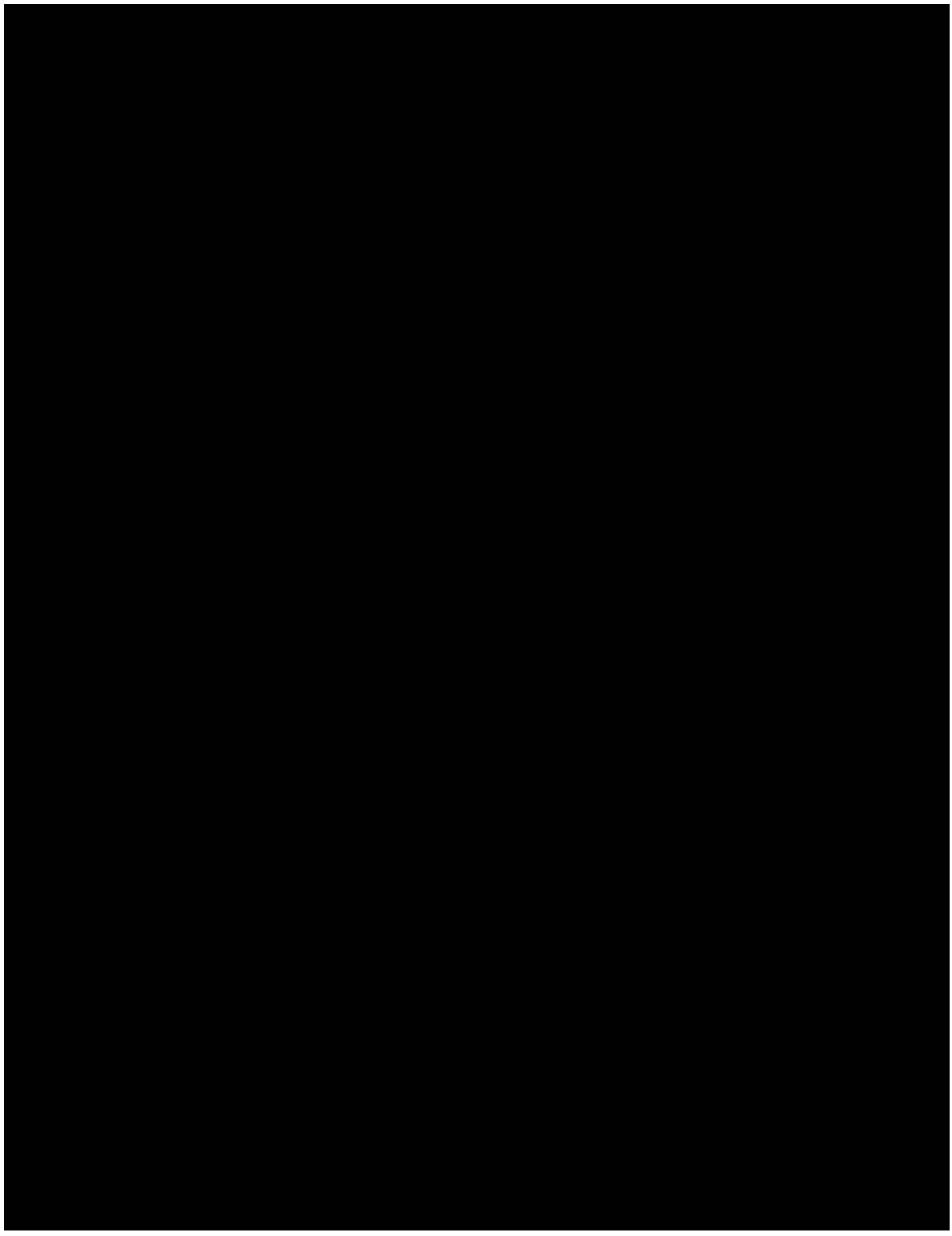

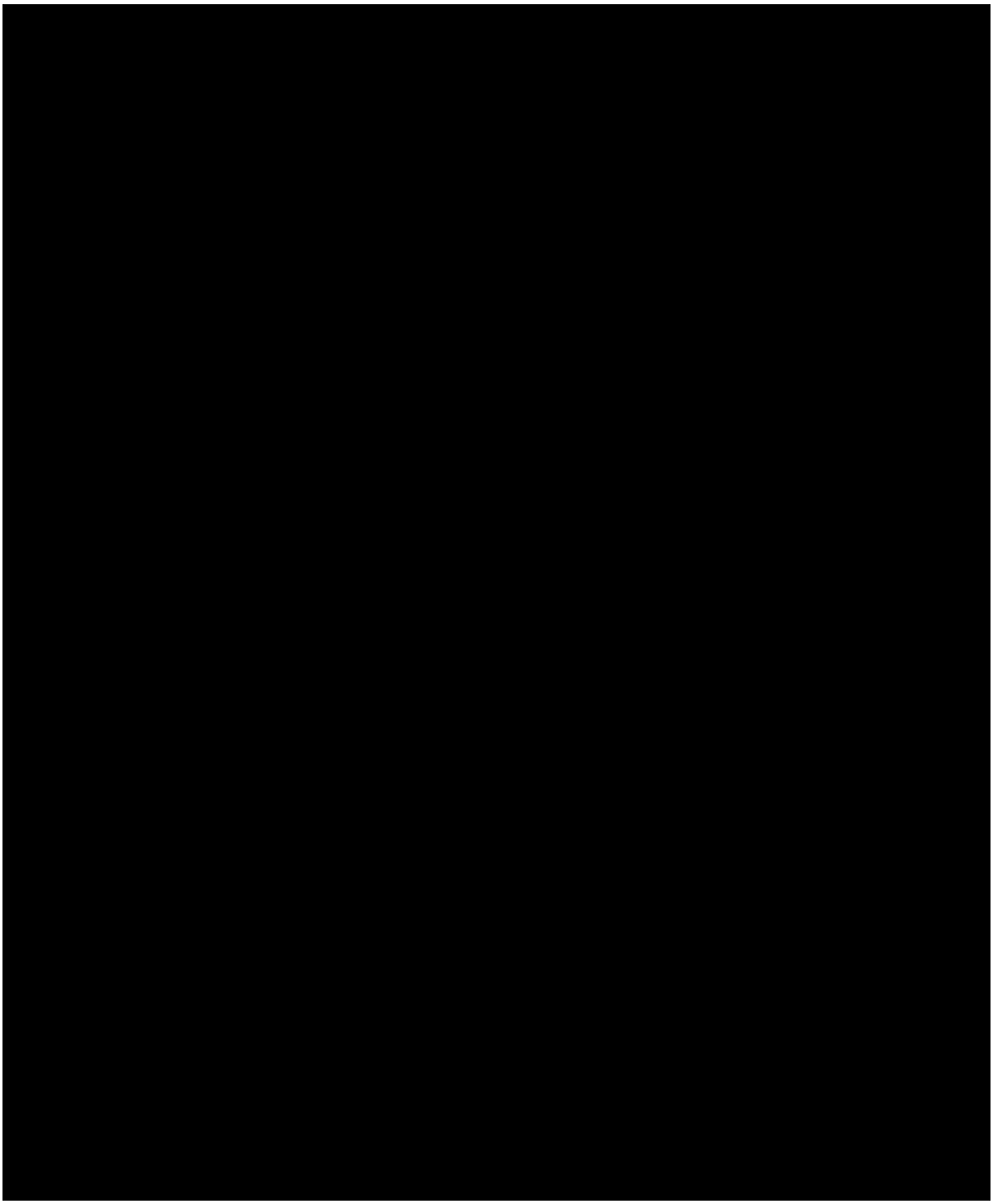

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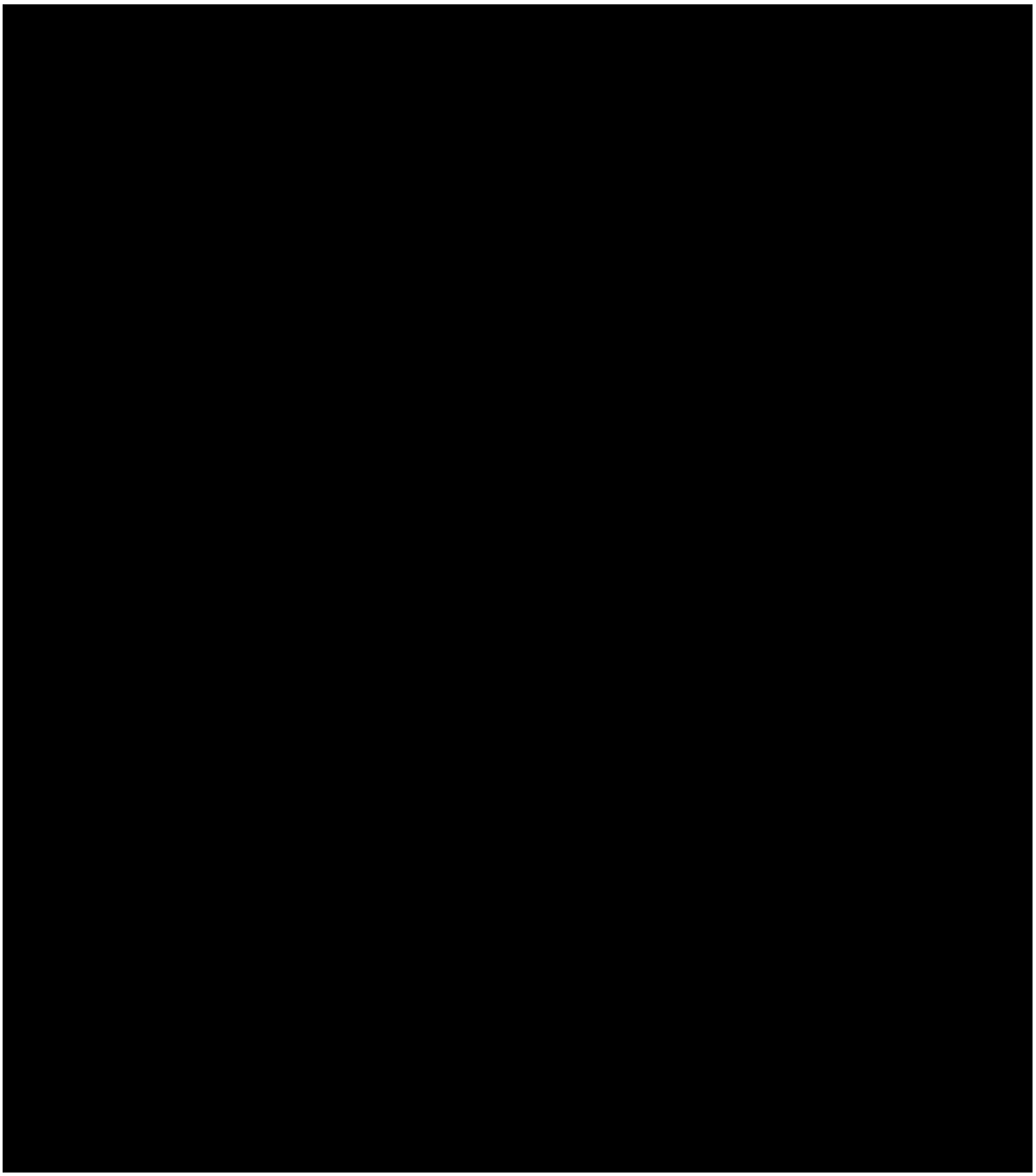

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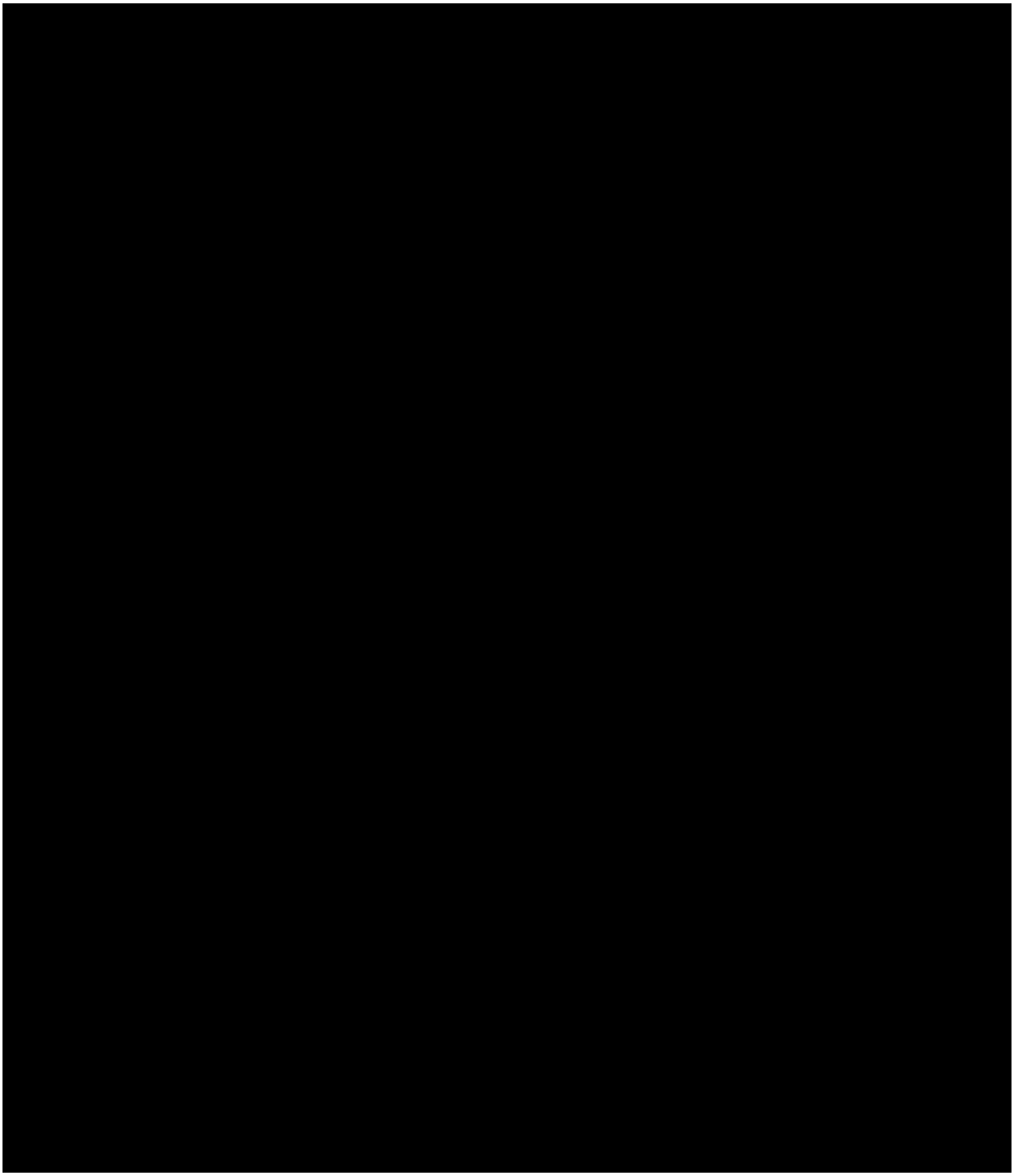

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Appendix 6
Schedule of Activities for Screening

Table 1 Schedule of Activities for Stage 1 Screening

Assessment or Procedure	Stage 1 Screening [a] (Days –28 to –1)
Informed consent	x [b]
Demographics (age, sex, and self-reported race/ethnicity)	x
Medical history and baseline conditions	x
Molecular profile of GC or GEJC (if available)	x
Vital signs [c]	x
Weight	x
Height	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
Hematology [f]	x [g]
Chemistry [h]	x [g]
Coagulation (INR and aPTT)	x [g]
TSH, free T3 (or total T3 [i]), and free T4	x [g]
[redacted]	
C-reactive protein	x [g]
Pregnancy test [k]	x [g]
Urinalysis [l]	x [g]
Baseline tumor tissue sample [m]	x
Baseline tumor assessments [n]	x
Concomitant medications [o]	x
Adverse events [p]	x

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

CT = computed tomography; [redacted] ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form;; GC = gastric carcinoma; GEJC = gastroesophageal carcinoma; [redacted] IHC = immunohistochemistry; MRI = magnetic resonance imaging; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; [redacted]

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 (within 14 days prior to Day 1 for laboratory tests) may be used; such tests do not need to be repeated for screening or re-screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[c] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[d] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. The physical examination should also include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[e] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[g] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if available), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate (or phosphorus), calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase (if available).

[i] Total T3 may be performed for sites where free T3 is not performed.

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

[j] [redacted]

