

Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized, Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer or Esophageal Cancer (Morpheus-Gastric and Esophageal Cancer)

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PROTOCOL

PROTOCOL TITLE: A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED, UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER OR ESOPHAGEAL CANCER (MORPHEUS–GASTRIC AND ESOPHAGEAL CANCER)

PROTOCOL NUMBER: YO39609

VERSION NUMBER: 11

TEST COMPOUNDS: Atezolizumab (RO5541267), BL-8040, Linagliptin, Tiragolumab (RO7092284)

STUDY PHASE: Phase Ib/II

REGULATORY AGENCY IDENTIFIER NUMBERS: IND Number: 133,155
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NCT Number: 03281369

SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS: F. Hoffmann-La Roche Ltd
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PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	Date Final	Country	Version	Date Final
11	See electronic date stamp on the final page of this document.	—	—	—
10	15 Dec 2022	—	—	—
9	6 December 2021	—	—	—
8	28 May 2021	—	—	—
7	11 October 2019	—	—	—
6	12 October 2018	—	—	—
1	19 May 2017	Spain	5	24 April 2018
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		United Kingdom	3	21 March 2018
		European Union	2	29 November 2017

PROTOCOL AMENDMENT, VERSION 11

RATIONALE

Protocol YO39609 has been amended primarily to align the adverse event management guidelines with the Atezolizumab Investigator's Brochure, Version 20. Changes to the protocol, along with a rationale for each change, are summarized below.

- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Sections 1.3.4, A12-1.1, A13-1.1, A17-1.1, A18-1.1, and A20-1.1).
- Language surrounding serum autoantibody collected at screening has been revised to align with the standard program language to retain the ability to test the baseline sample if needed (Section 4.5.6).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 6).

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 IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER OR ESOPHAGEAL CANCER (MORPHEUS-GASTRIC AND ESOPHAGEAL CANCER)

PROTOCOL NUMBER: YO39609

VERSION NUMBER: 11

TEST COMPOUNDS: Atezolizumab (RO5541267), BL-8040, Linagliptin, and 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 return 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 IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER OR ESOPHAGEAL CANCER (MORPHEUS-GASTRIC AND ESOPHAGEAL CANCER)**

REGULATORY AGENCY IND Number: 133,155

IDENTIFIER NUMBERS: EudraCT Number: 2016-004529-17

NCT Number: 03281369

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety and pharmacokinetics of multiple immunotherapy-based treatment combinations in patients with locally advanced, unresectable, or metastatic gastric or gastroesophageal junction cancer (hereafter referred to as gastric cancer) or esophageal cancer. With the current standard-of-care treatments, the majority of patients with locally advanced, unresectable, or metastatic gastric or esophageal cancer ultimately experience disease progression and succumb to the diseases within 1–2 years after diagnosis, suggesting high unmet medical need exists for these diseases.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints for Stage 1

Objectives	Corresponding Endpoint(s)
Primary Efficacy Objective:	
To evaluate the efficacy of immunotherapy-based treatment combinations in all arms during Stage 1	Objective response, defined as 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

ADA=anti-drug antibody; DOR=duration of response; 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.

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

Objectives	Corresponding Endpoint(s)
Secondary Efficacy Objective:	
To evaluate the efficacy of immunotherapy-based treatment combinations in all arms 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), as determined by the investigator according to RECIST v1.1 - OS after randomization, defined as the time after randomization to death from any cause - 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, defined as stable disease for ≥ 16 weeks for the Gastric Cancer Cohort or ≥ 12 weeks for the Esophageal Cancer Cohort, or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective:	
To evaluate the safety of immunotherapy-based treatment combinations in all arms during Stage 1	- Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 - Change from baseline in vital signs and ECG parameters - Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective:	
To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	Plasma or serum concentration of each drug (as appropriate) at specified timepoints
Immunogenicity Objective:	
To evaluate the immune response to drugs that are administered as part of an immunotherapy-based 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

ADA=anti-drug antibody; DOR=duration of response; 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.

Table 2 Objectives and Corresponding Endpoints for Stage 2

Objectives	Corresponding Endpoint(s)
Safety Objective:	
To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	- Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 - Change from baseline in vital signs and ECG parameters - Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective:	
To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	Plasma or serum concentration of each drug at specified timepoints
Immunogenicity Objective:	
To evaluate the immune response to drugs that are administered as part of an immunotherapy-based 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

ADA=anti-drug antibody; 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.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with gastric and esophageal cancer. 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, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status).

Two cohorts of patients with gastric cancer have been enrolled in parallel in this study: the second-line (2L) Gastric Cancer Cohort consists of patients with gastric cancer who have progressed after receiving a platinum-containing or fluoropyrimidine-containing chemotherapy regimen in the first-line setting, and the first-line (1L) Gastric Cancer Cohort consists of patients with gastric cancer who have not received prior chemotherapy in this setting. In each cohort, eligible patients will initially be assigned to one of several treatment arms (Stage 1). Patients in the 2L Gastric Cancer Cohort who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen in Stage 2.

Additionally, a cohort of patients with esophageal cancer who have not received prior systemic treatment for their disease will also be enrolled in this study. Eligible patients will be randomized to one of three treatment arms. Patients in the control arm of the Esophageal Cancer Cohort who experience disease progression or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen in Stage 2.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase Ib/II	Population Type:	Adult patients
Control Method:	Active comparator	Population Diagnosis or Condition:	Locally advanced, unresectable, or metastatic gastric or gastroesophageal junction cancer or esophageal cancer
Interventional Model:	Parallel group	Population Age:	≥ 18 years
Test Compound(s):	Atezolizumab, BL-8040, linagliptin, tiragolumab	Site Distribution:	Multi-site and multi-region
Active Comparator:	Cisplatin, 5-fluorouracil, ramucirumab, paclitaxel, oxaliplatin, leucovorin	Study Intervention Assignment Method:	Randomization
Number of Arms:	8	Number of Participants to Be Enrolled:	Approximately 195–410

STUDY TREATMENT

Table 3 Study Treatments for Gastric Cancer Cohort

Stage 1 Study Treatments		
First-Line Cohort		
Treatment Regimen	Cycle	Dose, Route, and Regimen
mFOLFOX6	28 days	- Oxaliplatin ^a 100 mg/m² administered concurrently (using a Y-connector) with leucovorin 100 mg/m² by IV infusion over 120 (± 15) minutes on Days 1 and 15 of each cycle 5-FU 2400 mg/m² administered by continuous IV infusion over 46 hours on Days 1 and 2 and on Days 15 and 16 of each cycle
Second-Line Cohort		
Ramucirumab and paclitaxel	28 days	- Ramucirumab 8 mg/kg administered by IV infusion over 60 minutes on Days 1 and 15 of each cycle - Paclitaxel 80 mg/m² administered by IV infusion over 60 minutes on Days 1, 8, and 15 of each cycle

Table 3 Study Treatments for Gastric Cancer Cohort (cont.)

Treatment Regimen	Cycle	Dose, Route, and Regimen
Atezolizumab and BL-8040	Priming period prior to Cycle 1 ^b (5 days)	• BL-8040 1.25 mg/kg administered by SC injection on Days 1–5^{b, c}
	Cycles 1 and beyond (combination treatment period) (21 days)	• Atezolizumab 1200 mg administered by IV infusion on Day 1 of each cycle^c • BL-8040 1.25 mg/kg administered by SC injection three times a week^d (Days 1, 3, 5, 8, 10, 12, 15, 17, and 19 of each cycle)^{c, e}
Atezolizumab and linagliptin	21 days	• Atezolizumab 1200 mg administered by IV infusion on Day 1 of each cycle • Linagliptin 5 mg orally QD
Stage 2 Study Treatments		
No Stage 2 treatment is currently available.		

5-FU = 5-fluorouracil; mFOLFOX6 = infusional 5-fluorouracil (5-FU), leucovorin (folic acid), and oxaliplatin; PK = pharmacokinetic; QD = once a day.

^a Oxaliplatin treatment will be discontinued after Cycle 4, and patients will continue on leucovorin and 5-FU treatment.

^b Day 1 of the priming period will begin 1 week prior to Day 1 of the combination treatment period.

^c It is recommended that Day 1 be scheduled on a Monday to allow for dosing to occur on Days 1–5 of the priming period and on Days 1, 3, and 5 during the combination treatment period.

^d Patients with a complete or partial response that is confirmed at the next scheduled tumor assessment and patients with stable disease for more than 6 cycles can receive BL-8040 two times a week (on Days 1, 4, 8, 11, 15, and 18 of each cycle) instead of three times a week.

^e On Day 1 of each cycle during the combination treatment, BL-8040 will be administered at least 30 minutes after the end of the atezolizumab infusion and after the appropriate PK blood samples have been collected.

Table 4 Study Treatments for Esophageal Cancer Cohort

Stage 1 Study Treatments		
Treatment Regimen	Cycle	Dose, Route, and Regimen
Atezolizumab, tiragolumab, cisplatin, and 5-FU	21 days	- Atezolizumab 1200 mg IV on Day 1 of each cycle - Tiragolumab 600 mg IV on Day 1 of each cycle - Cisplatin 80 mg/m² IV on Day 1 of each cycle ^{a, b} 5-FU 800 mg/m²/24 hours IV (continuous) on Days 1–5 of each cycle ^b
Atezolizumab, cisplatin, and 5-FU	21 days	- Atezolizumab 1200 mg IV on Day 1 of each cycle - Cisplatin 80 mg/m² IV on Day 1 of each cycle ^{a, b} 5-FU 800 mg/m²/24 hours IV (continuous) on Days 1–5 of each cycle ^b
Cisplatin and 5-FU	21 days	- Cisplatin 80 mg/m² IV on Day 1 of the first six cycles ^{a, b} 5-FU 800 mg/m²/24 hours IV (continuous) on Days 1–5 of each cycle ^b
Stage 2 Study Treatments		
Atezolizumab and tiragolumab	21 days	- Atezolizumab 1200 mg IV on Day 1 of each cycle - Tiragolumab 600 mg IV on Day 1 of each cycle

5-FU = 5-fluorouracil.

^a Cisplatin treatment will be capped after 6 doses. Initial cisplatin dose should take into consideration patient's creatinine clearance levels.

^b Infusion times for cisplatin and 5-FU may be adapted in accordance with local standard practice.

There will be no dose modifications for atezolizumab, BL-8040, linagliptin, or tiragolumab in this study.

The paclitaxel and ramucirumab doses can be modified as shown in [Table 5](#) for the management of study drug-related toxicities. Patients who require reductions more than two dose levels should be discontinued from that agent.

Table 5 Ramucirumab and Paclitaxel Dose Adjustment

	Ramucirumab	Paclitaxel
Starting dose	8 mg/kg	80 mg/m ²
– 1 dose level	6 mg/kg	70 mg/m ²
– 2 dose levels	5 mg/kg	60 mg/m ²

For modified FOLFOX6 (infusional 5-fluorouracil [5-FU], leucovorin, and oxaliplatin) treatment, dose adjustments at the start of each administration (every 14 days) will be based on nadir hematologic counts or the maximum non-hematologic toxicity from the preceding cycle of

therapy. After a dose reduction is made, the dose will not be re-escalated during subsequent administrations (see Table 6 for chemotherapy dose reduction levels).

Patients who require reductions below two dose levels should be discontinued from that chemotherapy agent.

Table 6 mFOLFOX6 Dose Adjustment

	Oxaliplatin	5-FU Infusion
Starting dose (mg/m ²)	100	2400
–1 dose level (mg/m ²)	75	2000
–2 dose levels (mg/m ²)	50	1600

mFOLFOX6 = infusional 5-fluorouracil (5-FU), leucovorin (folic acid), and oxaliplatin.

For management of drug-related toxicities, the dose of cisplatin may be reduced by 20 mg/m² (one dose level) up to two times and the dose of 5-FU may be reduced by 200 mg/m² (one dose level) up to two times, as outlined below:

Table 7 Cisplatin and 5-FU Dose Adjustment

	Initial Dose	First Dose Reduction	Second Dose Reduction
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²
5-FU	800 mg/m ² /24 hours	600 mg/m ² /24 hours	400 mg/m ² /24 hours

5-FU = 5-fluorouracil.

DURATION OF PARTICIPATION

Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. The total duration of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–6 years.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee and Safety Monitoring Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first-line (Cohort)
2L	second-line (Cohort)
5-FU	5-fluorouracil
ADA	anti-drug antibody, also known as anti-therapeutic antibody (ATA)
Atezo	atezolizumab
BSC	best supportive care
CF	cisplatin and fluorouracil
CI	confidence interval
CIN	chromosomal instability
CIT	cancer immunotherapy
Cobi	cobimetinib
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CPS	combined positive score
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	cysteine-X-cysteine chemokine receptor 4
DDP-4	dipeptidyl peptidase-4
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
ESMO	European Society for Medical Oncology
FEV ₁	forced expiratory volume in 1 second
FISH	fluorescence in situ hybridization
FFPE	formalin-fixed, paraffin-embedded
FLO	fluorouracil, leucovorin, and oxaliplatin

Abbreviation	Definition
FLP	fluorouracil, leucovorin, and cisplatin
FVC	forced vital capacity
GEJ	gastroesophageal junction
GI	gastrointestinal
GS	genomically stable
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
IC	(tumor-infiltrating) immune cell
ICH	International Council for Harmonisation
IFN	interferon
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
ISH	in situ hybridization
IxRS	interactive voice or web-based response system
LVEF	left ventricular ejection fraction
mFOLFOX6	modified FOLFOX6: infusional 5-fluorouracil, leucovorin (folic acid), and oxaliplatin
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stable
N1 + I3	1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab Q3W for 4 cycles followed by 3 mg/kg of nivolumab Q2W
N3	3 mg/kg of nivolumab Q2W
N3 + I1	3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab Q3W for 4 cycles followed by 3 mg/kg of nivolumab Q2W
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network®

Abbreviation	Definition
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PFS	progression-free survival
PK	pharmacokinetic
Q3W	every 3 weeks
Q2W	every 2 weeks
RBR	Research Biosample Repository
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
SOC	Scientific Oversight Committee
T3	triiodothyronine
TC	tumor cell
TCGA	The Cancer Genome Atlas
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
ULN	upper limit of normal
████	████████████████████
████	████████████████████
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON GASTRIC CANCER

Gastric cancer remains one of the most common malignancies in the world, with an estimated 951,600 new cases in 2012 (Torre et al. 2015). Gastric cancer also continues to be a deadly disease—being the third leading cause of cancer-related deaths in men and the fifth in women—accounting for 723,000 deaths worldwide in 2012 (Greenlee et al. 2001; International Agency for Research on Cancer; GLOBOCAN 2012). The incidence of gastric cancer varies widely across geographic regions, with the highest incidence observed in Eastern Asia (Korea, Mongolia, Japan, and China), central and eastern Europe, and South America, and the lowest in Northern America and most parts of Africa (Torre et al. 2012). Survival outcomes also differ between regions, with overall 5-year survival rates being 10%–30% in the Western world (Karim-Kos et al. 2008) and 69% in Asia (Jung et al. 2013; Nashimoto et al. 2013).

The majority of gastric cancers are adenocarcinomas, which are further subdivided into intestinal, diffuse, or mixed subtypes according to the Lauren classification (Lauren 1965). Another classification proposed by the World Health Organization (WHO) recognizes four histological subtypes (papillary, tubular, mucinous, and poorly cohesive) (International Agency for Research on Cancer and WHO 2010). However, these two classifications have little clinical utility to guide treatment decisions.

Recently, molecular landscapes of gastric cancer have been explored and two new classifications have been proposed. The Cancer Genome Atlas (TCGA) has characterized 295 primary gastric adenocarcinomas, and this integrated analysis has allowed the identification of four subtypes: Epstein-Barr virus (EBV)-positive type (9%), microsatellite instability (MSI)-high type (22%), genomically stable (GS) type (20%), and chromosomal instability type (50%) (Cancer Genome Atlas Research Network 2014). Overall, the authors of this work did not find systematic differences between Asian and non-Asian patients, and the four identified tumor types did not link to different prognoses. Similarly, the Asian Cancer Research Group provided a molecular classification of gastric cancer with four categories (Cristescu et al. 2015): MSI high (23%), microsatellite stable (MSS)/epithelial–mesenchymal transition (15%), MSS/TP53 positive (p53 active; 26%), and MSS/TP53 negative (p53 inactive; 36%). Even though MSI-high status seems to be a predictive factor of clinical benefit in immune checkpoint blockade in both colorectal and non-colorectal cancers (Le et al. 2015), its role has not been confirmed in gastric cancer to date.

1.2 BACKGROUND ON ESOPHAGEAL CANCER

Esophageal cancer is the seventh most commonly diagnosed cancer worldwide and the sixth most common cause of cancer-related death (incidence of approximately 572,000; mortality of 509,000 in 2018); the latter signifying that esophageal cancer will be responsible for an estimated 1 in every 20 cancer deaths in 2018 (Bray et al. 2018). Approximately 70% of cases occur in men, and there is a 2- to 3-fold difference in

incidence and mortality rates between the sexes worldwide (Bray et al. 2018). Most esophageal cancers can be categorized into two histologic subtypes: squamous cell carcinoma and adenocarcinoma, with differences in prevalence depending on the region. Squamous cell carcinoma is the most common esophageal cancer in Asia and Africa, while adenocarcinoma is increasing in frequency in North America and Western Europe (Lin et al. 2013; Noone et al. 2017; Bray et al. 2018;). Another major difference is the disease etiology: tobacco and alcohol abuse are the major risk factors for squamous cell carcinoma, whereas gastroesophageal reflux disease and Barrett's esophagus are the two major risk factors for adenocarcinoma (Engel et al. 2003). Treatment options for patients with advanced or metastatic esophageal cancer are limited and patients have a poor prognosis with minimal overall survival benefit from current treatments (see Section 1.4 on treatment for esophageal cancer). Hence, there remains a significant need for novel therapeutic agents in this population.

1.3 TREATMENT FOR GASTRIC CANCER

Despite differences in epidemiology, the general approach to the treatment of gastric cancer is consistent regardless of histologic and biologic subtypes. The only potentially curative treatment for gastric cancer is complete resection of localized disease, and the incidence of localized disease and the extent of surgical resection vary, depending on geographic region. Because of earlier detection and improved surgical techniques, survival rates for gastric cancer have improved significantly in Japan in recent years (Parkin et al. 2005). In contrast, in Europe, the United States, and China, gastric cancer is often diagnosed at an advanced stage when complete resection is not possible. As a result, of all patients with gastric cancer, 80%–90% are either diagnosed at an advanced stage, when the tumor is inoperable, or develop a recurrence within 5 years after surgery (Wagner et al. 2010). The prognosis for patients with advanced gastric cancer is very poor, with median overall survival (OS) ranging from 4 months, when treated only with best supportive care (BSC), to approximately 12 months with combination cytotoxic chemotherapy (Wagner et al. 2010).

1.3.1 First-Line Treatment for Advanced Gastric Cancer

For patients with newly diagnosed locally advanced and metastatic gastric cancer, systemic chemotherapy is the main treatment option (Wagner et al. 2010) and multiple agents are active, including fluoropyrimidines (fluorouracil, capecitabine, and S-1), anthracyclines, platinum agents, taxanes (paclitaxel and docetaxel), irinotecan, and others, as well as trastuzumab for HER2-overexpressing gastric cancer (Al-Batran et al. 2008; Bang et al. 2010).

Combination chemotherapy compared with single-agent chemotherapy provides a clear survival benefit according to a meta-analysis (Wagner et al. 2006), with a median survival of approximately 8.3 months in the combination chemotherapy arms versus 6.7 months in the single-agent arms. The combination of fluorouracil, leucovorin, and oxaliplatin (FLO) has been evaluated as an alternative to cisplatin and fluorouracil in

patients with advanced or metastatic gastric cancer. A Phase III trial conducted by the German Study Group (Al-Batran et al. 2008) showed that the combination of FLO had a trend toward improved median progression-free survival (PFS) compared with fluorouracil, leucovorin, and cisplatin (FLP) (5.8 vs. 3.9 months). However, there were no significant differences in median OS (10.7 vs. 8.8 months, respectively) between the two groups. FLO is associated with significantly less toxicity than FLP.

Different doses and schedules of administration of FLO have been investigated in several Phase II studies, showing an objective response rate (ORR) ranging from 43% to 56% and an OS of about 10 months (Louvret et al. 2002; Al-Batran et al. 2004; Chao et al. 2004; DeVita et al. 2005; Lordick et al. 2005). An alternative, modified FOLFOX6 (mFOLFOX6; infusional 5-fluorouracil [5-FU], leucovorin [folic acid], and oxaliplatin), has been investigated in patients with advanced gastric cancer in a Phase II study (Keam et al. 2008). The ORR of mFOLFOX6 was 43.8%, with a median time to progression and OS that were 6.0 months and 12.6 months, respectively. Toxicities were generally tolerable and manageable (Keam et al. 2008). mFOLFOX6 represents an appropriate 5-FU/platinum combination for patients and, thus, is considered an acceptable first-line treatment.

Recommended regimens for the first-line treatment of metastatic or locally advanced HER2-negative gastric and gastroesophageal cancers per guidelines established by the National Comprehensive Cancer Network® (NCCN 2017) and the European Society for Medical Oncology (ESMO) (Smyth et al. 2016) are summarized in [Table 1](#).

Table 1 Recommended Regimens for First-Line Treatment of Metastatic or Locally Advanced HER2-Negative Gastric and Gastroesophageal Cancers

NCCN	ESMO
Two-drug regimens are preferred because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation. <u>Preferred regimens:</u> • Cisplatin combined with either 5-FU or capecitabine • Oxaliplatin combined with either 5-FU or capecitabine <u>Other regimens:</u> • Paclitaxel combined with either cisplatin or carboplatin • Docetaxel and cisplatin • Docetaxel or paclitaxel or 5-FU or capecitabine • Docetaxel and irinotecan • Docetaxel and 5-FU combined with one of the following: oxaliplatin, carboplatin, or cisplatin • Epirubicin and 5-FU combined with either oxaliplatin or cisplatin • Epirubicin and capecitabine combined with either oxaliplatin or cisplatin • 5-FU and irinotecan • 5-FU	Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients. <u>Example regimens:</u> • Epirubicin and 5-FU combined with either oxaliplatin or cisplatin • Epirubicin and capecitabine combined with either oxaliplatin or cisplatin • Docetaxel, cisplatin, and 5-FU • Fluorouracil, leucovorin, oxaliplatin, and docetaxel

5-FU=5-fluorouracil; ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network®; PS=performance status.

1.3.2 Second-Line Treatment for Advanced Gastric Cancer

A systematic review and meta-analysis showed that second-line therapy for advanced gastric cancer leads to a reduction of the risk of death by 18% (hazard ratio [HR]=0.82; posterior probability of HR ≥ 1: <0.00001) over BSC (Iacovelli et al. 2014). This benefit translates into an increase of about 2 months in median OS compared with that for BSC. On the basis of these supportive data, the administration of second-line therapy is now established as a standard-of-care option. However, depending on a patient's clinical condition and local clinical practices, 20%–50% of patients with gastric cancer receive second-line treatment, primarily owing to the risk of exposing patients with quickly deteriorating performance status to treatment toxicity.

A variety of single agents, including docetaxel, paclitaxel, irinotecan, and ramucirumab, or the combination of ramucirumab with paclitaxel are considered valid second-line treatment choices (NCCN 2017).

A Phase III trial in 168 patients who had progressed during or within 6 months of treatment with a platinum-containing chemotherapy confirmed that docetaxel combined with active symptom control significantly increased OS compared with active symptom control alone (5.2 months vs. 3.6 months; $p=0.01$) (Ford et al. 2014).

In a Korean Phase III trial conducted in 202 patients with advanced gastric cancer after failure of either a fluoropyrimidine- or platinum-based chemotherapy or a fluoropyrimidines and platinum combination, median OS was improved significantly in patients treated with chemotherapy (docetaxel or irinotecan) compared with BSC (5.3 months vs. 3.8 months; one-sided $p=0.007$). However, the efficacy of irinotecan and docetaxel was comparable (Kang et al. 2012).

A recent Japanese Phase III study confirmed that irinotecan was not superior to paclitaxel in terms of median PFS (2.3 months vs. 3.6 months; $p<0.33$) or OS (8.4 months vs. 9.5 months; $p=0.38$) (Hironaka et al. 2013).

In gastric cancer, increased VEGF-A expression has been correlated with a poor prognosis (Maeda et al. 1996), supporting various studies with anti-angiogenic agents (Ohtsu et al. 2011). Indeed, recent data demonstrated a clear benefit of targeting angiogenesis in the second-line setting. Ramucirumab, an IgG1 monoclonal antibody and antagonist of the VEGF receptor-2 that blocks the binding of VEGF-A, -C, and -D, has been evaluated in a number of Phase III studies, as described below.

In the Phase III REGARD trial conducted in 355 patients with metastatic gastric cancer whose disease progressed after first-line chemotherapy, OS was significantly extended to 5.2 months in patients treated with ramucirumab plus BSC compared with 3.8 months in patients treated with placebo plus BSC (HR=0.776; $p=0.047$) (Fuchs et al. 2014).

The RAINBOW trial assessed ramucirumab in combination with paclitaxel versus paclitaxel alone for the second-line treatment of advanced gastric cancer. Six hundred sixty-five patients were randomly assigned in a 1:1 ratio to receive paclitaxel, with or without ramucirumab (Wilke et al. 2014). The study demonstrated an HR of 0.81, with an associated median survival of 9.6 months with the addition of ramucirumab to paclitaxel and 7.4 months with paclitaxel alone ($p=0.017$). Median PFS with ramucirumab plus paclitaxel was significantly longer than with placebo plus paclitaxel (4.4 months vs. 2.9 months $p<0.0001$). PFS for the ramucirumab plus paclitaxel was longer than for placebo plus paclitaxel in most subgroups. A significantly greater proportion of patients achieved an objective response in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (28% vs. 16%, respectively; $p=0.0001$).

Recommended regimens for the second-line treatment of metastatic or locally advanced gastric and gastroesophageal cancers per guidelines established by the NCCN (2017) and ESMO (Smyth et al. 2016) are summarized in [Table 2](#).

Table 2 Recommended Regimens for Second-Line Treatment of Metastatic or Locally Advanced HER2-Negative Gastric and Gastroesophageal Cancers

NCCN	ESMO
<u>Preferred regimens</u> • Ramucirumab and paclitaxel • Docetaxel • Paclitaxel • Irinotecan • Ramucirumab • 5-FU and irinotecan (if not used in first line) <u>Other regimens</u> • Irinotecan and cisplatin • Pembrolizumab for treatment of MSI-high or dMMR tumors • Docetaxel and irinotecan	• Ramucirumab and paclitaxel in patients with a performance status of 0 or 1 • Docetaxel • Paclitaxel • Irinotecan • Ramucirumab

5-FU=5-fluorouracil; dMMR=mismatch repair deficient; ESMO=European Society for Medical Oncology; MSI=microsatellite instability; NCCN=National Comprehensive Cancer Network®.

Although important advances have been achieved with the introduction of new anti-cancer agents, OS has been only marginally affected and the long-term prognosis of patients with gastric cancer who experience disease progression during or following a first-line chemotherapy regimen remains dismal.

1.3.3 Immunotherapy for Gastric Cancer

Promising new therapy for gastric cancer has emerged with use of immune checkpoint inhibitors (CPIs). These treatments are designed to unleash or enhance preexisting anti-cancer immune responses. Selected available clinical trial data involving PD-1 or PD-L1 inhibitors in gastric cancer are described below.

ONO-12 (ATTRACTION 2)—a Phase III, multicenter, double-blind, randomized study of nivolumab (PD-1 inhibitor) in patients with unresectable advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer who were refractory to or intolerant to two or more prior chemotherapy regimens—demonstrated for the first time that PD-1 inhibition could lead to an improvement in OS for patients with heavily pretreated gastric or gastroesophageal cancer. The median OS was 5.32 months (95% confidence interval [CI]: 4.63, 6.41) for patients treated with nivolumab, compared with 4.14 months (95% CI: 3.42, 4.86 for patients treated with placebo ($p < 0.0001$). In addition, OS rate at

12 months was 26.6% (95% CI: 21.1, 32.4) in the nivolumab group versus 10.9% (95% CI: 6.2, 17.0) in the placebo group (Kang et al. 2017).

CheckMate-032, a Phase I/II, open-label, randomized study, investigated nivolumab alone or in combination with ipilimumab in 160 patients with advanced or metastatic gastric or gastroesophageal cancer who had progressed while receiving standard chemotherapy, with most patients having received two or more prior regimens (Janjigian et al. 2016). Patients were randomized to receive one of the following regimens until disease progression or intolerable toxicity: 3 mg/kg of nivolumab every 2 weeks (Q2W) (N3 arm), 1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab every 3 weeks (Q3W) for 4 cycles followed by 3 mg/kg of nivolumab Q2W (N1 + I3 arm), or 3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab Q3W for 4 cycles followed by 3 mg/kg of nivolumab Q2W (N3 + I1 arm). The median OS was highest in the N1 + I3 arm. For patients with PD-L1–positive tumors, the response rate was 27% for the N3 arm and 44% for the N1 + I3 arm (the more active of the combination arms). For patients with PD-L1–negative tumors, the response rate was 12% for the N3 arm and 21% for the N1 + I3 arm.

KEYNOTE-012, a Phase Ib, multicenter, open-label, non-randomized, multicohort study evaluating single-agent pembrolizumab (PD-1 inhibitor) in 39 heavily pretreated patients with PD-L1–positive recurrent or metastatic gastric or GEJ adenocarcinoma (Muro et al. 2016). A partial response rate of 22% was observed among 36 efficacy-evaluable patients.

KEYNOTE-028 evaluated the role of pembrolizumab (10 mg/kg Q2W up to 2 years or until progression) in 23 patients with PD-L1–positive advanced solid tumors including esophageal or GEJ cancers (adenocarcinoma and squamous cell cancer) (Doi et al. 2016). The ORR was 30%, and the PFS rate at 6 and 12 months was 30.4% and 21.7%, respectively. In this trial, 74% of patients had squamous histology.

KEYNOTE-059 is a Phase II study of patients with HER2-negative advanced gastric or GEJ adenocarcinoma receiving first-line treatment consisting of pembrolizumab plus 5-FU (or capecitabine in Japan) plus cisplatin Q3W for 6 cycles, followed by pembrolizumab plus 5-FU/capecitabine maintenance for up to 2 years or until disease progression (Fuchs et al. 2016). Preliminary data suggest that combination treatment with a PD-1 inhibitor and chemotherapy has manageable toxicity for patients with advanced gastric cancer. Final efficacy data from this study are pending.

Avelumab (anti-PD-L1 IgG1 antibody) is currently being assessed in the JAVELIN program in expansion cohorts for selected tumor types, including gastric or GEJ tumors (Kelly et al. 2015). Preliminary data show a 9.7% response rate in patients receiving 10 mg/kg of avelumab Q2W in the second-line setting. For Japanese patients who had progressed while receiving prior chemotherapy, the reported ORR was 15% (3 of 20 patients), with 43.3% of patients achieving PFS at 12 weeks (Nishina et al. 2016).

Additionally, [Table 3](#) summarizes selected ongoing clinical trials involving first-line, second-line, third-line, and maintenance therapy involving PD-1 or PD-L1 inhibitors in gastric cancer.

Table 3 Selected Ongoing Gastric/Gastroesophageal Junction Cancer Trials Involving PD-1/PD-L1 Inhibitors

Investigational Compound	Clinical Trial Identifier	Phase	Study Design	Primary Endpoint
First-Line Therapy				
Nivolumab	NCT02746796	II	Nivolumab plus chemotherapy	ORR
Nivolumab	NCT02935634	III	Nivolumab plus ipilimumab vs. nivolumab plus IO (multiple lines)	ORR, DOR, PFS
Nivolumab	NCT01928394	I/II	Nivolumab with or without ipilimumab (multiple lines)	ORR
Pembrolizumab	NCT02393248	I/II	Pembrolizumab or chemotherapy plus INCB054828	Safety, MTD
Pembrolizumab	NCT02494583	III	Pembrolizumab with or without chemotherapy	OS, PFS (PD-L1+)
Pembrolizumab	NCT02335411	II	Pembrolizumab with or without chemotherapy	Safety, ORR
Durvalumab	NCT02304975	Ib/II	Durvalumab plus tremelimumab (multiple lines)	Safety, ORR, PFS
Durvalumab	NCT02735239	I/II	Durvalumab plus tremelimumab with or without chemotherapy with or without radiotherapy (multiple lines)	Safety
Second-Line Therapy				
Nivolumab	NCT01928394	I/II	Nivolumab with or without ipilimumab (multiple lines)	ORR
Nivolumab	NCT02935634	III	Nivolumab plus ipilimumab vs. nivolumab plus IO (multiple lines)	ORR, DOR, PFS
Pembrolizumab	NCT02564263	III	Pembrolizumab vs. chemotherapy	PFS, OS
Pembrolizumab	NCT02370498	III	Pembrolizumab vs. paclitaxel	PFS, OS (PD-L1+)
Durvalumab	NCT02318277	I/II	Durvalumab plus epacadostat	Safety, ORR
Durvalumab	NCT02572687	I	Durvalumab plus ramucirumab	Safety
Durvalumab	NCT02304975	Ib/II	Durvalumab plus tremelimumab (multiple lines)	Safety, ORR, PFS
Durvalumab	NCT02735239	I/II	Durvalumab plus tremelimumab with or without chemotherapy with or without radiotherapy (multiple lines)	Safety
Avelumab	NCT01772004	I	Monotherapy	Safety

DOR=duration of response; IO=immuno-oncology (compounds); irPFS=immune-related progression-free survival; MTD=maximum tolerated dose; ORR=objective response rate; OS=overall survival; PD-L1+=PD-L1-positive (tumors); PFS=progression-free survival.

Table 3 Selected Ongoing Gastric/ Gastroesophageal Junction Cancer Trials Involving PD-1/PD-L1 Inhibitors (cont.)

Investigational Compound	Clinical Trial Identifier	Phase	Study Design	Primary Endpoint
Third-Line Therapy				
Nivolumab	NCT02267343	III	Nivolumab vs. placebo	OS
Avelumab	NCT02625623	III	Avelumab vs. best supportive care	OS
Maintenance Therapy				
Avelumab	NCT01772004	I	Monotherapy	Safety, ORR
Durvalumab	NCT02678182	II	Durvalumab vs. capecitabine vs. trastuzumab vs. control	PFS
Ipilimumab	NCT01585987	II	Ipilimumab vs. best supportive care	irPFS

DOR=duration of response; IO=immuno-oncology (compounds); irPFS=immune-related progression-free survival; MTD=maximum tolerated dose; ORR=objective response rate; OS=overall survival; PD-L1+=PD-L1-positive (tumors); PFS=progression-free survival.

In summary, preliminary data from clinical trials involving single-agent CPIs in metastatic gastroesophageal cancer have demonstrated response rates of approximately 10%–17% overall (regardless of PD-L1 status) and approximately 22%–30% for the subset of patients with PD-L1-positive tumors. It is likely that the majority of patients who respond to single-agent checkpoint inhibition may present with special subtypes, such as the EBV subtype and the MSI subtype. TCGA investigators reported that the EBV subtype in gastric cancer displays recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, PD-L1, and PD-L2, and the MSI subtype shows elevated mutation rates that have yet to be determined (Cancer Genome Atlas Research Network 2014). Alternatively, patients with the GS subtype (mutations of RhoA or fusions involving Rho-family guanosine 5'-triphosphatase-activating proteins) and the chromosomal unstable subtype (marked aneuploidy and focal amplification of receptor tyrosine kinases) may need novel combination immunotherapies. However, a much greater understanding of tumor forces that dampen the T-cell immune response in gastric cancer is needed. This study will aid in the understanding of resistance mechanisms such as the interaction of immunosuppressive factors within the immune microenvironment, the effects of tumor reactive stroma or transforming growth factor beta biology, or the function of density of tumor-infiltrating lymphocytes or density of PD-L1 expression.

1.3.4 Background on Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude

and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to 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 advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab (Tecentriq®) 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.

1.3.4.1 Atezolizumab in the Treatment of Gastric Cancer

As of 10 May 2016, 42 studies were ongoing with atezolizumab given as a single agent or in combination with other therapies in solid tumors and three of them include a specific cohort with gastric cancer (see [Table 4](#)). Preliminary safety and efficacy data of atezolizumab as a single agent for the treatment of gastric cancer (Study PCD4989g) are promising and support further investigation of immune combinations in this indication.

Refer to the Atezolizumab Investigator's Brochure for efficacy and safety details.

Table 4 Ongoing Clinical Studies with Atezolizumab, Including a Patient-Specific Cohort with Gastric Cancer

Study	Study Description	Primary Endpoints
PCD4989g (GO27831)	A Phase Ia, first-in-human, open-label study of atezolizumab in patients with locally advanced or metastatic solid tumors or hematologic malignancies	Safety and tolerability, including MTD, DLTs, and RP2D
GO30140	A Phase Ib, open-label study of atezolizumab administered with bevacizumab (Arm A), with bevacizumab plus FOLFOX (Arm B), with gemcitabine and nab-paclitaxel (Arm C), and with vanucizumab (Arm D), in patients with solid tumors	Safety and tolerability
GP28328	A Phase Ib, open-label, non-controlled study of atezolizumab administered with bevacizumab alone (Arm A), with bevacizumab plus mFOLFOX6 (Arm B), with carboplatin and paclitaxel (Arm C), with carboplatin and pemetrexed (Arm D), with carboplatin and nab-paclitaxel (Arm E), or with nab-paclitaxel (Arm F) in patients with advanced solid tumors	Safety and tolerability

DLT=dose-limiting toxicity; FOLFOX6=infusional 5-fluorouracil, leucovorin [folic acid], and oxaliplatin; mFOLFOX6=modified FOLFOX6; MTD=maximum tolerated dose; nab-paclitaxel=nanoparticle albumin-bound paclitaxel; RP2D=recommended Phase II dose.

1.4 TREATMENT FOR ESOPHAGEAL CANCER

1.4.1 First-Line Treatment for Esophageal Cancer

Treatment options for patients with advanced or metastatic esophageal cancer are limited. Current NCCN guidelines for the first-line treatment of advanced or metastatic disease recommend platinum-based chemotherapy in combination with fluoropyrimidine (fluorouracil or capecitabine) (NCCN 2019; Lordick et al. 2016). Although ESMO guidelines recommend monotherapy or best supportive care as first-line therapy in patients with squamous cell carcinoma (Lordick et al. 2016), platinum doublet chemotherapy is commonly used without supportive evidence from randomized controlled trials in Asian countries, with response rates of only 20%–40% (Lorenzen et al. 2009; Kato et al. 2014). Targeted agents have also been investigated as first-line therapy in patients with esophageal squamous cell carcinoma, but these earlier attempts failed to demonstrate a clear benefit over chemotherapy alone (Lorenzen et al. 2009; Weidmann and Mössner 2013; Adenis et al. 2016; Moehler et al. 2017). More recently, immune CPIs are being investigated in Phase III trials: KEYNOTE-590 (NCT03189719) is evaluating pembrolizumab in combination with chemotherapy (5-FU and cisplatin) compared with chemotherapy as first-line treatment in patients with advanced or metastatic esophageal cancer; CheckMate-648 study (NCT03143153) is evaluating the

efficacy of nivolumab and ipilimumab compared with nivolumab combined with fluorouracil plus cisplatin, and compared with fluorouracil plus cisplatin in patients with advanced or metastatic previously untreated esophageal squamous cell cancer.

Hence, there remains a significant need for novel therapeutic agents for the first-line treatment of advanced or metastatic esophageal cancer. Thus, other novel agents are worth exploring further in esophageal cancer.

1.4.2 Second-Line Treatment for Esophageal Cancer

Patients with advanced esophageal cancer after first-line chemotherapy have a poor prognosis and limited treatment options. Docetaxel, paclitaxel, and irinotecan are commonly used for both histologic subtypes, but there is no consensus on a second-line regimen for patients whose disease progresses on first-line therapy (Lordick et al. 2016; Ilson et al. 2018). Notably, there was no overall survival benefit demonstrated with chemotherapy in a Phase III Study (Ilson et al. 2018). Molecular targeted therapy has also been explored, but outcomes were also poor (Weidmann and Mössner 2013).