[k] All women of childbearing potential will have a serum pregnancy test at screening.

[l] Urinalysis includes pH, specific gravity, glucose, protein (or albumin), ketones, and blood; dipstick permitted.

[m] Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that tumor tissue was obtained from a previous surgery or biopsy within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. See Section 4.5.7 for tissue sample requirements.

[n] All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care 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 CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., 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. Bone scans, CT or MRI scans of the neck, and CT or MRI scans of the brain should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease according to RECIST v1.1 may be used. See Section 4.5.6 for further details on tumor assessments.

[o] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment.

[p] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 7
Study Details Specific to Atezo+CAPOX Arm (Control)

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A7–1 BACKGROUND ON ATEZO + CAPOX ARM

A7–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death–1 (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 (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor 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 with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

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

A7–1.2 BACKGROUND ON CAPOX

The combination of capecitabine and oxaliplatin (CAPOX) in the first-line treatment setting of human epidermal growth factor 2 (HER2)-negative gastric carcinoma (GC) is the standard of care recommended by oncology guidelines (National Comprehensive Cancer Network 2021; Wang et al. 2021). The CAPOX regimen demonstrated survival benefit in patients with GC in the first-line treatment Phase II studies, with median progression-free survival (PFS) of about 6–7 months and overall survival (OS) of about 12–13 months (Park et al. 2008; Kim et al. 2012). In addition, the convenience of the CAPOX regimen (oral capecitabine every 2 weeks plus oxaliplatin administered by IV infusion in a 3-week cycle) has favored increased implementation of this regimen in clinical practice globally.

A7–2 RATIONALE FOR ATEZO + CAPOX ARM

A7–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, GC, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

A number of studies have indicated a role for PD-L1 in gastric carcinogenesis. In case studies, PD-L1 was expressed in tumor cells in 42%–65% of patients with GC (Wu et al. 2006; Geng et al. 2015; Kim et al. 2016). Anti–PD-1 inhibitors (i.e., nivolumab and pembrolizumab) have been investigated in the treatment of GC and have demonstrated anti-tumor activity. In the Phase III ATTRACTION-2 study, nivolumab monotherapy demonstrated superior OS benefit versus placebo (hazard ratio [HR]: 0.63) in the third- or subsequent-line setting of GC and gastroesophageal junction carcinoma (GEJC) (Kang et al. 2017). In the Phase II KEYNOTE-059 study, pembrolizumab monotherapy achieved a 33% objective response rate (ORR) by investigator assessment and 22% by central data review of patients with GC with PD-L1–expressing tumors (Bang et al. 2015).

A7–2.2 EFFECT OF CAPOX ON THE IMMUNE TUMOR MICROENVIRONMENT

There is increasing evidence that in addition to causing tumor cell death, certain conventional chemotherapies may have immunogenic effects (Zitvogel et al. 2008). Oxaliplatin, a component of CAPOX, is one of a limited number of anti-cancer agents that has been shown to induce immunogenic cell death, eliciting immune responses as a result of calreticulin exposure and release of adenosine triphosphate and high-mobility group protein (Green et al. 2009; Tesniere et al. 2010; Michaud et al. 2011). In a murine nonclinical model with transplantable and transgene-driven cancers, oxaliplatin has been shown to trigger tumor-targeting immune responses (Shalapour et al. 2015). Capecitabine, an orally administered tumor-activated 5-fluorouracil (5-FU) prodrug, is metabolized to 5-FU by means of a three-step enzymatic cascade after oral administration (Reigner et al. 2001). The treatment of tumor-bearing mice with 5-FU results in selective reduction of myeloid-derived suppressor cells in the tumor bed, without significant depletion of T cells, natural killer cells, dendritic cells, or B cells, a corresponding increase in interferon-γ production by CD8-positive tumor-infiltrating lymphocytes was observed (Vincent et al. 2010). These nonclinical results suggesting that treatment with oxaliplatin and capecitabine may enhance anti-tumor immunity.

A7–2.3 COMBINATION TREATMENT WITH ATEZOLIZUMAB AND CAPOX

Chemotherapy may modulate tumor and immune system interactions in favor of the immune system, resulting in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing the number of T-regulatory cells. Immunogenic chemotherapy such as oxaliplatin combined with immune checkpoint inhibitors can trigger T-cell infiltration to tumors and provide additive or synergistic anti-tumor activity in vivo and is expected to contribute to durable anti-tumor responses (Pfirschke and Engblom 2016).

Recently, CheckMate-649 (NCT02872116), a Phase III trial investigating nivolumab plus chemotherapy or nivolumab plus ipilimumab compared with chemotherapy alone in the first-line treatment of metastatic HER2-negative GC and GEJC, showed improved OS (14.4 vs. 11.1 months; HR: 0.71) and improved PFS (7.7 vs. 6.1 months; HR: 0.74) in patients with a PD-L1 combined positive score (CPS) ≥ 5 receiving nivolumab plus chemotherapy compared with chemotherapy alone (Moehler et al. 2020). An OS benefit (13.8 vs. 11.6 months; HR: 0.80) was also seen in an all-randomized population. With the recent regulatory approval by the U.S. Food and Drug Administration, this practice-changing study has established chemotherapy plus nivolumab as a new

standard of care for the first-line treatment of patients with HER2-negative GC and GEJC.

Nivolumab and atezolizumab are both approved for the treatment of patients with metastatic NSCLC who experienced disease progression during or following a platinum-containing chemotherapy, irrespective of PD-L1 expression. Nivolumab demonstrated superiority in OS over docetaxel based on two Phase III trials, CheckMate-017 for the treatment of squamous NSCLC and CheckMate-057 for the treatment of non-squamous NSCLC, and atezolizumab was based on the Phase III OAK trial. Of note, the two drugs showed comparable survival benefit in non-squamous populations. In the CheckMate-057 study (Borghaei et al. 2015), the median OS for nivolumab and docetaxel was 12.2 versus 9.4 months (HR: 0.73). In the OAK study (Rittmeyer et al. 2017), the median OS for atezolizumab and docetaxel was 15.6 versus 11.2 months (HR: 0.73).

In light of the totality of evidence described above, together with the anticipated evaluation of standard of care for the first-line treatment of patients with HER2-negative GC and GJEC following the positive readout of CheckMate-649, blockade of the PD-L1/PD-1 pathway with atezolizumab in combination with CAPOX chemotherapy may result in an enhanced protective anti-tumor immune response, supporting the selection of this treatment combination to be a control for other experimental arms with innovative combination therapies.

A7–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH CAPOX

Capecitabine, an orally administered tumor-activated 5-FU prodrug, is metabolized to 5-FU by means of a three-step enzymatic cascade after oral administration (Reigner et al. 2001). The safety and the preliminary anti-tumor activity of the combination of atezolizumab, bevacizumab, and FOLFOX (5-FU in combination with oxaliplatin) have been evaluated in the Phase I study GP28328 in oxaliplatin treatment–naive patients with solid tumors, including metastatic colorectal cancer. Adverse events observed thus far are consistent with the known risks of each study treatment. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with additive severe (Grade ≥ 3) toxicities, indicating that atezolizumab can be safely combined with standard chemotherapy.

As of the clinical cutoff date, 1 September 2015, 23 efficacy-evaluable oxaliplatin treatment–naive patients with metastatic colorectal cancer had been treated in the first-line setting. Investigator-assessed ORR (confirmed response per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]) was 52.2%, and all 12 responders had partial responses. The median investigator-assessed duration of

response per RECIST v1.1 for the 12 responders was 11.4 months. The median investigator-assessed PFS per RECIST v1.1 was 14.1 months.

Detailed clinical study results for atezolizumab can be found in the Atezolizumab Investigator's Brochure.

A7–2.5 BENEFIT–RISK ASSESSMENT

Capecitabine is the prodrug of 5-FU and taking into account the manageable and tolerable safety profile of FOLFOX (5-FU in combination with oxaliplatin) plus atezolizumab described in Study GP28328, the combination of CAPOX appears to have promising therapeutic potential in the treatment of solid tumors such as GC.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please see Section 1.4.

A7–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + CAPOX ARM

A7–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. Package Insert).

A7–3.2 RATIONALE FOR CAPOX DOSE AND SCHEDULE

The CAPOX regimen (1000 mg/m^2 capecitabine taken orally twice a day for 14 days followed by 7 days off and 130 mg/m^2 oxaliplatin administered intravenously on Day 1 Q3W) at the recommended doses has been used in multiple Phase III trials (Boku et al. 2019; Moehler et al. 2020) represents an acceptable combination of capecitabine and oxaliplatin for patients with GC or GEJC.

Standard treatment for late-stage GC is recommended to be 4–6 months by Chinese Society of Clinical Oncology guidelines (Wang et al. 2021). In this study, the discontinuation of chemotherapy beyond Cycle 6 (administered in 21-day cycles) will occur because the majority of patients with GC and GEJC achieve maximum tumor reduction by Cycle 6 and discontinuation of chemotherapy will improve the tolerability of continued dosing with maintenance treatment with atezolizumab.

A7–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + CAPOX ARM

A7–4.1 TREATMENT IN ATEZO + CAPOX ARM

A7–4.1.1 Formulation and Packaging

A7–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a [redacted]-mL glass vial. The vial contains approximately [redacted] mL (1200 mg) of atezolizumab solution.

For information on the formulation of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A7–4.1.1.2 CAPOX

Refer to the oxaliplatin and capecitabine prescribing information for details on the respective formulations and storage instructions. Oxaliplatin and capecitabine will be either provided by Sponsor or sourced commercially by sites.

For information on the formulation, packaging, and handling of the CAPOX agents, refer to the local prescribing information for each agent.

A7–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus CAPOX (Atezo + CAPOX) arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.2 for details). [redacted]

Table 1 Treatment Regimen for Atezo + CAPOX Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Capecitabine 1000 mg/m^2 orally twice daily on Days 1–14 [a] • Oxaliplatin 130 mg/m^2 by IV infusion on Day 1 [a]

Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin.

[a] Treatment for up to six cycles.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12. No safety data related to overdosing of atezolizumab are available to date.

A7–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 4. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, 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 and 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics 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 clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 5.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A7–5.1.4. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures).

The acceptable length of treatment interruption 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. The Medical Monitor is available to advise as needed.

A7–4.1.2.2 CAPOX

Treatment will be administered as follows during each 21-day cycle for up to 6 cycles:

- Capecitabine (1000 mg/m^2) orally twice a day on Days 1–14
- Oxaliplatin (130 mg/m^2) by IV infusion on Day 1 at least 5 minutes after completion of the atezolizumab infusion

The rates of drug administration for oxaliplatin may follow the institutional guidelines. Patients may be premedicated with 5-HT$_3$–receptor antagonists or other standard-of-care methods to control nausea and vomiting. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A7–5.1.4. CAPOX treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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. The Medical Monitor is available to advise as needed.