Immune CPIs have recently been evaluated in various trials in patients with advanced and metastatic esophageal cancer. Clinical trials that utilized PD-1 monoclonal antibodies reported preliminary evidence of activity in a subset of participants with esophageal cancer. In the KEYNOTE-028 trial (NCT02054806), which was limited to participants with PD-L1–positive tumors, the Esophageal Cancer Cohort showed objective responses after pembrolizumab therapy in 5 of 18 patients with squamous cell carcinoma (28%) (Doi et al. 2017). A separate Phase II trial of nivolumab from Japan in a purely squamous cell carcinoma cohort, not pre-selected for PD-L1 status, reported objective responses in 11 of 64 patients (17.2%), including one complete responder and 16 of 64 patients (25.0%) had stable disease (Kudo et al. 2017).

Successor studies include two trials evaluating pembrolizumab in the second- and third-line settings for advanced esophageal cancer (NCT02564263 [KEYNOTE-181] and NCT02559687 [KEYNOTE-180]) and two ongoing trials evaluating nivolumab in unresectable advanced or recurrent esophageal cancer (NCT02569242) and nivolumab plus ipilimumab for second-line therapy in elderly patients with advanced esophageal cancer (NCT03416244).

Results from KEYNOTE-180, a Phase II study evaluating pembrolizumab in heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, demonstrated durable responses with an ORR of 14.3% among patients with squamous cell carcinoma, 5.2% among patients with adenocarcinoma, and 13.8% among patients with PD-L1–positive tumors (Shah et al. 2019). In KEYNOTE-181, a Phase III study evaluating pembrolizumab compared with chemotherapy, patients with metastatic esophageal cancer, who had progressed after

one prior therapy, and whose tumors showed PD-L1 combined positive score (CPS) ≥ 10 , experienced a significant increase in survival (12-month OS rate of 42% vs. 20%). This benefit extended to patients with squamous cell carcinoma (12-month OS rate of 39% vs. 25%) (Kojima et al. 2019; Shah et al. 2019).

Based on the data from KEYNOTE-181, recent NCCN guidelines recommend pembrolizumab for second-line therapy for esophageal squamous cell carcinoma, esophageal adenocarcinoma, and GEJ adenocarcinoma with PD-L1 expression levels by CPS ≥ 10 [NCCN 2019].

While these immune CPIs certainly hold considerable promise, it is apparent that only a subset of participants derived benefit from this class of agents (Wang et al. 2016). Hence, there remains a significant need for novel therapeutic agents for the second-line treatment of locally advanced or metastatic esophageal cancer. Thus, other novel agents are worth exploring further in esophageal cancer.

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study will enroll patients with locally advanced unresectable or metastatic gastric cancer or GEJ cancer (hereafter referred to as gastric cancer). Patients will be allocated to two cohorts: Patients with gastric cancer who have not received prior chemotherapy in the locally advanced or metastatic setting (the first-line [1L] Cohort), and patients with gastric cancer who have progressed after receiving a platinum-containing or fluoropyrimidine-containing chemotherapy regimen in the first-line setting (i.e., the second-line [2L] Cohort). Given the relatively poor prognosis and limited treatment options for these patients, these populations are considered appropriate for trials of novel therapeutic candidates. As of October 2019, the gastric cancer cohorts are not enrolling patients into the current treatment arms.

This study will also enroll patients with esophageal cancer. Patients with locally advanced unresectable or metastatic esophageal cancer who have not received prior systemic treatment will be allocated to an Esophageal Cancer Cohort. Because of the relatively poor prognosis and limited treatment options for these patients, this population is also considered appropriate for trials evaluating novel therapeutic agents.

CIT has demonstrated extraordinary success, with significant survival benefits observed across multiple advanced malignancies. Currently, the prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by identifying and targeting T-cell co-inhibitory surface receptors such as CTLA-4 and PD-L1/PD-1. Although these targets have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates a series of stepwise events necessary for the generation of a continuous anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune evasion mechanisms. Thus, the need to

identify and circumvent the various factors involved in tumor immune evasion will be critical for propagating the anti-tumor immune response and advancing the field of CIT, most likely through combination regimens.

This Phase Ib/II umbrella study is designed to accelerate the development of CIT combinations by identifying early signals and establishing proof-of-concept clinical data in patients with gastric and esophageal cancer. This study is designed with the flexibility to open new treatment arms as new treatments become available and to close treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms within 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 mechanisms of immune escape through immune cell (IC) 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. Moreover, patients who experience disease progression or loss of clinical benefit with the initial treatment regimen (Stage 1) may be eligible to continue treatment with a different CIT combination regimen (Stage 2), which may advance the scientific understanding of immune escape mechanisms in patients who do not respond or experience disease progression during treatment with CIT or control regimens.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) are summarized in [Table 5](#). The control and experimental treatment regimens are described in Sections [3.1.1](#), [3.1.3](#), and [3.1.4](#) (see also [Table 8](#), [Table 10](#), [Table 11](#), and [Table 12](#)). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agents, are provided in the respective appendix for that treatment arm, as outlined in [Table 8](#), [Table 10](#), [Table 11](#), and [Table 12](#).

Table 5 Target and Proposed Mechanism-of-Action Classification for Investigational Medicinal Products

Experimental IMP	Target	Proposed MOA Classification
Atezolizumab	PD-L1	Checkpoint inhibitor
BL-8040 ^a	CXCR4	Tumor micro-environment recruitment ^b
Linagliptin ^a	DPP-4	Tumor micro-environment recruitment ^c
Tiragolumab	TIGIT	TIGIT antagonist, improves the activation and effectiveness of T-cell and NK-cell tumor-killing activity ^d

CXCR4 = cysteine-X-cysteine chemokine receptor 4; DPP-4 = dipeptidyl peptidase-4; IMP = investigational medicinal product; MOA = mechanism of action; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

^a As of October 2019, experimental treatment arms with this IMP are no longer enrolling patients in this study.

^b Fearon 2014.

^c Barreira da Silva et al. 2015.

^d Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014.

1.6 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). 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.

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). While 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 CPI therapies (e.g., atezolizumab). At this time, there is insufficient evidence for causal association

between immune CPI therapies and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with immune CPI 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.

A number of COVID-19 vaccines have received emergency use authorization or temporary authorization. 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 the recommendations of the NCCN COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune CPIs and chemotherapy) with the understanding that there are limited safety and efficacy data in these patients (NCCN 2021). 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 treatment with CIT (SITC 2020). For patients enrolling in this study and receiving atezolizumab and tiragolumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, 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 immunotherapy-based treatment combinations in patients with gastric cancer and esophageal cancer. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 6) and Stage 2 (see Table 7).

Table 6 Objectives and Corresponding Endpoints for Stage 1

Objectives	Corresponding Endpoint(s)
Primary Efficacy Objective:	
To evaluate the efficacy of immunotherapy-based treatment combinations in all arms during Stage 1	Objective response, defined as 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:	
To evaluate the efficacy of immunotherapy-based treatment combinations in all arms 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), as determined by the investigator according to RECIST v1.1 - OS after randomization, defined as the time after randomization to death from any cause - 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, defined as stable disease for ≥ 16 weeks for the Gastric Cancer Cohort or ≥ 12 weeks for the Esophageal Cancer Cohort, or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective:	
To evaluate the safety of immunotherapy-based treatment combinations in all arms during Stage 1	- Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 - Change from baseline in vital signs and ECG parameters - Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective:	
To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	Plasma or serum concentration of each drug (as appropriate) at specified timepoints

ADA=anti-drug antibody; DOR=duration of response; eCRF=electronic case report form; IC=immune cell; IHC=immunohistochemistry; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; TC=tumor cell; TIGIT=T-cell immunoreceptor with Ig and ITIM domains.

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

Table 6 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Objectives	Corresponding Endpoints
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]
Immunogenicity Objective:	
To evaluate the immune response to drugs that are administered as part of an immunotherapy-based 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
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]

ADA=anti-drug antibody; DOR=duration of response; eCRF=electronic case report form; [REDACTED] OS=overall survival; PFS=progression-free survival; [REDACTED] RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; [REDACTED]

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

Table 7 Objectives and Corresponding Endpoints for Stage 2

Objectives	Corresponding Endpoints
• [REDACTED]	• [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]
Safety Objective:	
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective:	
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug at specified timepoints

ADA=anti-drug antibody; [REDACTED]

OS=overall survival; [REDACTED]

eCRF=electronic case report form; [REDACTED]

PK=pharmacokinetic; [REDACTED]

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

Table 7 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Objectives	Corresponding Endpoints
[REDACTED]	
• [REDACTED]	• [REDACTED] • [REDACTED]
Immunogenicity Objective:	
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based 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
Exploratory Immunogenicity Objective:	
• 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
[REDACTED]	
• [REDACTED]	• [REDACTED]

ADA= anti-drug antibody;

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

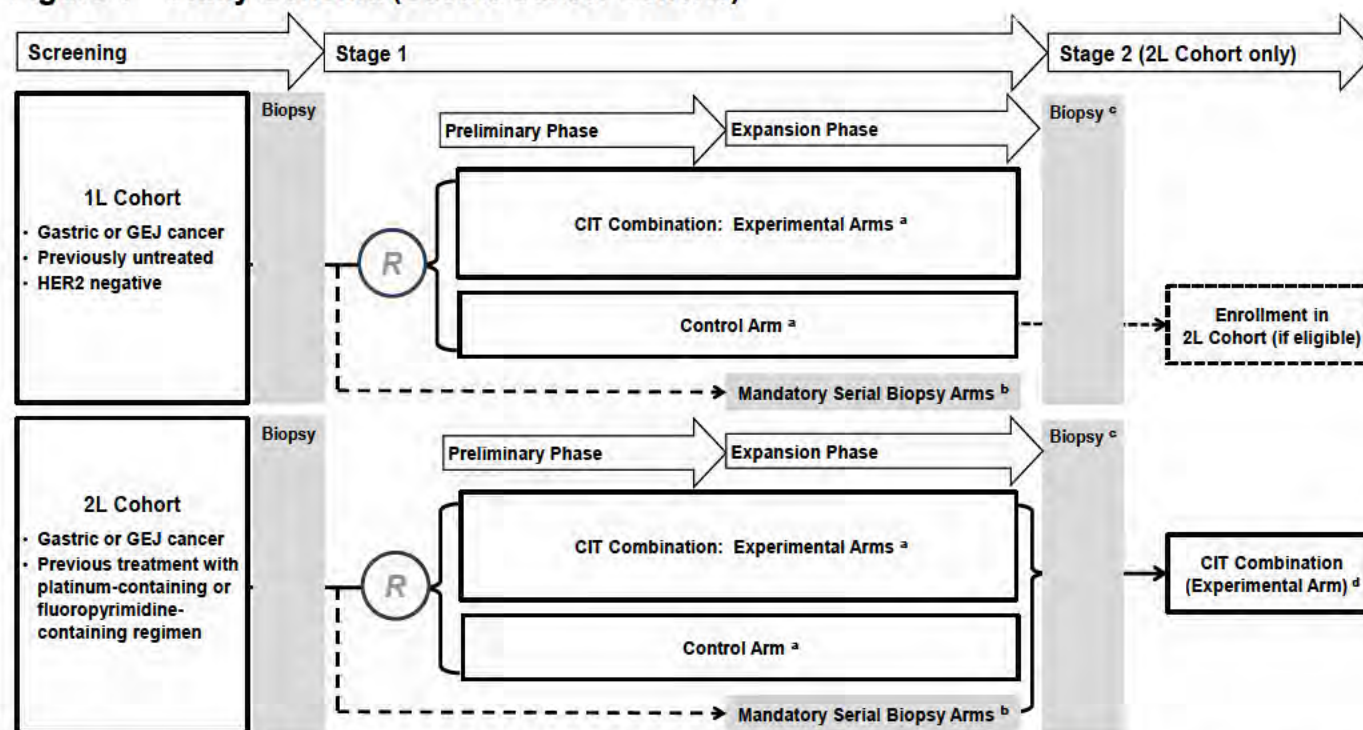
This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with gastric and esophageal cancer. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity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

Two cohorts of patients with gastric cancer have been enrolled in parallel in this study: the 2L Gastric Cancer Cohort consists of patients with gastric cancer who have progressed after receiving a platinum-containing or fluoropyrimidine-containing chemotherapy regimen in the first-line setting, and the 1L Gastric Cancer Cohort consists of patients with gastric cancer who have not received prior chemotherapy in this setting (see [Figure 1](#)). In each cohort, eligible patients will initially be assigned to one of several treatment arms (Stage 1; see Section 3.1.1). Patients in the 2L Gastric Cancer Cohort who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen in Stage 2 (see Section 3.1.3). Because the combination of atezolizumab plus cobimetinib did not meet its primary endpoint of OS when compared with regorafenib in a Phase III study in patients with locally advanced or metastatic colorectal cancer (Study GO30182 [IMblaze370]), patients will no longer be enrolled in cobimetinib-containing arms, but all enrolled patients will continue to be treated and monitored per the protocol. In addition, patient enrollment in the 1L Cohort (including the safety run-in phase) has been suspended until additional arms can be added (with a substantial amendment). As of October 2019, the 2L Gastric Cancer Cohort has completed enrollment in the preliminary phase and will not undergo the expansion phase. All enrolled patients in the gastric cancer cohorts will continue to be treated and monitored per the protocol. [Table 9](#) lists treatment arms for which enrollment and patient follow-up has been completed.

Additionally, a cohort of patients with esophageal cancer who have not received prior systemic treatment for their disease will also be enrolled in this study (see [Figure 2](#)). Eligible patients will be randomized to one of three treatment arms (see Section 3.1.1). Patients in the control arm of the Esophageal Cancer Cohort who experience disease progression or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen in Stage 2 (see Section 3.1.4).

Overall, approximately 195–410 patients will enroll in this study across both the Gastric and Esophageal Cancer Cohorts.

Figure 1 Study Schema (Gastric Cancer Cohorts)



1L = first-line; 2L = second-line; CIT = cancer immunotherapy; GEJ = gastroesophageal junction; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Further enrollment in the 1L Cohort was suspended as of June 2018 (see Section 3.1 for details). As of October 2019, patients with gastric cancer are not being enrolled (see Section 3.1 for details).

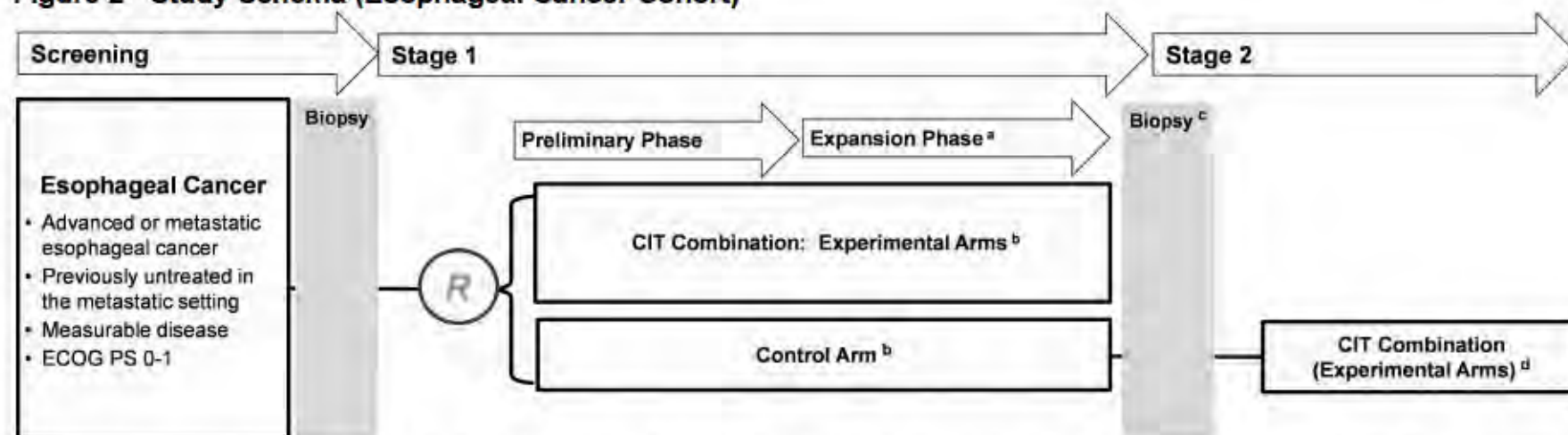
^a Refer to Table 8 for a summary of available Stage 1 treatment regimens for the 1L and 2L Gastric Cancer Cohorts.

^b The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.1.2 for details).

^c A biopsy (if clinically feasible) will be performed for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see details on tissue sample collection in Section 4.5.6).

^d Refer to Table 11 for a summary of available Stage 2 treatment regimens for the 2L Gastric Cancer Cohort.

Figure 2 Study Schema (Esophageal Cancer Cohort)



CIT = cancer immunotherapy; ECOG = Eastern Cooperative Oncology Group; PS = Performance Status R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

- ^a If deemed clinically feasible by the investigator, patients enrolled in an experimental arm during the expansion phase will undergo an on-treatment biopsy 4 weeks after initiation of Stage 1 treatment.
- ^b Refer to [Table 10](#) for a summary of available Stage 1 treatment regimens for the Esophageal Cancer Cohort.
- ^c A biopsy (if clinically feasible) will be performed for patients who discontinue Stage 1 because of unacceptable toxicity or disease progression per RECIST v1.1 (see details on tissue sample collection in [Section 4.5.6](#)).
- ^d Refer to [Table 12](#) for a summary of available Stage 2 treatment regimens for the Esophageal Cancer Cohort.

3.1.1 Stage 1

Gastric Cancer

During Stage 1, patients will be randomly assigned to control or experimental treatment arms with the exception of the mandatory serial biopsy arms. Patients in the 2L Gastric Cancer Cohort will be randomly assigned to a control arm (Ramucirumab + Paclitaxel) or an experimental arm consisting of atezolizumab in combination with BL-8040 (Atezo + BL-8040), or linagliptin (Atezo + Linagliptin). As of June 2018, further enrollment in the 1L Gastric Cancer Cohort was suspended and the experimental arm of mFOLFOX6 combined with atezolizumab plus cobimetinib (mFOLFOX6 + Atezo + Cobi) was closed for further enrollment (see Section 3.1 for details). At that time, 5 patients had been enrolled in the mFOLFOX6 + Atezo + Cobi arm during the safety run-in phase. As of October 2019, the 2L Gastric Cancer Cohort has completed enrollment in the preliminary phase and will not undergo the expansion phase. All enrolled patients in the gastric cancer cohorts will continue to be treated and monitored per the protocol. Details on the treatment regimens for Stage 1 are provided in [Appendix 8–Appendix 9](#) and [Appendix 12–Appendix 13](#), as specified in [Table 8](#). [Table 9](#) lists treatment arms for which enrollment and patient follow-up has been completed.

Enrollment for all experimental arms will take place in two phases: a preliminary phase followed by an expansion phase, as outlined in [Table 8](#) and shown in [Figure 3](#) and [Figure 4](#).

A total of up to 95–245 patients will be enrolled during Stage 1. Approximately 15 patients will be enrolled in all arms during the preliminary phase. 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. The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

The Sponsor may also decide to open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase (see Section 3.1.1.2 for details). Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be enrolled to ensure balance among 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 (see Section 9.6).

Table 8 Stage 1 Treatment Regimens (Gastric Cancer Cohorts)

Cohort (Enrollment Status)	Study Treatment	No. of Patients (Sponsor Assignment) ^a	No. of Patients (Random Assignment) ^b		Appendix
		Safety Run-In Phase	Preliminary Phase	Expansion Phase ^{c, d}	
1L Gastric Cancer (Not Enrolling) ^e	mFOLFOX6	—	Variable ^b		Appendix 9
2L Gastric Cancer (Not Enrolling) ^e	Atezo+BL-8040	—	15	25	Appendix 12
	Atezo+Linagliptin	—	15	25	Appendix 13
	Ramucirumab+Paclitaxel	—	Variable ^b		Appendix 8

1L=first-line; 2L=second-line; Atezo=atezolizumab; mFOLFOX6=infusional 5-fluorouracil, leucovorin (folic acid), and oxaliplatin.

^a During the safety run-in phase, patients will be assigned to available treatment arms. The treatment assignment ratio will depend on the number of experimental arms that are open for enrollment (see Section 4.2 for details).

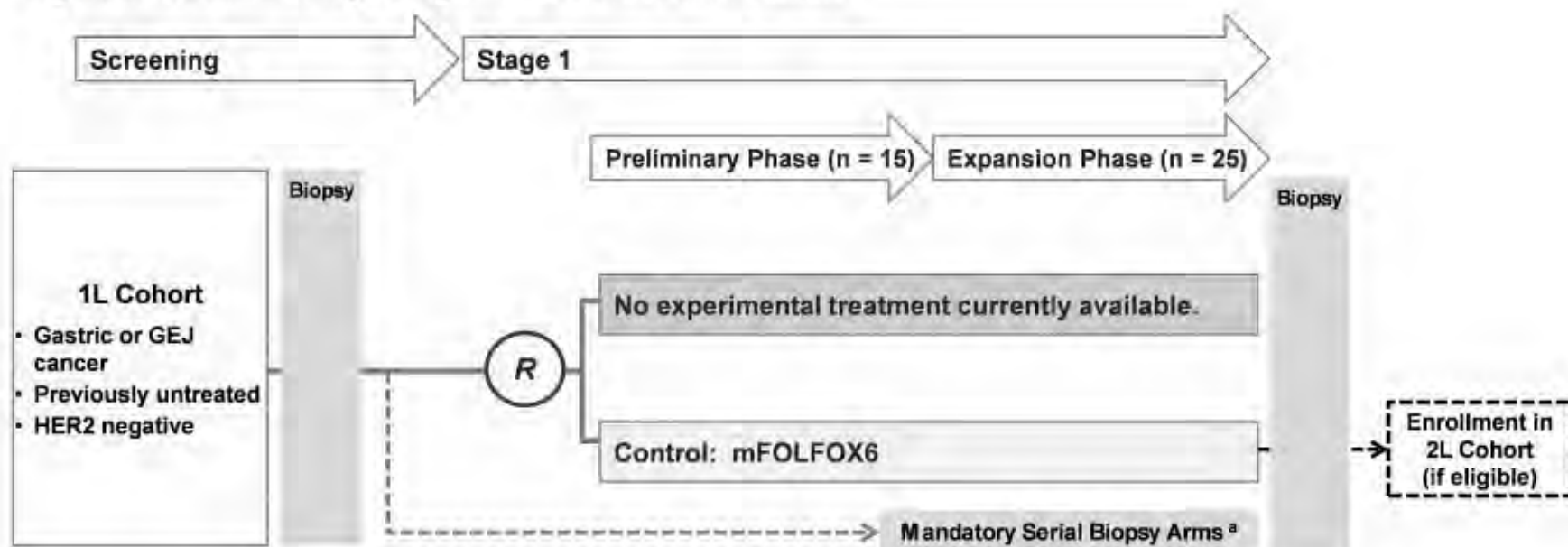
^b The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 35% of patients will be randomly allocated to the control arm at a given time. The randomization ratios may be altered to increase enrollment in an experimental arm that has demonstrated promising clinical activity (see Section 4.2 for details).

^c If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients will be enrolled in that arm during the expansion phase.

^d The Sponsor may decide to open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.1.2 for details).

^e Further enrollment in the 1L Gastric Cancer Cohort was suspended as of June 2018. As of October 2019, the 2L Gastric Cancer Cohort has completed enrollment in the preliminary phase and will not undergo the expansion phase (see Section 3.1 for details). As of November 2021, 2 patients are on treatment in the Atezo+BL-8040 arm and 1 patient is on treatment in the Atezo+Linagliptin arm; no patients are on treatment or in follow-up in the mFOLFOX arm or the Ramucirumab+Paclitaxel arm.

Figure 3 Detailed Study Design: 1L Gastric Cancer Cohort

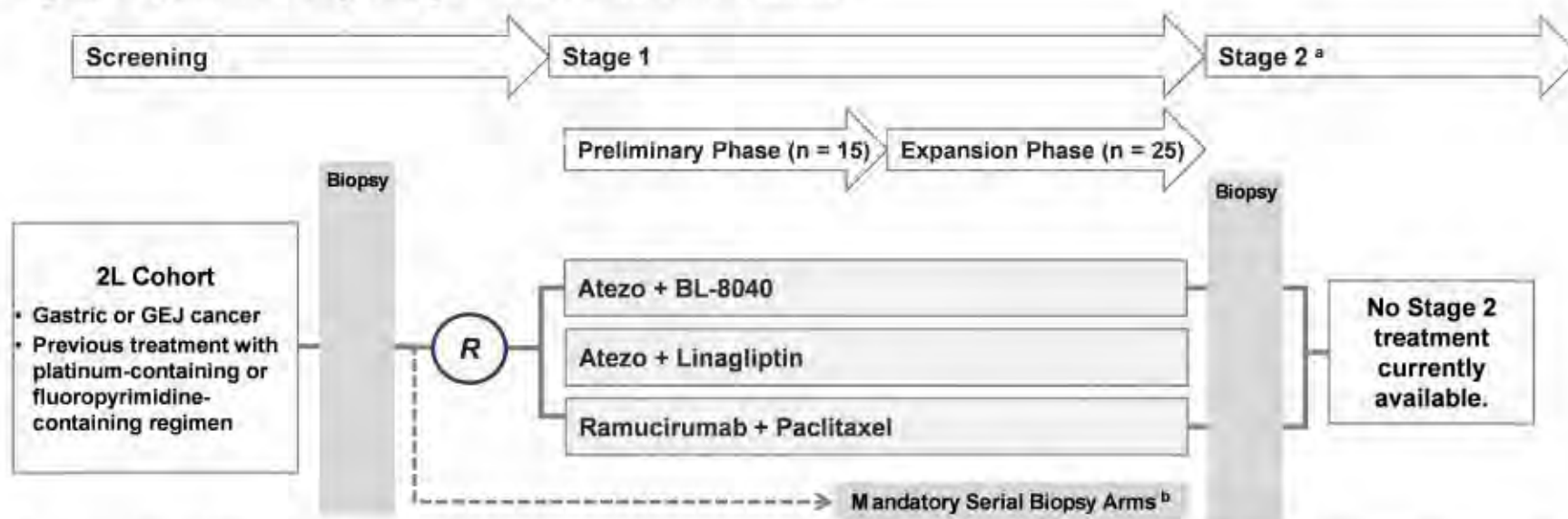


1L = first-line; 2L = second-line; Atezo = atezolizumab; GEJ = gastroesophageal junction; mFOLFOX6 = infusional 5-fluorouracil, leucovorin (folic acid), and oxaliplatin; R = randomization.

Notes: As of January 2021, all 1L gastric cancer experimental treatment arms have been removed.

^a The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.1.2 for details).

Figure 4 Detailed Study Design: 2L Gastric Cancer Cohort



2L = second-line; Atezo = atezolizumab; GEJ = gastroesophageal junction; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: As of October 2019, the 2L Gastric Cancer Cohort has completed enrollment in the preliminary phase and will not undergo the expansion phase (see Sections 3.1 and 3.1.1 for details).

^a Patients in the 2L Gastric Cancer Cohort who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment combination during Stage 2, provided they meet eligibility criteria and the Stage 2 arm is open for enrollment. Details are provided in Section 3.1.3 and the respective appendix for each treatment arm (see Appendix 8, Appendix 10, Appendix 12–Appendix 13, and Appendix 16).

^b The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.1.2 for details).

Table 9 Treatment Arms with Completed Enrollment and Patient Follow-Up

Stage	Cohort	Arm	Number of Patients Enrolled		Protocol Versions Describing Arm
			Preliminary Stage	Expansion Phase	
1	1L	mFOLFOX6+Atezo+Cobi	5	0	1–7
	2L	Atezo+PEGPH20	15	0	1–7

Atezo=atezolizumab; Cobi=cobimetinib; mFOLFOX6=infusional 5-fluorouracil, leucovorin (folic acid), and oxaliplatin.

Patients in Stage 1 will be randomly assigned to treatment arms, with the exception of the mandatory serial biopsy arms, and the randomization ratio will depend on the number of experimental arms that are available (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 no more than 35% of patients will be randomly allocated to the control arm at a given time. 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.

Patients in the control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 1). Patients in the experimental arms will be treated 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 IC infiltration in the setting of a T-cell response (termed pseudoprogression) with CITs (such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study 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 anatomic sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- An additional patient's written consent form to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

Esophageal Cancer

During Stage 1, patients with esophageal cancer will be randomly assigned to a chemotherapy control arm (Cisplatin+5-FU) or one of two experimental arms: atezolizumab in combination with tiragolumab and chemotherapy (Atezo+ Tiragolumab+ Cisplatin+5-FU), or atezolizumab in combination with chemotherapy (Atezo+ Cisplatin+5-FU). Details on the treatment regimens for Stage 1 are provided in [Appendix 17–Appendix 19](#), as specified in [Table 10](#).

Enrollment for the two experimental arms will take place in two phases: a preliminary phase followed by an expansion phase, as outlined in [Table 10](#) and shown in [Figure 5](#).

Approximately 100–165 patients will be enrolled during Stage 1. Up to approximately 40 patients will be enrolled in the two experimental arms during the preliminary phase to ensure a sufficient number of patients with high TIGIT and PD-L1 expression to facilitate the evaluation of benefit and risk within this subpopulation. 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. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Enrollment in the Atezo+ Tiragolumab+ Cisplatin+ 5-FU arm will be suspended to allow for a safety evaluation in a minimum of 6 patients (see [Section 3.1.1.1](#) for details).

Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. New experimental arms may be added during the study by amending the protocol (see [Section 9.6](#)).

Table 10 Stage 1 Treatment Regimens (Esophageal Cancer Cohort)

Cohort (Enrollment Status)	Study Treatment	No. of Patients (Random Assignment) ^a		Appendix
		Preliminary Phase	Expansion Phase ^d	
1L Esophageal Cancer (Enrolling) ^b	Atezo + Tiragolumab + Cisplatin + 5-FU	40 ^c	25	Appendix 17
	Atezo + Cisplatin + 5-FU	40	25	Appendix 18
	Cisplatin + 5-FU	Variable		Appendix 19

1L = first-line; 5-FU = 5-fluorouracil; Atezo = atezolizumab.

^a 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 no more than 35% of patients will be randomly allocated to the control arm at a given time. The randomization ratios may be altered to increase enrollment in an experimental arm that has demonstrated promising clinical activity (see Section 4.2 for details).

^b The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

^c Enrollment will be suspended in the Atezo + Tiragolumab + Cisplatin + 5-FU arm to allow for a safety evaluation in a minimum of 6 patients (see Section 3.1.1.1 for details).

^d If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients will be enrolled in that arm during the expansion phase.

Figure 5 Detailed Study Design: Esophageal Cancer Cohort



5-FU = 5-fluorouracil; Atezo = atezolizumab; ECOG = Eastern Cooperative Oncology Group; PS = Performance Status R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

^a Patients in the control arm who experience disease progression per RECIST v1.1 or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment combination during Stage 2 (if arm open for enrollment), provided they meet the eligibility criteria. Details are provided in the respective appendix for the control arm (see [Appendix 19](#)).

Patients in Stage 1 will be randomly assigned to treatment arms, and the randomization ratio will depend on the number of experimental arms that are available (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 no more than 35% of patients will be randomly allocated to the control arm at a given time. 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 4.1.4). Details on treatment assignment and randomization are provided in Section 4.2.

Patients in the control arm will continue to receive treatment until unacceptable toxicity or disease progression per RECIST v1.1; see Appendix 1. Patients in the experimental arms will be treated 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 IC infiltration in the setting of a T-cell response (termed pseudoprogression) with CITs (such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study 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 ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomic sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- An additional patient's written consent form to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

3.1.1.1 Safety Evaluation Phase

To account for potential overlapping toxicities in the Atezo+Tiragolumab+Cisplatin+5-FU arm, enrollment will be suspended after approximately █ patients have been enrolled to allow for a safety evaluation. The safety evaluation will be based on safety data from a minimum of █ patients who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and completed safety follow-up during █ treatment cycle. If the combination is determined to be sufficiently safe, enrollment will be resumed in the arm.

3.1.1.2 Mandatory Serial Biopsy Arms (Participating Sites) (Gastric Cancer Cohorts)

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial biopsy arm consisting of patients at participating sites who are willing to undergo an on-treatment biopsy.

Enrollment in a mandatory serial biopsy arm is contingent upon the review and approval of mandatory serial biopsies by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for mandatory serial biopsies, this section of the protocol (see Section 3.1.1.2) will not be applicable at that site.

The objective of the mandatory serial biopsy arms is to perform analysis of serial tissue samples, including pre-treatment, on-treatment, and post-progression samples, to better understand the biological changes occurring during treatment with CIT combinations, as well as immune escape. The biomarkers to be evaluated include those that will be used to inform stromal and immune biology (Turley et al. 2015). Changes in the associated markers will be used to provide evidence of pharmacodynamic measures and confirm hypothesized mechanisms of action.

Patients enrolled in Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial biopsy arm rather than undergo assignment to other arms that are open for enrollment. If more than one mandatory serial biopsy arm is open, patients will be assigned to one of the available cohorts by the Sponsor.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm. However, the number of patients will be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to a total of approximately 15 patients per CIT combination within each cohort.

Patients enrolled in a mandatory serial biopsy arm will undergo the same assessments as other patients receiving the same treatment combination but will have an additional mandatory on-treatment biopsy at 4 weeks (± 7 days) after initiation of CIT combination treatment (if deemed clinically feasible by the investigator). Details about the timing of biopsy sample collection are provided in the schedule of activities for each arm (see [Appendix 10–Appendix 16](#)).

To be eligible for a mandatory serial biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred])

without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥ 1 cm apart.

Patients enrolled in a mandatory serial biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

3.1.2 Second-Line Treatment for 1L Gastric Cancer Cohort Control Arm

Patients in the 1L Cohort control arm who experience disease progression per RECIST v1.1 or unacceptable toxicity will be given the option of enrolling in the 2L Cohort (if open for enrollment), provided they meet eligibility criteria (see Section 4.1).

3.1.3 Stage 2 Treatment for 2L Gastric Cancer Cohort

Patients in the 2L Gastric Cancer Cohort control arm who experience disease progression per RECIST v1.1 and patients in a 2L Cohort 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 11, provided they meet eligibility criteria (see Section 4.1) and the Stage 2 arm is open for enrollment. Patients in the control arm who experience unacceptable toxicity and patients in an experimental arm who experience unacceptable toxicity not related to atezolizumab may be eligible for Stage 2 treatment.

Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1 (control arm), loss of clinical benefit (experimental arms), or unacceptable toxicity in Stage 1 and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1). However, it is recommended that patients begin Stage 2 treatment as soon as possible.

Table 11 Stage 2 Treatment Regimens for 2L Gastric Cancer Cohort

Cohort	Study Treatment	Appendix
2L Gastric Cancer	No Stage 2 treatment currently available	—

2L = second-line.

The Sponsor may also decide to discontinue enrollment in the Stage 2 treatment arm on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., [REDACTED]), as appropriate.

3.1.4 Stage 2 Treatment for Esophageal Cancer Cohort

Patients in the Esophageal Cancer Cohort control arm who experience disease progression per RECIST v1.1 will be given the option of receiving a different treatment combination during Stage 2, as outlined in [Table 12](#), provided they meet eligibility criteria (see Section [4.1.3](#)) and the Stage 2 arm is open for enrollment. Patients in the control arm who experience unacceptable toxicity may be eligible for Stage 2 treatment based on the investigator's judgement. The Medical Monitor is available to advise if needed.

Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1 or unacceptable toxicity in Stage 1 and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (for details, see Section [3.1.1](#)). However, it is recommended that patients begin Stage 2 treatment as soon as possible.

Table 12 Stage 2 Treatment Regimens for Esophageal Cancer Cohort

Cohort	Study Treatment	Appendix
Esophageal Cancer	Atezo + Tiragolumab	Appendix 20

Atezo = atezolizumab.

The Sponsor may also decide to discontinue enrollment in the Stage 2 treatment arm on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g. [REDACTED]), as appropriate.

3.1.5 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 4.0 (NCI CTCAE v4.0). [REDACTED]

Patients in the gastric cancer cohorts will undergo tumor assessments every 8 weeks (starting on Day 1 of Cycle 1) for the first 12 months and then every 8 or 12 weeks thereafter (see Section [4.5.5](#) and [Appendix 8–Appendix 16](#) for details). Patients in the Esophageal Cancer Cohort will undergo tumor assessments every 6 weeks (starting on Day 1 of Cycle 1) for the first 12 months and then every 6 or 12 weeks thereafter (see Section [4.5.5](#) and [Appendix 17–Appendix 20](#) for details).

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 reading 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. If deemed clinically feasible by the investigator, tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (control arm), or loss of clinical benefit as determined by the investigator (experimental arms). For patients with gastric cancer enrolled in a mandatory serial biopsy arm at participating sites, an additional tumor tissue sample will be collected during treatment (if clinically feasible). For patients with esophageal cancer enrolled in an experimental arm during the expansion phase, an on-treatment tumor tissue sample will be collected 4 weeks after initiation of Stage 1 treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for [REDACTED] research (see [REDACTED] and details on tissue sample collection in Section 4.5.6).

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

On the basis of 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 8–Appendix 20](#).

3.1.6 Internal Monitoring Committee

An internal monitoring committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from Clinical Science, Safety Science, 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.

3.1.7 Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study.

This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, [REDACTED] from the time of the first meeting of the SOC. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

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, including survival follow-up visits conducted by telephone or onsite visit.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–6 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population (Gastric Cancer Cohorts)

This study will enroll patients with locally advanced unresectable or metastatic gastric or GEJ cancer who have not received any prior systemic therapy for the locally advanced or metastatic setting (1L Gastric Cancer Cohort) and who have progressed during or following a first-line platinum-containing or fluoropyrimidine-containing chemotherapy regimen (2L Gastric Cancer Cohort).

Patients affected by signet ring cell dominant carcinoma will be excluded from both 1L Gastric Cancer Cohort and 2L Gastric Cancer Cohort. 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). Although for early stages of the disease, the prognosis of patients with signet ring cell adenocarcinoma has been reported to be equivalent to or better than that of other gastric adenocarcinomas, at the advanced stage prognosis of signet ring cell adenocarcinoma is more controversial and is commonly thought to be poor. Moreover, signet ring cell carcinoma seems to have a different chemosensitivity profile, and in particular, recent data suggest that a taxane-based therapy could be more effective in this histotype (Pernot et al. 2015a, 2015b).

Patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinomas who have not received any prior systemic therapy in this setting will be excluded from the 1L Gastric Cancer Cohort based on the ToGA trial that demonstrated clinical benefit with the addition of trastuzumab to a first-line chemotherapy regimen (Bang et al. 2010). Patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinomas are eligible for the 2L Gastric Cancer Cohort.

Combination chemotherapy, given as first-line treatment, for advanced gastric cancer is associated with rates of response $\geq 40\%$, but most patients still have a median survival of 1 year, and survival at 2 years is rare. Herein lies the primary rationale to include this patient population in this study. Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in multiple tumor types (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In case studies, PD-L1 was expressed on tumor cells in 42%–65% of patients with gastric cancer (Wu et al. 2006; Geng et al. 2015; Kim et al. 2016). PD-L1 immunodetection was significantly correlated with tumor size, invasion, lymph node metastasis, and survival time of patients. PD-L1 immunolabeling was significantly enhanced ($p < 0.01$) when the tumor infiltrated into the deep muscular layers, with lymph node metastasis or survival time of < 2 years (Wu et al. 2006; Geng et al. 2015). High expression of PD-L1 was associated with poor prognosis (Geng et al. 2015). The anti-PD-L1 antibody atezolizumab demonstrated preliminary activity against gastric cancer in Study PCD4989g (Roche unpublished data). The data provide a rationale for evaluating the efficacy of atezolizumab in combination with other therapies in patients with advanced gastric cancer. The rationale for each combination is presented in the corresponding appendix as indicated in [Table 8](#).