A7–4.2 CONCOMITANT THERAPY FOR ATEZO + CAPOX ARM

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 from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A7–4.2.1 Permitted Therapy for Atezo + CAPOX Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see A7–4.2.3).
- Megestrol acetate administered as an appetite stimulant

- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and CAPOX may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab 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 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; see Appendix 4).

A7–4.2.2 Cautionary Therapy for Atezo + CAPOX Arm

A7–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, 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 therapy (refer to Appendix 5 for details).

A7–4.2.2.2 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 (see Section A7–4.2.3) may be used during the study at the discretion of the investigator.

A7–4.2.2.3 Medications Given with Precaution Concomitantly with CAPOX

The following medications should be used with precaution during treatment with CAPOX:

- Anticoagulants: Patients who receive concomitant capecitabine and oral coumadin-derivative anticoagulant therapy such as warfarin should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose.
- Phenytoin: Monitor phenytoin levels in patients taking capecitabine concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- Leucovorin: The concentration of 5-FU is increased and its toxicity may be enhanced by leucovorin.
- CYP2C9 substrates: Patients who are treated with capecitabine and other sensitive CYP2C9 substrate or a CYP2C9 substrate with narrow therapeutic index should be closely monitored for toxicity.
- Because platinum-containing species are eliminated primarily through the kidneys, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds. Co-administration of oxaliplatin with medicinal products known to cause nephrotoxicity is not recommended.

A7–4.2.3 Prohibited Therapy for Atezo + CAPOX Arm

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, for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A7–4.2.1
- Concomitant use of herbal therapies and traditional Chinese medicine with anti-cancer activity included in the label
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Use of allopurinol during treatment with capecitabine
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the final dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) 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

A7–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + CAPOX ARM

Contraception requirements for women and men in the Atezo + CAPOX arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent 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 capecitabine, and 9 months after the final dose of oxaliplatin.

  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), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (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 pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 3 months after the final dose of capecitabine, and 6 months after the final dose of oxaliplatin 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 preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

  Male patients should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from therapy with capecitabine and oxaliplatin.

A7–5 ASSESSMENT OF SAFETY FOR ATEZO + CAPOX ARM

A7–5.1 SAFETY PLAN FOR ATEZO + CAPOX ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and CAPOX in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A7–5.1.1, A7–5.1.2, and A7–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A7–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study.

Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.4–5.6.

A7–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 5 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A7–5.1.2 Risks Associated with CAPOX

In prior clinical trials of capecitabine, the following safety signals were identified: diarrhea, nausea, vomiting, stomatitis, cardiotoxicity, hepatotoxicity, hand–foot syndrome, and hematologic toxicity. Patients should be advised to avoid prolonged exposure to sunlight because of the risk of photosensitivity with capecitabine.

In prior clinical trials of oxaliplatin, the following safety signals were identified: sensory and/or motor neuropathy, allergic reactions, pharyngolaryngeal dysesthesia, interstitial lung disease and pulmonary fibrosis, hepatotoxicity, and hematologic toxicity.

For more details regarding the safety profile of capecitabine and oxaliplatin, see the respective local prescribing information.

A7–5.1.3 Risks Associated with Combination Use of Atezolizumab and CAPOX

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and CAPOX: hepatic, gastrointestinal (primarily, diarrhea), hepatotoxicity, and pulmonary events.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing infection in patients receiving atezolizumab in combination with chemotherapy.

A7–5.1.4 Management of Patients Who Experience Specific Adverse Events in the Atezolizumab + CAPOX Arm

A7–5.1.4.1 Dose Modifications

Atezolizumab

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

Capecitabine

The capecitabine dose can be modified as presented in the Table 3 for the management of drug-related toxicities. Once the dose has been reduced, it cannot be increased later. Omitted doses of capecitabine because of toxicity will not be replaced.

Table 3 Dose Modification for Capecitabine for Drug-Related Toxicities

Toxicity [a]	Action to Be Taken for Current Treatment	Dose Modification for the Next Treatment (% of Starting Dose)
Grade 1	Maintain dose level.	Maintain dose level.
Grade 2		
First occurrence	Withhold until resolved to Grade 1 or better.	100% (1000 mg/m^2)
Second occurrence		75% (750 mg/m^2)
Third occurrence		50% (500 mg/m^2)
Fourth occurrence	Discontinue permanently.	—
Grade 3		
First occurrence	Withhold until resolved to Grade 1 or better.	75% (750 mg/m^2)
Second occurrence		50% (500 mg/m^2)
Third occurrence	Discontinue permanently.	—
Grade 4		
First occurrence	Discontinue permanently or continue at the discretion of the investigator once the event has resolved to Grade 1 or better.	50% (500 mg/m^2)

[a] Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Oxaliplatin

Dose Modifications for Patients with Neurotoxicity

- For Grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia) or limiting instrumental activities of daily living, omit oxaliplatin. When toxicity resolves to Grade 1 or better, resume oxaliplatin to 75% of the initial dose.
  If oxaliplatin is omitted for 6 weeks (two consecutive cycles) for neurologic toxicity, discontinue oxaliplatin.

- For Grade 3 and 4 peripheral sensory neuropathy (severe paresthesia or dysesthesia) or limiting self-care activities of daily living), discontinue oxaliplatin.

Dose Modifications for Patients with Renal Impairment

- For normal renal function or mild to moderate renal impairment (creatinine clearance >50 mL/min), the full dose of oxaliplatin can be administered.
- For severe renal impairment, the oxaliplatin dose should be reduced to 75% of the initial dose.

Dose Modifications for Patients with Hematologic Toxicity

- For Grade 2 and 3 thrombocytopenia, the oxaliplatin dose should be reduced to 75% of the initial dose. For Grade 4 thrombocytopenia, the dose should be reduced to 50% of the initial dose.
- For Grade 3 and 4 neutropenia or febrile neutropenia, the oxaliplatin dose should be reduced to 75% of the initial dose.

A7–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab 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 can be resumed. If atezolizumab is withheld for >12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

The CAPOX treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If CAPOX has been withheld for >21 days because of toxicity, the patient should be discontinued from CAPOX, unless the patient is likely to derive clinical benefit. The decision to re-challenge patients with CAPOX should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If one component of the combination (atezolizumab or CAPOX) is discontinued, the other component may be continued if the patient is likely to derive clinical benefit, as determined by the investigator. The Medical Monitor is available to advise as needed. Treatment with CAPOX will continue for up to six cycles and patients will be offered continued treatment with atezolizumab as long as they are experiencing clinical benefit in the opinion of the investigator. If oxaliplatin treatment is discontinued during the first six cycles, patients are encouraged to continue chemotherapy with capecitabine and

atezolizumab, as long as they are experiencing clinical benefit in the opinion of the investigator. The Medical Monitor is available to advise as needed. If capecitabine treatment is discontinued during the first six cycles, patients are encouraged to continue chemotherapy with oxaliplatin and atezolizumab, provided they are experiencing clinical benefit in the opinion of the investigator. The Medical Monitor is available to advise as needed.

A7–5.1.4.3 Management Guidelines for Adverse Events

Appendix 5 provides guidelines for the management of patients who experience atezolizumab-associated adverse events. It is recommended that atezolizumab be withheld or discontinued per the guidelines provided in Appendix 5.

For cases in which management guidelines are not covered in Appendix 5, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Guidelines for management of patients who experience specific adverse events related to CAPOX regimen are provided in Section A7–5.1.4.1. The treating physician may use discretion in modifying the dose modification guidelines, depending on the severity of toxicity and an assessment of the benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care.

Chemotherapy should be discontinued if ANC and platelets do not recover to ≥1000/μL and ≥75,000/μL, respectively, after treatment is delayed by 3 weeks.

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

A7–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + CAPOX ARM

A7–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, 6 months after the final dose of capecitabine, or 9 months after the final dose of oxaliplatin. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the

Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A7–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the final dose of capecitabine or 6 months after the final dose of oxaliplatin. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A7–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no

more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A7–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly or birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A7–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + CAPOX ARM

Table 4 Schedule of Activities for Atezo + CAPOX Arm

Assessment or Procedure	Stage 1 Screening (see Appendix 6) Days −28 to −1	Treatment Cycles (21-day cycles) [a] Cycle 1 [b] Day 1	Treatment Cycles (21-day cycles) [a] Cycles ≥ 2 Day 1 (± 3 days)	Treatment Discontinuation [c]	Follow-Up Every 3 Months
Molecular profile of GC or GEJC (if available)	See Appendix 6.	Whenever updated information becomes available			
Vital signs [d, e]		x	x	x	
Weight [e]		x	x	x	
Complete physical examination [f]				x	
Limited physical examination [e, g]		x	x		
ECOG Performance Status [e]		x	x	x	
ECG [e, h]		Perform as clinically indicated.			
Hematology [i]		x [j, k]	x [j]	x	
Chemistry [l]		x [j. k]	x [j]	x	
TSH, free T3 (or total T3),and free T4 [m]		x [j, k, m]		x	
[redacted]					
C-reactive protein		x [j, k]			
Pregnancy test [o]		x [j, k]	x [j]	x	x [o]
Urinalysis [p]		Perform as clinically indicated.			

Table 4 Schedule of Activities for Atezo + CAPOX Arm (Control) (cont.)

Assessment or Procedure	Stage 1 Screening (see Appendix 6)	Treatment Cycles (21-day cycles) [a]			Follow-Up
		Cycle 1 [b]	Cycles ≥ 2		
	Days −28 to −1	Day 1	Day 1 (± 3 days)	Treatment Discontinuation [c]	Every 3 Months
Biomarker sample (blood, serum, plasma, and WBC)	See Appendix 6.	See Table 5.			
Tumor biopsy		x [q]			
Tumor biopsy (optional)		x [r]			
Stool sample *(optional)*		x [s]	x [s]		
Tumor response assessments		x [t, u]			
Concomitant medications [v]		x	x	x	
Adverse events [w]		x	x	x [w]	x [w]
Atezolizumab administration [x, y]		x	x		
CAPOX administration [x, z]		x	x		
Survival follow-up and anti-cancer treatment					x [aa]

Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; GC = gastric carcinoma; GEJC = gastroesophageal junction carcinoma; [redacted]

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] [redacted]

[c] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.2 for details) may be used as the treatment discontinuation visit.

Table 4 Schedule of Activities for Atezo + CAPOX Arm (Control) (cont.)

[d] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. During visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. During visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[j] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if available), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate (or phosphorus), calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase (if available).

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, and so on).

[n] [redacted]

[o] All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment and at 3 months and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Table 4 Schedule of Activities for Atezo + CAPOX Arm (Control) (cont.)

[p] Urinalysis includes pH, specific gravity, glucose, protein (or albumin), ketones, and blood; dipstick permitted.

[q] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.7 for tissue sample requirements.

[r] Patients who consent to optional biopsies will undergo tumor biopsy sample collection *8* weeks (±7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[s] Patients *who consent to providing optional* stool sample *will receive the collection device for the stool sample* prior to Day1 of Cycle1 and Day 1 of Cycle 3. Samples to be collected by predose (i.e., before the visit). Patients will be instructed to return the collection device with the stool sample to the site on the Day 1, Cycle 1 and Day 1, Cycle 3 (±1 week) visit. If a patient does not return the collection device at the Day 1, Cycle 3 visit, he or she may return the collection device at the Day 1, Cycle 4 visit.

[t] Patients will undergo tumor assessments every 6 weeks (±1 week) during the first 48 weeks (from Day 1 of Cycle 1) and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays until confirmed radiographic disease progression, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 4.5.6 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new non−protocol-specified anti-cancer therapy.

[u] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the tumor assessment schedule. 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 (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. 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).

[v] Concomitant medication includes 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 from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Table 4 Schedule of Activities for Atezo + CAPOX Arm (Control) (cont.)

[w] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[x] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

[y] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. See Section A7–4.1.2.1 for details on atezolizumab infusions (including measurement of vital signs).

[z] Capecitabine (1000 mg/m^2) will be administered orally twice daily on Days 1–14 and oxaliplatin (130 mg/m^2) will be administered by IV infusion on Day 1 and at least 5 minutes after completion of the atezolizumab infusion. Treatment will continue for up to six cycles.

[aa] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only. For an experimental arm, in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining approximately 20% of patients will be discontinued from the study).

Table 5 Schedule of Pharmacokinetic, Anti-Drug Antibody, and Blood Biomarker Samples for Atezo+CAPOX Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (serum and blood) • Biomarker (plasma and WBC) [a]
	30 (± 10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycles 2, 3, 4, 8, 12, and 16	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (serum and blood) on Day 1 of Cycles 2 and 3 only
Treatment discontinuation visit (≤ 30 days after final dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (serum and blood) • Biomarker (plasma) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin; ctDNA = circulating tumor DNA; PK = pharmacokinetic; WES = whole exome sequencing.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. Blood collections for biomarker assessment (e.g., cytokines, chemokines, gene expression profiling, ctDNA and WES of WBC-derived DNA as germline control) are applicable only after approval from local regulatory authorities. Based on emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Blood collected at site for central processing of plasma and WBC samples.

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Appendix 8
Study Details Specific to Atezo+CAPOX+Tira Arm

TABLE OF CONTENTS

A8–1 BACKGROUND ON ATEZO + CAPOX + TIRA ARM

A8–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death–1 (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 (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor 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 with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

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

A8–1.2 BACKGROUND ON CAPOX

The combination of capecitabine and oxaliplatin (CAPOX) in the first-line treatment setting of human epidermal growth factor 2 (HER2)-negative gastric carcinoma (GC) is the standard of care recommended by oncology guidelines (National Comprehensive Cancer Network 2021; Wang et al. 2021). The CAPOX regimen demonstrated survival benefit in patients with GC in the first-line treatment Phase II studies, with median progression-free survival (PFS) of about 6–7 months and overall survival (OS) of about 12–13 months (Park et al. 2008; Kim et al. 2012). In addition, the convenience of the CAPOX regimen (oral capecitabine every 2 weeks plus oxaliplatin administered by IV infusion in a 3-week cycle) has favored increased implementation of this regimen in clinical practice globally.

A8–1.3 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). 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 used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients.

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

A8–2 RATIONALE FOR ATEZO + CAPOX + TIRA ARM

A8–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, GC, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

A number of studies have indicated a role for PD-L1 in gastric carcinogenesis. In case studies, PD-L1 was expressed in tumor cells in 42%–65% of patients with GC (Wu et al. 2006; Geng et al. 2015; Kim et al. 2016). Anti–PD-1 inhibitors (i.e., nivolumab and

pembrolizumab) have been investigated in the treatment of GC and have demonstrated anti-tumor activity. In the Phase III ATTRACTION-2 study, nivolumab monotherapy has demonstrated superior OS benefit versus placebo (hazard ratio [HR]: 0.63) in the third- and subsequent-line GC and gastroesophageal carcinoma (GEJC) settings (Kang et al. 2017). In the Phase II KEYNOTE-059 study, pembrolizumab monotherapy achieved a 33% overall response rate (ORR) by investigator assessment and 22% by central data review in patients with GC with PD-L1–expressing tumors (Bang et al. 2015).

A8–2.2 EFFECT OF CAPOX ON THE IMMUNE TUMOR MICROENVIRONMENT

There is increasing evidence that in addition to causing tumor cell death, certain conventional chemotherapies may have immunogenic effects (Zitvogel et al. 2008). Oxaliplatin, a component of CAPOX, is one of a limited number of anti-cancer agents that has been shown to induce immunogenic cell death, eliciting immune responses as a result of calreticulin exposure and release of adenosine triphosphate and high-mobility group protein (Green et al. 2009; Tesniere et al. 2010; Michaud et al. 2011). In a murine nonclinical model with transplantable and transgene-driven cancers, oxaliplatin has been shown to trigger tumor-targeting immune responses (Shalapour et al. 2015). Capecitabine, an orally administered tumor-activated 5-fluorouracil (5-FU) prodrug, is metabolized to 5-FU by means of a three-step enzymatic cascade after oral administration (Reigner et al. 2012). The treatment of tumor-bearing mice with 5-FU results in selective reduction of myeloid-derived suppressor cells in the tumor bed, without significant depletion of T cells, natural killer (NK) cells, dendritic cells, or B cells, a corresponding increase in interferon-γ production by CD8-positive tumor-infiltrating lymphocytes was observed (Vincent et al. 2010). The preclinical results suggesting that treatment with oxaliplatin and capecitabine may enhance anti-tumor immunity.

A8–2.3 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily. TIGIT is expressed on the surface of activated T-cell and NK-cell subsets and interacts with high affinity with CD155 (also known as PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other immune checkpoint receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells

(Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including most solid tumors, such as NSCLC, breast cancer, hepatocellular carcinoma, and melanoma, and hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma, and fluorescence-activated cell sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; He et al. 2017; Yang 2016; Guillerey at al. 2018; Duan et al. 2019). TIGIT expression was 30%–80% and 50%–80% on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, respectively (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic intervention, aimed at restoring the immune response against the tumor. Agents that inhibit TIGIT interaction with PVR may inhibit an important source of tumor-associated immune suppression and therefore may enhance the activity of other immune-based therapies. Nonclinical studies using blocking antibodies in genetically deficient mice have revealed a key role for TIGIT in regulating T-cell responses in cancer. Together, the data support the hypothesis that anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A8–2.4 COMBINATION TREATMENT WITH ATEZOLIZUMAB, CAPOX, AND TIRAGOLUMAB

Chemotherapy may modulate tumor and immune-system interactions in favor of the immune system, resulting in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing the number of T-regulatory cells. Immunogenic chemotherapy such as oxaliplatin combination with immune checkpoint can trigger T-cell infiltration to tumors and provide additive or synergistic anti-tumor activity in vivo and is expected to contribute to durable anti-tumor responses (Pfirschke and Engblom 2016).