Patients with gastric cancer from different geographic localities are known to have different clinical outcomes, with overall 5-year survival rates being 10%–15% in North America and 45%–50% in East Asia. These differences cannot be simply explained by improved early diagnosis in Asian countries, as they persist even after stratification for disease stage (Fuchs and Mayer 1995). Recent Phase III clinical trials (the AVAGAST and LOGiC trials) with standardized treatment arms demonstrated differences in gastric cancer outcomes by geographic locality (Ohtsu et al. 2011; Hecht et al. 2013). A gene expression study performed on more than 1600 gastric cancers suggested that tumor immunity signatures may differ significantly between Asian and non-Asian gastric cancers with potential impact on immune-therapy outcome (Lin et al. 2015).

3.3.2 Rationale for Patient Population (Esophageal Cancer Cohorts)

Studies characterizing the genomics of esophageal and gastric cancer have found that they share biology (Cancer Genome Atlas Research Network 2014 and 2017). Esophageal cancer is subclassified into two histological subtypes: adenocarcinoma and squamous cell carcinoma. Adenocarcinomas are more prevalent in western countries and are associated with obesity, gastroesophageal reflux disease, and Barrett's esophagus. The incidence of adenocarcinoma has risen concordantly with the incidence of gastroesophageal junction cancer and proximal gastric cancers, and the anatomic demarcation between gastroesophageal cancers and esophageal is the subject of ongoing discussion. In contrast, squamous cell carcinoma subtypes occur predominately in the upper- and mid-esophagus and are associated with smoking and

alcohol consumption. This subtype is less frequent in western countries, but is more frequent in East Asia.

Gene signatures from TCGA studies evaluating both gastroesophageal and gastric adenocarcinomas revealed that they could both be divided into four subtypes based: 1) EBV infection, 2) MSI, 3) chromosomal instability (CIN) and 4) genomic stability. In trying to further identify differences between esophageal and gastroesophageal adenocarcinomas, the authors found that no esophageal carcinomas fit within the EBV and MSI subtypes, but were enriched in the CIN subtype (71/72 samples). Furthermore, esophageal adenocarcinomas shared more chromosomal abnormalities with gastric adenocarcinoma than esophageal squamous cell carcinoma. Following integrative clustering analysis, the authors declared that they could not find a consistent separation between esophageal and gastric CIN cancers, and argued against classifying these as distinct diseases.

This study will also enroll patients with esophageal cancer who have not received prior systemic treatment for their disease.

Esophageal cancer is a disease of high unmet medical need with 5-year survival rates of 5% in the metastatic and 24% in the locally advanced disease settings (Noone et al. 2018). Treatment options for patients with advanced or metastatic esophageal cancer are limited and have poor prognosis with minimal overall survival benefit (Weidmann and Mössnew 2013; Lordick et al. 2016; Wang et al. 2016; Ilson et al. 2018; NCCN 2019). Therefore, there is a continuing need for more efficacious and better-tolerated treatments for this patient population.

The available safety and efficacy data from Studies GO30103 and GO40290 evaluating the combination of tiragolumab with atezolizumab in multiple solid tumors (including an esophageal cancer cohort) and NSCLC, respectively, and the safety and efficacy data from Study GO30140 evaluating the combination of atezolizumab with 5-FU and cisplatin (see [Appendix 17](#) and [Appendix 18](#) for more details), support additional investigation of this CIT combination with chemotherapy as a treatment option for patients with esophageal cancer.

3.3.3 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, a complete response, a 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 IC 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 ICs 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 to be favorable by the investigator. 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 3.1.1 for details).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria (Gastric Cancer Cohorts)

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 3](#))
- Life expectancy ≥ 3 months, as determined by the investigator
- Histologically or cytologically confirmed locally advanced unresectable according to 2018 NCCN Gastric Cancer Guidelines (i.e., there is evidence of peritoneal involvement including positive peritoneal cytology or locally advanced disease [N3 or N4 lymph node involvement] or invasion or encasement of major vascular structures, excluding the splenic vessels) or metastatic adenocarcinoma of gastric or GEJ

For patients in the 1L Gastric Cancer Cohort: no prior systemic therapy for the locally advanced or metastatic disease

- Patients who experience disease progression more than 6 months after the last dose of adjuvant and/or neoadjuvant therapy are eligible for the 1L Gastric Cancer Cohort.

For patients in the 2L Gastric Cancer Cohort: disease progression during or following a first-line platinum-containing or fluoropyrimidine-containing chemotherapy regimen

- Patients whose disease progresses or recurs within ≤ 6 months after completion of their adjuvant or neoadjuvant therapy may be allowed to participate in the 2L Gastric Cancer Cohort, provided their neo-adjuvant or adjuvant regimen included a combination of at least a platinum (e.g., cisplatin, carboplatin, or oxaliplatin) and a fluoropyrimidine (e.g., 5-FU, capecitabine, or S-1). In these cases, the adjuvant or neoadjuvant therapy will count as one prior (first-line) therapy for gastric cancer.

- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by means of 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 the tissue was obtained from a biopsy performed within 6 months prior to enrollment and the patient has not received any anti-cancer therapy since the time of the biopsy.

A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 10–16 slides (16 slides preferred) containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening.

- Only for the 1L Gastric Cancer Cohort: patients whose tumors are without HER2 amplification documented by fluorescence in situ hybridization (FISH) or in situ hybridization (ISH) or are negative by immunohistochemistry (IHC) 0 or +1 on previously collected and assessed tumor tissue upon 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, eligibility of the patient should be determined by the investigator's judgement. The Medical Monitor is available to advise as needed.

At the Sponsor's discretion, HER2 negativity may be retrospectively confirmed by central laboratory testing after enrollment. If done, HER2-negative status will be determined on the basis of archival or, if not available, prescreening biopsy material and defined as:

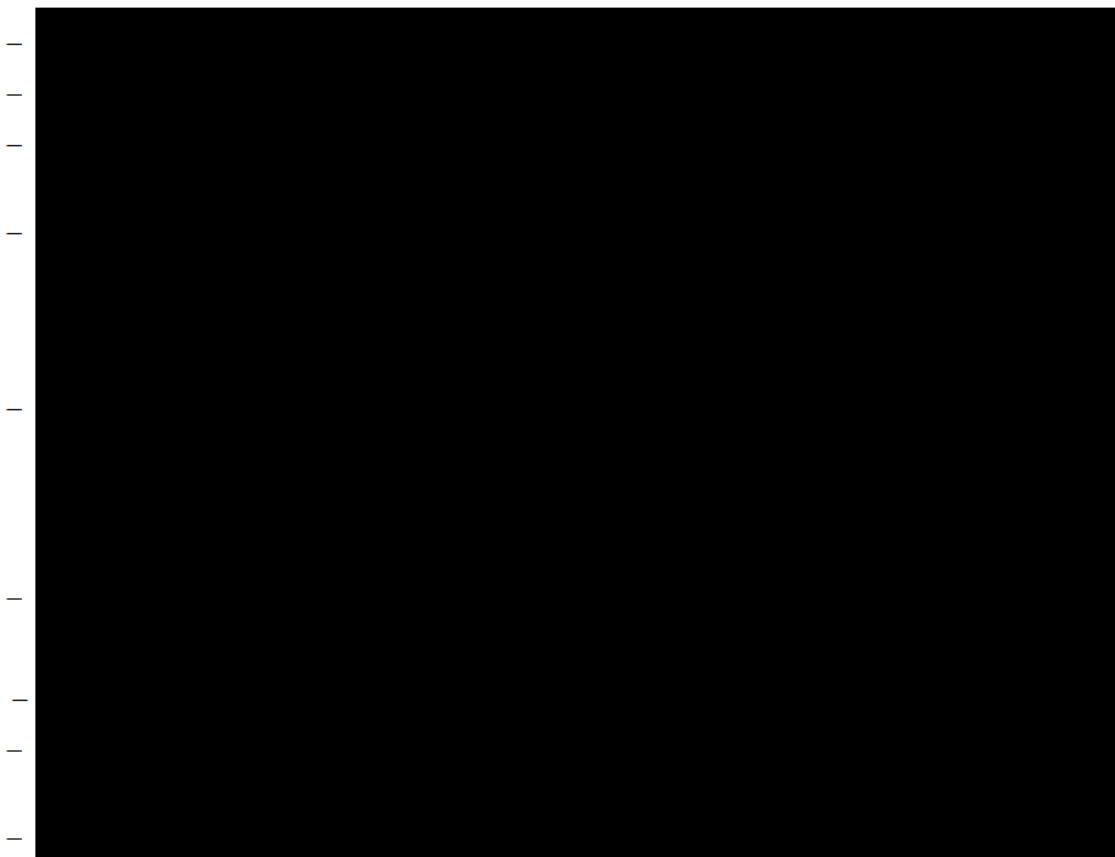
- FISH or ISH non-amplified (ratio of HER2 to CEP17 <2.0 or single probe average HER2 gene copy number <4 signals/cell), or
- IHC 0 or IHC 1+

4.1.1.2 Inclusion Criteria for Stages 1 and 2

Patients must meet all of the following criteria to qualify for Stages 1 and 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
 - Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to initiation of study treatment:

–



- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
 - [Redacted]
- [Redacted]
- [Redacted]
 - [Redacted]
- [Redacted]
 - [Redacted]
- [Redacted]
 - [Redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as outlined for each specific treatment arm (see [Appendix 8–Appendix 16](#))

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm (see [Appendix 8–Appendix 16](#))

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 0–2 (see [Appendix 3](#))
- Patients in a control arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity, or disease progression per RECIST v1.1 while receiving treatment
- Patients in an experimental arm during Stage 1: 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 3.1.1](#) for details) while receiving 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 (Gastric Cancer Cohorts)

There are specific exclusion criteria for both cohorts and all the arms. Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the criteria outlined in subsequent sections, as summarized by treatment arm in [Table 13](#).

Table 13 Gastric Cancer Cohort and Treatment Arm–Specific Exclusion Criteria

Stage	Cohort (Enrollment Status)	Treatment Arm	Applicable Exclusion Criteria
1	1L (Not Enrolling) ^a	mFOLFOX6	Sections 4.1.2.2 and 4.1.2.3
	2L (Not Enrolling) ^b	Paclitaxel + Ramucirumab	Sections 4.1.2.1 , 4.1.2.2 , and 4.1.2.3
		Atezo + BL-8040	Sections 4.1.2.1 , 4.1.2.2 , and 4.1.2.3
		Atezo + Linagliptin	Sections 4.1.2.1 , 4.1.2.2 , and 4.1.2.3

1L = first-line; 2L = second-line; Atezo = atezolizumab; mFOLFOX6 = infusional 5-fluorouracil, leucovorin (folic acid), and oxaliplatin.

^a Further enrollment in the 1L Gastric Cancer Cohort was suspended as of June 2018 (see [Section 3.1](#) for details).

^b As of October 2019, patients with gastric cancer are not being enrolled.

4.1.2.1 Exclusion Criteria for 2L Gastric Cancer Cohort, Stage 1

Patients who meet any of the following criteria will be excluded from the 2L Gastric Cancer Cohort, Stage 1:

- Urinary protein is > 1+ on dipstick and the required following 24-hour urine collection shows urinary protein > 2 g (24-hour urine collection is required only if urinary protein is > 1+ on dipstick; see Section 4.5.6)
- Serious or non-healing wound, peptic ulcer, or bone fracture within 28 days prior to initiation of study treatment
- History of gastrointestinal (GI) perforation and/or fistulae within 6 months prior to initiation of study treatment
- Presence of a bowel obstruction, history or presence of inflammatory enteropathy, or extensive intestinal resection (e.g., hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn disease, ulcerative colitis, or chronic diarrhea
- Uncontrolled arterial hypertension, defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 95 mmHg (average of at least three readings at two or more sessions), despite standard medical management
- Chronic therapy with nonsteroidal anti-inflammatory agents (e.g., indomethacin, ibuprofen, naproxen or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide, or similar agents)

Aspirin use at doses of up to 325 mg/day is permitted.

4.1.2.2 Exclusion Criteria for Stage 1

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

- Systemic treatment for gastric cancer within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Prior treatment with any of the protocol-specified study treatments, with the exception of chemotherapy
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Patients with Type 2 diabetes mellitus currently under treatment with DPP-4 inhibitors
- Known dihydropyrimidine dehydrogenase deficiency
- Eligible only for the control arm

4.1.2.3 Exclusion Criteria for Stages 1 and 2

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

- Weight loss > 5% within 4 weeks prior to screening

- Uncontrolled pleural effusion, pericardial effusion, or ascites
- Uncontrolled tumor-related pain

Patients requiring narcotic 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 initiation of study treatment. Patients should be recovered from the 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 presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the initiation of study treatment.

- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

Patients who are receiving bisphosphonate therapy for other reasons (e.g., bone metastases or osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible for the study.

- Symptomatic, untreated, or actively progressing CNS metastases

Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:

- [REDACTED]
- The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
- 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 the screening brain scan.
- The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 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.
- 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
- Active or history of autoimmune disease or immune deficiency [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

[REDACTED]

- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease, and inherited liver disease
- Active tuberculosis
- 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 [COPD] exacerbation) are eligible for the study.
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, carotid artery disease requiring intervention or treatment, or cerebrovascular accident) within 12 months prior to initiation of study treatment, or unstable arrhythmia or unstable angina within 3 months prior to initiation of study treatment
- Significant bleeding disorder, vasculitis, Grade ≥ 3 hemorrhage, or significant bleeding episode from a GI tract event within 3 months prior to initiation of study treatment

- History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") within 3 months prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- 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
 - Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Treatment with anticoagulation with warfarin, low-molecular-weight heparin, or similar agents for therapeutic purposes
 - Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria are met.
- History of malignancy other than gastric or GEJ carcinoma within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 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
- Any other diseases, 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 intention of becoming pregnant during the study
 - Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to the first study treatment administration.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with atezolizumab and within 5 months after the last dose of atezolizumab
- 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 their excipients
- Known dihydropyrimidine dehydrogenase deficiency or thymidylate synthase gene polymorphism predisposing the patient to 5-FU toxicity
- Treatment with systemic immunostimulatory medication (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor- α agents) within 2 weeks prior to initiation of study treatment, or anticipation of the need for systemic immunosuppressant medication during the study, with the following exceptions:

[REDACTED]

[REDACTED]

- Adverse events from prior anti-cancer therapy that have not resolved to Grade 1 or better, with the exception of alopecia of any grade and Grade ≤ 2 peripheral neuropathy
- 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

4.1.3 Inclusion Criteria (Esophageal Cancer Cohort)

Patients must meet all of the criteria outlined in Sections 4.1.3.1 and 4.1.3.2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 4.1.3.2 and 4.1.3.3 to qualify for Stage 2.

4.1.3.1 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 3](#))
- Histologically or cytologically confirmed diagnosis of squamous cell carcinoma or adenocarcinoma of the esophagus in locally advanced or metastatic disease

The definitive diagnosis of metastatic esophageal cancer is made by evaluating the histopathologic data within the context of clinical and radiographic data.
- No prior systemic treatment for esophageal cancer, with the following exception:

For patients treated with chemotherapy in the locally advanced setting: occurrence of metastasis after 6 months from the last dose of chemotherapy
- For patients with adenocarcinoma: absence of HER2 expression as documented as ISH-negative on previously collected and assessed tumor tissue upon initial diagnosis of disease

HER2-negative status will be determined on the basis of an ISH non-amplified (ratio of HER2 to CEP17 < 2.0 or single probe average HER2 gene copy number < 4 signals/cell) IHC 0 or IHC 1+ (if more than one test result is

available and not all results meet the inclusion criterion definition, eligibility of the patient should be determined by the investigator's judgement. The Medical Monitor is available to advise as needed).

- Life expectancy ≥ 3 months as determined by the investigator
- Creatinine clearance (CrCl) ≥ 50 mL/min (calculated using the Cockcroft-Gault formula)

CrCl is calculated by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} (\times 0.85 \text{ if female})$$

Where: CrCl=creatinine clearance in mL/min
age=patient's age in years
wt=patient's weight in kg
Scr=serum creatinine in mg/dL

- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and TIGIT levels by IHC and/or additional biomarker status by means of retrospective 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.

A FFPE tumor specimen in a paraffin block (preferred) or 10–16 slides (16 slides preferred) containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening.

4.1.3.2 Inclusion Criteria for Stage 1 and Stage 2

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

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease per RECIST v1.1

Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:

—
—
—

- [REDACTED]
- Negative HIV test at screening, with the following exception:
[REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- Negative 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.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as outlined for each specific treatment arm (see [Appendix 17–Appendix 20](#))
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm (see [Appendix 17–Appendix 20](#))

4.1.3.3 Inclusion Criteria for Stage 2

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

- ECOG Performance Status of 0, 1, or 2 (see [Appendix 3](#))
- Patients randomly allocated to the control arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity, or disease progression per RECIST v1.1 while receiving control treatment

- Availability of a tumor specimen (if deemed clinically feasible) from a biopsy performed upon discontinuation of Stage 1 because of unacceptable toxicity, or disease progression per RECIST v1.1

4.1.4 Exclusion Criteria (Esophageal Cancer Cohort)

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the criteria outlined in subsequent sections.

4.1.4.1 Exclusion Criteria for Stage 1

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

- Prior treatment with any of the protocol-specified study treatments
- Patients with known hearing impairment
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria
- Known dihydropyrimidine dehydrogenase deficiency or thymidylate synthase gene polymorphism predisposing the patient to 5-FU toxicity

4.1.4.2 Exclusion Criteria for Stage 1 and Stage 2

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

- High risk for developing esophageal fistula by clinical assessment or imaging, such as prior history or associated symptoms of esophageal fistula or T4 classification by endoscopic ultrasound
- 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. Anticonvulsant 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.

- Positive EBV viral capsid antigen IgM test at screening

[REDACTED]

- 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 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 loco-regional 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 > ULN)
- Active or history of autoimmune disease or immune deficiency, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

— [REDACTED]
— [REDACTED]
— [REDACTED]

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



- 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 esophageal cancer within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, 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 COPD 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
- 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 treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-TIGIT therapeutic antibodies

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-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:
 - [REDACTED]
 - [REDACTED]
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab and tiragolumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab

Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

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 interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment through the use of the IxRS and will retain the same patient identification number that was 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, with the stipulation that the likelihood of being allocated to the control arm will be no more than [REDACTED]. The randomization ratio may be altered to increase enrollment in an experimental arm that has demonstrated promising clinical activity.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Sections 4.1.1, 4.1.2, 4.1.3, and 4.1.4. For example, a treatment arm will be removed as an option for patients who are ineligible for that arm. If a patient is eligible only for the control arm, the patient will not be enrolled in the study.

If more than one mandatory biopsy cohort is open for enrollment at a time, eligible patients (at participating sites) will be assigned to one of the available cohorts by the Sponsor.

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 randomized in Stage 1 to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 8 and Table 10 for Stage 1 and Table 11 and Table 12 for Stage 2.

4.3.1 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, BL-8040, linagliptin, ramucirumab, paclitaxel, oxaliplatin, leucovorin, tiragolumab, cisplatin, and infusional 5-FU. All IMPs required for completion of this study will be provided by the Sponsor where required by local practices. 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.

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 Sponsor-supplied IMP destruction 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 the Drug Inventory Log.

4.3.2 Continued 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

Details about concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided for each treatment arm in [Appendix 8–Appendix 20](#). 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 are to be performed within 28 days prior to initiation of study treatment in Stage 1 or 2 (Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Patients who fail their first screening for study eligibility (Stage 1 or 2) 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.

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, will be recorded at baseline. The patient's molecular profile for gastric cancer or esophageal cancer, 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 period of time prior to initiation of study treatment (see [Appendix 8–Appendix 20](#) and [Table 8](#), [Table 10](#), [Table 11](#), and [Table 12](#)) will be recorded. 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 and Weight

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, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological 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.

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, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

Vital signs should be measured within 60 minutes prior to administration of each study treatment and, if clinically indicated, during or after treatment administration. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see [Appendix 8–Appendix 20](#)).

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 8 weeks (± 1 week) in the gastric cancer cohorts and every 6 weeks (± 1 week) in the Esophageal Cancer Cohort for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 except in the case of patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 8 weeks (± 1 week) for the gastric cancer cohorts and every 6 weeks (± 1 week) in the Esophageal Cancer Cohort until loss of clinical benefit as determined by the investigator (see [Section 3.1.1](#) for details).

Thus, in all cohorts, tumor assessments are to continue according to schedule for patients who discontinue treatment for reasons other than disease progression or 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). For patients who are eligible for Stage 2, tumor assessments performed prior to, or at the time of unacceptable toxicity or disease progression per RECIST v1.1 (control arm) or loss of clinical benefit (experimental arms) 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 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 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 oral and/or IV contrast) or magnetic resonance imaging (MRI) scans 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 and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease according to 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. 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 CT 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). To facilitate evaluation of post-progression tumor changes while treatment is ongoing, 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. Available results must be reviewed by the investigator prior to treatment administration.

4.5.6 Laboratory, Biomarker, and Other Biologic 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, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): amylase, and lipase (performed as applicable; details provided in schedules of activities); bicarbonate or carbon dioxide (if considered standard of care for the region); sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin (only needed for Gastric Cancer Cohort), albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST
- Coagulation: INR and aPTT
- Thyroid-function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 at sites where free T3 is not performed), and free thyroxine (also known as T4)
- C-reactive protein
- LDH
- CA19-9 (gastric cancer cohorts only)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Pregnancy test

All women of childbearing potential must have a negative 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 postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

Refer to [Appendix 8–Appendix 20](#) for arm-specific local laboratory requirements.

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

- Serum samples for analysis of autoantibodies: anti-citrullinated peptide antibody, anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody

Serum samples collected for the assessment of pharmacokinetics, anti-drug antibodies (ADAs), or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.
- Plasma or serum samples for PK analysis through use of validated assays (see [Appendix 10–Appendix 18](#) and [Appendix 20](#))
- Plasma or serum samples for immunogenicity analysis through use of validated assays (see [Appendix 10–Appendix 18](#) and [Appendix 20](#))
- [REDACTED]

[REDACTED]
- Tumor tissue sample collected at baseline for determination of PD-L1 and TIGIT expression and for [REDACTED]

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.

A representative FFPE tumor specimen in a paraffin block (preferred) or at 10–16 slides (16 slides 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 (at least three cores, 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.

Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

- Patients with esophageal cancer enrolled in an experimental arm during the expansion phase: tumor tissue sample collected 4 weeks ($\pm$ 7 days) after initiation of Stage 1 treatment (if deemed clinically feasible by the investigator) for [REDACTED]

Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

- Tumor tissue samples collected during Stage 1, at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator, for [REDACTED]

[REDACTED] are applicable only after approval from local regulatory authorities.

Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anticancer 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.

- Patients with gastric cancer enrolled in a mandatory serial biopsy arm at participating sites (see Section 3.1.1.2): tumor tissue samples collected 4 weeks ($\pm$ 7 days) after initiation of Stage 1 treatment, if deemed clinically feasible by the investigator, for [REDACTED]

[REDACTED] are applicable only after approval from local regulatory authorities.

Patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of

a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥ 1 cm apart.

The Informed Consent Form will contain a separate section that addresses the mandatory serial biopsy arm. A separate, specific signature will be required to document a patient's agreement to participate in this cohort.

Refer to [Appendix 8–Appendix 20](#) for arm-specific central laboratory requirements.



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

Unless the patient gives specific consent for his or her remaining samples to be stored for optional [REDACTED] (see Section 4.5.10), biologic samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum and plasma samples collected for PK analysis and/or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and 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.
- [REDACTED] will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of samples that undergo [REDACTED], which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the [REDACTED] samples will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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 will be subject to the confidentiality standards described in Section 8.4.

Given the [REDACTED]
[REDACTED] will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. Patients in arms that require additional ECG monitoring will undergo ECGs at specified timepoints during the study. 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.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.5.9 Optional Tumor Tissue Samples (Gastric Cancer Cohorts)

Consenting patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (± 7 days) after treatment initiation and may undergo additional on-treatment biopsies 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. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of collecting optional biopsies. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional biopsies. Patients who decline to participate will not provide a separate signature.

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 [REDACTED] as described in Section 4.5.6. Refer to Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data derived from [REDACTED].

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, and peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of [REDACTED], which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of [REDACTED] with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop [REDACTED] assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the [REDACTED] and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on [REDACTED] related to CIT or diseases:

- Blood samples collected on Day 1, Cycle 1, during Stages 1 and 2
- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, and peptides), including

remaining tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the study

The above samples may be sent to one or more laboratories for analysis of germ-line or somatic mutations [REDACTED].

Genomics is increasingly informing researcher's understanding of disease pathobiology. [REDACTED] provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens 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.

Given the [REDACTED] of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

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 RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study YO39609 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study YO39609.

4.5.10.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits,

IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

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
- Experimental arms: 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 3.1.1 for details)
- Control arm: radiographic disease progression per RECIST v1.1

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease 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 (see [Appendix 8–Appendix 20](#) for each treatment arm).

After treatment discontinuation, information on survival follow-up and initiation of new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 2 weeks) (unless the patient withdraws consent or the Sponsor terminates the study or concludes the treatment arm) until death. 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, 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 ~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 withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- 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.

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 investigators 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, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided for each treatment arm in [Appendix 8–Appendix 20](#).

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).

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), except as described in Section [5.3.5.10](#)
- 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/birth defect in a neonate/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.



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



Adverse events of special interest are listed for each treatment arm in [Appendix 8–Appendix 20](#).

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor) (Gastric Cancer Cohorts)

During the dose-limiting toxicity (DLT) assessment window, adverse events identified as DLTs 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).

5.3 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).



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 (v4.0) will be used for assessing adverse event severity. Table 14 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 14 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 (v4.0), 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.

[REDACTED]

[REDACTED]

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 the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also [Table 16](#)):

- 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 16 Casual 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	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> 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 or Injection Reactions and [REDACTED]

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, [REDACTED] 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 or injection should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction," "injection-site reaction," or [REDACTED]). Avoid ambiguous terms such as "systemic reaction." [REDACTED]

██████████ on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF, Injection-Site Reaction eCRF, or ██████████, 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, Injection-Site Reaction eCRF, or ██████████

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 6](#).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section [5.3.5.1](#)), 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 GI 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 $5 \times$ 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 ($> 3 \times$ baseline value) 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 $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ 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 gastric or esophageal cancer 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 Esophageal Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any

uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

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 Overdose, 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 (RO5541267), BL-8040, linagliptin, tiragolumab (RO7092284), ramucirumab, paclitaxel, oxaliplatin, leucovorin, 5-FU, and cisplatin, 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, BL-8040, linagliptin, tiragolumab, ramucirumab, paclitaxel, oxaliplatin, leucovorin, 5-FU, and cisplatin, 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 (see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (see Section 5.4.2 for details on reporting requirements)
- DLTs (see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events 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 IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, 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, Adverse Events of Special Interest, and Dose-Limiting Toxicities

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

 DLTs will be reported during the DLT assessment window. 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 > 135 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

Reporting requirements for pregnancies are described for each treatment arm in Appendix 8–Appendix 20.

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.

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, electronic mail, 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 adverse event reporting period [REDACTED], all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. Reporting of deaths may be stopped in arms concluded by the Sponsor (see Section 4.6.1).

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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 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 the regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

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.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- BL-8040 Investigator's Brochure
- Tiragolumab Investigator's Brochure
- Summary of Product Characteristics for linagliptin, ramucirumab, paclitaxel, oxaliplatin, leucovorin, infusional 5-FU, and cisplatin

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. For all cohorts, 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.

In all cohorts, the analysis results will be summarized by the treatment that patients actually received. Results will also be summarized by stage (Stage 1 or 2) whenever Stage 2 treatment is available. 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 place 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 4.5.5. 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 gastric cancer and esophageal cancer.

6.1.1 Gastric Cancer Cohorts

The 1L Gastric Cancer Cohort will enroll patients with gastric cancer who have not received prior systemic therapy in this setting, and the 2L Gastric Cancer Cohort will enroll patients with gastric cancer who have progressed after receiving a platinum-containing or fluoropyrimidine-containing chemotherapy regimen in the first-line setting.

As of June 2018, further enrollment in the 1L Cohort was suspended and the mFOLFOX6+Atezo+Cobi arm was closed for further enrollment (see Sections 3.1 and 3.1.1 for details). At that time, 5 patients had been enrolled in the mFOLFOX6+Atezo+Cobi arm during the safety run-in phase. As of October 2019, the 2L Gastric Cancer Cohort has completed enrollment in the preliminary phase and will not undergo the expansion phase. At that time, 62 patients had been enrolled. No patients had been enrolled in any biopsy arm.

6.1.2 Esophageal Cancer Cohort

The Esophageal Cancer Cohort will enroll patients with esophageal cancer who have not received prior systemic therapy in this setting. Approximately 100–165 patients will be randomized 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 within the two stages. Patient disposition will be summarized by treatment arm within each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm within each stage.

For the safety-evaluable population, study drug administration data will be tabulated or listed by treatment arm within 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 cohort and treatment arm within each stage.

6.4 EFFICACY ANALYSES

The efficacy-evaluable populations will be defined as follows:

- All patients who received at least one dose of each drug for their assigned treatment regimen

Efficacy endpoints will be summarized by actual treatment arm.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR during Stage 1 based on RECIST v1.1, defined as the proportion of patients with an objective response. An objective response is defined as a complete response or a partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator using RECIST v1.1. Patients not meeting this criterion, including patients without a post-baseline tumor assessment, will be considered non-responders. ORR, the proportion of patients with a complete or partial response

The analysis population for ORR is the efficacy-evaluable population.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, OS, OS at specific timepoints (e.g., 6 months and 12 months), duration of response (DOR), and disease control during Stage 1, as defined in Section 2 (see [Table 6](#)). 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 confirmed complete or partial response.

For patients who do not have documented disease progression or death in a study stage, 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 Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% CIs constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated using the Kaplan-Meier method, with 95% CIs calculated on the basis of Greenwood's estimate for the variance.

Disease control rate, defined as the proportion of patients with stable disease for ≥ 16 weeks for the Gastric Cancer Cohort or ≥ 12 weeks for the Esophageal Cancer Cohort, a partial response, or a complete response, will be calculated for each treatment arm, with 95% CIs estimated through use of Clopper-Pearson's exact method.

[REDACTED]

6.5 SAFETY ANALYSES

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 v4.0, [REDACTED]

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.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each patient, the maximum reported severity of each adverse event will be used in the summaries by severity grade. All treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of study treatment, Grade ≥ 3 adverse events, deaths, and causes of death will be listed and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Relevant laboratory, vital sign (pulse rate, respiratory rate, pulse oximetry, blood pressure, 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.

Safety analysis will include all patients who receive at least one dose of any component of study treatment. Exposure to study treatment will be summarized overall and by actual treatment arm within each stage.

Adverse events will be summarized by mapped terms, appropriate thesaurus level, and toxicity grade. For each patient, the maximum severity reported will be used in the summaries. Adverse events, study treatment-related adverse events, adverse events leading to withdrawal of study drug, Grade ≥ 3 adverse events, serious adverse events, and adverse events of special interest will be summarized. All deaths and causes of death will be summarized.

Change in NCI CTCAE grade for selected laboratory tests will be tabulated by actual treatment arm.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for 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 will 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 will be plotted by treatment arm, cycle, and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab 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 will be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses for atezolizumab will include all patients with at least one 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 number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (postbaseline incidence) will be summarized by treatment arm. When determining postbaseline incidence, patients are considered to be treatment-emergent ADA positive if they are ADA negative or have 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 post-baseline samples is at least

[REDACTED]

The interim analyses will be performed and interpreted by the Sponsor's study team personnel.

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, patient-reported outcomes, 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 into 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 into 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 IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

The Sponsor will retain study data for 25 years after the final study results have been reported 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). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

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 of 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.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. 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.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

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 9.6).

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 [REDACTED], data derived from these analyses will generally not be provided to study investigators or 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 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.

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 study and for 1 year after completion of the study (i.e., the date when the last patient completes the last visit) (see definition of end of study in Section 3.2).

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 study 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, [REDACTED], and PK analyses), as specified in Section 4.5.6.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, [REDACTED], and PK analyses), as specified in Section 4.5.6. 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. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 PUBLICATION 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, both at scientific congresses 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 [REDACTED] 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 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 study participants.

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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 ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and 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 $\geq$ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, AND 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 since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 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, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.

Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

- Complete response (CR): Disappearance of all target lesions
Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)
In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

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

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more 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 A1-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A1-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

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

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 A1-1](#).

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.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.

Appendix 2

Placeholder for Future Arm

The Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) appendix has been removed as the Sponsor no longer plans to perform these analyses. Appendix 2 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 3

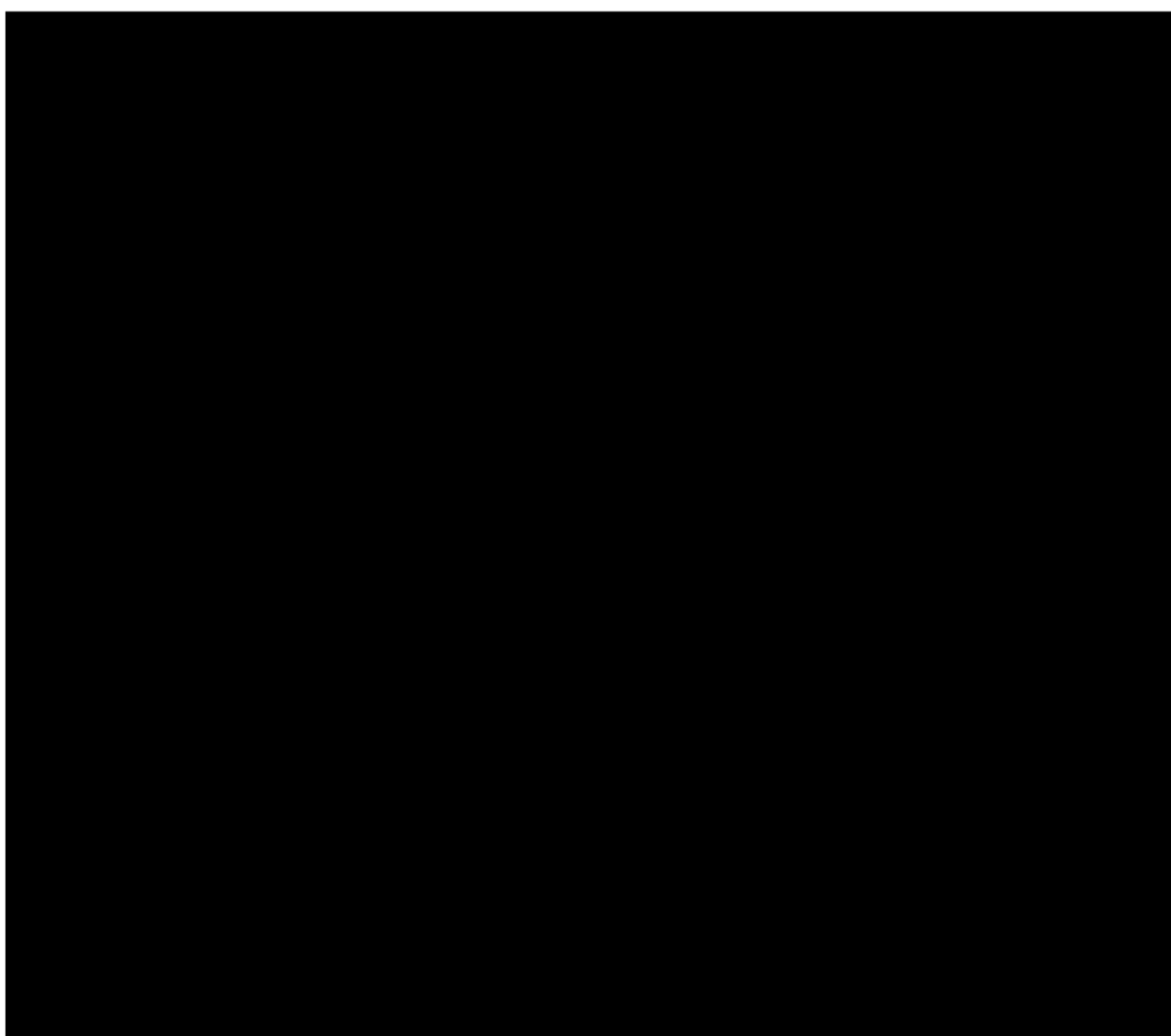
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 4

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 for which 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 autoimmune exclusions.