Recently, CheckMate-649 (NCT02872116), a Phase III trial investigating nivolumab plus chemotherapy or nivolumab plus ipilimumab compared with chemotherapy alone in the first-line treatment of patients with metastatic HER2-negative GC and GEJC, showed improved OS (14.4 vs. 11.1 months; HR: 0.71) (Moehler et al. 2020). An OS benefit (13.8 vs. 11.6 months; HR: 0.80) was also seen in the all-randomized population. With the recent regulatory approval, this practice changing study has established chemotherapy plus nivolumab as a new standard of care for the first-line treatment of patients with HER2-negative GC and GEJC.

Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppresses the effector function of chronically stimulated $CD8^+$ T cells and that inhibiting both TIGIT and PD-L1/PD-1 results in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Higher levels of $PD\text{-}1^+$, $TIGIT^+$, $CD8^+$ T cells have been reported in GC and are associated with hyporesponsive anti-tumor immunity and poor prognosis (Xu et al. 2020). Hence, targeting TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including GC and GEJC (see Section A8–2.6 for a description of clinical studies of tiragolumab combined with atezolizumab).

Based on the above-described data, it is hypothesized that combination treatment with atezolizumab, CAPOX, and tiragolumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit in patients with GC and GEJC.

A8–2.5 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH CAPOX

Capecitabine, an orally administered tumor-activated 5-FU prodrug, is metabolized to 5-FU by means of a three-step enzymatic cascade after oral administration (Reigner et al. 2001). The safety and the preliminary anti-tumor activity of the combination of atezolizumab, bevacizumab, and FOLFOX (5-FU + oxaliplatin) have been evaluated in the Phase I Study GP28328 in oxaliplatin treatment–naive patients with solid tumors, including metastatic colorectal cancer. Adverse events observed thus far are consistent with the known risks of each study treatment. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with additive severe (Grade ≥ 3) toxicities, indicating that atezolizumab can be safely combined with standard chemotherapy.

As of the clinical cutoff date, 1 September 2015, 23 efficacy-evaluable oxaliplatin treatment–naive patients with metastatic colorectal cancer had been treated in the first-line setting. Investigator-assessed ORR (confirmed response as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]) was 52.2% and all 12 responders had partial responses. The median investigator-assessed duration of response per RECIST v1.1 for the 12 responders was 11.4 months. The median investigator-assessed PFS according to RECIST v1.1 was 14.1 months.

Detailed clinical study results for atezolizumab can be found in the Atezolizumab Investigator's Brochure.

A8–2.6 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies (GO30103 and GO40290) in patients with solid tumors.

A8–2.6.1 Study GO30103

Study GO30103 is a first-in-human, Phase I, open-label, dose-escalation, and dose-expansion study of tiragolumab as a single agent and in combination with atezolizumab in patients with locally advanced, recurrent, or metastatic incurable tumors, including urothelial carcinoma, renal cell carcinoma, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, colorectal cancer, GC, cholangiocarcinoma, and triple-negative breast cancer.

As of 2 December 2020, a total of 236 patients had been enrolled in Study GO30103. Of the 236 patients, 42 patents were enrolled in the Phase Ia portion of the study across tiragolumab dose levels from 2 mg to 1200 mg every 3 weeks (Q3W) and 217 patients were enrolled in the Phase Ib portion of the study across tiragolumab dose levels from 2 mg to 1200 mg Q3W in combination with 1200 mg atezolizumab Q3W, including 23 patients who crossed over from the Phase Ia portion. One patient in the Phase Ib portion of the study was enrolled in the study at the 30-mg tiragolumab dose level but was not treated with any study drug.

Overall, from the combined Phase Ia and Ib portions of Study GO30103, the Eastern Cooperative Oncology Group (ECOG) Performance Status at screening for the safety-evaluable population was 0 or 1 in 29.8% and 70.2% of patients, respectively. The most common cancer types reported in $\geq$10 patients in this study population were NSCLC (19.1%), breast, and head and neck cancer (9.8% each), esophageal and colon cancer (8.5% each), ovarian cancer (6.4%), and kidney, melanoma, and stomach cancer (4.7% each).

A8–2.6.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in previously untreated patients with locally advanced unresectable or metastatic PD-L1–positive (defined as tumor proportion score [TPS] $\geq$1%) NSCLC.

As of the data cutoff date, 30 June 2019, a total of 135 patients with a PD-L1 TPS $\geq$1% had received tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). In the intent-to-treat (ITT) population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than the placebo plus atezolizumab arm (16.2%). In the subgroup of patients with TPS $\geq$50%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n=29; 55.2% [95% CI: 35.4% to 75.0%]) than

the placebo plus atezolizumab arm (n = 29; 17.2% [95% CI: 1.8% to 32.7%]). Of note, responders in the tiragolumab plus atezolizumab arm included patients with both squamous and non-squamous histology.

In the ITT population, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm (stratified HR: 0.57 [95% CI: 0.37 to 0.90]; median PFS: 5.4 vs. 3.6 months, respectively). In the subgroup of patients with TPS ≥ 50%, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm (unstratified HR: 0.33 [95% CI: 0.15 to 0.72]; median PFS: not estimable vs. 3.9 months, respectively).

As of the data cutoff date, most adverse events have been Grade 1 or Grade 2. Serious adverse events, Grade 3–5 adverse events, adverse events leading to discontinuation, and adverse events leading to death have been balanced between the two treatment arms. Serious and high-grade treatment-related adverse events have also been balanced between the two treatment arms. [redacted] have been balanced between the two treatment arms, with the exception of a higher frequency of infusion-related reaction (IRR) and rash reported in the atezolizumab plus tiragolumab arm.

[redacted]

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A8–2.7 BENEFIT–RISK ASSESSMENT

Taking into account the potentially synergistic mechanisms of action of tiragolumab and atezolizumab, as well as the preliminary efficacy and manageable safety profiles of the above-described combinations, treatment with atezolizumab, CAPOX, and tiragolumab (Atezo + CAPOX + Tira) may have therapeutic potential in solid tumors such as GC and GEJC.

For the evaluation of the impact of the (coronavirus disease 2019) COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A8–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + CAPOX + TIRA ARM

A8–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. Package Insert).

A8–3.2 RATIONALE FOR CAPOX DOSE AND SCHEDULE

The CAPOX regimen (1000 mg/m^2 capecitabine taken orally twice a day for 14 days followed by 7 days off and 130 mg/m^2 oxaliplatin administered intravenously on Day 1 Q3W) at the recommended doses has been used in multiple Phase III trials (Boku et al. 2019; Moehler et al. 2020) and represents an acceptable capecitabine/oxaliplatin combination for patients with GC and GEJC.

Standard treatment for late-stage GC is recommended to be 4–6 months according to the Chinese Society of Clinical Oncology guidelines (Wang et al. 2021). In this study, the discontinuation of chemotherapy beyond Cycle 6 (administered in 21-day cycles) will occur because the majority of patients with GC and GEJC achieve maximum tumor reduction by Cycle 6, and discontinuation of chemotherapy will improve the tolerability of continued dosing with maintenance treatment with atezolizumab.

[redacted]

[redacted]

[redacted]

A8–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + CAPOX

A8–4.1 TREATMENT IN ATEZO + CAPOX + TIRA ARM

A8–4.1.1 Formulation and Packaging

A8–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a [redacted]-mL glass vial. The vial contains approximately [redacted]) of atezolizumab solution.

For information on the formulation of atezolizumab, refer to the pharmacy manual and the Atezolizumab Investigator's Brochure.

A8–4.1.1.2 CAPOX

Refer to the oxaliplatin and capecitabine prescribing information for details on the respective formulations and storage instructions. Oxaliplatin and capecitabine will be either provided by Sponsor or sourced commercially by sites.

For information on the formulation, packaging, and handling of the CAPOX agents, refer to the local prescribing information for each agent.

A8–4.1.1.3 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor in [redacted]-mL glass vials. The vial contains [redacted] mL of tiragolumab. The approximate concentration of tiragolumab antibody in each vial is [redacted] mg/mL.

For information on the formulation of tiragolumab, refer to the pharmacy manual and the Tiragolumab Investigator's Brochure.

A8–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus CAPOX plus tiragolumab (Atezo + CAPOX + Tira) arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.2 for details). [redacted]

Table 1 Treatment Regimen for Atezo + CAPOX + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	Atezolizumab 1200 mg by IV infusion on Day 1 Tiragolumab 600 mg by IV infusion on Day 1 Capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 [a] Oxaliplatin 130 mg/m^2 by IV infusion on Day 1 [a]

Atezo + atezolizumab; CAPOX = capecitabine plus oxaliplatin; Tira = tiragolumab.

[a] Treatment for up to six cycles.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12. No safety data related to overdosing of atezolizumab or tiragolumab are available to date.

A8–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 4. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, 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 and 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretic medications, and/or analgesics 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 clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 5.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A8–5.1.5. Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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. The Medical Monitor is available to advise as needed.