Appendix 5

Anaphylaxis Precautions

Equipment Needed

- Oxygen
- Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

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

- Stop the study treatment infusion.
- Maintain an adequate airway.
- Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 6

Management of Atezolizumab-Specific Adverse Events

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Appendix 6: Management of Atezolizumab-Specific Adverse Events

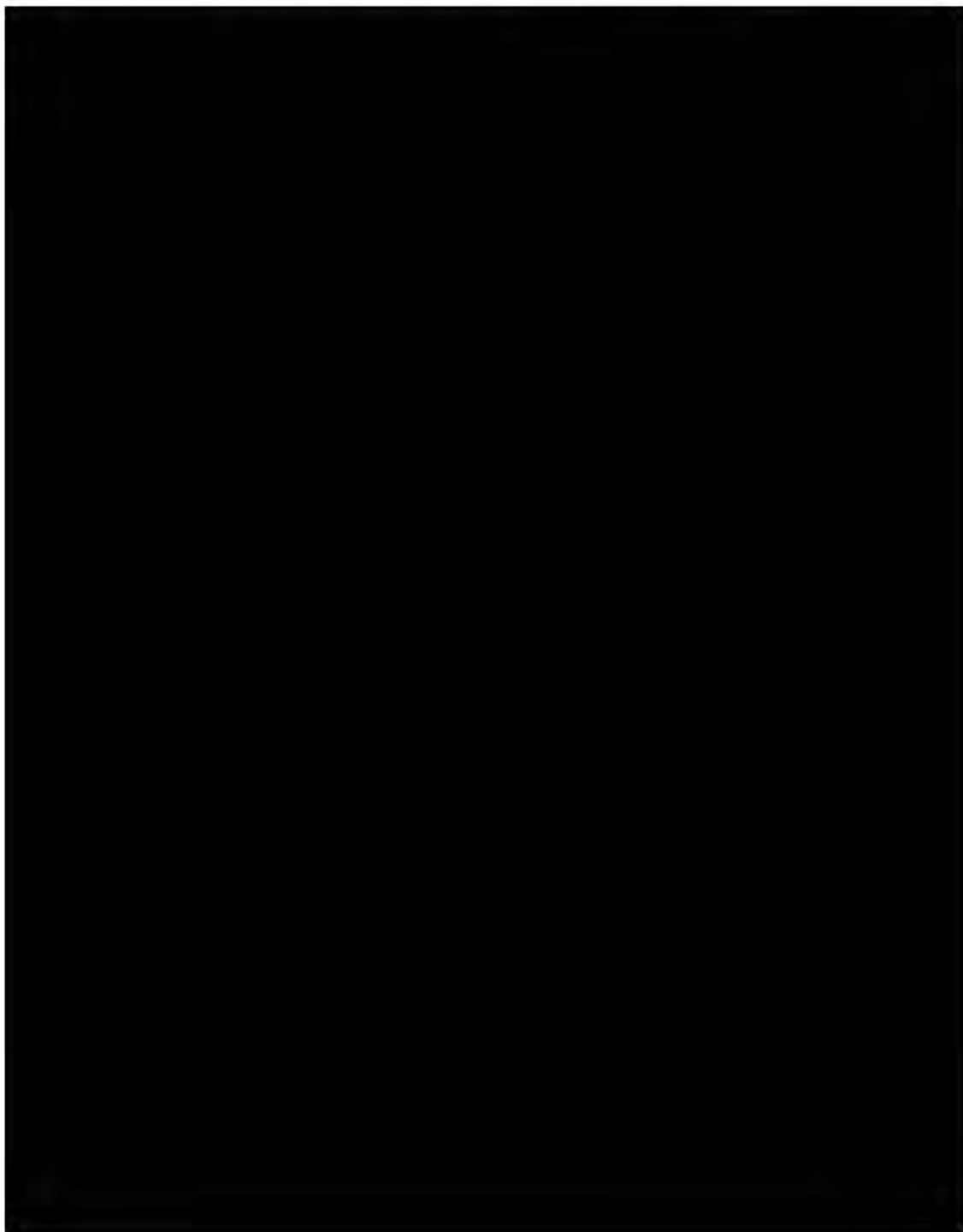
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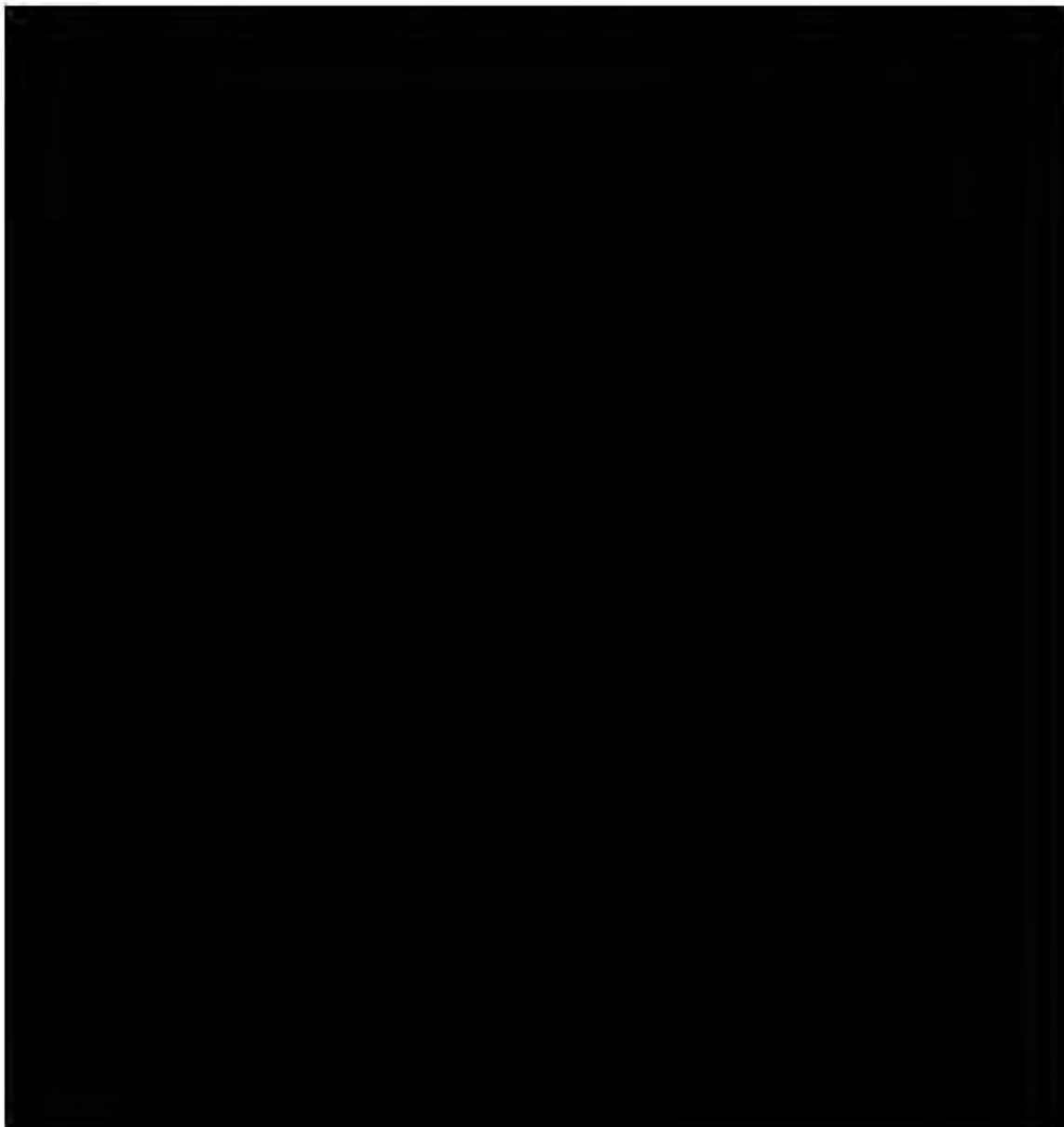
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Appendix 6: Management of Atezolizumab-Specific Adverse Events



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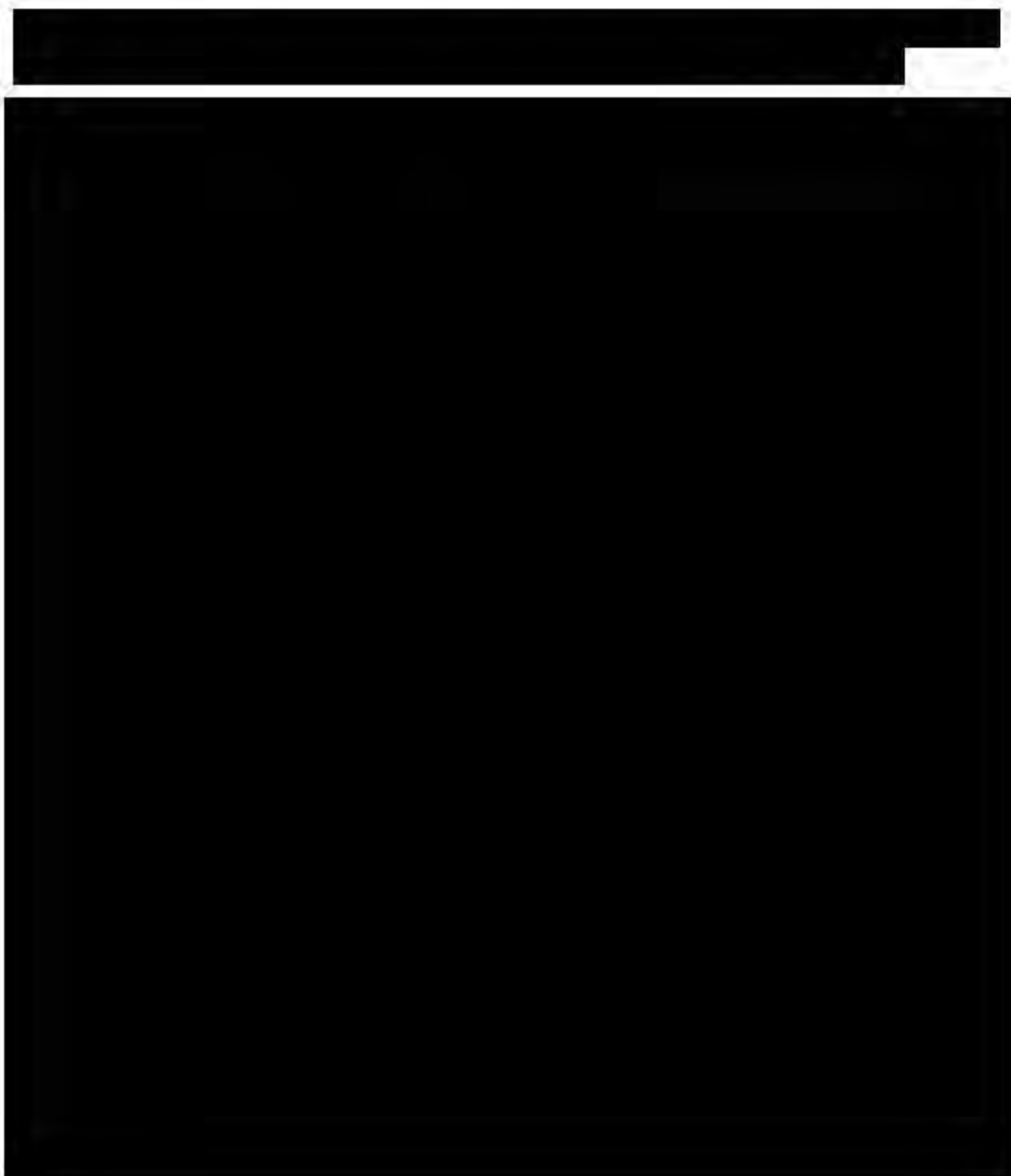


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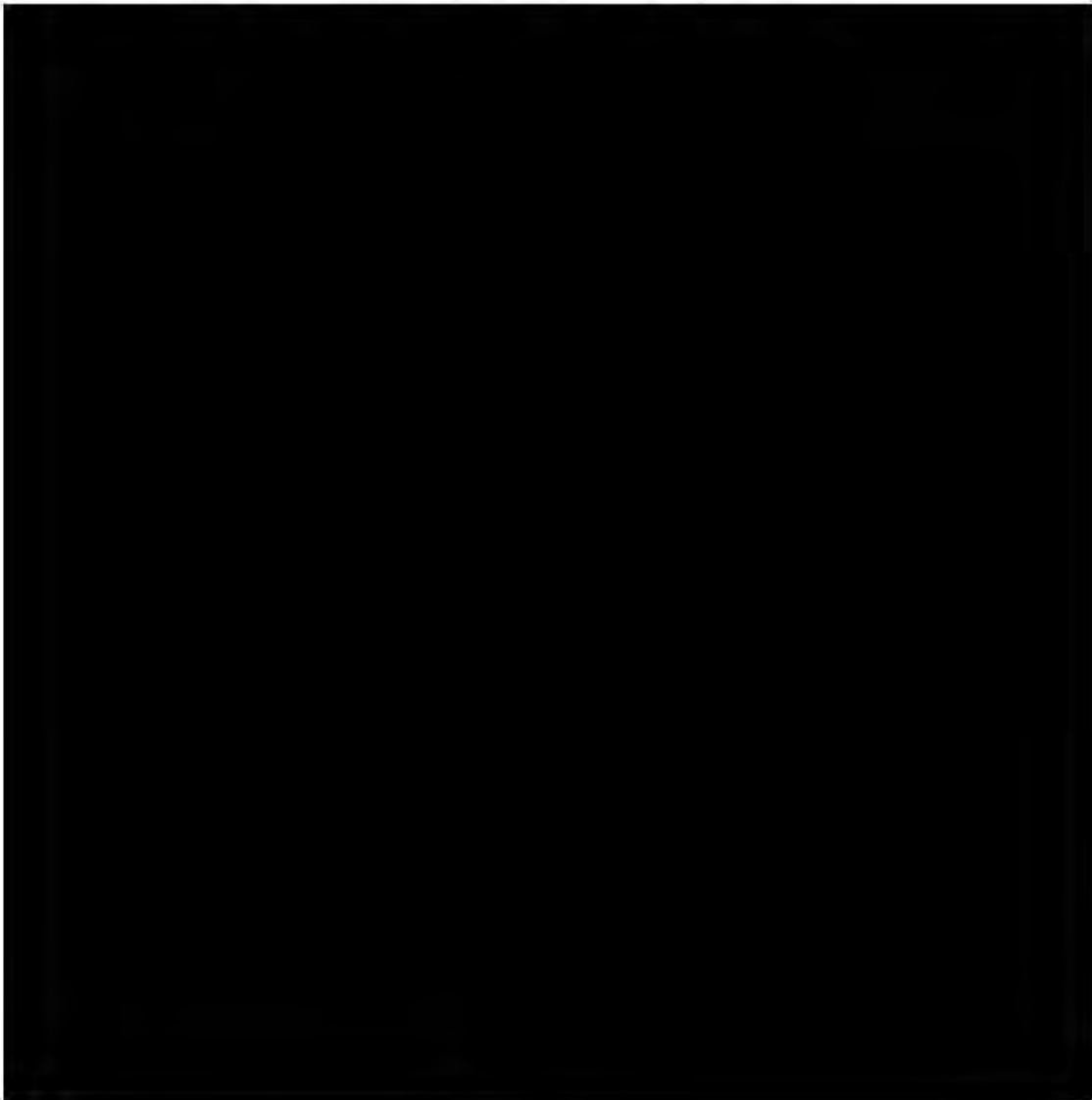
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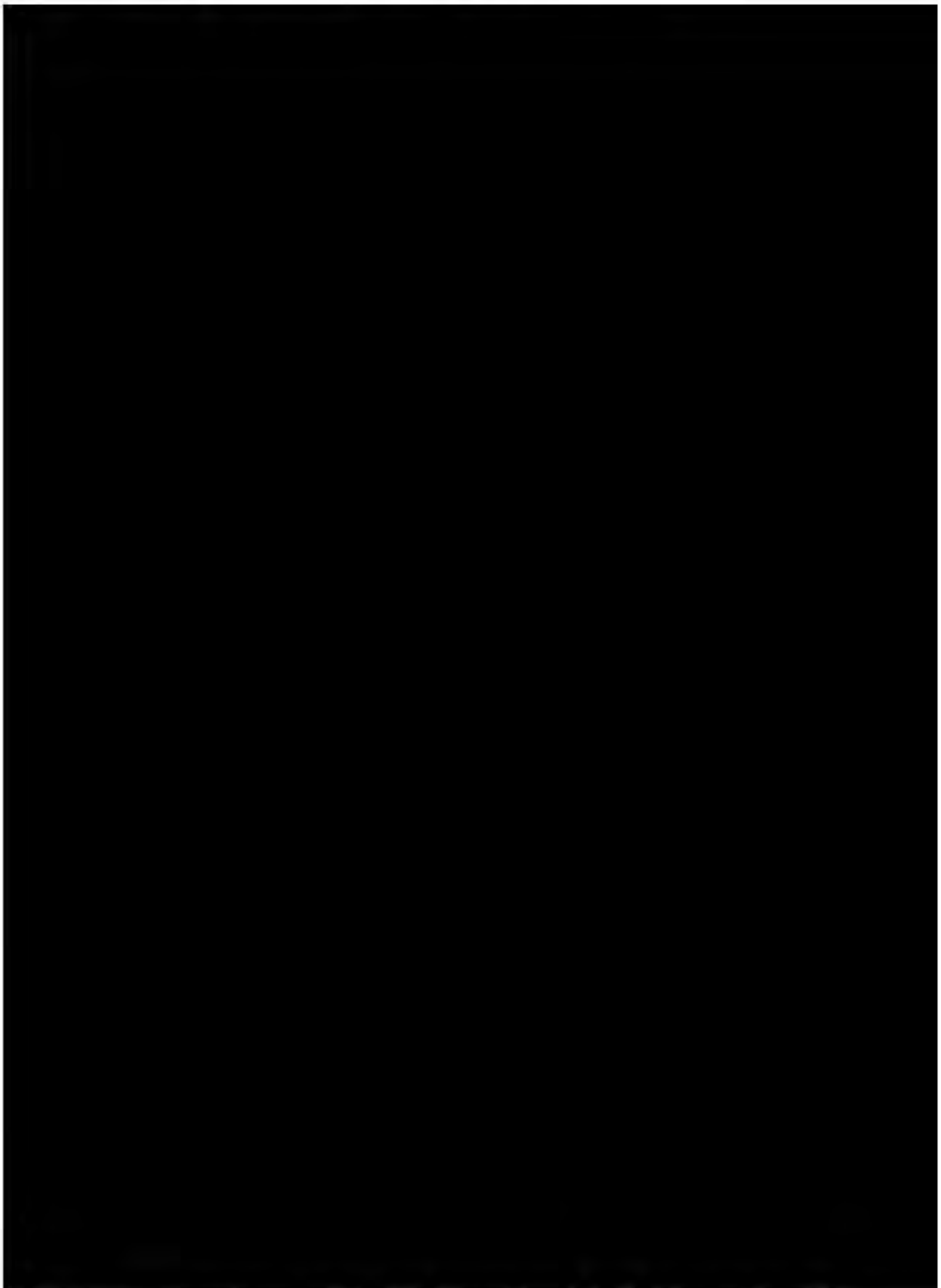


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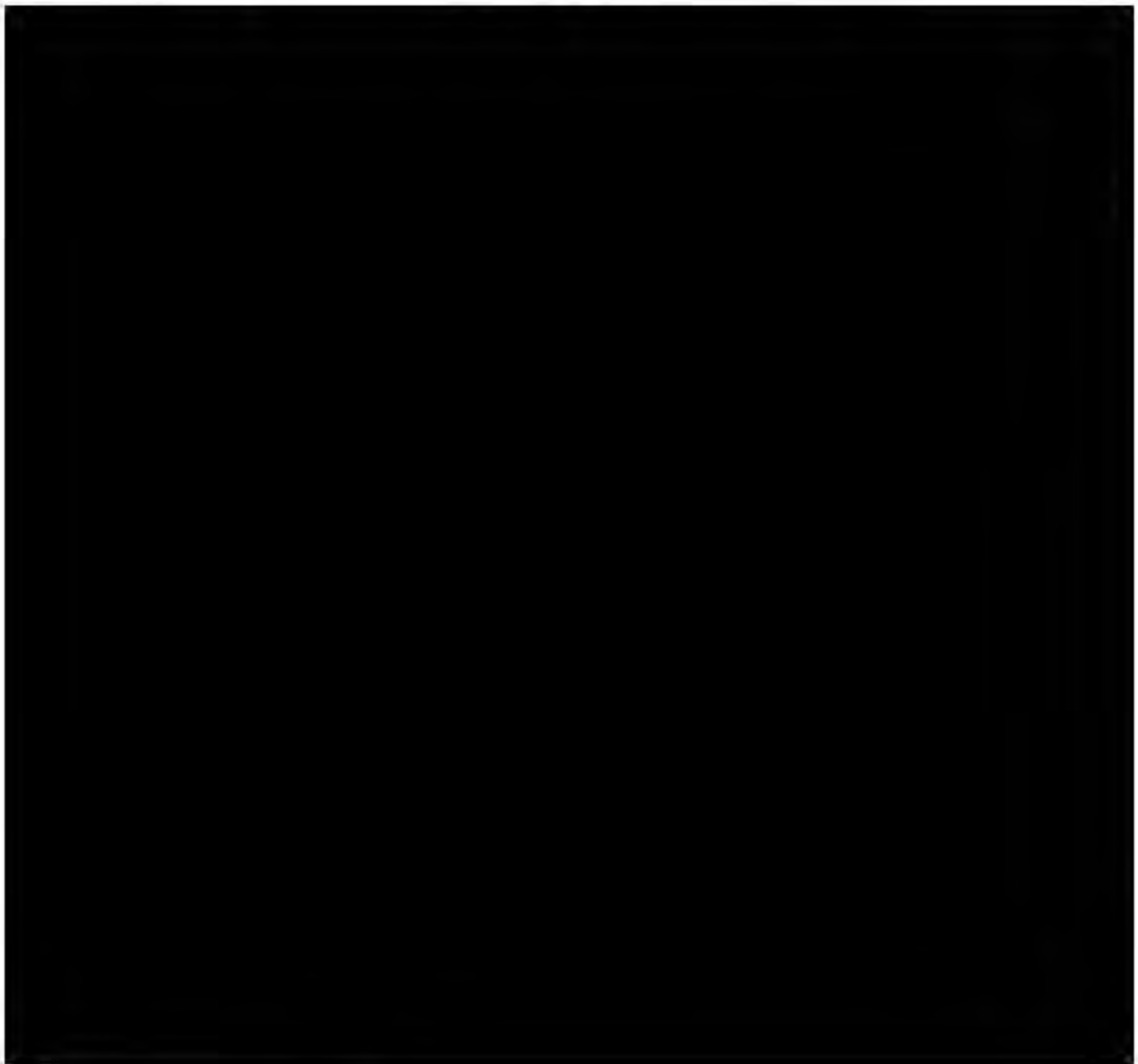
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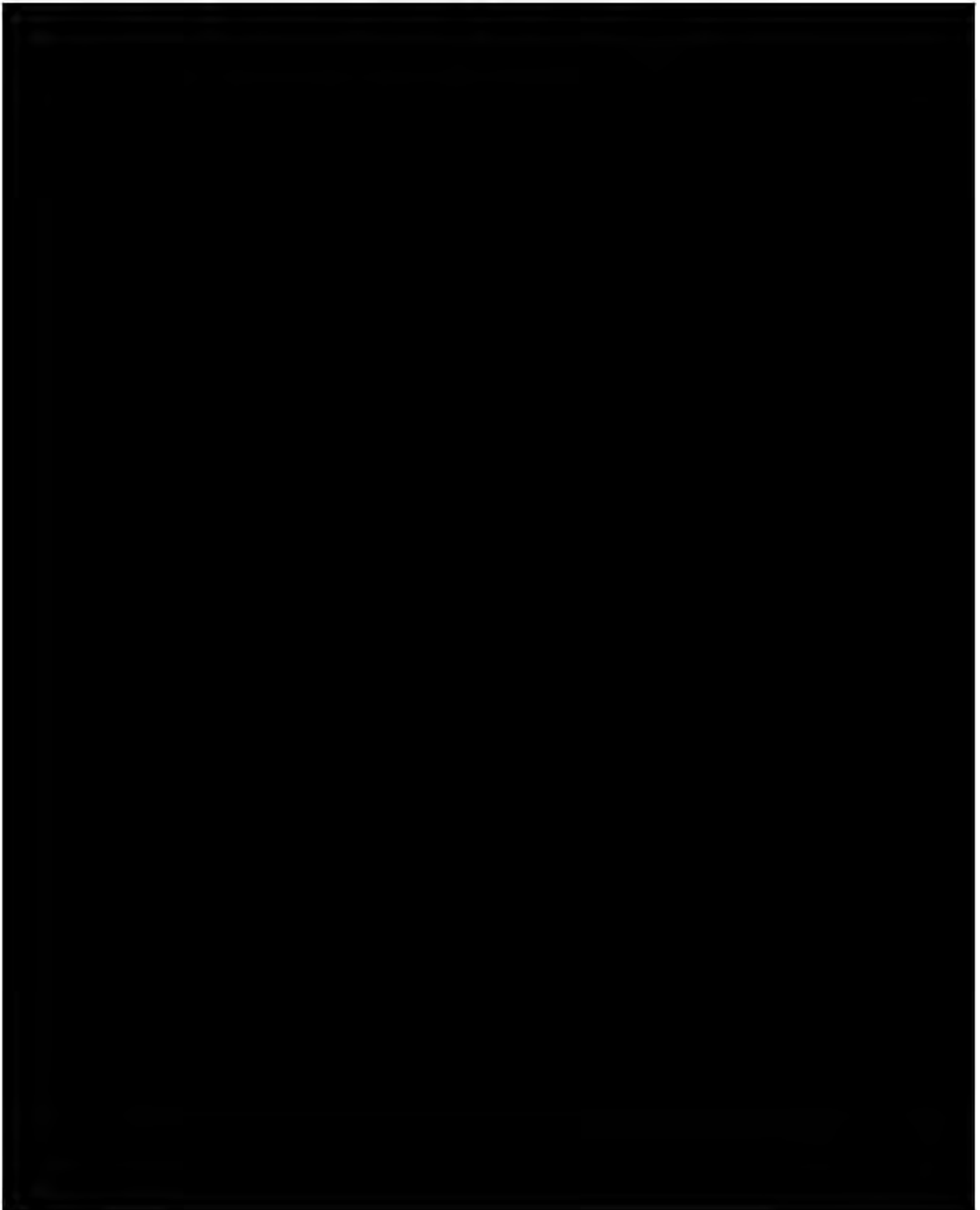
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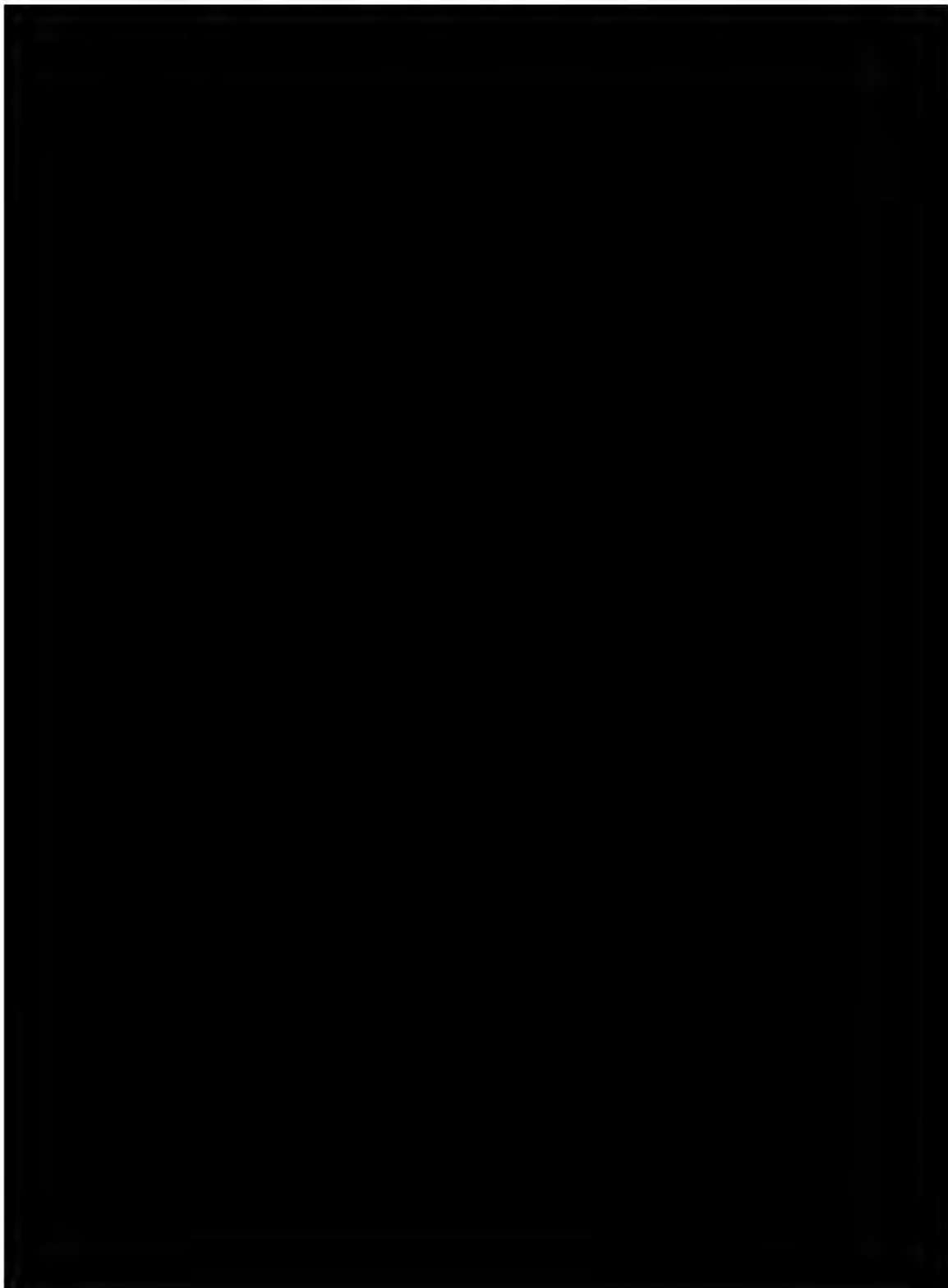
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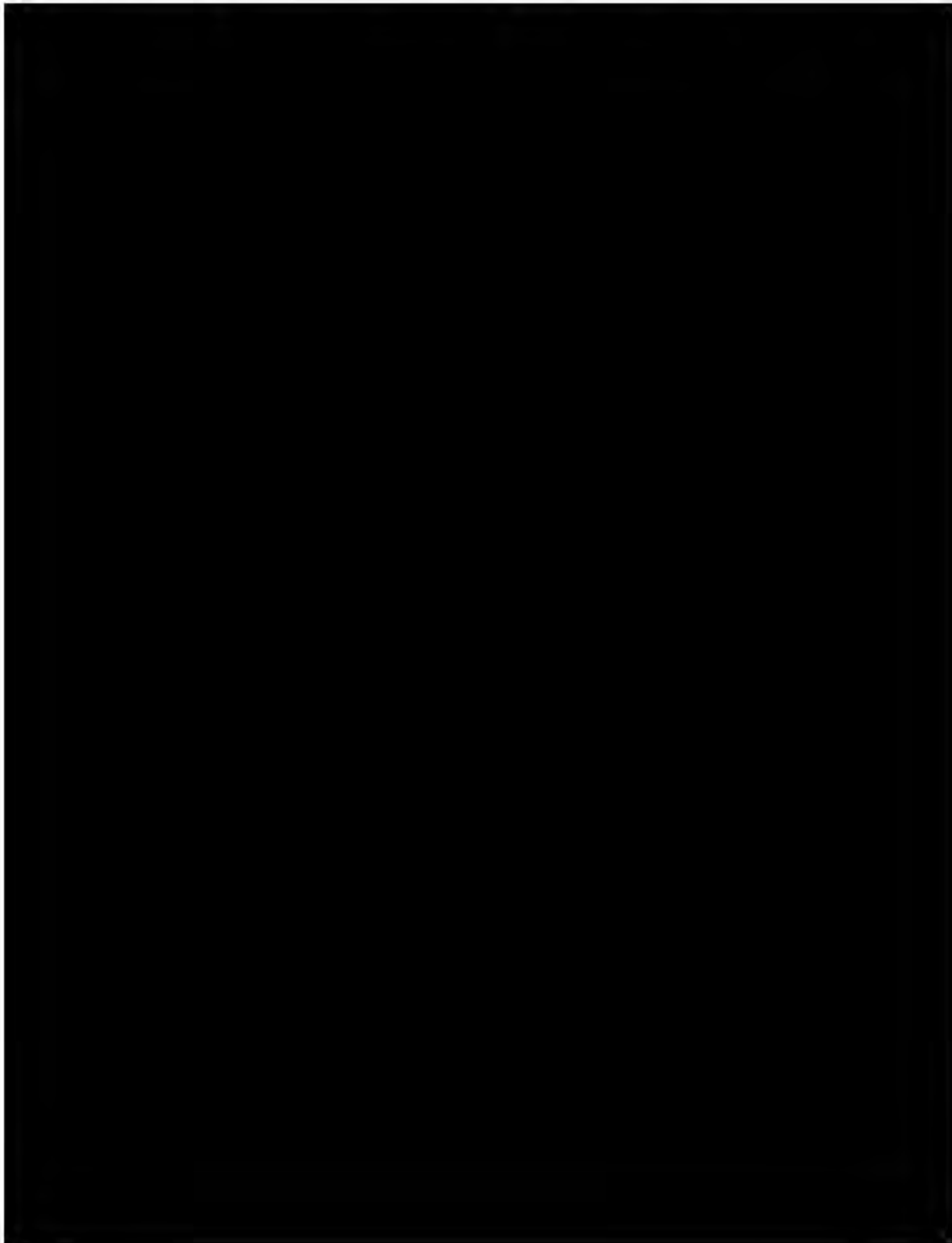
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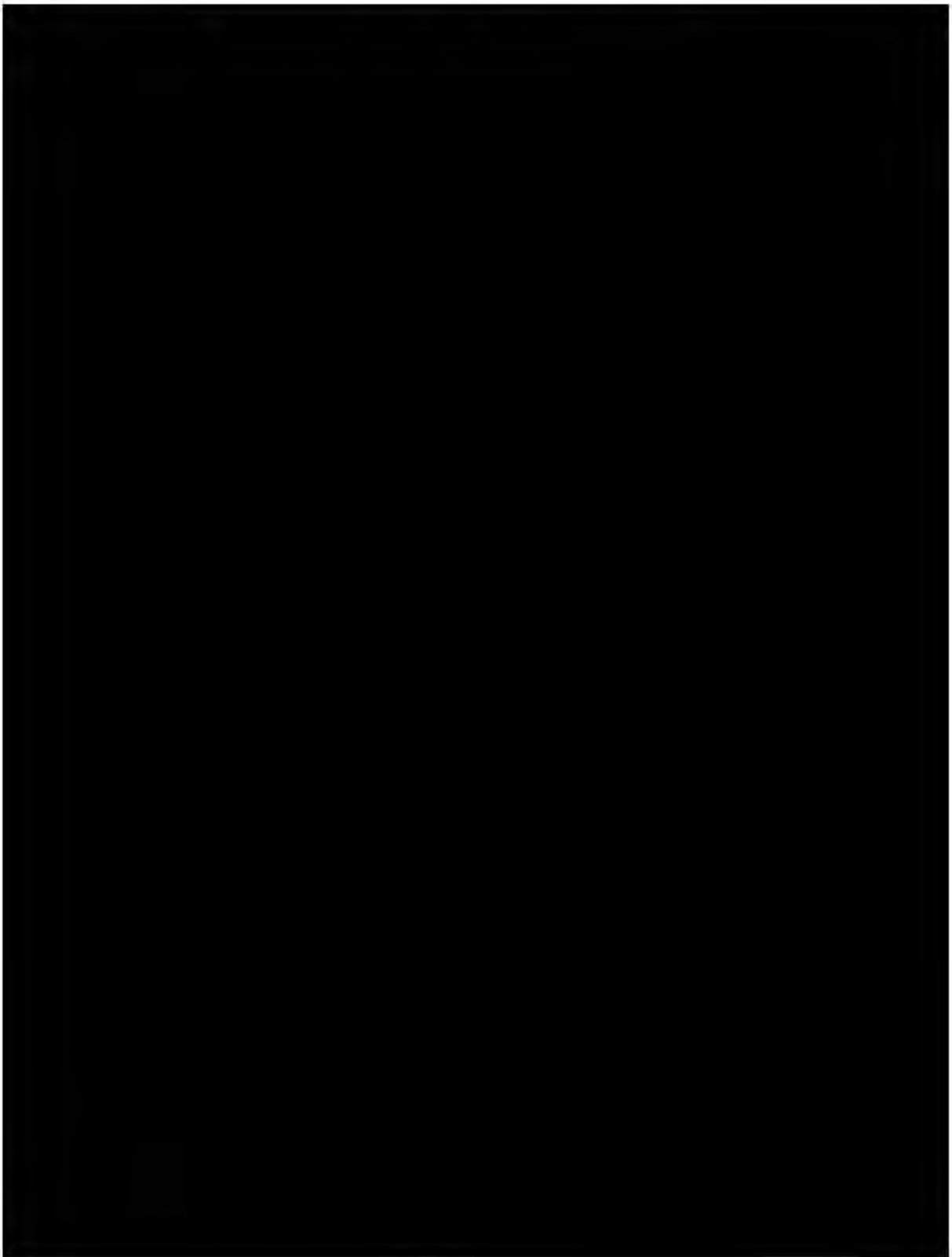
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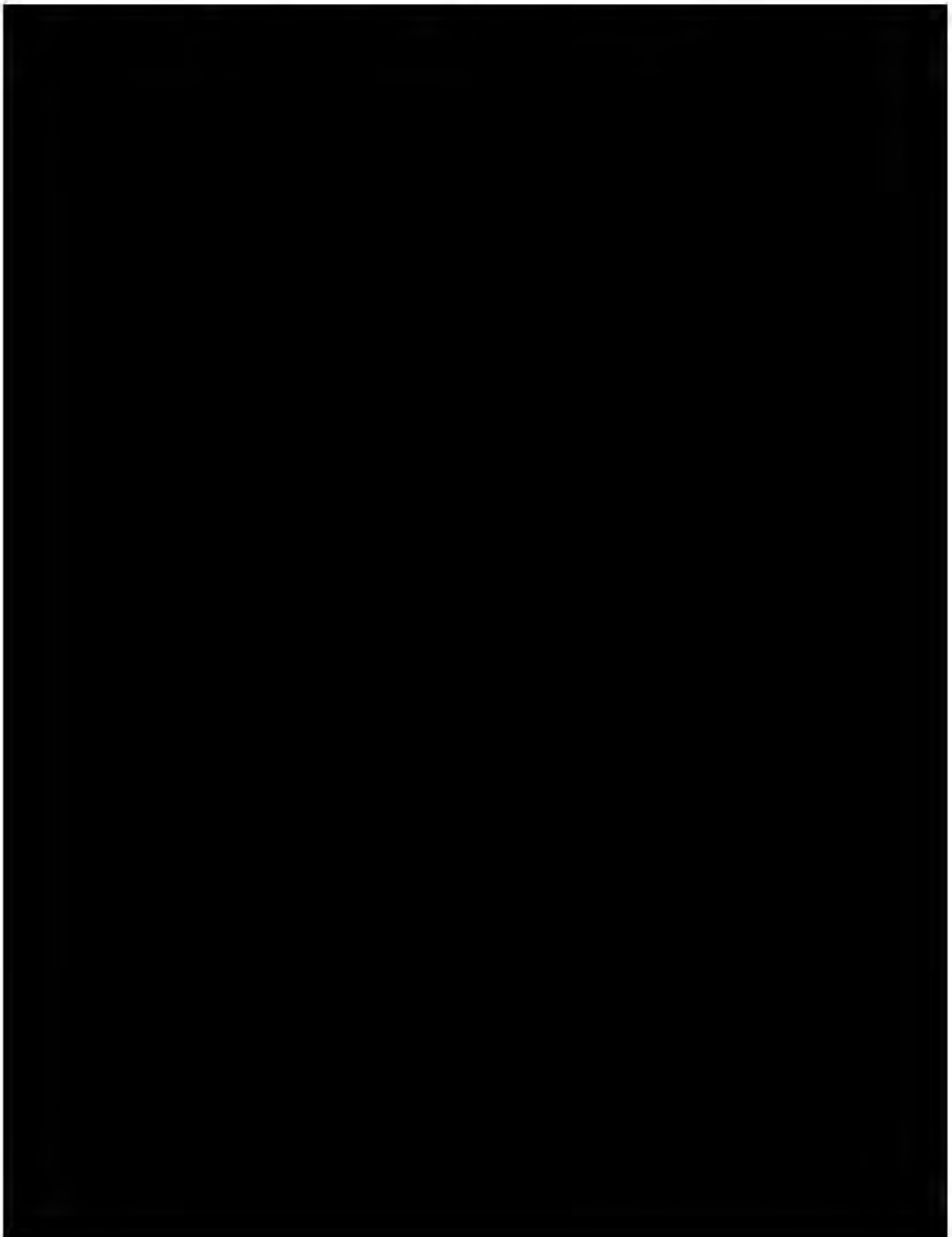
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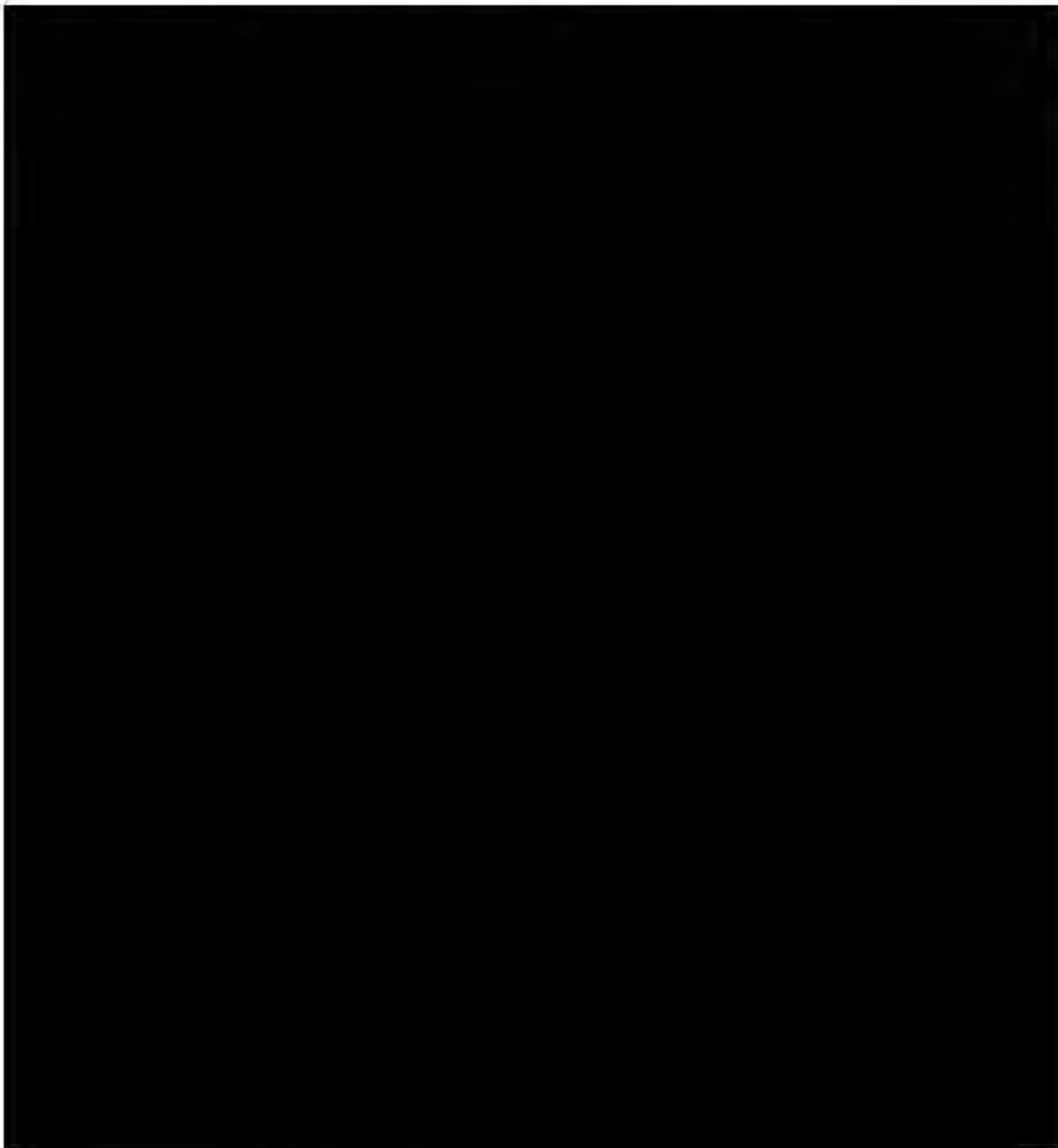
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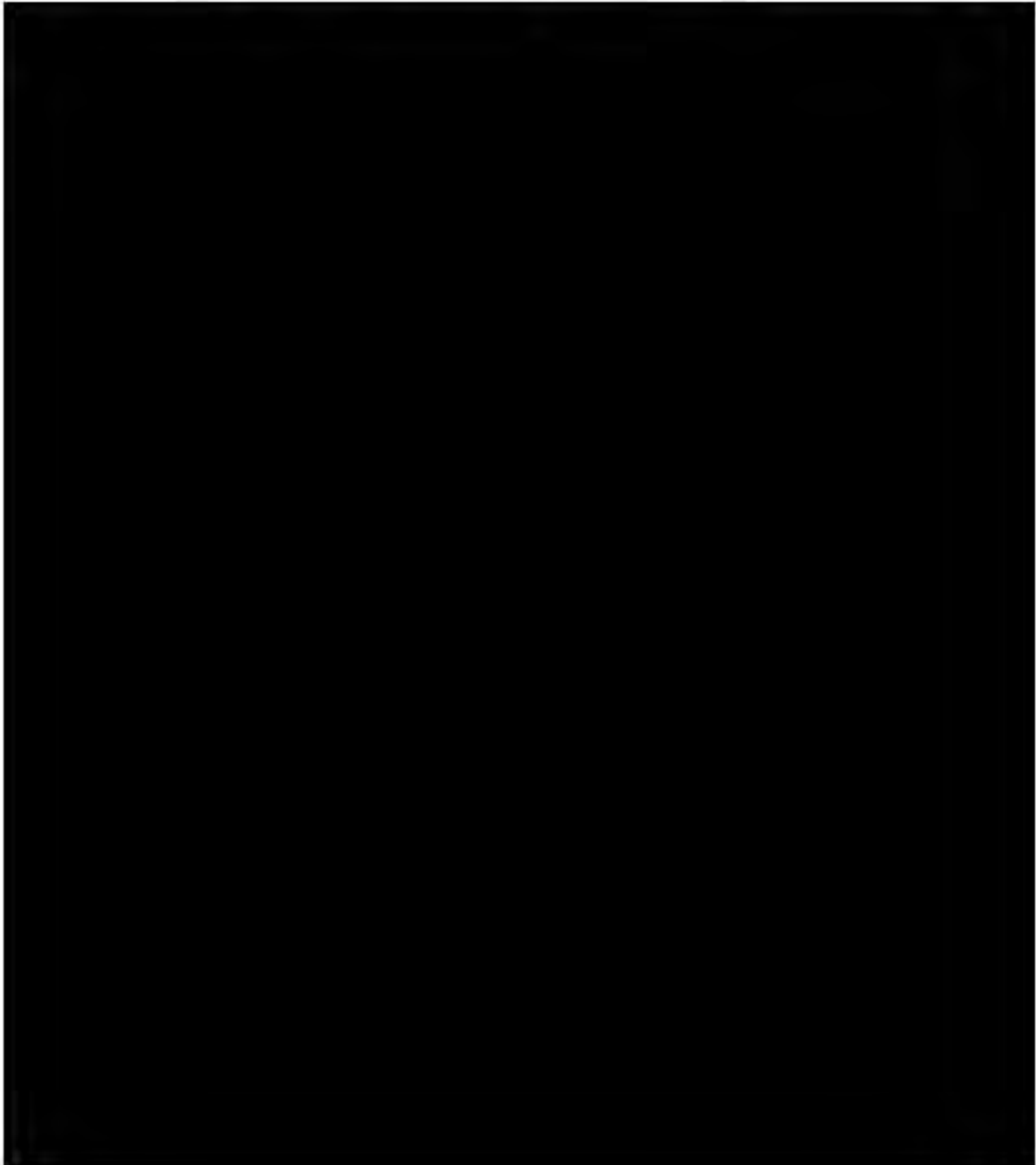
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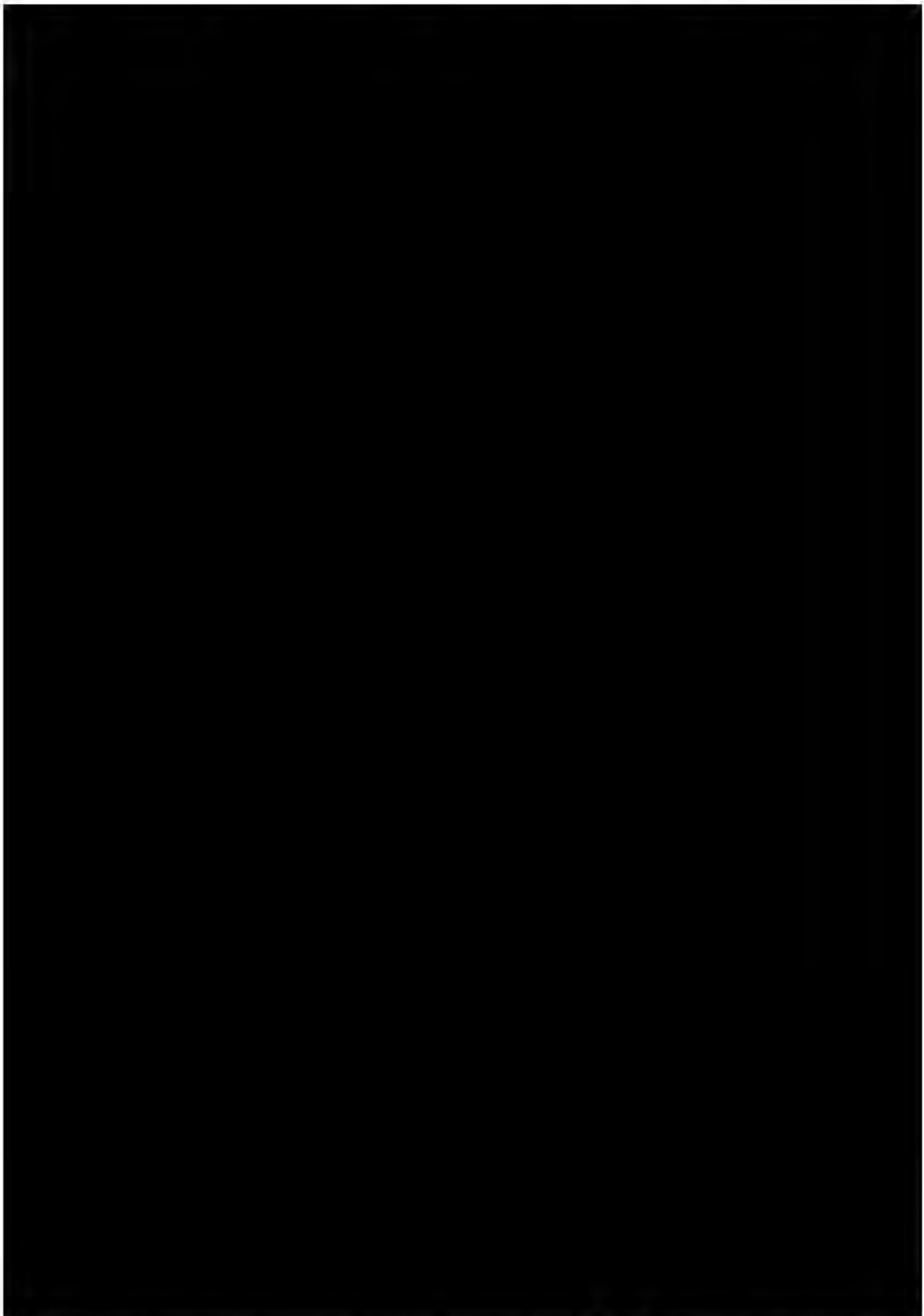
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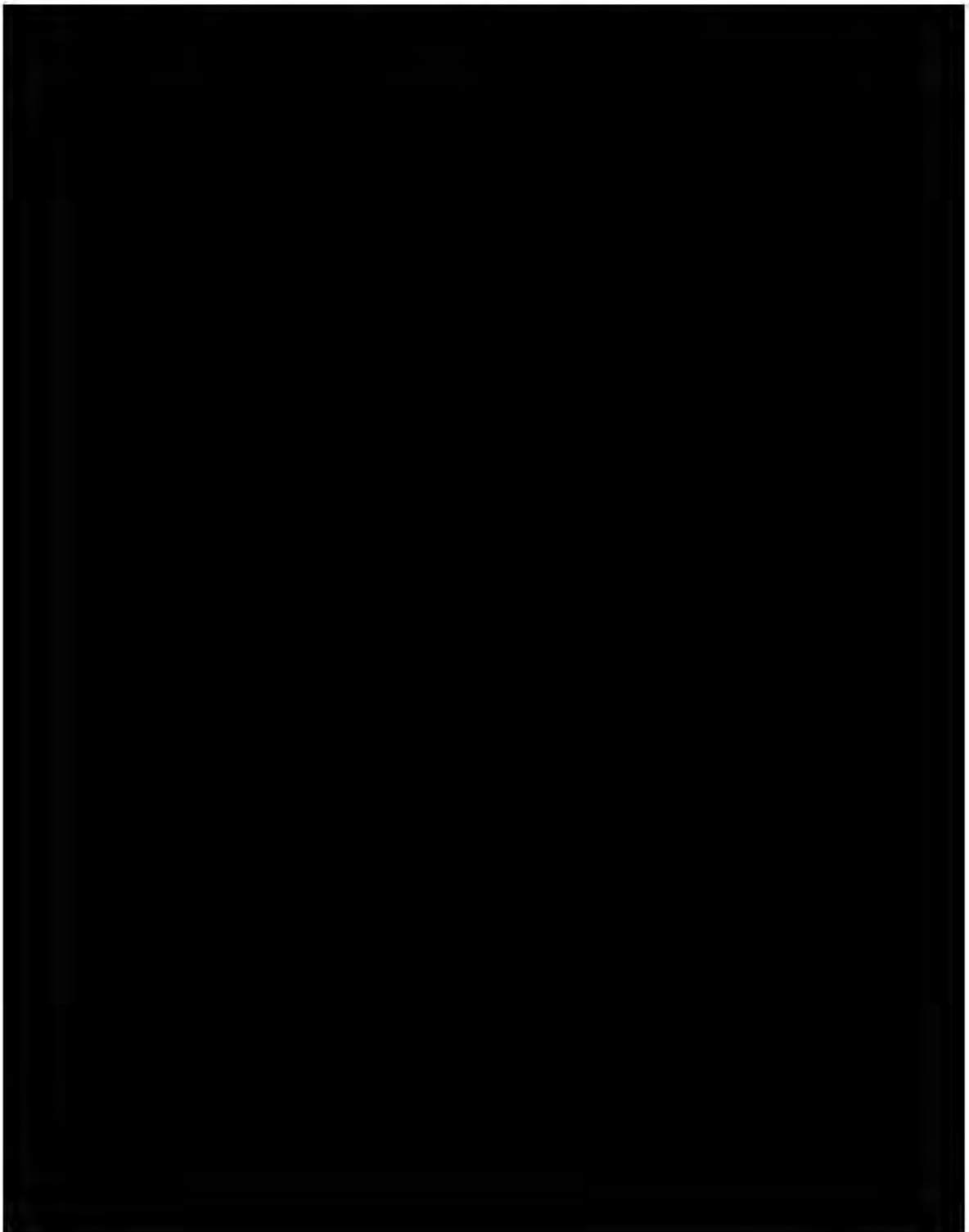
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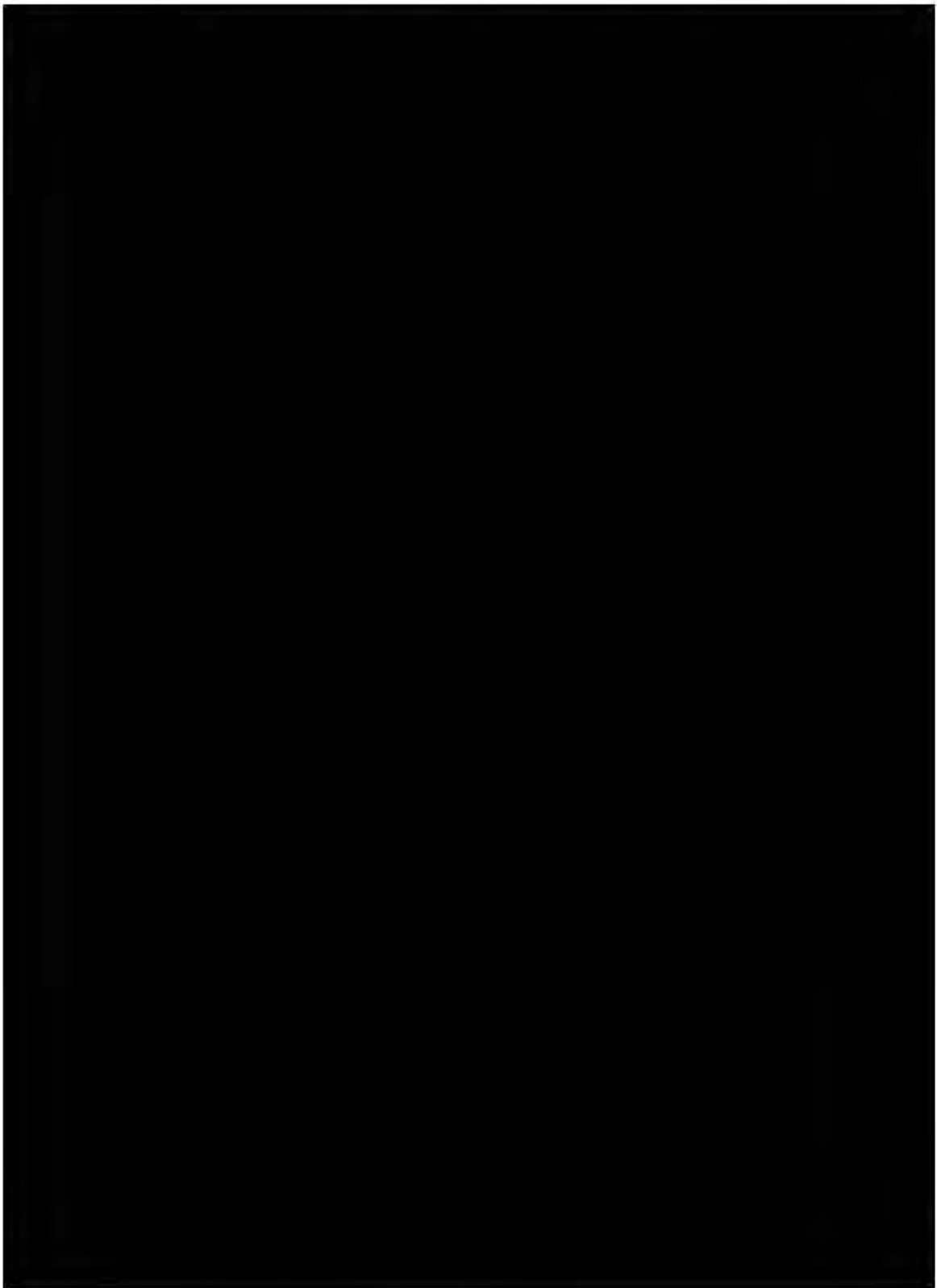
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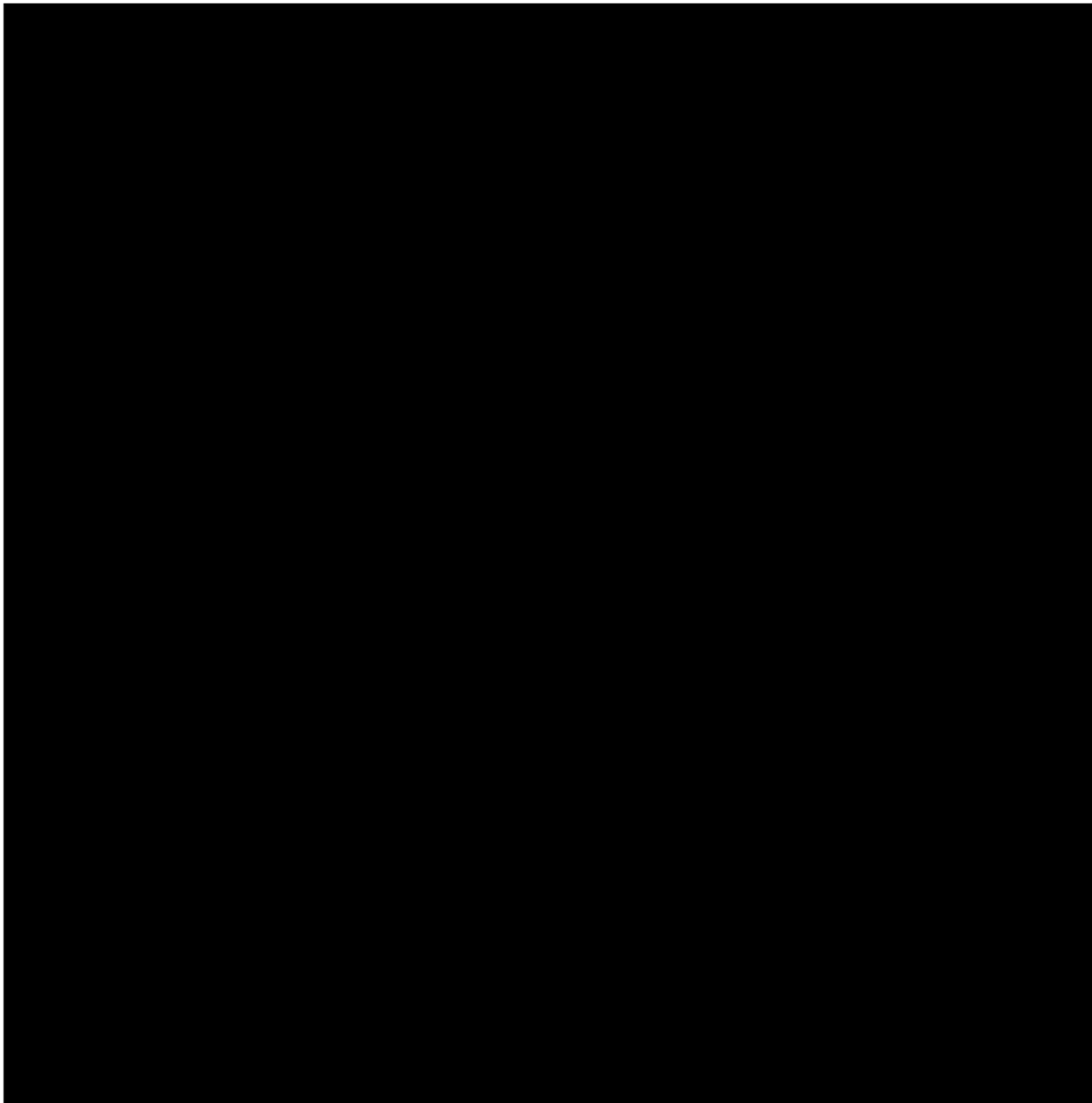
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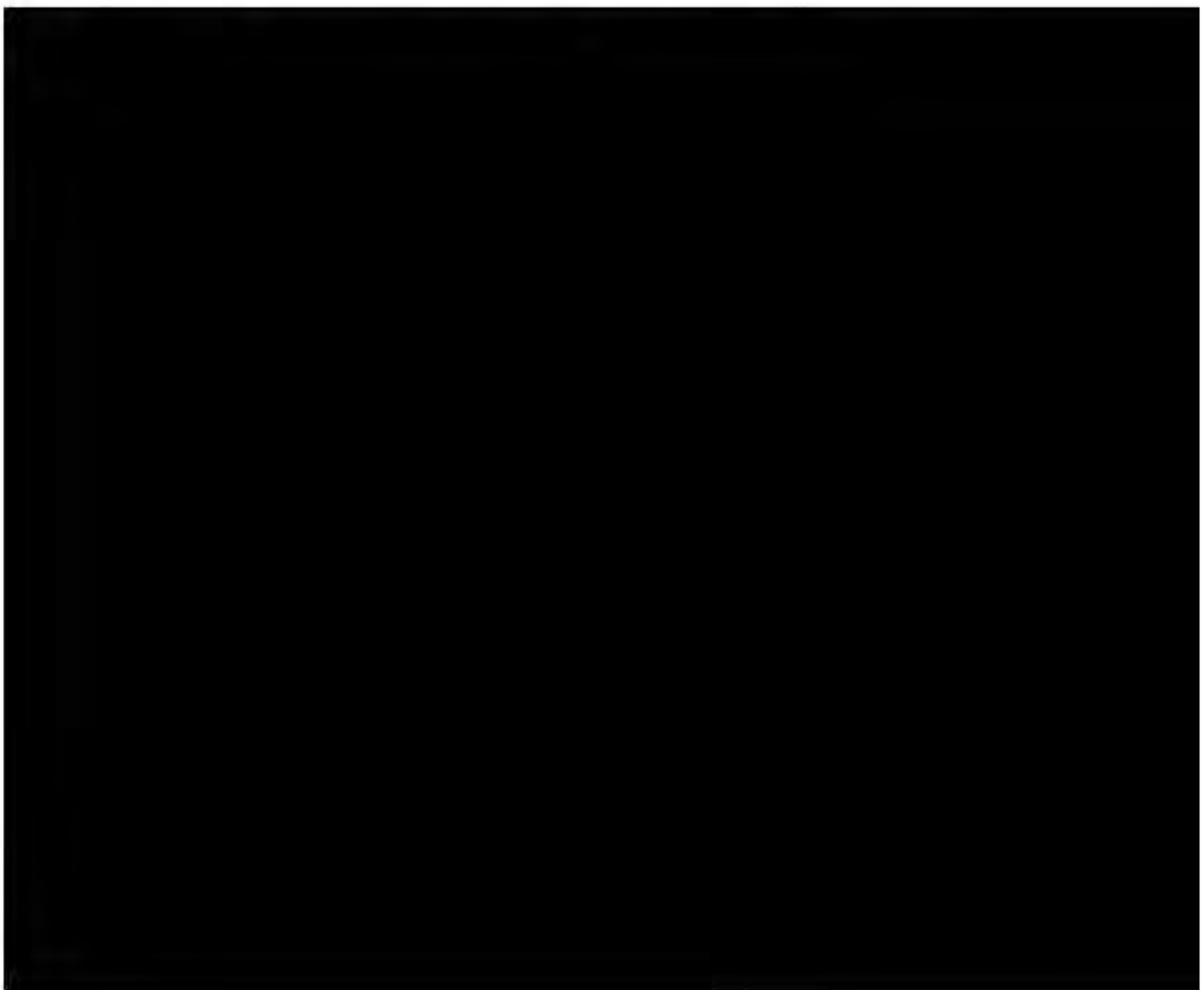
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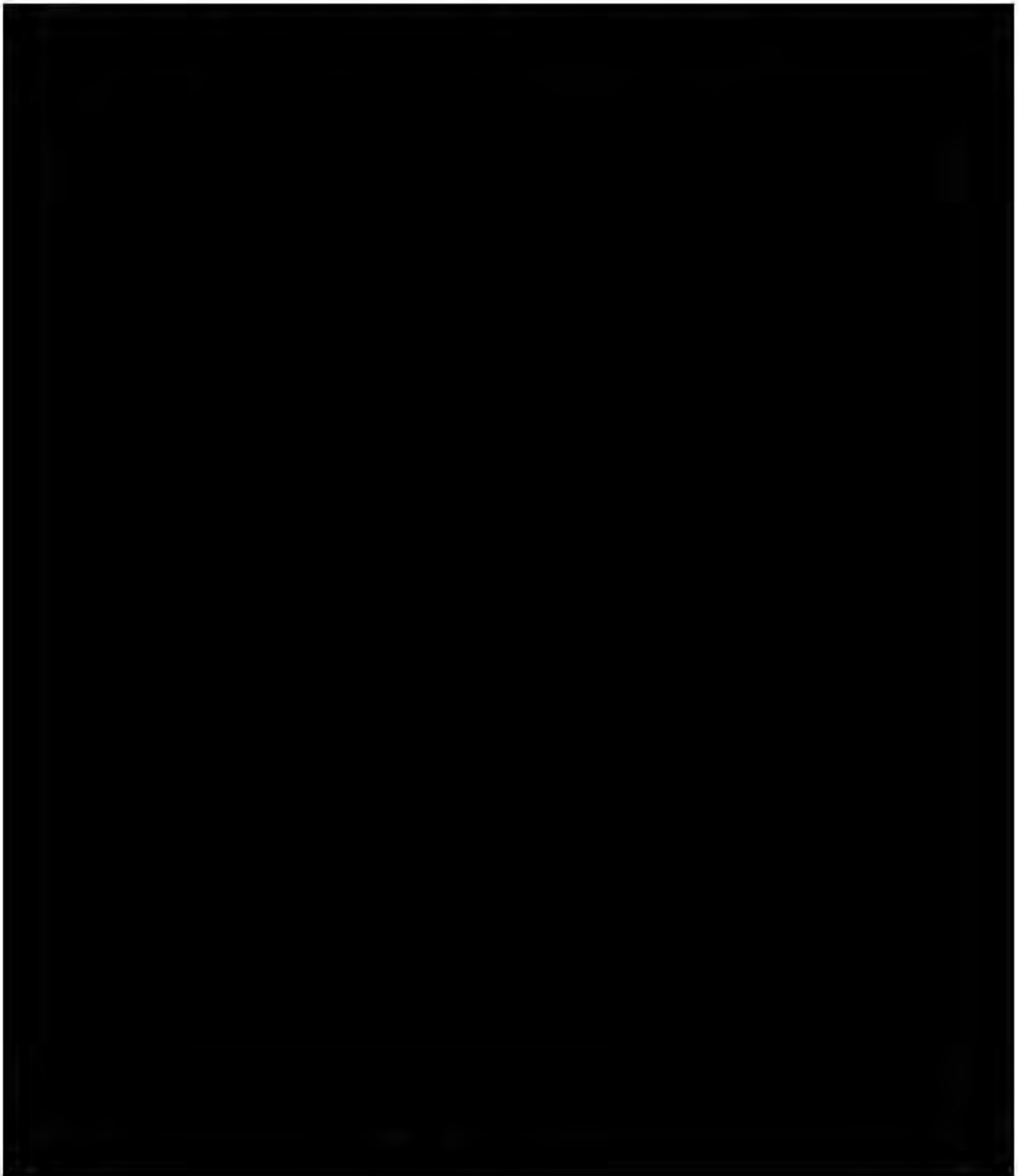
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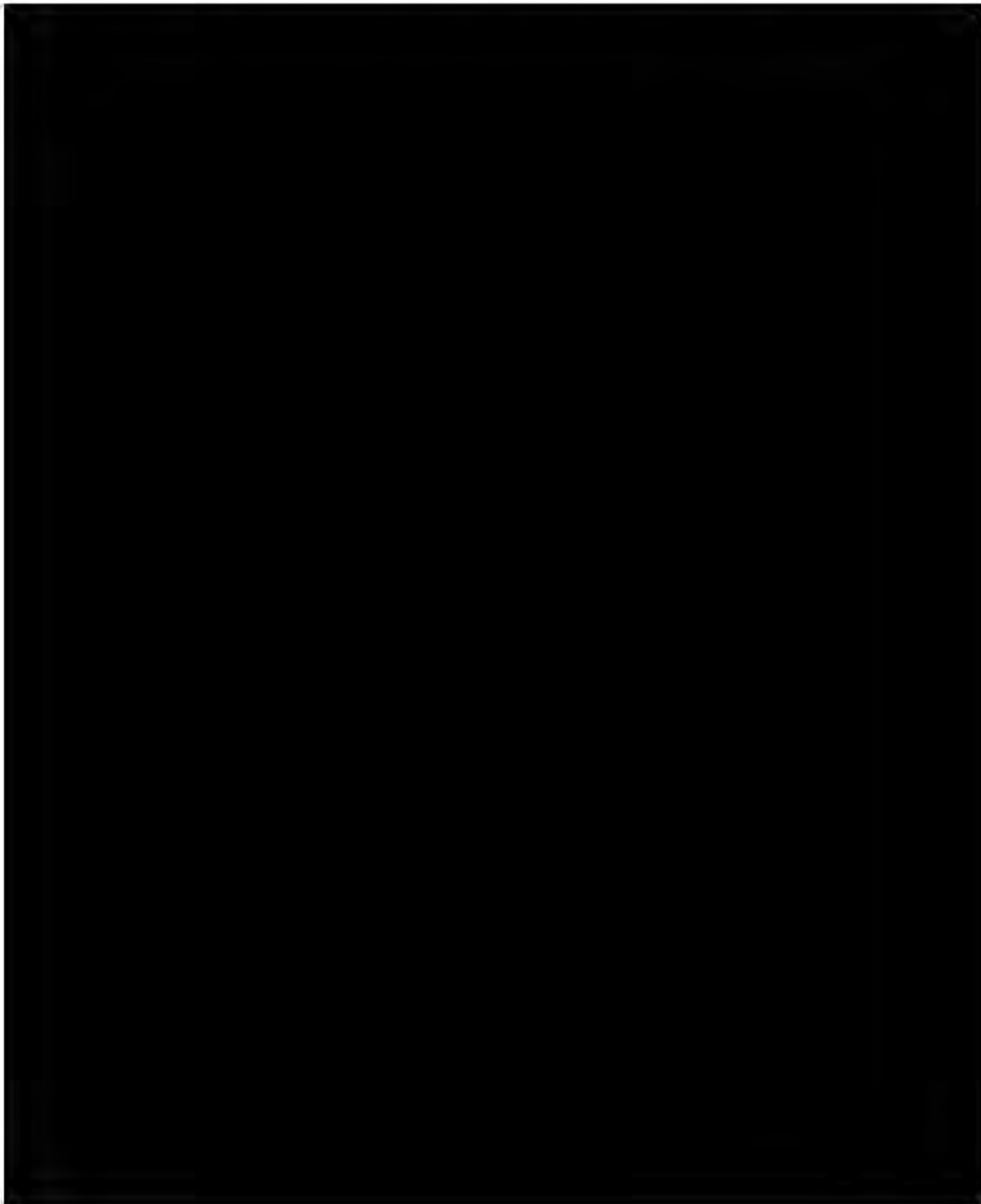
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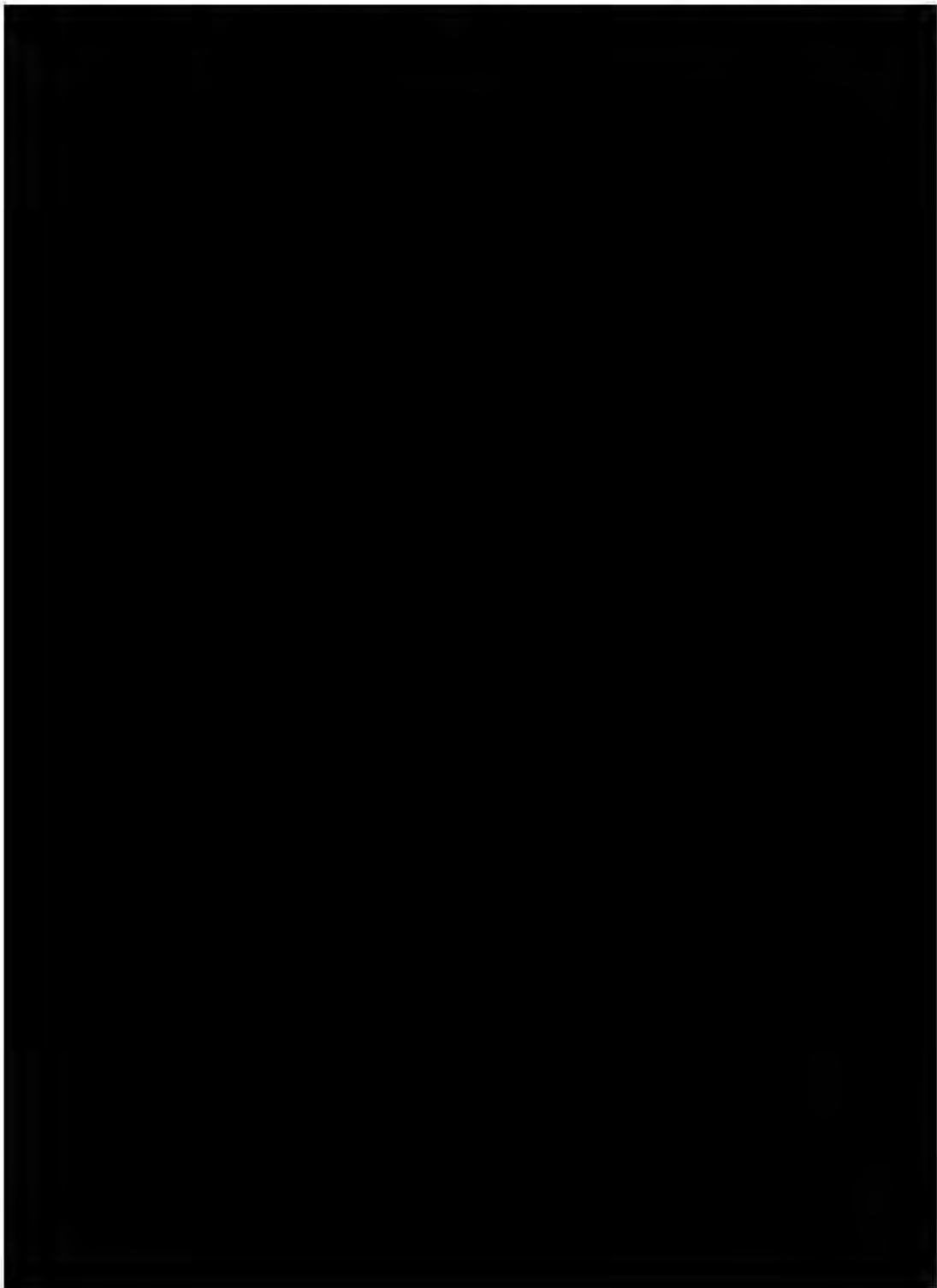
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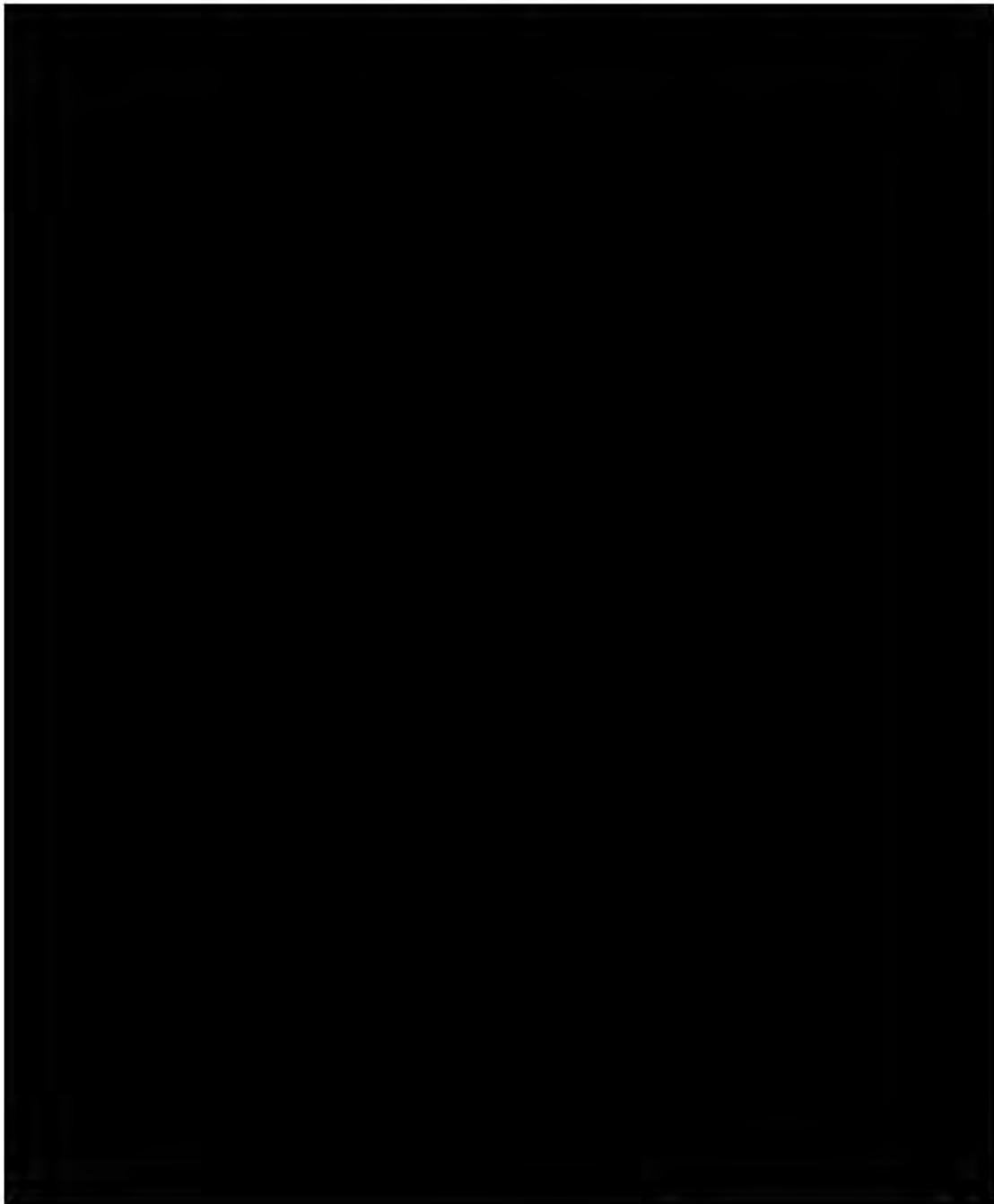
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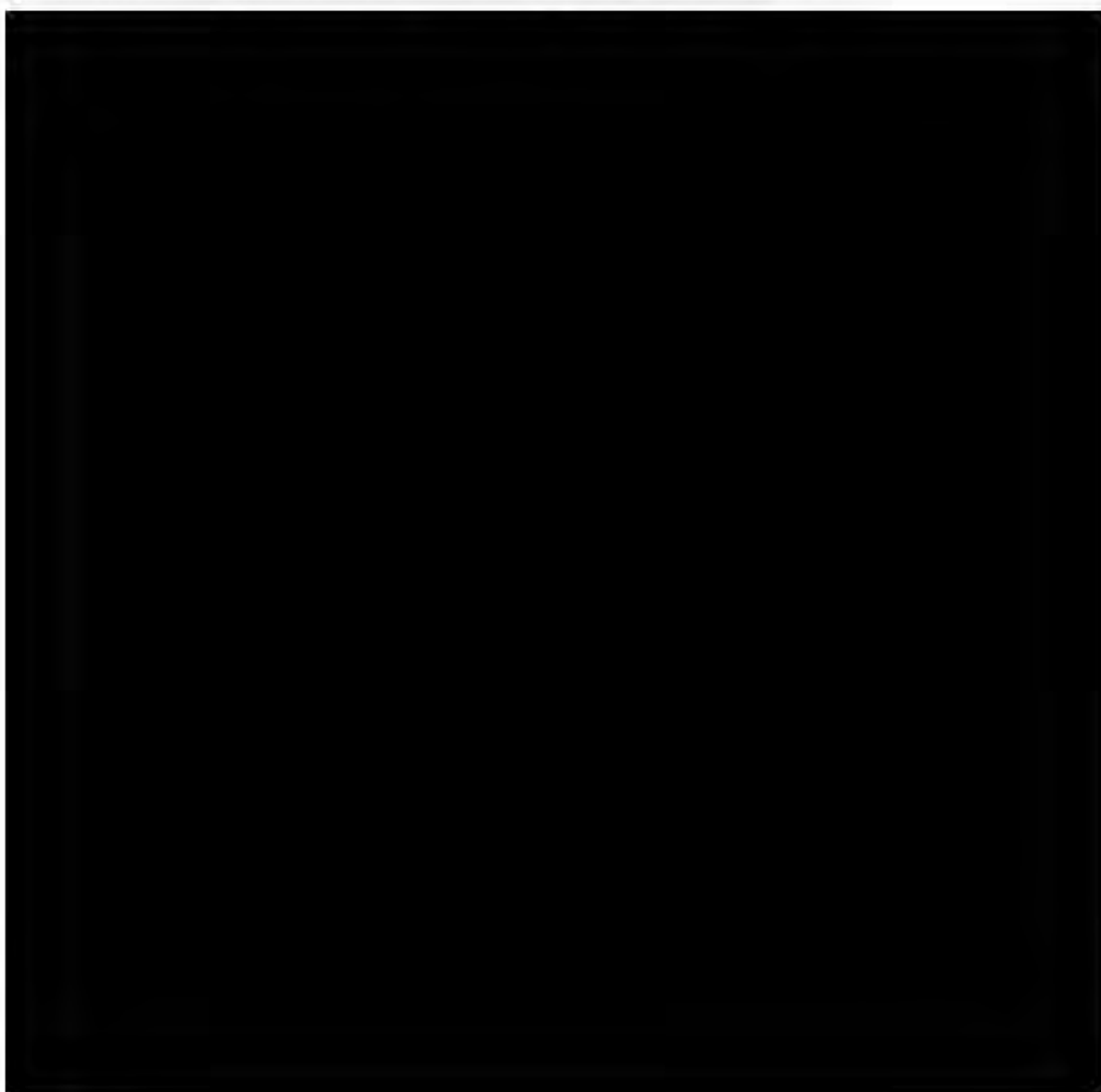
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This image shows a blank, aged, cream-colored page, likely an endpaper or flyleaf of a book. The paper has a slightly textured appearance with some faint smudges and discoloration, characteristic of old paper. The left edge of the page shows the binding of the book, and the overall tone is a warm, off-white or light beige.