A8–4.1.2.2 CAPOX

Treatment will be administered as follows during each 21-day cycle for up to six cycles:

- Capecitabine (1000 mg/m^2) orally twice a day on Days 1–14
- Oxaliplatin (130 mg/m^2) by IV infusion on Day 1 and at least 5 minutes after completion of the tiragolumab infusion

The rates of drug administration for oxaliplatin may follow the institutional guidelines. Patients may be premedicated with 5-HT$_3$–receptor antagonists or other standard of care methods to control nausea and vomiting. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A8–5.1.5. CAPOX treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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. The Medical Monitor is available to advise as needed.

A8–4.1.2.3 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in Table 3.
On Day 1 of Cycle 1, tiragolumab will be administered 60 minutes after completion of the atezolizumab infusion. The interval between subsequent infusions will be 30 minutes if the previous atezolizumab infusion was given without premedication and tolerated without an IRR or 60 minutes if the patient experienced an IRR with the previous atezolizumab infusion.

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 4.
Tiragolumab infusions will be administered per the instructions in Table 3.

Guidelines for medical management of IRRs for tiragolumab are provided in Appendix 5.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A8–5.1.5. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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. The Medical Monitor is available to advise as needed.

A8–4.2 CONCOMITANT THERAPY FOR ATEZO + CAPOX + TIRA ARM

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 from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A8–4.2.1 Permitted Therapy for Atezo + CAPOX + Tira Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy
- Vaccinations (such as influenza, COVID-19)
    - Live, attenuated vaccines are not permitted (see Section A8–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

    Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab, tiragolumab, and CAPOX may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

    Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiotherapy) provided that all of the following criteria are met:

    – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

    – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

- Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab and tiragolumab 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 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; see Appendix 4).

A8–4.2.2 Cautionary Therapy for Atezo + CAPOX + Tira Arm

A8–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, 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 5 for details).

A8–4.2.2.2 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 (see Section A8–4.2.3) may be used during the study at the discretion of the investigator.

A8–4.2.2.3 Medications Given with Precaution Concomitantly with CAPOX

The following medications should be used with precaution during treatment with CAPOX:

- Anticoagulants: Patients who receive concomitant capecitabine and oral coumadin-derivative anticoagulant therapy such as warfarin should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose.
- Phenytoin: Monitor phenytoin levels in patients taking capecitabine concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- Leucovorin: The concentration 5-FU is increased and its toxicity may be enhanced by leucovorin.
- CYP2C9 substrates: Patients who are treated with capecitabine and other sensitive CYP2C9 substrate or a CYP2C9 substrate with narrow therapeutic index should be closely monitored for toxicity.
- Because platinum-containing species are eliminated primarily through the kidneys, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds. Co-administration of oxaliplatin with medicinal products known to cause nephrotoxicity is not recommended.

A8–4.2.3 Prohibited Therapy for Atezo + CAPOX + Tira Arm

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, for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A8–4.2.1
- Concomitant use of herbal therapies and traditional Chinese medicine with anti-cancer activity included in the label
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Use of allopurinol during treatment with capecitabine
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and/or tiragolumab, and for 5 months after the final dose of atezolizumab or 90 days after the final dose of tiragolumab, whichever is later

- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because such agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and/or tiragolumab

A8–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + CAPOX + TIRA ARM

Contraception requirements for women and men in the Atezo + CAPOX + Tira arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, 6 months after the final dose of capecitabine, and 9 months after the final dose of oxaliplatin.

  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), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (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 pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 3 months after final dose of capecitabine, 6 months after final dose of oxaliplatin, and for 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 preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Male patients should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from therapy with capecitabine and oxaliplatin.

A8–5 ASSESSMENT OF SAFETY FOR ATEZO + CAPOX + TIRA ARM

A8–5.1 SAFETY PLAN FOR ATEZO + CAPOX + TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, CAPOX, and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A8–5.1.1, A8–5.1.2, A8–5.1.3, and A8–5.1.4). Guidelines for management of patients who experience specific adverse events are provided in Section A8–5.1.5.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study.

Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.4–5.6.

A8–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 5 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A8–5.1.2 Risks Associated with CAPOX

In prior clinical trials of capecitabine, the following safety signals were identified: diarrhea, nausea, vomiting, stomatitis, cardiotoxicity, hepatotoxicity, hand–foot

syndrome, and hematologic toxicity. Patients should be advised to avoid prolonged exposure to sunlight because of the risk of photosensitivity with capecitabine.

In prior clinical trials of oxaliplatin, the following safety signals were identified: sensory and/or motor neuropathy, allergic reactions, pharyngolaryngeal dysesthesia, interstitial lung disease and pulmonary fibrosis, hepatotoxicity, and hematologic toxicity.

For more details regarding the safety profile of capecitabine and oxaliplatin, see the respective local prescribing information.

A8–5.1.3 Risks Associated with Tiragolumab

[redacted] While clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as [redacted]

A8–5.1.3.1 Infusion-Related Reactions

[redacted] Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. [redacted] The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, [redacted]
Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

See Section A8–4.1.2.3 detailed guidance on administration of tiragolumab in this study. See Appendix 4 for guidance on anaphylaxis precautions and Appendix 5 for guidance on the management of IRRs.

[redacted]

[redacted]

A8–5.1.3.5 Embryofetal Toxicity

[redacted] No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A8–5.1.4 Risks Associated with Combination Use of Atezolizumab, CAPOX, and Tiragolumab

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab with tiragolumab and CAPOX: [redacted]

Neutropenia and [redacted] associated with chemotherapy may aggravate the known adverse reaction of [redacted] for tiragolumab in combination with atezolizumab, and increase the risk for developing infection in patients receiving atezolizumab and tiragolumab in combination with chemotherapy.

Given the mechanism of action for atezolizumab and tiragolumab, [redacted] are potential overlapping toxicities associated with combination use of these two agents.

A8–5.1.5 Management of Patients Who Experience Specific Adverse Events in Atezo + CAPOX + Tira Arm

A8–5.1.5.1 Dose Modifications

Atezolizumab and Tiragolumab

There will be no dose modifications for atezolizumab and tiragolumab in this study.

Capecitabine

The capecitabine dose can be modified as presented in Table 4 for the management of drug-related toxicities. Once the dose has been reduced, it cannot be increased later. Omitted doses of capecitabine because of toxicity will not be replaced.

Table 4 Dose Modifications for Capecitabine Drug-Related Toxicities

Toxicity [a]	Action to Be Taken for Current Treatment	Dose Modification for the Next Treatment (% of Starting Dose)
Grade 1	Maintain dose level.	Maintain dose level.
Grade 2		
First occurrence	Withhold until resolved to Grade 1 or better.	100% (1000 mg/m^2)
Second occurrence		75% (750 mg/m^2)
Third occurrence		50% (500 mg/m^2)
Fourth occurrence	Discontinue permanently.	—
Grade 3		
First occurrence	Withhold until resolved to Grade 1 or better.	75% (750 mg/m^2)
Second occurrence		50% (500 mg/m^2)
Third occurrence	Discontinue permanently.	—
Grade 4		
First occurrence	Discontinue permanently or continue at the discretion of the investigator until resolved to Grade 1 or better.	50% (500 mg/m^2)

[a] Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Oxaliplatin

Dose Modifications for Patients with Neurotoxicity

The following dose modifications will be made for patients with neurotoxicity:

- For Grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia), or limiting instrumental activities of daily living, omit oxaliplatin. When toxicity resolves to Grade 1 or better, resume oxaliplatin to 75% of the initial dose. If oxaliplatin is omitted for 6 weeks (two consecutive cycles) for neurologic toxicity, discontinue oxaliplatin.
- For Grade 3 and 4 peripheral sensory neuropathy (severe paresthesia or dysesthesia) or limiting self-care activities of daily living), discontinue oxaliplatin.

Dose Modifications for Patients with Renal Impairment

The following dose modifications will be made for patients with renal impairment:

- For normal renal function or mild to moderate renal impairment (creatinine clearance $>$50 mL/min), the full dose of oxaliplatin can be administered.
- For severe renal impairment, the oxaliplatin dose should be reduced to 75% of the initial dose.

Dose Modifications for Patients with Hematologic Toxicity

The following dose modifications will be made for patients with hematologic toxicity:

- For Grade 2 and 3 thrombocytopenia, the oxaliplatin dose should be reduced to 75% of the initial dose. For Grade 4 thrombocytopenia, the dose should be reduced to 50% of the initial dose.
- For Grade 3 and 4 neutropenia or febrile neutropenia, the oxaliplatin dose should be reduced to 75% of the initial dose.

A8–5.1.5.2 Treatment Interruption for Toxicities

[redacted] The Medical Monitor is available to advise as needed.

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, [redacted] should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to [redacted] should be applied to both tiragolumab and atezolizumab.