Appendix 6: Management of Atezolizumab-Specific Adverse Events



Appendix 7 Schedules of Activities for Screening

Table A7-1 Schedule of Activities for Stage 1 Screening: 1L Gastric Cancer Cohort

Assessment/Procedure	Stage 1 Screening ^a (Day -28 to -1)
Informed consent	x ^b
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of gastric cancer (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, aPTT)	x ^g
TSH, free T3 (or total T3 ⁱ), and free T4	x ^g
C-reactive protein	x ^g
LDH	x ^g
Pregnancy test ^k	x ^g
Urinalysis ^l	x ^g
Serum autoantibody sample ^m	x
Tumor biopsy ⁿ	x
Baseline tumor assessments ^o	x ^o
Concomitant medications ^p	x
Adverse events ^q	x

1L=first-line; CT=computed tomography; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

Table A7-1 Schedule of Activities for Stage 1 Screening: 1L Gastric Cancer Cohort (cont.)

- ^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, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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 considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ Total T3 may be performed for sites where free T3 is not performed.
- ^j 
- ^k All women of childbearing potential will have a serum pregnancy test at screening.
- ^l Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. If urinary protein is > 1+ on dipstick and there is no explanation for the positive dipstick result (e.g., menses), a 24-hour urine collection is required to check total urinary protein.
- ^m Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.
- ⁿ 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 from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Refer to Section 4.5.6 for tissue sample requirements.

Table A7-1 Schedule of Activities for Stage 1 Screening: 1L Gastric Cancer Cohort (cont.)

- ° All measurable and 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 and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.
- ° Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.
- ° 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: Schedules of Activities for Screening

Table A7-2 Schedule of Activities for Stage 1 Screening: 2L Gastric Cancer Cohort

Assessment/Procedure	Stage 1 Screening ^a (Day –28 to –1)
Informed consent	x ^b
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of gastric cancer (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, aPTT)	x ^g
TSH, free T3 (or total T3 ⁱ), and free T4	x ^g
C-reactive protein	x ^g
LDH	x ^g
Pregnancy test ^k	x ^g
Urinalysis ^l	x ^g
Serum autoantibody sample ^m	x
Tumor biopsy ⁿ	x ^g
Baseline tumor assessments ^o	x ^o
Concomitant medications ^p	x
Adverse events ^q	x

2L = second-line; CT = computed tomography; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Appendix 7: Schedules of Activities for Screening

Table A7-2 Schedule of Activities for Stage 1 Screening: 2L Gastric Cancer Cohort (cont.)

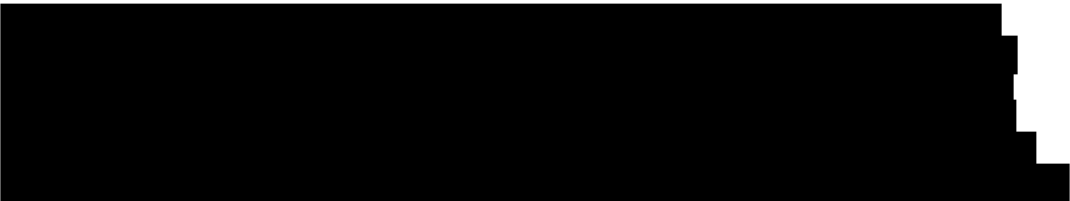
- ^a Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations 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, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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 considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ Total T3 may be performed for sites where free T3 is not performed.
- ^j 
- ^k All women of childbearing potential will have a serum pregnancy test at screening.
- ^l Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^m Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.
- ⁿ 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 from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. Refer to Section 4.5.6 for tissue sample requirements.

Table A7-2 Schedule of Activities for Stage 1 Screening: 2L Gastric Cancer Cohort (cont.)

- ° All measurable and 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 and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.
- ° Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.
- ° 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: Schedules of Activities for Screening

Table A7-3 Schedule of Activities for Stage 2 Screening: 2L Gastric Cancer Cohort

Assessment/Procedure	Stage 2 Screening ^a
Informed consent	x ^b
Molecular profile of gastric cancer (if available)	x
Vital signs ^c	x
Weight	x
Complete physical examination ^d	x
ECOG Performance Status	x
ECG ^e	x
Hematology ^f	x ^g
Chemistry ^h	x ^g
Coagulation (INR, aPTT)	x ^g
TSH, free T3 (or total T3 ⁱ), and free T4	x ^g
C-reactive protein	x ^g
LDH	x ^g
Pregnancy test ^k	x ^g
Urinalysis ^l	x ^g
Baseline tumor assessments ^m	x ^{m, n}
Concomitant medications ^o	x
Adverse events ^p	x

2L=second-line; CT=computed tomography; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

- ^a The visit at which response assessment shows progressive disease may be used as the Stage 2 screening visit. 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.
- ^b Written informed consent must be obtained before performing screening evaluations for Stage 2 except as noted in footnote "o" below.
- ^c Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

Appendix 7: Schedules of Activities for Screening

Table A7-3 Schedule of Activities for Stage 2 Screening: 2L Gastric Cancer Cohort (cont.)

- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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 considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ Total T3 may be performed for sites where free T3 is not performed.
- ^j 
- ^k All women of childbearing potential will have a urine or serum pregnancy test at screening.
- ^l Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. If urinary protein is > 1+ on dipstick and there is no explanation for the positive dipstick result (e.g., menses), a 24-hour urine collection is required to check total urinary protein.
- ^m All measurable and 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 and CT scans of the neck should 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ⁿ 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 loss of clinical benefit or unacceptable toxicity 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.

Table A7-3 Schedule of Activities for Stage 2 Screening: 2L Gastric Cancer Cohort (cont.)

- Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.
- 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: Schedules of Activities for Screening

Table A7-4 Schedule of Activities for Stage 1 Screening: Esophageal Cancer Cohort

Assessment/Procedure	Stage 1 Screening ^a (Day -28 to -1)
Informed consent	x ^b
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of cancer (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
Creatinine clearance ⁱ	x
Coagulation (INR, aPTT)	x ^g
TSH, free T3 (or total T3 ^j), and free T4	x ^g
C-reactive protein	x ^g
LDH	x ^g
Pregnancy test ^l	x ^g
Urinalysis ^m	x ^g
Serum autoantibody sample ⁿ	x
Tumor biopsy ^o	x
Baseline tumor assessments ^p	x ^p
Concomitant medications ^q	x
Adverse events ^r	x

CT = computed tomography; EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table A7-4 Schedule of Activities for Stage 1 Screening: Esophageal Cancer Cohort (cont.)

- ^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, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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 considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ Creatinine clearance is calculated by the method of Cockcroft and Gault (1976) (see Section 4.1.3.1).
- ^j Total T3 may be performed for sites where free T3 is not performed.
- ^k 
- ^l All women of childbearing potential will have a serum pregnancy test at screening.
- ^m Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ⁿ Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

Table A7-4 Schedule of Activities for Stage 1 Screening: Esophageal Cancer Cohort (cont.)

- ° 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. Refer to Section 4.5.6 for tissue sample requirements.
- ° All measurable and 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 and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.
- ° Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.
- ° 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: Schedules of Activities for Screening

Table A7-5 Schedule of Activities for Stage 2 Screening: Esophageal Cancer Cohort

Assessment/Procedure	Stage 2 Screening ^a (Day –28 to –1)
Informed consent	x ^b
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of cancer (if available)	x
Vital signs ^c	x
Weight	x
Complete physical examination ^d	x
ECOG Performance Status	x
ECG ^e	x
Hematology ^f	x ^g
Chemistry ^h	x ^g
Coagulation (INR, aPTT)	x ^g
TSH, free T3 (or total T3 ⁱ), and free T4	x ^g
C-reactive protein	x ^g
LDH	x ^g
Pregnancy test ^k	x ^g
Urinalysis ^l	x ^g
Tumor biopsy ^m	x ^m
Baseline tumor assessments ⁿ	x ^{n, o}
Concomitant medications ^p	x
Adverse events ^q	x

CT= computed tomography; EBNA=Epstein-Barr nuclear antigen; EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

^a The visit at which response assessment shows progressive disease may be used as the Stage 2 screening visit. 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.

^b Written informed consent must be obtained before performing screening evaluations for Stage 2 except as noted in footnote "n" below.

Table A7-5 Schedule of Activities for Stage 2 Screening: Esophageal Cancer Cohort (cont.)

- ^c Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
- ^d Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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 considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ⁱ Total T3 may be performed for sites where free T3 is not performed.
- ^j 
- ^k All women of childbearing potential will have a serum pregnancy test at screening.
- ^l Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^m Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at Stage 2 screening, if deemed clinically feasible by the investigator.
- ⁿ All measurable and 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 and CT scans of the neck should 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. Refer to Section 4.5.5 for further details on tumor assessments.

Table A7-5 Schedule of Activities for Stage 2 Screening: Esophageal Cancer Cohort (cont.)

- ° 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 loss of disease progression per RECIST v1.1 or unacceptable toxicity 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.
- ° Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.
- ° 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 8

Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

**NOTE: THE RAMUCIRUMAB + PACLITAXEL CONTROL ARM IS NOT
CURRENTLY ENROLLING NEW PATIENTS AS OF OCTOBER 2019.**

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Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

A8-1 MATERIALS AND METHODS SPECIFIC TO RAMUCIRUMAB+PACLITAXEL CONTROL ARM

A8-1.1 TREATMENT IN RAMUCIRUMAB+PACLITAXEL CONTROL ARM

A8-1.1.1 Formulation, Packaging, and Handling

For information on the formulation, packaging, and handling of paclitaxel and ramucirumab, refer to the local label.

A8-1.1.2 Dosage, Administration, and Compliance

Patients in the control arm will receive treatment with ramucirumab plus paclitaxel as outlined in [Table A8-1](#), until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).

It is recommended that treatment be initiated no later than 7 days after randomization. Treatment will be administered according to institutional standards in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Table A8-1 Treatment Regimen for Ramucirumab+Paclitaxel Control Arm

Treatment Regimen	Cycle Length	Dose, Route, and Regimen (Drugs Listed in Order of Administration)
Ramucirumab and paclitaxel	28 days	• Ramucirumab 8 mg/kg administered by IV infusion over 60 minutes on Days 1 and 15 of each cycle • Paclitaxel 80 mg/m² administered by IV infusion over 60 minutes on Days 1, 8, and 15 of each cycle

Prior to each ramucirumab infusion, patients should be premedicated with an IV histamine H₁ antagonist (e.g., diphenhydramine hydrochloride).

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.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under "special situations" as explained in [Section 5.3.5.12](#). Adverse events associated

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

A8-1.1.3 Stage 2 Treatment

Patients who experience disease progression per RECIST v1.1 will be given the option of receiving a different treatment combination during Stage 2 of the study, as outlined in [Table A8-2](#), provided they meet eligibility criteria (see [Section 4.1](#)) and the Stage 2 arm is open for enrollment. Patients who experience unacceptable toxicity may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of disease progression or unacceptable toxicity 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 (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A8-2 Stage 2 Treatment Regimen Available for the Ramucirumab + Paclitaxel Control Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

A8-1.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR RAMUCIRUMAB + PACLITAXEL CONTROL ARM

Concomitant therapy 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 10 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.

Paclitaxel can cause severe allergic reaction due to the drug carrier. Therefore, patients should receive a pre-medication prior to each paclitaxel dose, including corticosteroids, in alignment with local guidelines.

Owing to the risk of gastrointestinal (GI) perforation during treatment with ramucirumab, chronic daily treatment with non-steroidal anti-inflammatory drug and chronic daily treatment with systemic corticosteroids (dose > 10 mg/day methylprednisolone or

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

equivalent) is discouraged. However, occasional use for the symptomatic relief of medical conditions (e.g., headache) is allowed when co-administered with proton-pump inhibitors to reduce potential GI damage.

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for the control agents, refer to the local label for each agent.

A8-1.3 CONTRACEPTION REQUIREMENTS FOR RAMUCIRUMAB + PACLITAXEL CONTROL ARM

Contraception requirements for women and men in the control arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, 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 6 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

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

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male 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 acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of study treatment. Men must refrain from donating sperm during this same period.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of study treatment to avoid exposing the embryo.

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 acceptable methods of contraception.

A8-2 ASSESSMENT OF SAFETY FOR RAMUCIRUMAB + PACLITAXEL CONTROL ARM

A8-2.1 SAFETY PLAN FOR RAMUCIRUMAB + PACLITAXEL CONTROL ARM

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 paclitaxel and ramucirumab 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. An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections 3.1.6 and 3.1.7.

A8-2.1.1 Risks Associated with Paclitaxel or Ramucirumab

Risks associated with paclitaxel or with ramucirumab are described in the local prescribing information for each agent.

A8-2.1.2 Management of Patients Who Experience Specific Adverse Events in the Ramucirumab + Paclitaxel Control Arm

Guidelines for management of patients who experience specific adverse events related to paclitaxel or ramucirumab (including dose modifications and treatment interruptions) can be found below. The treating physician may use discretion in modifying the dose modification guidelines described below, 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.

A8-2.1.2.1 Dose Modifications

The paclitaxel and ramucirumab doses can be modified as shown in [Table A8-3](#) for the management of study drug-related toxicities. Patients who require reductions more than two dose levels should be discontinued from that agent.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

Table A8-3 Ramucirumab and Paclitaxel Dose Adjustment

	Ramucirumab	Paclitaxel
Starting dose	8 mg/kg	80 mg/m ²
– 1 dose level	6 mg/kg	70 mg/m ²
– 2 dose levels	5 mg/kg	60 mg/m ²

The dose of ramucirumab and paclitaxel can be reduced by one dose level decrements up to two times for management of study drug–related toxicities. If the dose of ramucirumab and/or paclitaxel is reduced, subsequent dose increases are not permitted. Paclitaxel will be permanently discontinued if a dose reduction to <60 mg/m² would be required, or in case of any paclitaxel-related event that is deemed life threatening, regardless of grade.

A8–2.1.2.2 Treatment Interruption

Paclitaxel and/or ramucirumab treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If paclitaxel and/or ramucirumab has been withheld for >28 days because of toxicity, paclitaxel and/or ramucirumab should be permanently discontinued.

If one component of the regimen (paclitaxel or ramucirumab) is discontinued, the remaining component should be continued if the patient is likely to derive clinical benefit according to the investigator.

A8–2.1.2.3 Management of Specific Adverse Events: Guidelines for Ramucirumab

Infusion-Related Reactions

If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR), the infusion rate of ramucirumab should be reduced by 50% for the duration of the infusion and for all subsequent infusions.

For patients who experiences a Grade 1 or 2 IRR, premedication with dexamethasone (or equivalent) and acetaminophen prior to each subsequent ramucirumab infusion.

Ramucirumab should be immediately and permanently discontinued in the event of a Grade 3 or 4 IRR.

Hypertension

Ramucirumab therapy should be temporarily discontinued in the event of Grade 3 or 4 hypertension, until controlled with medical management. If there is medically significant hypertension that cannot be controlled safely with antihypertensive therapy, ramucirumab therapy should be permanently discontinued.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

Proteinuria

Ramucirumab therapy should be temporarily discontinued if the urine protein level is ≥ 2 g/24 hr. Once the urine protein level returns to < 2 g/24 hr, treatment should be resumed by one dose level reduction. A second dose reduction is recommended if a urine protein level ≥ 2 g/24 hr recurs.

Ramucirumab therapy should be permanently discontinued if the urine protein level is > 3 g/24 hr or in the event of nephrotic syndrome.

Elective Surgery or Impaired Wound Healing

Ramucirumab therapy should be temporarily discontinued for at least 4 weeks prior to elective surgery. Ramucirumab therapy should be temporarily discontinued if there are wound-healing complications, until the wound is fully healed.

Modifications for Other Toxicities

Ramucirumab therapy should be permanently discontinued in the event of:

- Severe arterial thromboembolic events
- GI perforations
- Severe bleeding: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or 4 bleeding
- Spontaneous development of fistula
- Reversible posterior leukoencephalopathy syndrome

A8-2.1.2.4 Management of Specific Adverse Events: Guidelines for Paclitaxel

The criteria to be met prior to each paclitaxel infusion are provided in [Table A8-4](#).

Table A8-4 Criteria to Be Met prior to Each Paclitaxel Administration

Criteria	
Neutrophils	Day 1: $\geq 1.5 \times 10^9/\text{L}$ Days 8 and 15: $> 1.0 \times 10^9/\text{L}$
Platelets	Day 1: $\geq 100 \times 10^9/\text{L}$ Days 8 and 15: $\geq 75 \times 10^9/\text{L}$
Bilirubin	$< 1.5 \times \text{ULN}$
AST/ALT	No liver metastases: $\text{ALT/AST} \leq 3 \times \text{ULN}$ Liver metastases: $\text{ALT/AST} \leq 5 \times \text{ULN}$

ULN = upper limit of normal.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

Paclitaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. For NCI CTCAE Grade 4 hematologic toxicity or Grade 3 paclitaxel-related non-hematological toxicity, it is recommended to reduce the dose of paclitaxel by 10 mg/m² for all following cycles. A second dose reduction of 10 mg/m² is recommended if these toxicities persist or recur.

A8-2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR RAMUCIRUMAB + PACLITAXEL CONTROL ARM (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 the Ramucirumab + Paclitaxel arm include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A8-2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN RAMUCIRUMAB + PACLITAXEL CONTROL ARM

A8-2.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of study treatment. A 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/birth defect in the child) should be reported on the

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

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.

A8-2.3.2 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 6 months after the last dose of study treatment. A 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. 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 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 when updated information on the course and outcome of the pregnancy becomes available. 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 investigator and/or obstetrician.

A8-2.3.3 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.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

A8–2.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/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](#)).

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

A8-3 SCHEDULE OF ACTIVITIES FOR RAMUCIRUMAB+PACLITAXEL CONTROL ARM

Table A8-5 Schedule of Activities for Ramucirumab+Paclitaxel Control Arm (2L Gastric Cancer Cohort)

Assessment/Procedure	Stage 1 Screening (see Appendix 7)	Treatment Cycles (28-Day Cycles) ^a						Stage 2 Screening (see Appendix 7) ^c or Treat. Discon. ^d	Follow- Up ^d Every 3 Months
		Cycle 1 ^b			Cycles ≥ 2				
	Days –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)		
Molecular profile of gastric cancer (if available)	See Appendix 7.	Whenever updated information becomes available							
Vital signs ^e		X	X	X	X	X	X	X	
Weight ^{dd}		X			X			X	
Complete physical examination ^f								X	
Limited physical examination ^{g, dd}		X	X	X	X	X	X		
ECOG Performance Status ^{dd}		X			X			X	
ECG ^{h, dd}		Perform as clinically indicated.							
Hematology ⁱ		X ^{j, k}	X ^j	X ^j	X ^j	X ^j	X ^j	X	
Chemistry ^l		X ^{j, k}			X ^j			X	
CA19-9		X			X			X	
Pregnancy test ^m		X ^{j, k}			X ^j			X	X ^m
Urinalysis ⁿ		X ^o		X ^o	X ^o		X ^o	X	
Plasma and serum samples for biomarkers ^p		X		X	X ^p			X ^p	
PBMC sample for biomarkers ^q		X			X ^q				

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

Assessment/Procedure	Stage 1 Screening (see Appendix 7)	Treatment Cycles (28-Day Cycles) ^a						Stage 2 Screening (see Appendix 7) ^c or Treat. Discon. ^d	Follow- Up ^d
	Days –28 to –1	Cycle 1 ^b			Cycles ≥2				
		Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)		Every 3 Months
Blood sample for RBR (optional) ^r	See Appendix 7.	x							
Tumor biopsy		x ^s							
Tumor biopsy (optional)		x ^t							
Tumor response assessments		Any time after treatment initiation per investigator discretion ^{u, v, w}							
Concomitant medications ^x		x	x	x	x	x	x	x	
Adverse events ^y		x	x	x	x	x	x	x ^y	x ^y
Paclitaxel administration ^{z, aa}		x	x	x	x	x	x		
Ramucirumab administration ^{aa, bb}		x		x	x		x		
Survival follow-up and anti-cancer treatment								x ^{cc}	

2L=second-line; App.=Appendix; CT=computed tomography; Discon.=Discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Treat.=Treatment.

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 It is recommended that treatment be initiated no later than 7 days after randomization.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

- ^c Patients who experience disease progression per RECIST v1.1 and patients who experience unacceptable toxicity will be given the option of receiving a different treatment combination during Stage 2 of the study (provided Stage 2 is open for enrollment; see Section A8-1.1.3) and will undergo screening assessments to determine eligibility (see Appendix 7). Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Written informed consent must be obtained before performing screening evaluations for Stage 2, except as noted in footnote "w" below.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which disease progression is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments after completing the treatment discontinuation visit.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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. 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 carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ^m 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 treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ⁿ Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^o If there is a clinically significant positive result, urine will be sent to the laboratory for 24-hour urine protein analysis, microscopy, and culture. Urinalysis has to be obtained within 72 hours prior to Day 1 and Day 15 of each cycle. Results must be obtained prior to ramucirumab administration.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

- ^p Plasma and serum samples for biomarker analyses will be collected prior to study treatment on Days 1 and 15 of Cycle 1, Day 1 of Cycles 2, 4, and 8, and at the treatment discontinuation visit.
- ^q PBMC samples for biomarker analyses will be collected prior to study treatment on Day 1 of Cycles 1 and 2.
- ^r Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.
- ^s Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or disease progression per RECIST v1.1, if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.
- ^t Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible by the investigator, and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.
- ^u Patients will undergo tumor assessments at baseline, every 8 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non-protocol-specified anti-cancer therapy.
- ^v 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 CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ^w For patients who undergo screening for Stage 2: 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 disease progression per RECIST v1.1 or unacceptable toxicity 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.
- ^x 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 8: Study Details Specific to Ramucirumab + Paclitaxel Control Arm (2L Gastric Cancer Cohort)

- ^y After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events will continue to be reported until 135 days after the last dose of study treatment or until initiation of 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.
- ^z Paclitaxel (80 mg/m²) will be administered by IV infusion over 60 minutes.
- ^{aa} Treatment will continue until unacceptable toxicity or disease progression per RECIST v1.1.
- ^{bb} Ramucirumab (8 mg/kg) will be administered by IV infusion over 60 minutes.
- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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 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 ~20% of patients will be discontinued from the study).
- ^{dd} Assessment may be performed within 24 hours prior to dosing during the treatment period.

Appendix 9

Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

**NOTE: ENROLLMENT IN THE MFOLFOX6 CONTROL ARM WAS
SUSPENDED AS OF JUNE 2018.**

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A9-1 MATERIALS AND METHODS SPECIFIC TO MFOLFOX6 CONTROL ARM

A9-1.1 TREATMENT IN MFOLFOX6 CONTROL ARM

A9-1.1.1 Formulation, Packaging, and Handling

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

A9-1.1.2 Dosage, Administration, and Compliance

The modified FOLFOX6 (mFOLFOX6) regimen (oxaliplatin 100 mg/m² administered concurrently with leucovorin 100 mg/m² by IV infusion over 2 hours on Days 1 and 15, followed by 5-fluorouracil [5-FU] 2400 mg/m² administered by continuous IV infusion over 46 hours on Days 1 and 2 and Days 15 and 16 of every 28-day cycle) at the recommended doses (Kearm et al. 2008; Lee et al. 2010) represents an acceptable 5-FU/platinum combination for patients with gastric or gastroesophageal junction cancer.

Consistent with prior Phase III studies that used the backbone of platinum/5-FU to treat gastric and gastroesophageal junction cancer, the platinum component in this study (oxaliplatin) will be restricted to four 28-days cycles (Cunningham et al. 2010).

The discontinuation of oxaliplatin beyond Cycle 4 (28-day cycles) will occur because the majority of patients with gastric and gastroesophageal junction cancer achieve maximum tumor reduction by Cycle 4, and discontinuation of oxaliplatin will improve the tolerability of continued dosing with maintenance chemotherapy in combination with 5-FU and leucovorin.

Patients in the mFOLFOX6 arm will receive treatment as outlined in [Table A9-1](#) until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). It is recommended that treatment be initiated no later than 7 days after randomization.

Treatment will be administered according to institutional standards in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

Table A9-1 Treatment Regimen for mFOLFOX6 Control Arm

Cycle Length	Dose, Route, and Regimen (Drugs Listed in Order of Administration)
28 days	• Oxaliplatin ^a 100 mg/m² administered concurrently (using a Y-connector) with leucovorin 100 mg/m² by IV infusion over 120 (± 15) minutes on Days 1 and 15 of each cycle • 5-FU 2400 mg/m² administered by continuous IV infusion over 46 hours on Days 1 and 2 and on Days 15 and 16 of each cycle

mFOLFOX6=infusional 5-fluorouracil (5-FU), leucovorin (folic acid), and oxaliplatin.

^a Oxaliplatin treatment will be discontinued after Cycle 4, and patients will continue on leucovorin and 5-FU treatment.

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.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under "special situations" as explained in Section 5.3.5.12. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

A9-1.1.3 Second-Line Treatment

Patients in the mFOLFOX6 control arm who experience disease progression per RECIST v1.1 or unacceptable toxicity will be given the option of enrolling in the 2L Cohort (if open for enrollment), provided they meet eligibility criteria (see Section 4.1).

A9-1.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR MFOLFOX6 CONTROL ARM

Concomitant therapy 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 10 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.

Live, attenuated vaccines (e.g., FluMist[®]) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with 5-FU, and for 6 months after the last dose of 5-FU. For more information on permitted, prohibited, or cautionary therapy, prohibited

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

foods, and other restrictions (as applicable) for the control agents, refer to the local label for each agent.

A9–1.3 CONTRACEPTION REQUIREMENTS FOR MFOLFOX6 CONTROL ARM

Contraception requirements for women and men in the control arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, 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 6 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

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

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male 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 acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for 6 months after the last dose of study treatment. Men must refrain from donating sperm during this same period.

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of study treatment to avoid exposing the embryo.

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 acceptable methods of contraception.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

Male patients should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from therapy with 5-FU and oxaliplatin.

A9-2 ASSESSMENT OF SAFETY FOR MFOLFOX6 CONTROL ARM

A9-2.1 SAFETY PLAN FOR MFOLFOX6 CONTROL ARM

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 control agents 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. An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections 3.1.6 and 3.1.7.

A9-2.1.1 Risks Associated with Control Agents

Risks associated with each control agent can be found in the local prescribing information for that agent. Patients receiving mFOLFOX6 should be advised to avoid prolonged exposure to sunlight because of the risk of photosensitivity with 5-FU.

A9-2.1.2 Management of Patients Who Experience Specific Adverse Events in the mFOLFOX6 Control Arm

Dose modification guidelines are for the management of chemotherapy-specific toxicities. The treating physician may use discretion in modifying the dose modification guidelines described below, 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.

Dose adjustments at the start of each administration (every 14 days) will be based on nadir hematologic counts or the maximum non-hematologic toxicity from the preceding cycle of therapy. After a dose reduction is made, the dose will not be re-escalated during subsequent administrations (see Table A9-2 for chemotherapy dose reduction levels).

Patients who require reductions below two dose levels should be discontinued from that chemotherapy agent.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

Table A9-2 mFOLFOX6 Dose Adjustment

	Oxaliplatin	5-FU Infusion
Starting dose (mg/m ²)	100	2400
–1 dose level (mg/m ²)	75	2000
–2 dose levels (mg/m ²)	50	1600

mFOLFOX6 = infusional 5-fluorouracil (5-FU), leucovorin (folic acid), and oxaliplatin.

A9–2.1.2.1 Modifications for Hematologic Toxicity

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, and febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity. Colony-stimulating factors may be used.

Chemotherapy treatment should not be administered until ANC $\geq 1000/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$.

For Grade 4 neutropenia or febrile neutropenia, Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, or a >2-week dose delay because of prolonged decreased ANC or platelet counts:

- First occurrence: reduce infusional 5-FU and oxaliplatin by one dose level each for subsequent administration.
- Second occurrence: reduce infusional 5-FU and oxaliplatin by an additional dose level each for subsequent administration.
- Third occurrence: discontinue chemotherapy.

For the first occurrence of Grade 3 neutropenia without fever or Grade 3 thrombocytopenia without bleeding, withhold chemotherapy until ANC and platelet counts have recovered to a permissible level and then restart chemotherapy at the initial dose level. If the hematologic toxicity recurs, consideration should be given to reducing the doses of infusional 5-FU and oxaliplatin for subsequent administration.

Chemotherapy should be discontinued if ANC and platelets do not recover to $\geq 1000/\mu\text{L}$ and $\geq 75,000/\mu\text{L}$, respectively, after treatment is delayed by 3 weeks.

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A9–2.1.2.2 Modifications for Oxaliplatin-Induced Neurotoxicity

For neuropathy (sensory, motor, or cranial neuropathy, according to the adverse event grading in [Table A9-3](#)):

- For Grade 1 neuropathy: continue planned treatment.
- For Grade 2 or Grade 3 neuropathy:
 - First occurrence: withhold oxaliplatin until symptoms resolve (for up to 2 weeks) to Grade ≤ 1 and then reduce the dose of oxaliplatin by one dose level.
 - Second occurrence: withhold oxaliplatin until symptoms resolve (for up to 2 weeks) to Grade ≤ 1 and then reduce the dose of oxaliplatin by one dose level.
 - Third occurrence, requirement to reduce oxaliplatin dose below two dose levels or failure to resolve to Grade 1 within 2 weeks: discontinue oxaliplatin.
- For Grade 4 neuropathy, discontinue oxaliplatin therapy.

Table A9-3 Adverse Event Grading for Neuropathy

Grade	Description
1	Asymptomatic; loss of deep tendon reflexes or paresthesia
2	Moderate symptoms; limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

ADL = activities of daily living.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

If pseudo-laryngopharyngeal dysesthesia occurs, subsequent doses of oxaliplatin may be administered as a 6-hour infusion, and leucovorin should be administered during the last 2 hours of the infusion.

A9–2.1.2.3 Modifications for Other Non-Hematologic Toxicity

For other Grade 3 or 4 or persistent intolerable Grade 2 non-hematologic toxicity (e.g., fatigue, diarrhea, hand-foot syndrome, hepatic toxicity, respiratory symptoms, etc.) attributed to chemotherapy, chemotherapy can be withheld until adverse event resolution (Grade ≤ 1), for up to a maximum of 4 weeks:

- First occurrence: reduce the 5-FU infusional dose by one dose level, and/or reduce oxaliplatin by one dose level for subsequent administrations.
- Second occurrence of Grade 4 toxicity: discontinue the chemotherapy regimen.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

- Second and third occurrences of Grade 3 or intolerable Grade 2 toxicity: if indicated, reduce the 5-FU infusional dose by one dose level and/or reduce oxaliplatin by one dose level for subsequent administrations.
- Fourth occurrence of Grade 3 or intolerable Grade 2 toxicity: discontinue the chemotherapy regimen.

No dose reduction should be made for Grade 1 or 2 toxicities, except for those considered intolerable to the patient because of prolonged duration or adverse effects on quality of life.

Any contraindications and special warnings and precautions for the use of mFOLFOX6 should be observed.

A9–2.1.2.4 Modifications for Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient recovers completely or to Grade 1 toxicity for up to a maximum of 4 weeks.

A9–2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR MFOLFOX6 CONTROL ARM (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 the control arm include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A9–2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN MFOLFOX6 CONTROL ARM

A9–2.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

last dose of study treatment. A 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/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.

A9–2.3.2 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 6 months after the last dose of study treatment. A 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. 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 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 when updated information on the course and outcome of the pregnancy becomes available. 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 investigator and/or obstetrician.

A9–2.3.3 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

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

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.

A9–2.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/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).

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A9-3 SCHEDULE OF ACTIVITIES FOR MFOLFOX6 CONTROL ARM

Table A9-4 Schedule of Activities for mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

Assessment/Procedure	Stage 1 Screening (see Appendix 7)	Treatment Cycles (28-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^e
		Cycle 1 ^b		Cycles ≥ 2			
		Days –28 to –1	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		Day 15 (± 3 days)
Molecular profile of gastric cancer (if available)	See Appendix 7.	Whenever updated information becomes available					
Vital signs ^d		x	x	x	x	x	
Weight ^z		x	x	x	x	x	
Complete physical examination ^e						x	
Limited physical examination ^{f, z}		x	x	x	x		
ECOG Performance Status ^z		x		x		x	
ECG ^{g, z}		Perform as clinically indicated.					
Hematology ^h		x ^{i, j}	x ⁱ	x ⁱ	x ⁱ	x	
Chemistry ^k		x ^{i, j}	x ⁱ	x ⁱ	x ⁱ	x	
CA19-9		x		x		x	
Pregnancy test ^l		x ^{i, j}		x ⁱ		x	x ^l
Urinalysis ^m		Perform as clinically indicated ⁱ .					
Plasma and serum sample for biomarkers ⁿ		x	x	x ⁿ		x	
PBMC sample for biomarkers ^o		x		x ^o			

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Assessment/Procedure	Stage 1 Screening (see Appendix 7)	Treatment Cycles (28-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^e
		Cycle 1 ^b		Cycles ≥ 2			
		Days –28 to –1	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		Day 15 (± 3 days)
Blood sample for RBR (optional) ^p	See Appendix 7.	x					
Tumor biopsy		x ^q					
Tumor biopsy (optional)		x ^r					
Tumor response assessments		x ^{s, t}					
Concomitant medications ^u		x	x	x	x	x	
Adverse events ^v		x	x	x	x	x ^v	x ^v
mFOLFOX6 administration ^{w, x}		x	x	x	x		
Survival follow-up and anti-cancer treatment							x ^y

1L = first-line; App. = Appendix; CT = computed tomography; Discon. = Discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; mFOLFOX6 = infusional 5-fluorouracil (5-FU), leucovorin (folic acid), and oxaliplatin; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Treat. = Treatment.

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 It is recommended that treatment be initiated no later than 7 days after randomization.

^c Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which disease progression is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments every 3 months.

^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

- ^e Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording
- ^h Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ⁱ Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.
- ^j If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^k Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.
- ^l All women of childbearing potential will have urine or serum pregnancy tests performed at specified subsequent visits during treatment and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^m Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. If urinary protein is > 1+ on dipstick and there is no explanation for the positive dipstick result (e.g., menses), a 24-hour urine collection is required to check total urinary protein.
- ⁿ Plasma and serum samples for biomarker analyses will be collected prior to study treatment on Days 1 and 15 of Cycle 1 and on Day 1 of Cycles 2, 4, and 8, and at the treatment discontinuation visit.
- ^o PBMC samples for biomarker analyses will be collected prior to study treatment on Day 1 of Cycles 1 and 2.
- ^p Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.
- ^q Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or disease progression per RECIST v1.1, if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.
- ^r Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible by the investigator, and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.
- ^s Patients will undergo tumor assessments at baseline, every 8 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non-protocol-specified anti-cancer therapy.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

- ^t 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 CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ^u 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.
- ^v After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events will continue to be reported until 135 days after the last dose of study treatment or until initiation of 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.
- ^w Oxaliplatin (100 mg/m²) will be administered concurrently (using a Y-connector) with leucovorin (100 mg/m²) by IV infusion over 120 (± 15) minutes, followed by 5-FU (2400 mg/m²) administered by continuous IV infusion over 46 hours. Oxaliplatin treatment will be discontinued after Cycle 4. After Cycle 4, patients will continue to be treated with maintenance chemotherapy with leucovorin and 5-FU.
- ^x Treatment will continue until unacceptable toxicity or disease progression per RECIST v1.1.
- ^y After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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 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 ~20% of patients will be discontinued from the study).
- ^z Assessment may be performed within 24 hours prior to dosing during the treatment period.

Appendix 9: Study Details Specific to mFOLFOX6 Control Arm (1L Gastric Cancer Cohort)

A9-4 REFERENCES

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Keam B, Im S-I, Han S-W, et al. mFOLFOX6 chemotherapy in advanced gastric cancer: results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. *BMC Cancer* 2008;8:48.

Lee HH, Hur H, Kim SH, et al. Outcomes of modified FOLFOX-6 as first line treatment in patients with advanced gastric cancer in a single institution; retrospective analysis. *Cancer Res Treat* 2010;42:18–23.

Appendix 10

Placeholder for Future Arm

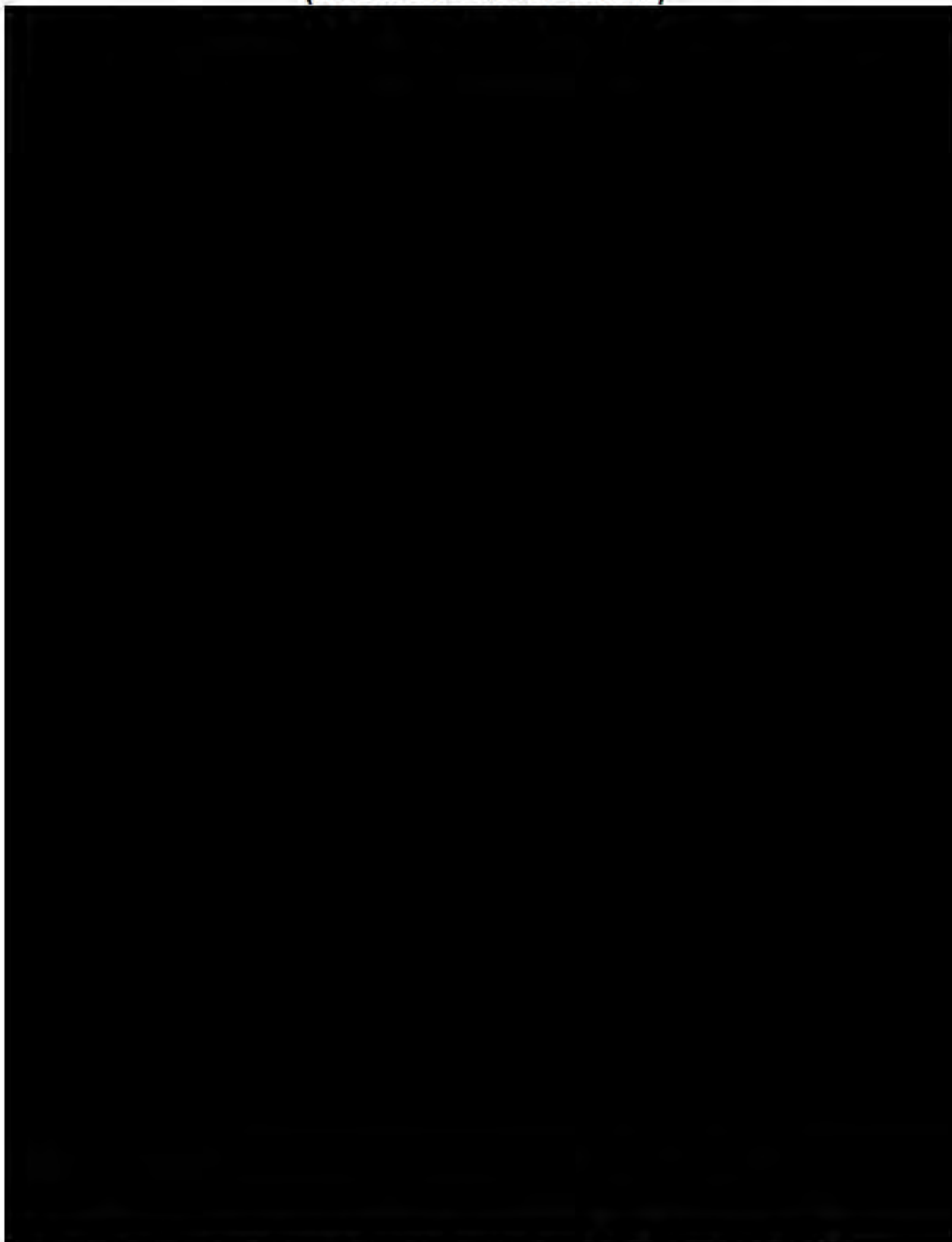
The atezolizumab plus RO6874281 arm has been removed, with no patients enrolled in that arm, and the content of Appendix 10 (previously Appendix 9, entitled "Study Details Specific to Atezo+RO6874281 Arm [2L Gastric Cancer Cohort]") has been deleted. Appendix 10 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 11

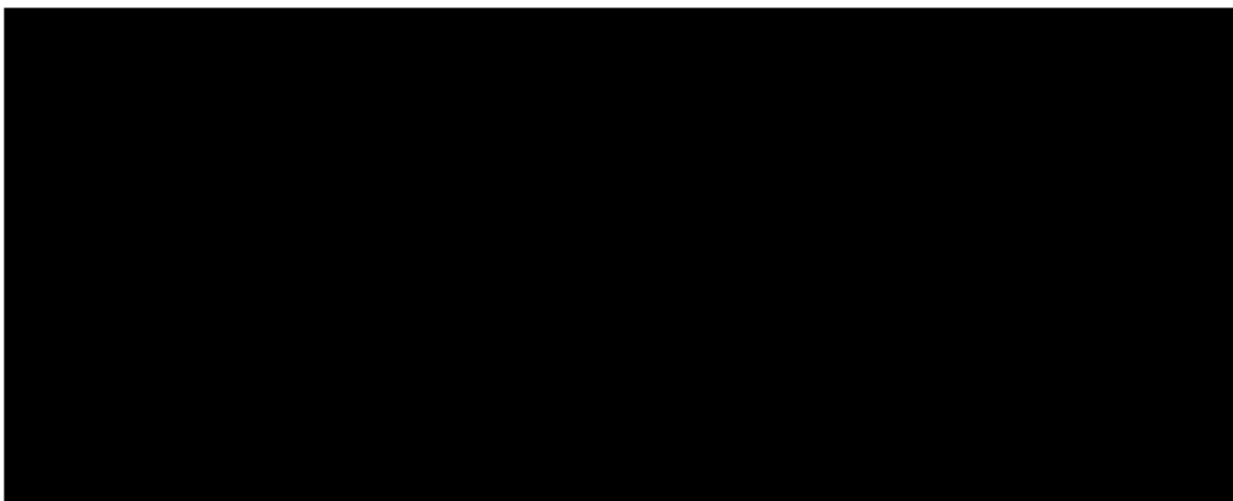
Placeholder for Future Arm

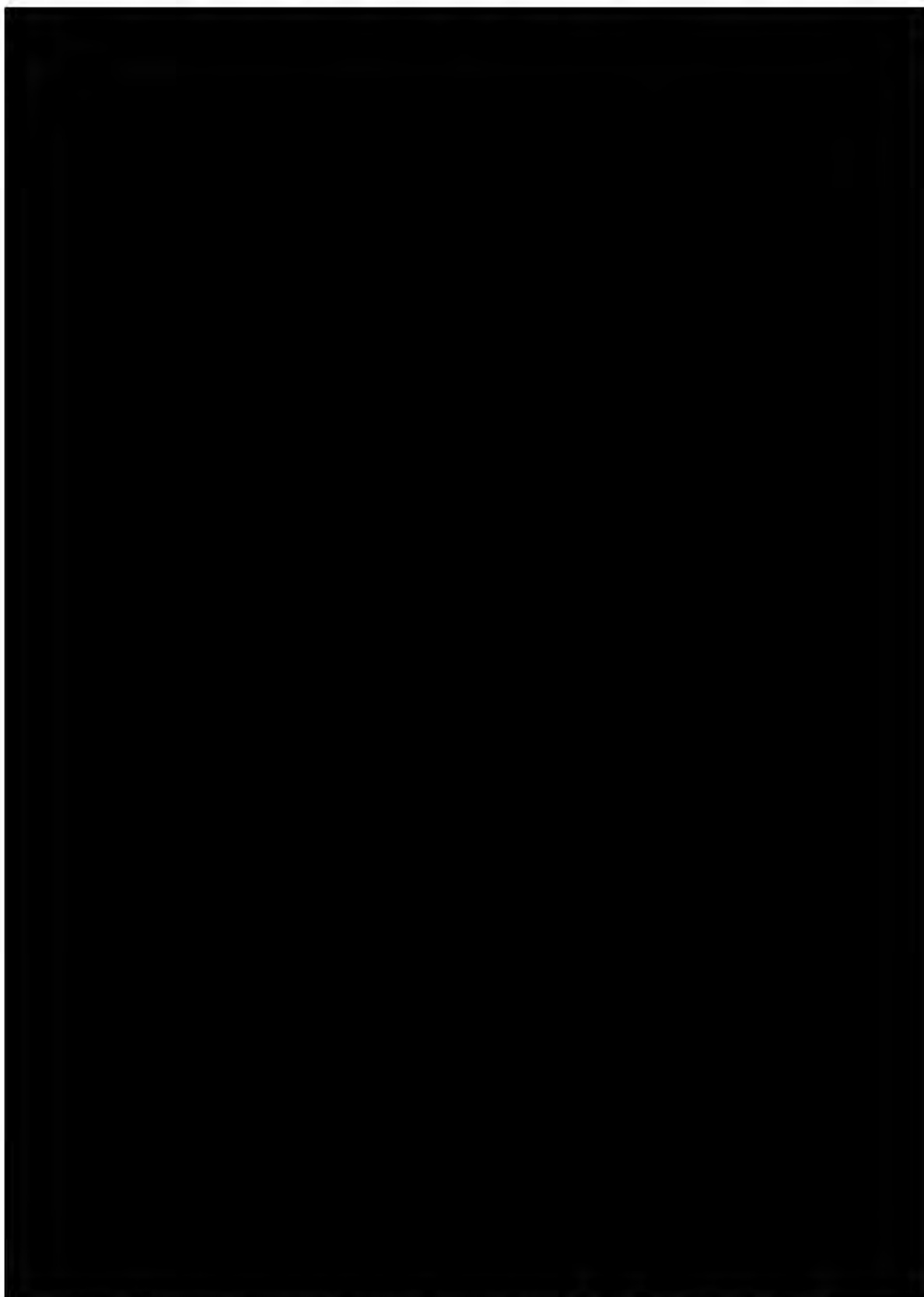
The atezolizumab plus PEGPH20 arm has been removed as all randomized patients have completed treatment and follow-up. The content of Appendix 11 (previously Appendix 10, entitled "Study Details Specific to Atezo + PEGPH20 Arm [2L Gastric Cancer Cohort]") has been deleted. Appendix 11 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 12
Study Details Specific to Atezo + BL-8040 Arm
(2L Gastric Cancer Cohort)

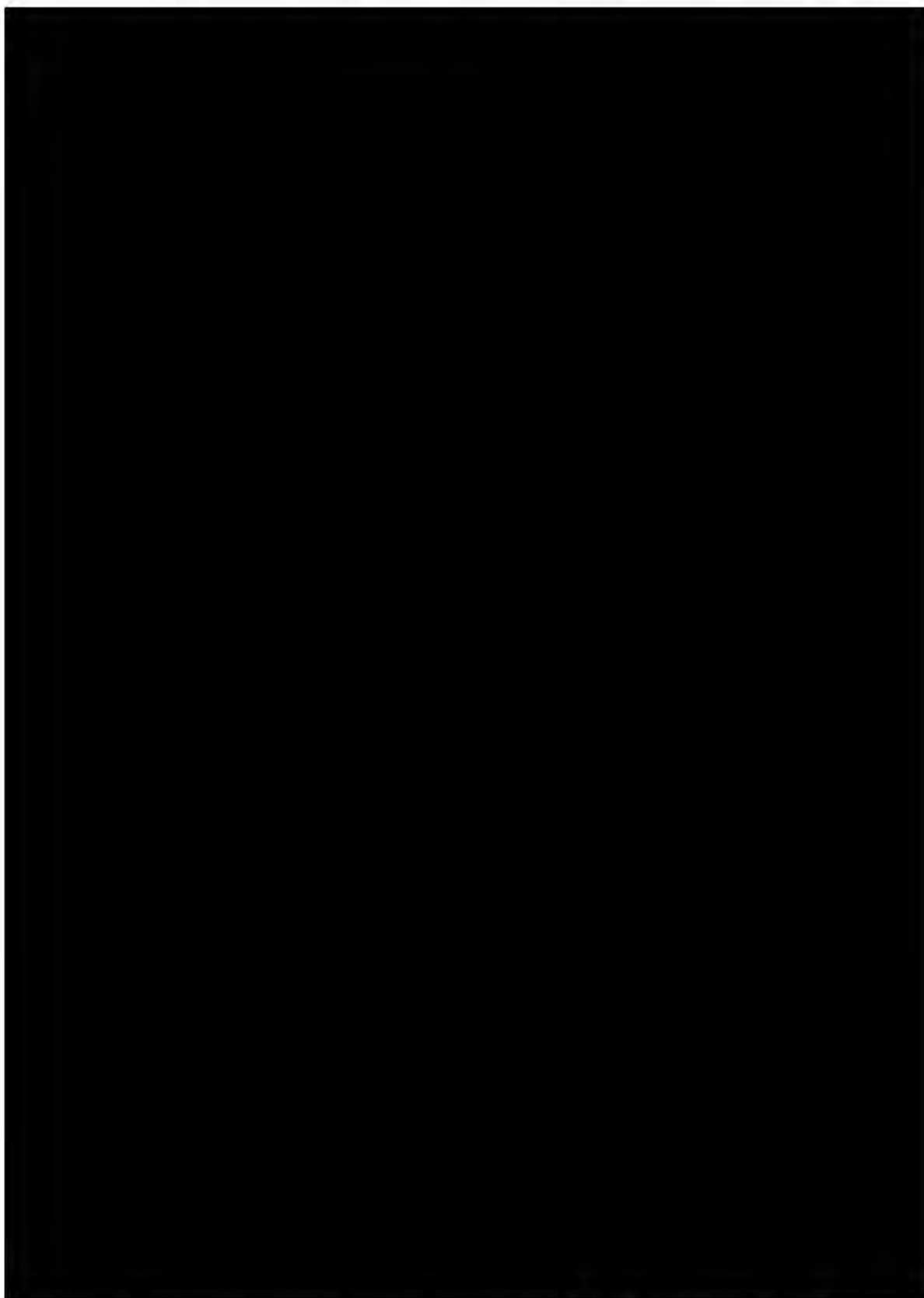


Appendix 12: Study Details Specific to Atezo+BL-8040 Arm (2L Gastric Cancer Cohort)

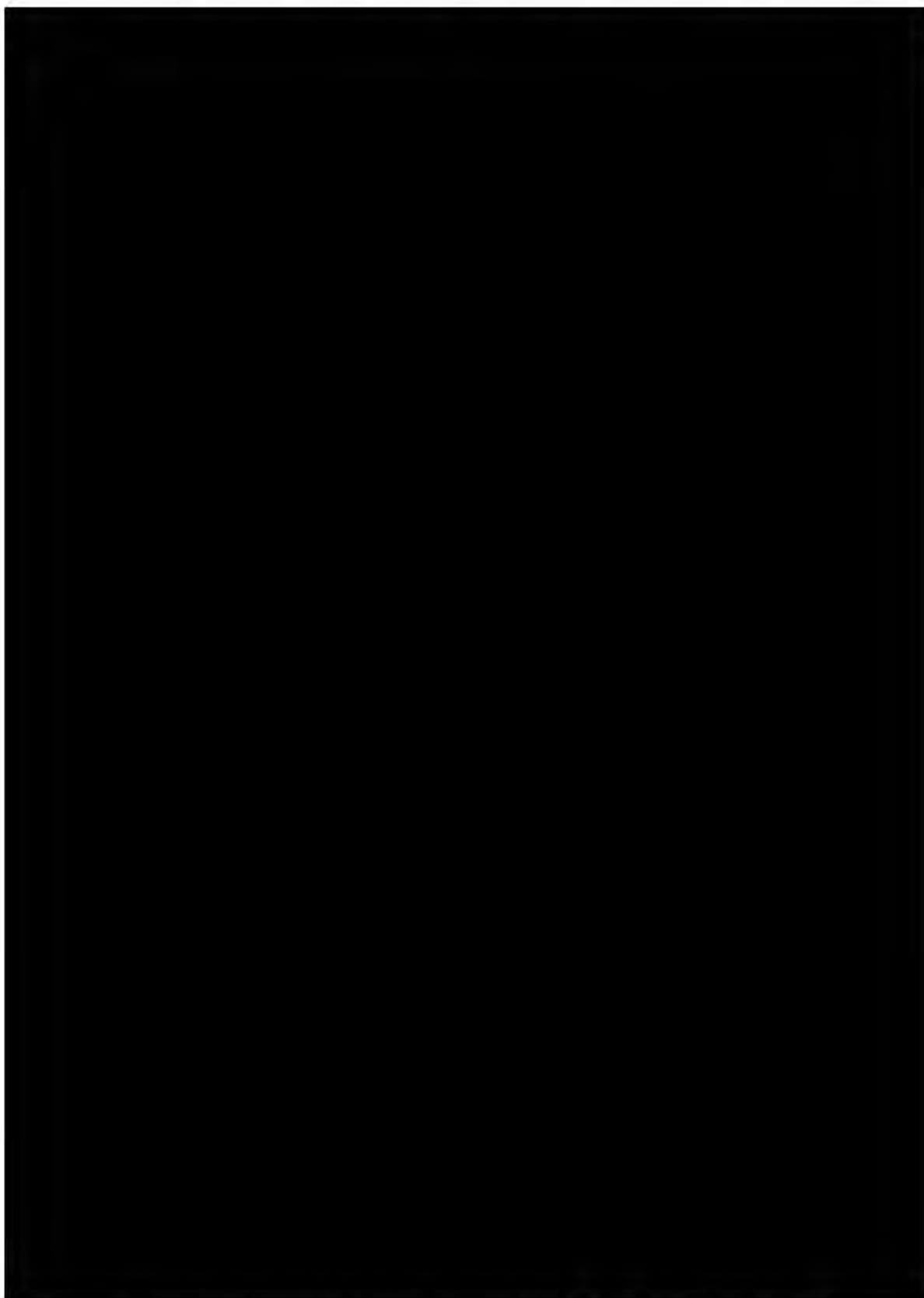




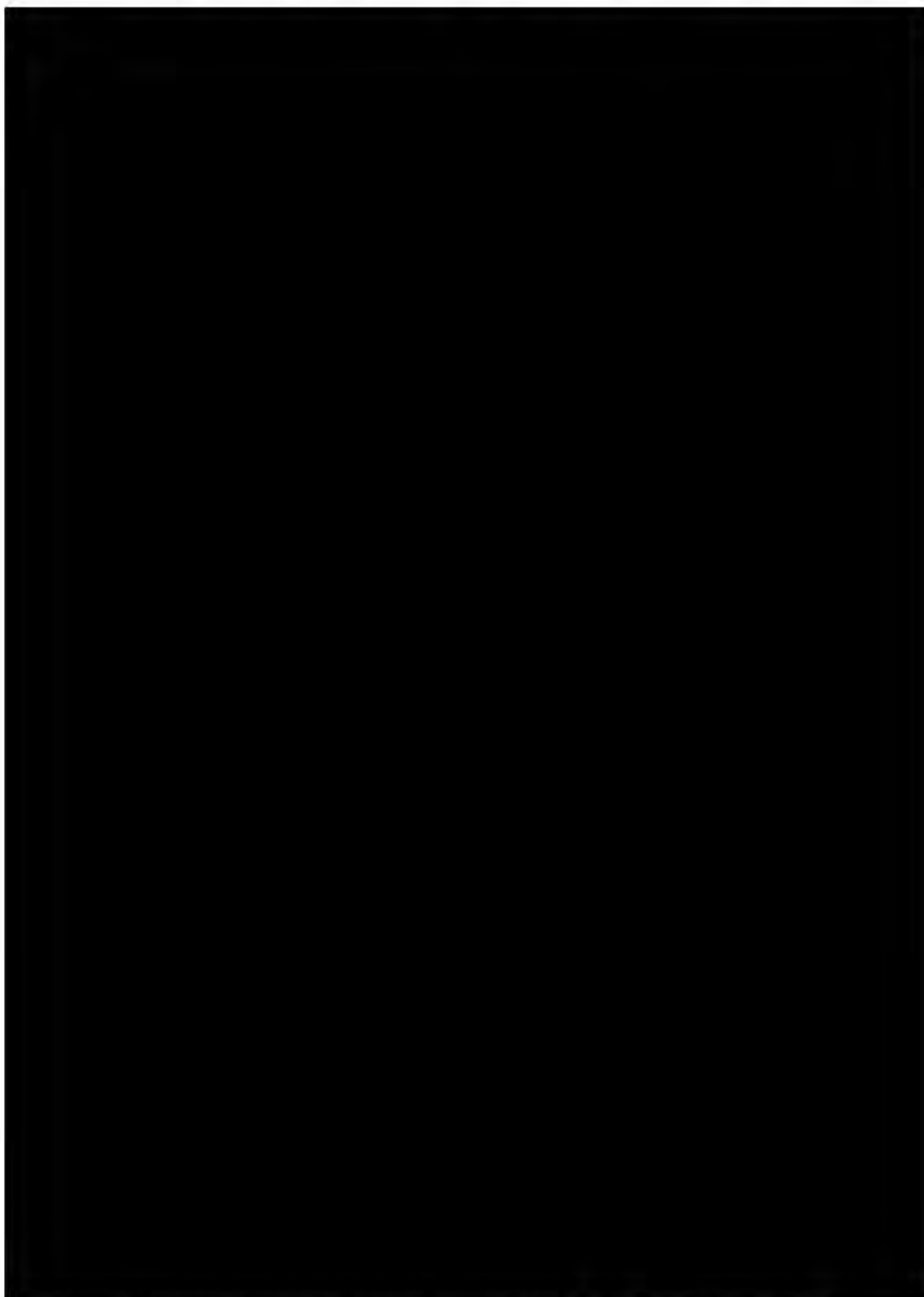
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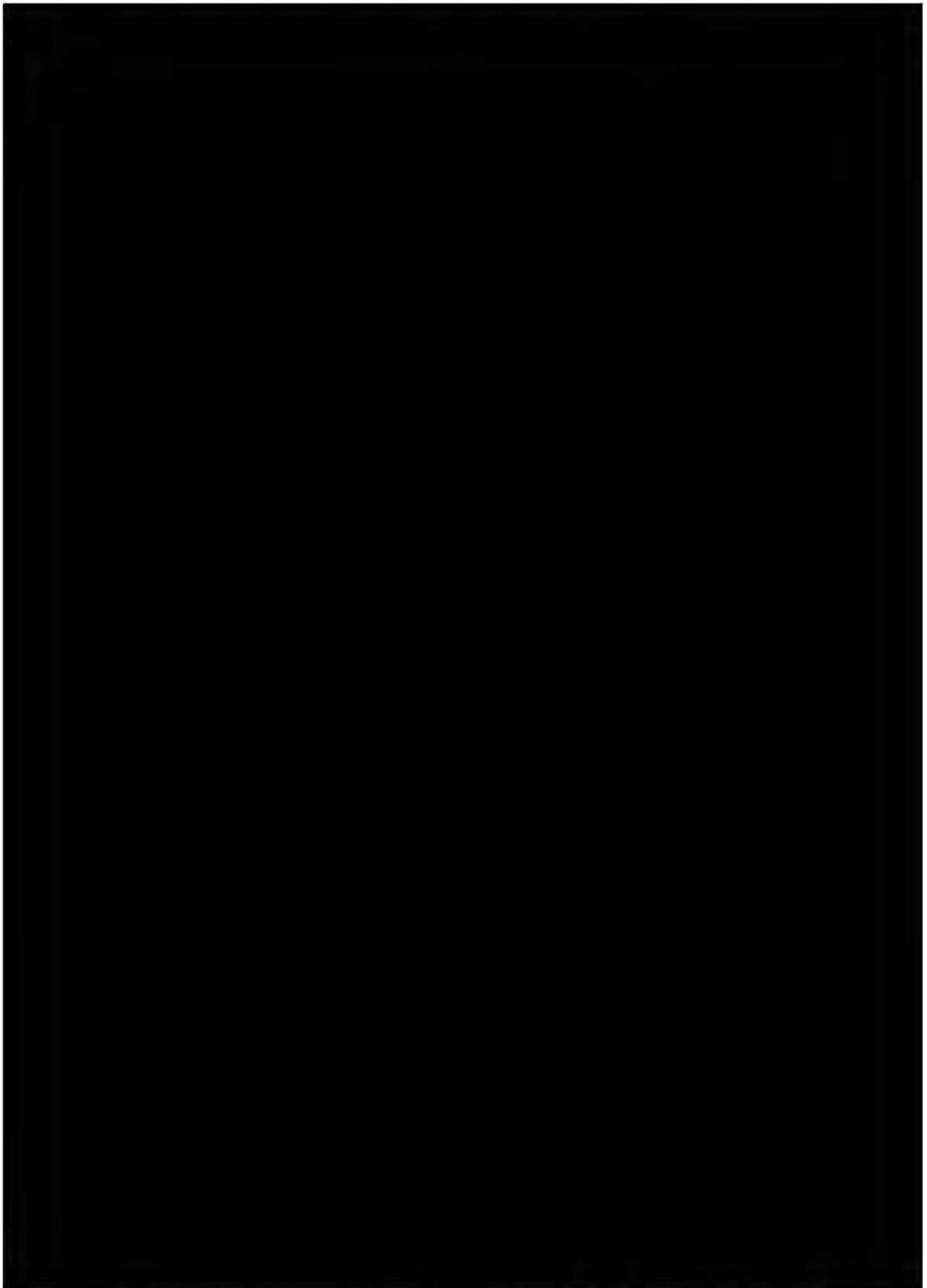
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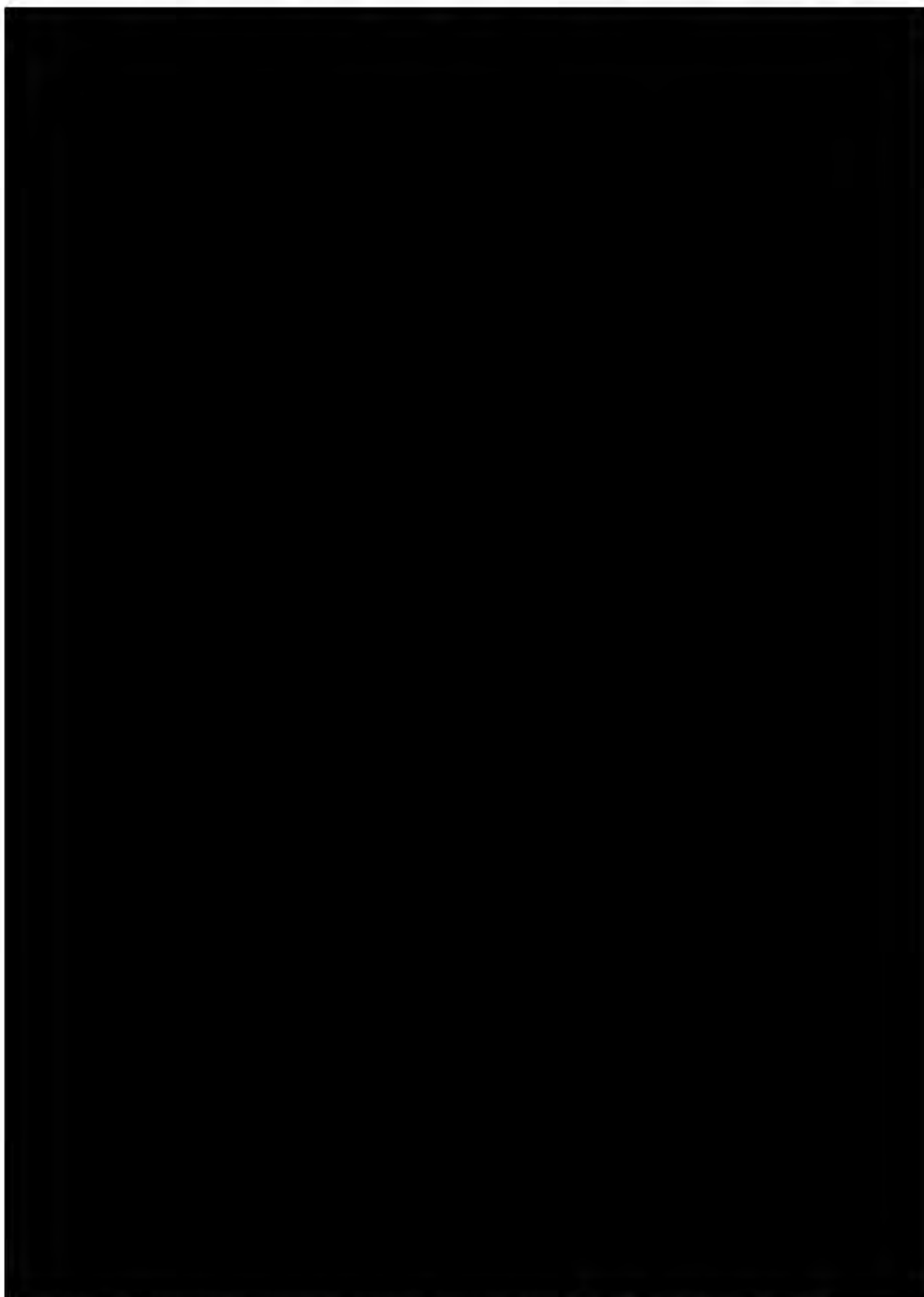
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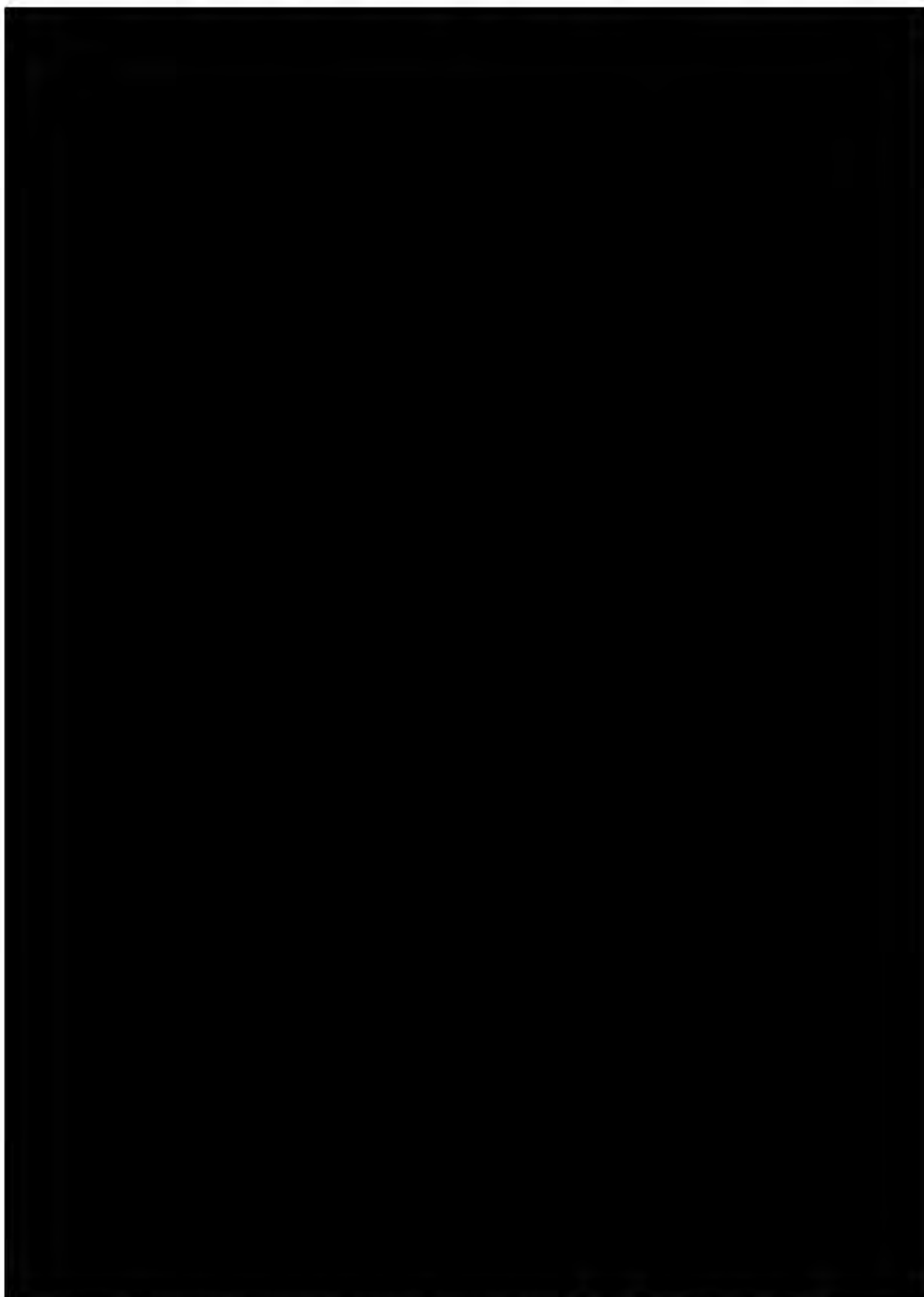
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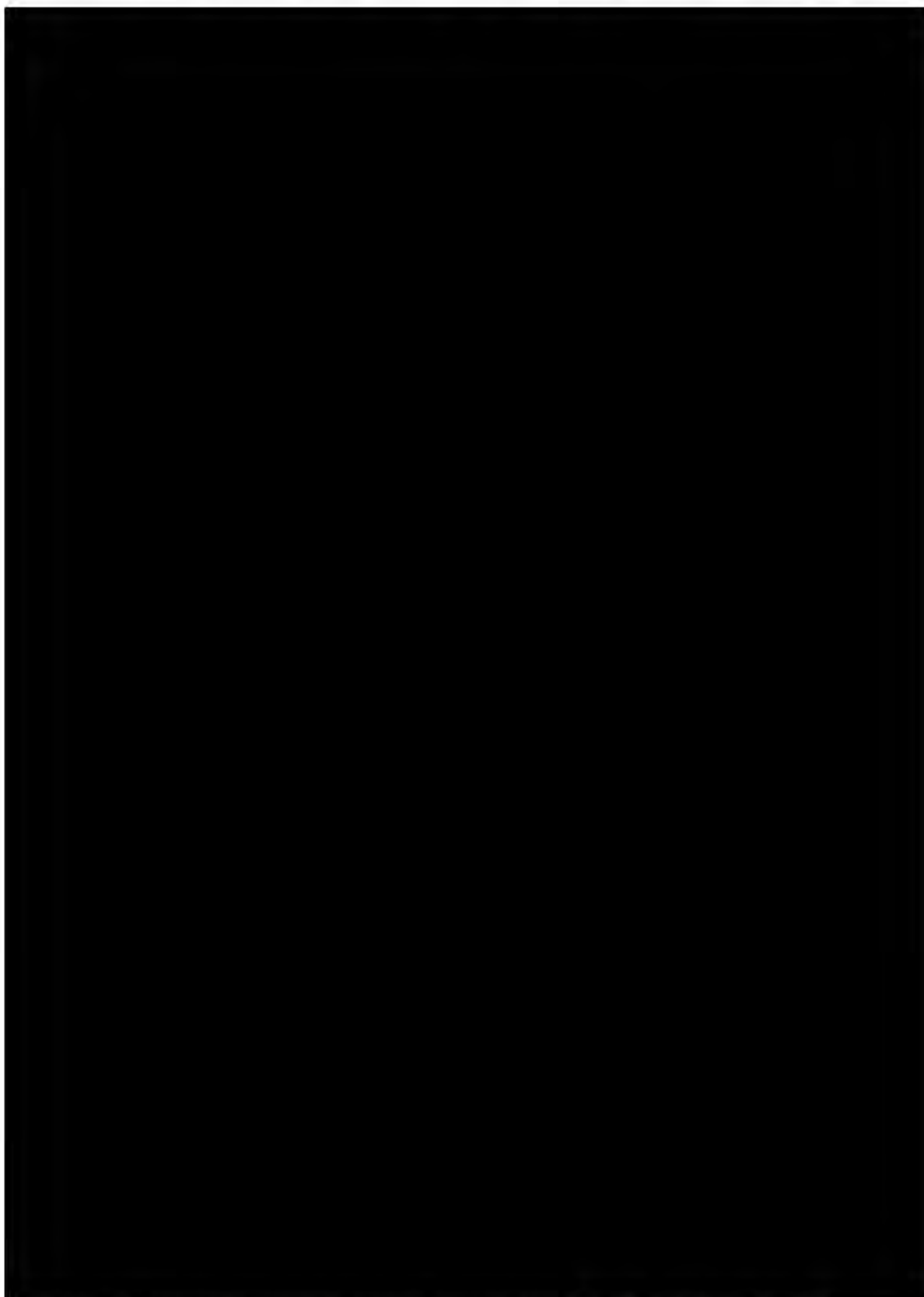
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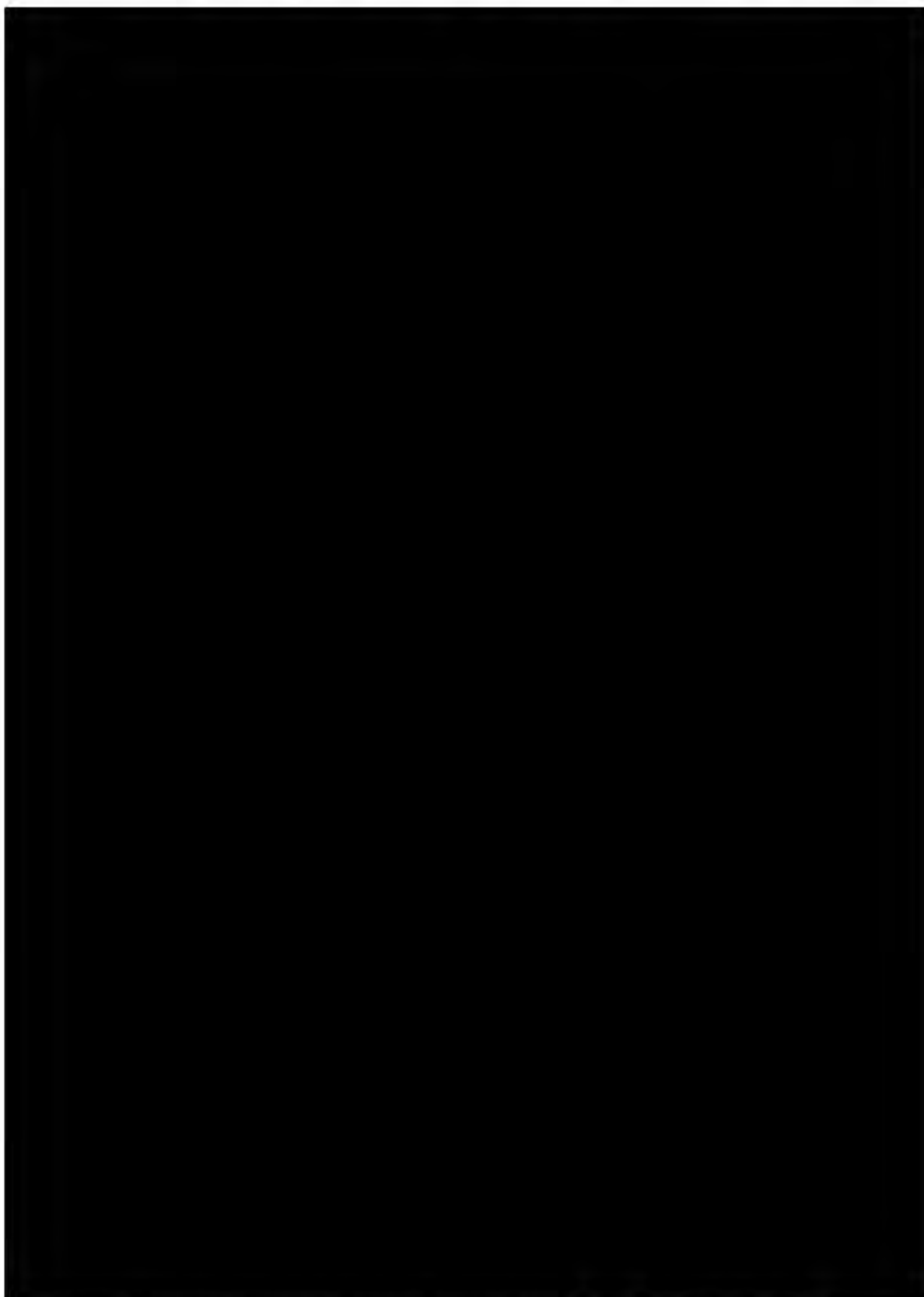
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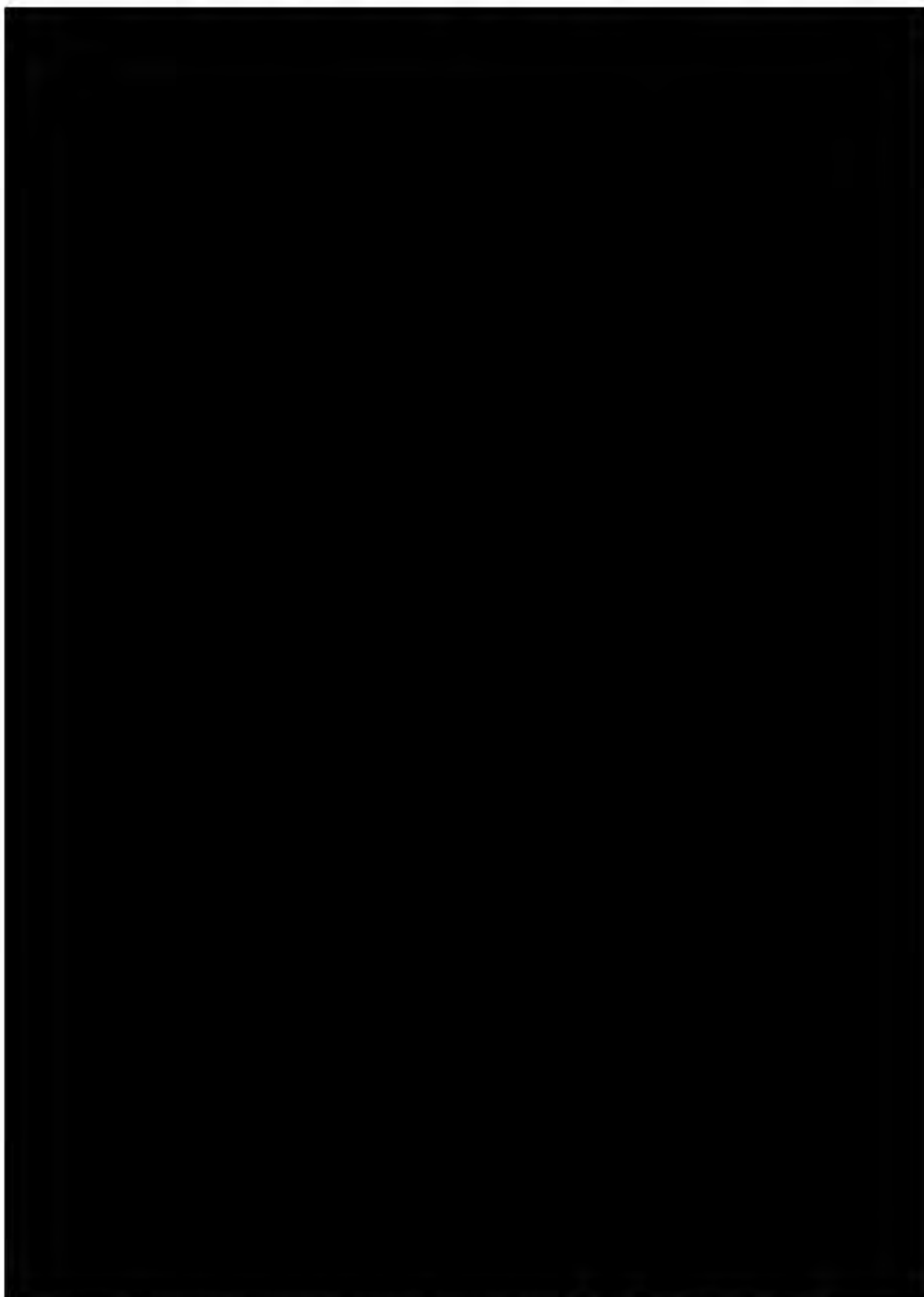
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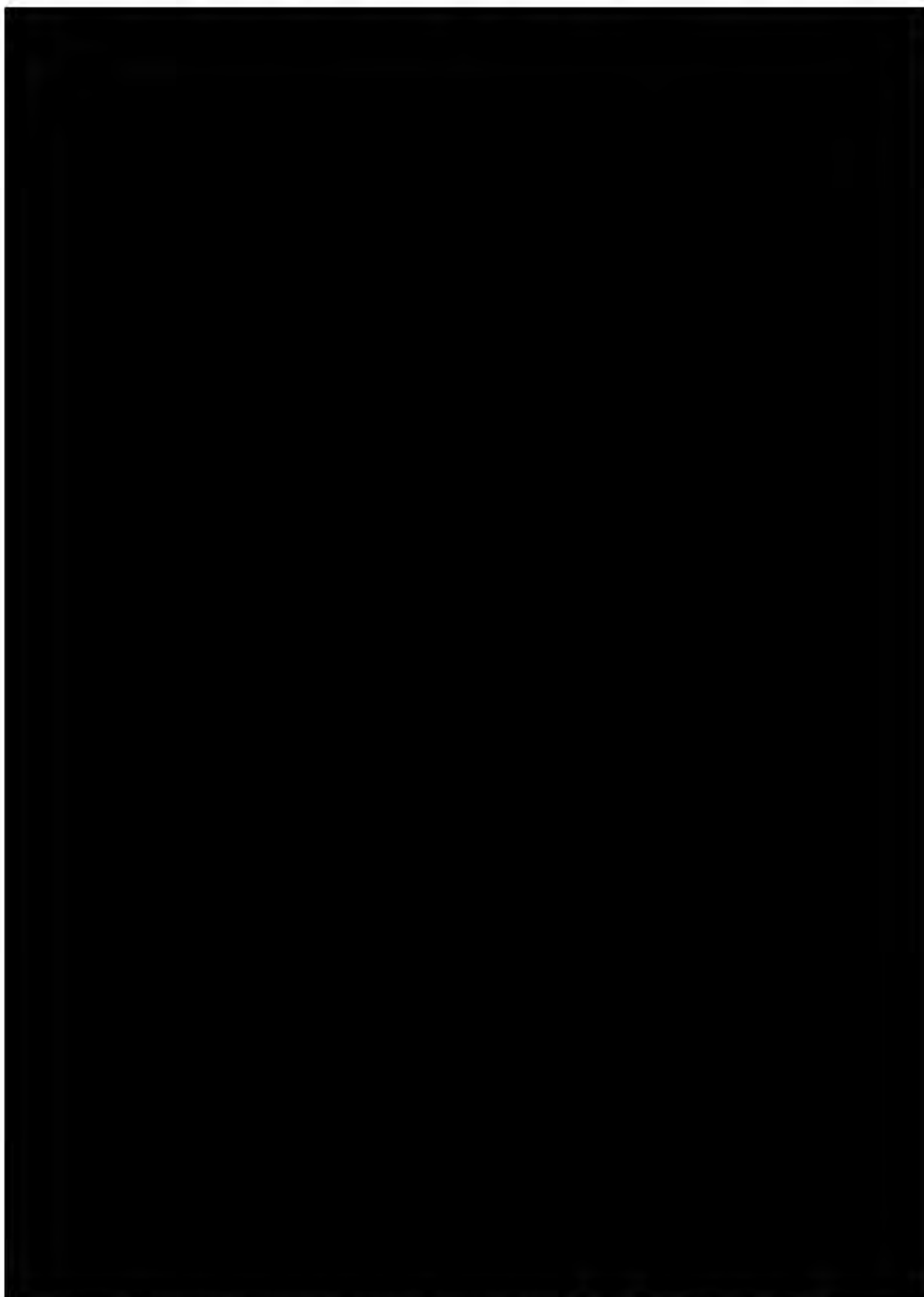
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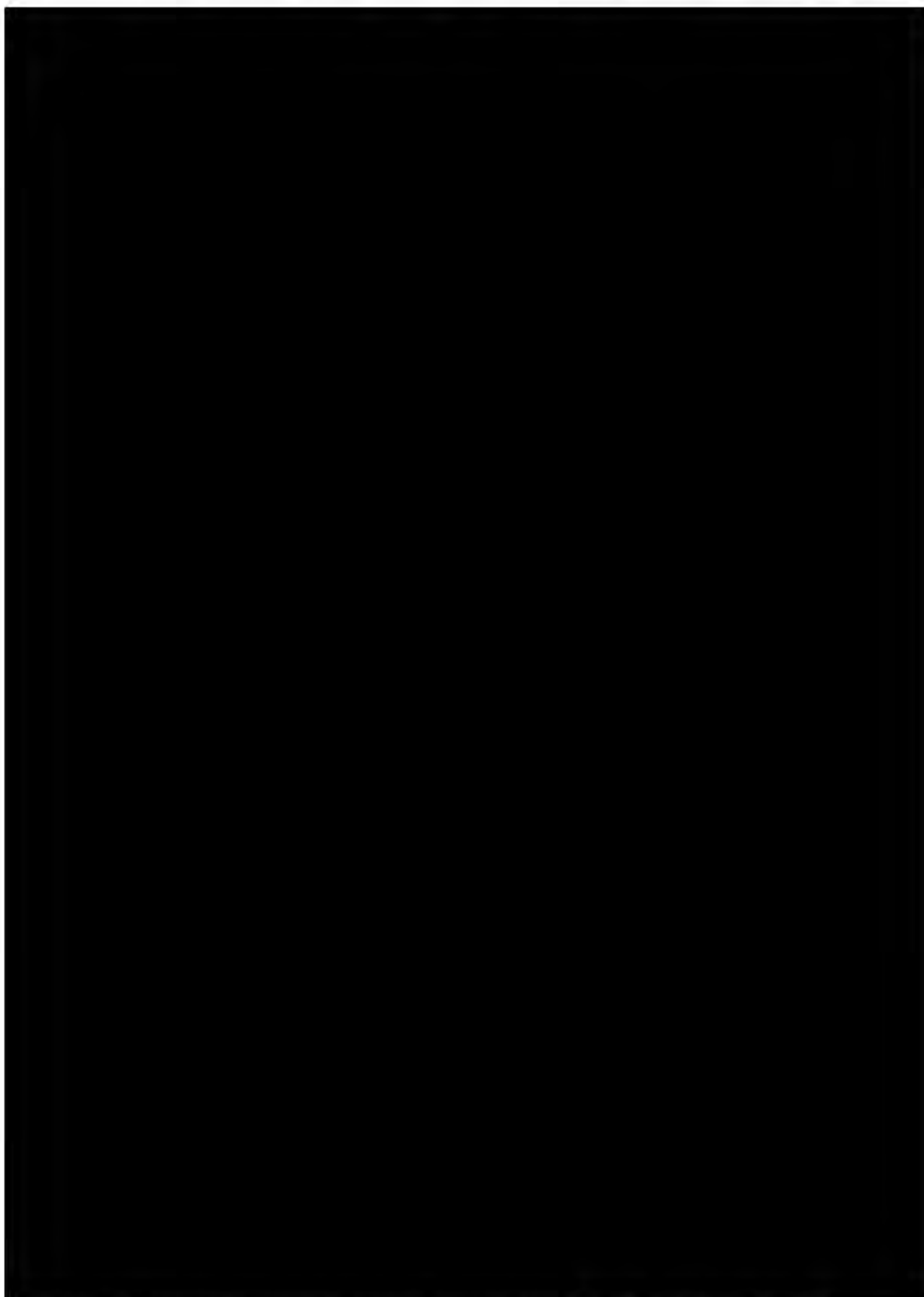
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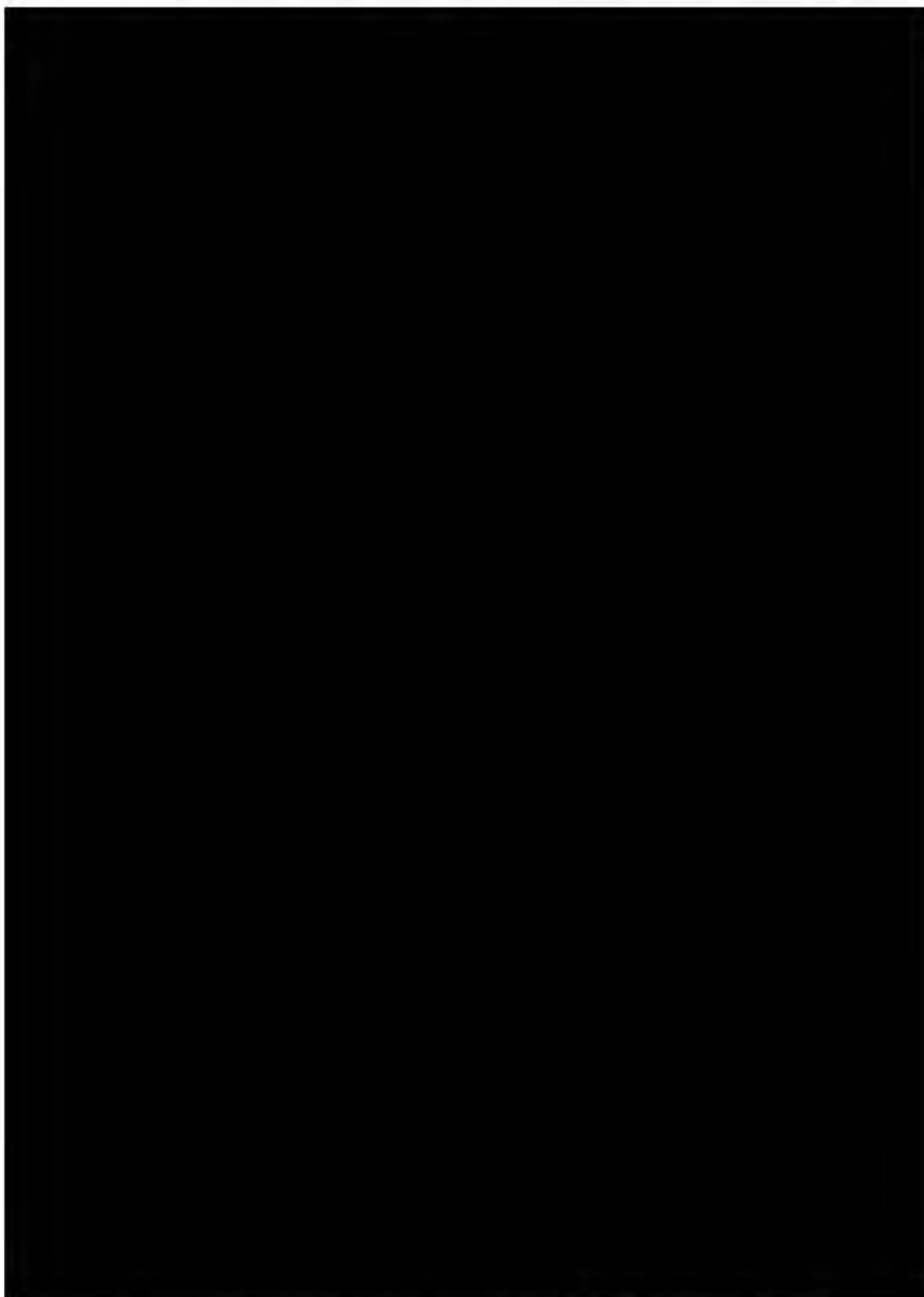
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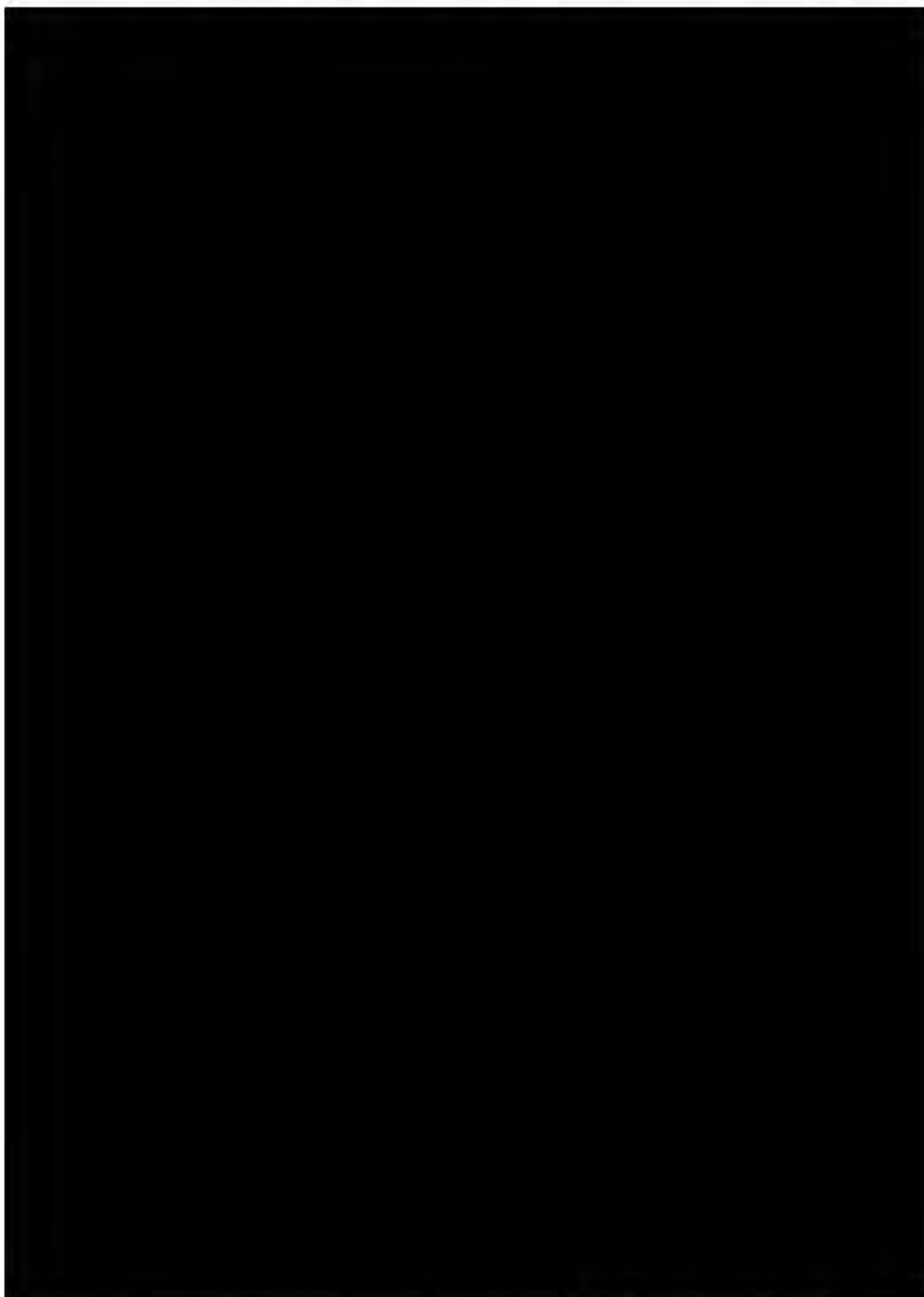