The CAPOX treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If CAPOX has been withheld for $>$21 days because of toxicity, the patient should be discontinued from CAPOX, unless the patient is likely to derive clinical benefit. The decision to re-challenge patients with CAPOX should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

If atezolizumab is withheld or discontinued, tiragolumab should also be withheld or discontinued, but CAPOX may be continued if the patient is likely to derive clinical benefit, as determined by the investigator per medical judgment. If CAPOX or tiragolumab is discontinued, the other drugs can be continued if the patient is likely to derive clinical benefit according to the investigator's medical judgment. Treatment with

CAPOX will continue for up to six cycles and patients will be offered continued treatment with atezolizumab as long as they are experiencing clinical benefit in the opinion of the investigator. If oxaliplatin treatment is discontinued during the first six cycles, patients are encouraged to continue chemotherapy with capecitabine, atezolizumab, and tiragolumab as long as they are experiencing clinical benefit in the opinion of the investigator. The Medical Monitor is available to advise as needed. If capecitabine treatment is discontinued during the first six cycles, patients are encouraged to continue chemotherapy with oxaliplatin, atezolizumab, and tiragolumab as long as they are experiencing clinical benefit in the opinion of the investigator, the Medical Monitor is available to advise as needed.

A8–5.1.5.3 Management Guidelines for Adverse Events

Appendix 5 provides guidelines for the management of patients who experience atezolizumab- and/or tiragolumab-associated adverse events. It is recommended that atezolizumab and/or tiragolumab be withheld or discontinued per the guidelines provided in Appendix 5.

For cases in which management guidelines are not covered in Appendix 5, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Guidelines for management of patients who experience specific adverse events related to CAPOX regimen are provided in Section A8–5.1.5.1. The treating physician may use discretion in modifying the dose modification guidelines, depending on the severity of toxicity and an assessment of the benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care.

Chemotherapy should be discontinued if ANC and platelets do not recover to ≥1000/μL and ≥75,000/μL, respectively, after treatment is delayed by 3 weeks.

[redacted]

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
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- [redacted]
- [redacted]

A8–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + CAPOX + TIRA ARM

A8–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, 90 days after the final dose of tiragolumab, 6 months after the final dose of capecitabine, or 9 months after the final

dose of oxaliplatin. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A8–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the final dose of capecitabine, 6 months after the final dose of oxaliplatin, or 90 days after the final dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information

would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A8–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A8–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly or birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A8–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + CAPOX + TIRA ARM

Table 5 Schedule of Activities for Atezo + CAPOX + Tira Arm

Assessment/Procedure	Stage 1 Screening (see Appendix 6) Days −28 to −1	Treatment Cycles (21-day cycles) [a] Cycle 1 [b] Day 1	Treatment Cycles (21-day cycles) [a] Cycles ≥ 2 Day 1 (±3 days)	Treatment Discontinuation [c]	Follow-Up Every 3 Months
Molecular profile of GC and GEJC (if available)	See Appendix 6.	Whenever updated information becomes available			
Vital signs [d, e]		x	x	x	
Weight [e]		x	x	x	
Complete physical examination [f]				x	
Limited physical examination [e, g]		x	x		
ECOG Performance Status [e]		x	x	x	
ECG [e, h]		Perform as clinically indicated.			
Hematology [i]		x [j, k]	x [j]	x	
Chemistry [l]		x [j, k]	x [j]	x	
TSH, free T3 (or total T3),and free T4 [m]		x [j, k, m]		x	
[redacted]					
C-reactive protein		x [j, k]			
Pregnancy test [o]		x [j, k]	x [j]	x	x [o]
Urinalysis [p]		Perform as clinically indicated.			

Table 5 Schedule of Activities for Atezo + CAPOX + Tira Arm (cont.)

Assessment/Procedure	Stage 1 Screening (see Appendix 6)	Treatment Cycles (21-day cycles) [a]			Follow-Up
		Cycle 1 [b]	Cycles ≥ 2		
	Days −28 to −1	Day 1	Day 1 (±3 days)	Treatment Discontinuation [c]	Every 3 Months
[redacted]					
Blood (for plasma and WBC central processing) and serum for biomarkers	See Appendix 6.	See Table 6.			
Tumor biopsy		x [q]			
Tumor biopsy (optional)		x [r]			
Stool sample *(optional)*		x [s]	x [s]		
Tumor response assessments		x [t, u]			
Concomitant medications [v]		x	x	x	
Adverse events [w]		x	x	x [w]	x [w]
Atezolizumab administration [x, y]		x	x		
CAPOX administration [x, z]		x	x		
Tiragolumab administration [x, aa]		x	x		
Survival follow-up and anti-cancer treatment					x [bb]

ADA = anti-drug antibody; Atezo = atezolizumab; CAPOX = capecitabine plus oxaliplatin; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; GC = gastric carcinoma; GEJC = gastroesophageal junction carcinoma; [redacted] IRR = infusion-related reaction; PK = pharmacokinetic.

Table 5 Schedule of Activities for Atezo + CAPOX + Tira Arm (cont.)

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] [redacted]

[c] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.2 for details) may be used as the treatment discontinuation visit.

[d] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. During visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. During visits when a patient will undergo a tumor assessment, the physical examination should include an evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[j] Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if available), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate (or phosphorus), calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase (if available).

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, and so on).

Table 5 Schedule of Activities for Atezo + CAPOX + Tira Arm (cont.)

[n] [redacted]

[o] All women of childbearing potential will have urine or serum pregnancy tests performed at specified visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Urinalysis includes pH, specific gravity, glucose, protein (or albumin), ketones, and blood; dipstick permitted.

[q] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Refer to Section 4.5.7 for tissue sample requirements.

[r] Patients who consent to optional biopsies will undergo tumor biopsy sample collection *8* weeks (±7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[s] Patients *who consent to providing optional* stool sample *will* receive the collection device for the stool sample prior to Day 1 of Cycle 1 and Day 1 of Cycle 3. Samples to be collected predose (i.e., before the visit). Patients will be instructed to return the collection device with the stool sample to the site on the Day 1, Cycle 1 and Day 1, Cycle 3 (±1 week) visits. If a patient does not return the collection device at the Day 1, Cycle 3 visit, he or she may return the collection device at the Day 1, Cycle 4 visit.

[t] Patients will undergo tumor assessments every 6 weeks (±1 week) during the first 48 weeks (from Day 1 of Cycle 1) and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays until confirmed radiographic disease progression, except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 4.5.6 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[u] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the tumor assessment schedule described above. 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 (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. 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).

Table 5 Schedule of Activities for Atezo + CAPOX + Tira Arm (cont.)

[v] Includes 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 from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[w] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[x] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details).

[y] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. See Section A8–4.1.2.1 for details on atezolizumab infusions (including measurement of vital signs).

[z] Capecitabine (1000 mg/m^2) will be administered orally twice daily on Days 1–14 and oxaliplatin (130 mg/m^2) will be administered by IV infusion on Day 1 and at least 5 minutes after completion of the tiragolumab infusion. Treatment will continue for up to six cycles.

[aa] Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle. The initial dose of tiragolumab will be delivered over 60 (±10) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±10) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. On Day 1 of Cycle 1, tiragolumab will be administered 60 minutes after completion of the atezolizumab infusion. The interval between subsequent infusions will be 30 minutes if the previous atezolizumab infusion was tolerated without an IRR or 60 minutes if the patient experienced an IRR with the previous atezolizumab infusion. See Section A8–4.1.2.3 for details on tiragolumab infusions (including measurement of vital signs and patient observation after infusions).

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm, in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining approximately 20% of patients will be discontinued from the study).

Table 6 Schedule of Pharmacokinetic, Immunogenicity, and Blood Biomarker Samples for Atezo+CAPOX+Tira Arm

Visit	Timepoint(s)	Sample Type(s)
Day 1 of Cycle 1	Prior to first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted] • Biomarker (serum) • Biomarker (plasma and WBC) [a]
	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
	30 (±10) minutes after end of tiragolumab infusion	• [redacted]
Day 1 of Cycle 2	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted]
Day 1 of Cycle 3	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted] • Biomarker (serum)
Day 1 of Cycle 4	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted]
Day 1 of Cycle 8	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted]

ADA=anti-drug antibody; Atezo+CAPOX+Tira=atezolizumab plus capecitabine plus oxaliplatin plus tiragolumab; ctDNA=circulating tumor DNA; PK=pharmacokinetic; WES=whole exome sequencing.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. Blood collections for biomarker assessment (e.g., cytokines, chemokines, ctDNA, and WES of WBC-derived DNA as germline control) are applicable only after approval from local regulatory authorities. Based on emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Blood collected at site for central processing of plasma and WBC samples.

Table 6 Schedule of Pharmacokinetic, Immunogenicity, and Liquid Biomarker Samples for Atezo+CAPOX+Tira Arm (cont.)

Visit	Timepoint(s)	Sample Type(s)
Day 1 of Cycles 12 and 16	Prior to infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted]
Treatment discontinuation visit (≤30 days after final dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • [redacted] • [redacted] • Biomarker (serum) • Biomarker (plasma)[a]

ADA=anti-drug antibody; Atezo+CAPOX+Tira=atezolizumab plus capecitabine plus oxaliplatin plus tiragolumab; ctDNA=circulating tumor DNA; PK=pharmacokinetic; WES=whole exome sequencing.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. Blood collections for biomarker assessment (e.g., cytokines, chemokines, ctDNA, and WES of WBC-derived DNA as germline control) are applicable only after approval from local regulatory authorities. Based on emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Blood collected at site for central processing of plasma and WBC samples.

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