Appendix 12: Study Details Specific to Atezo+BL-8040 Arm (2L Gastric Cancer Cohort)

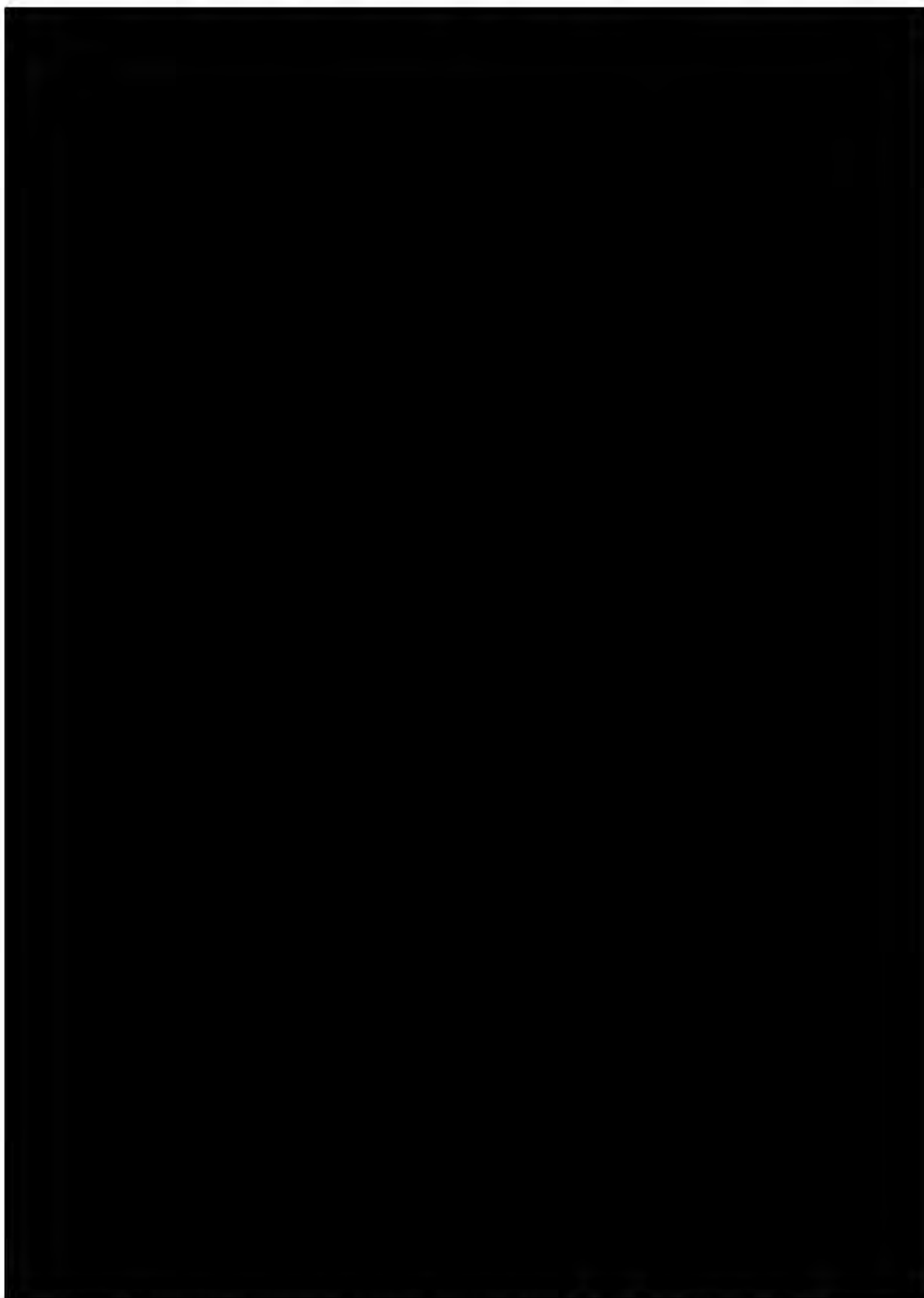


Appendix 12: Study Details Specific to Atezo+BL-8040 Arm (2L Gastric Cancer Cohort)

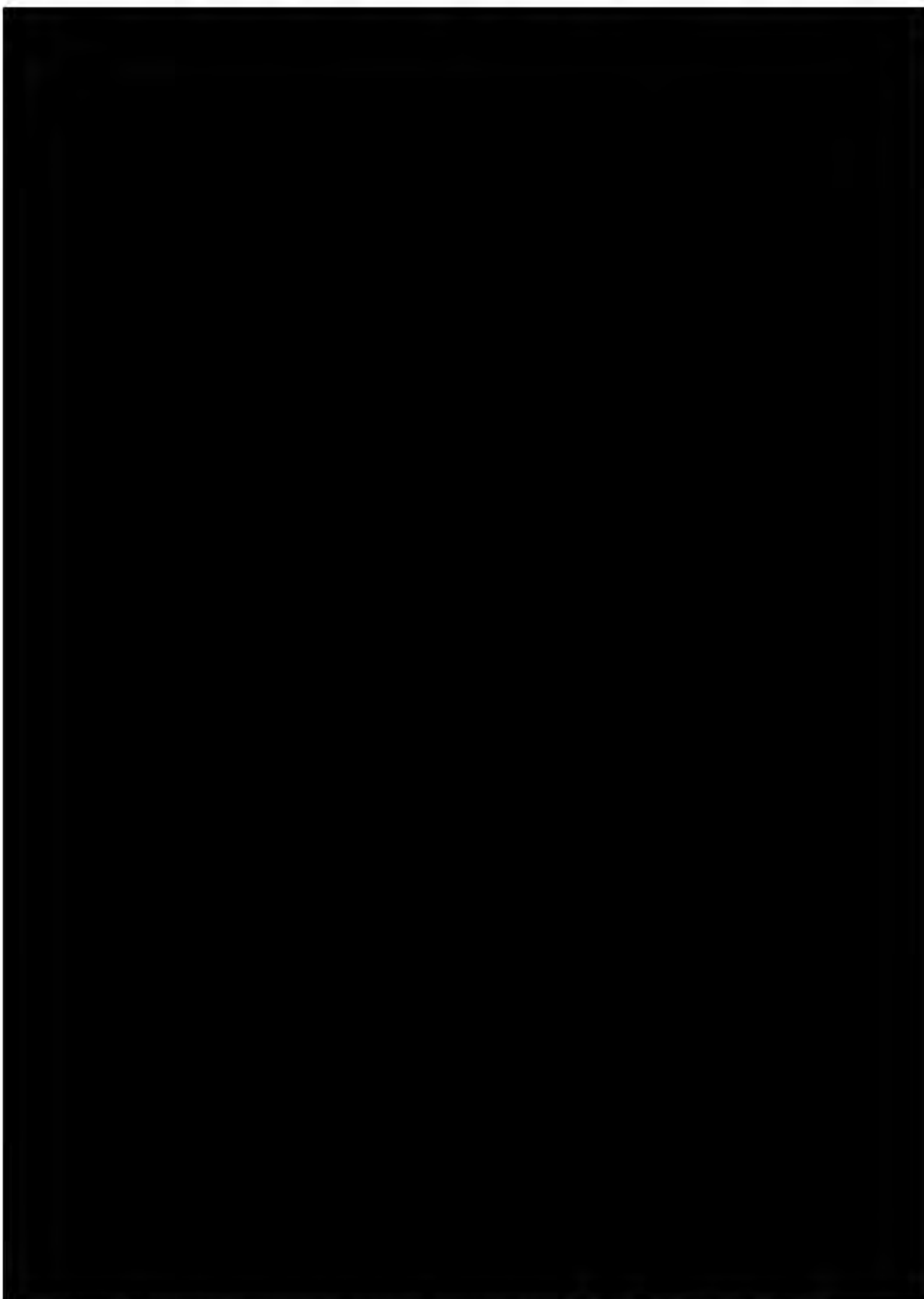




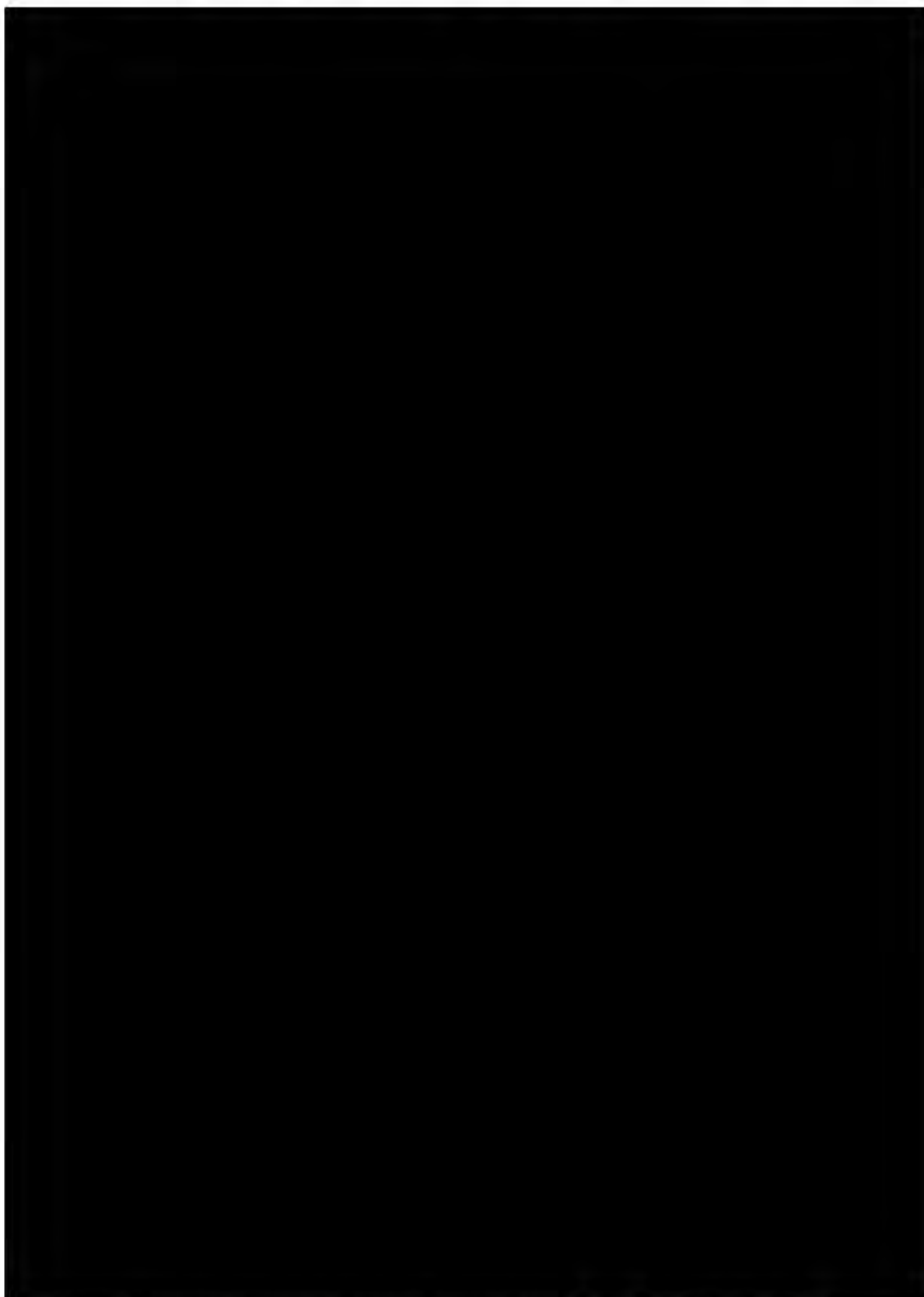
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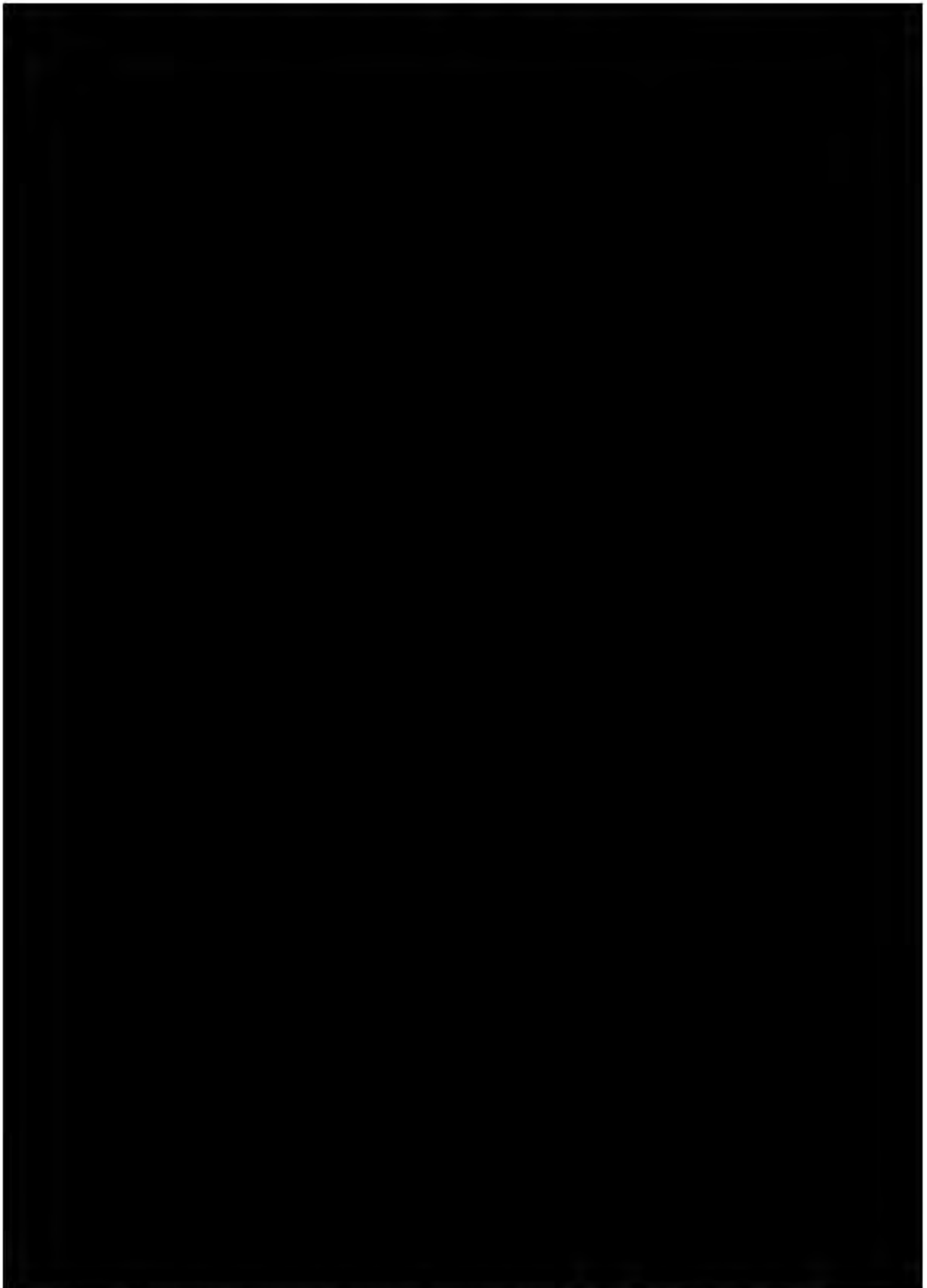
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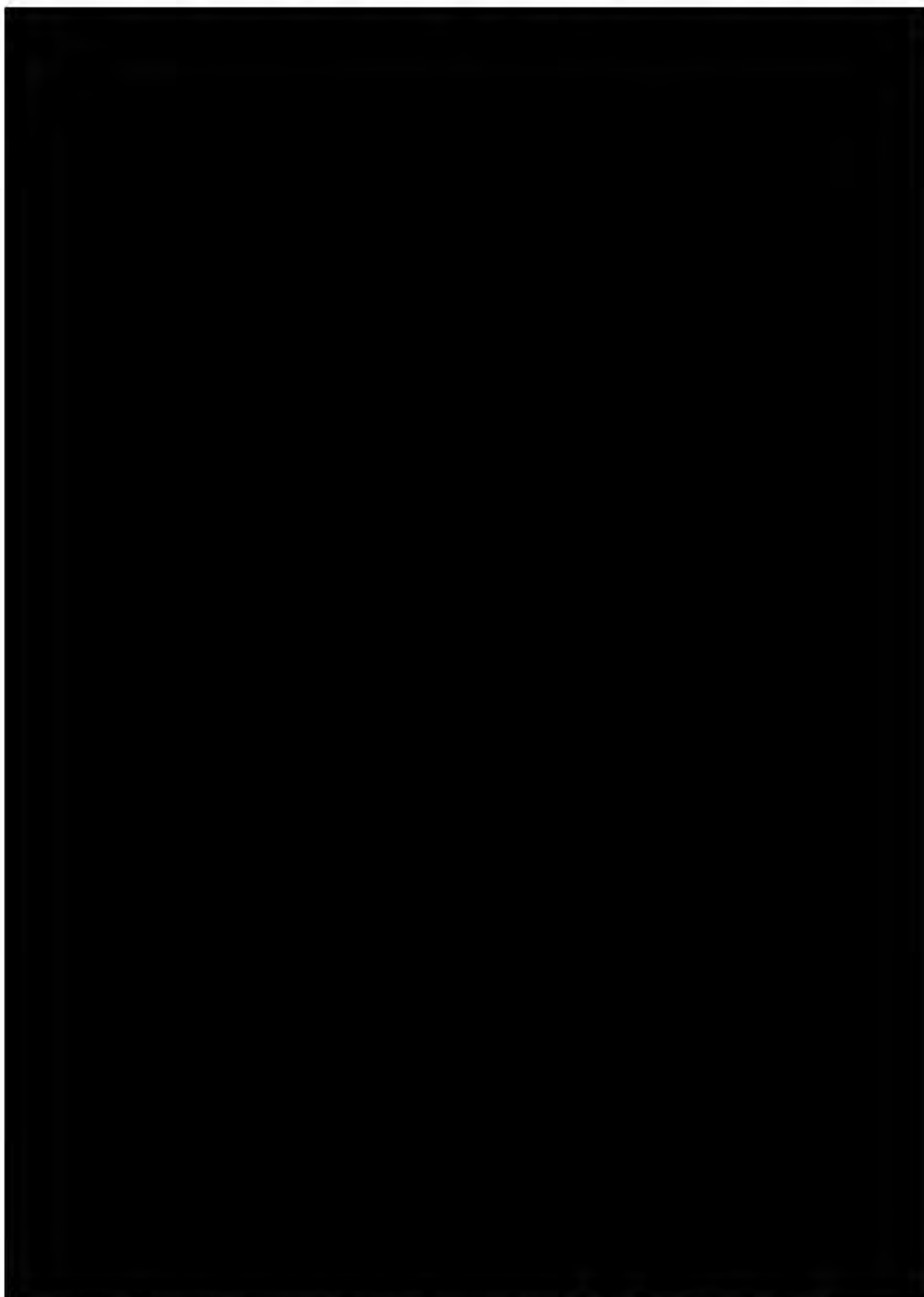


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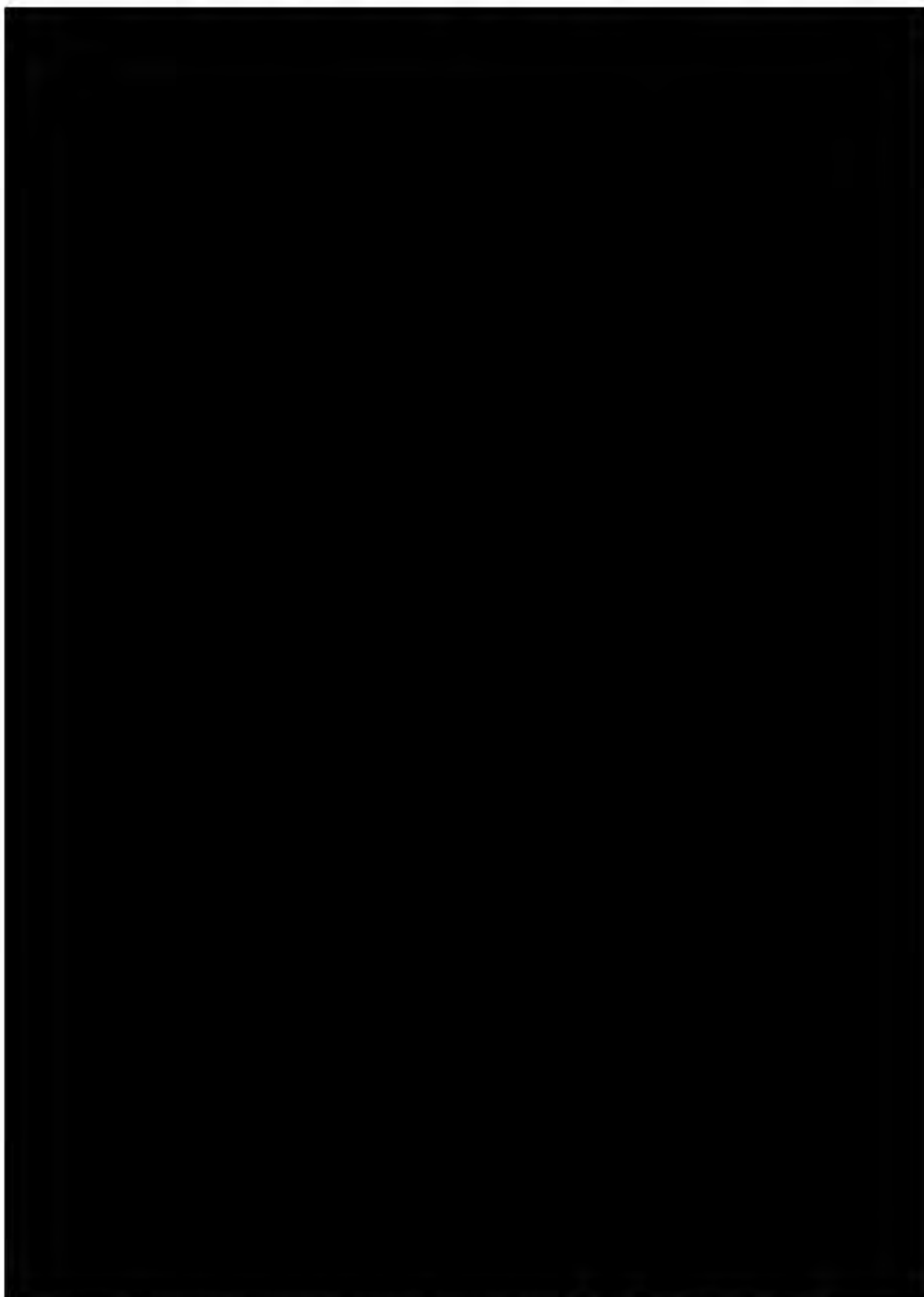


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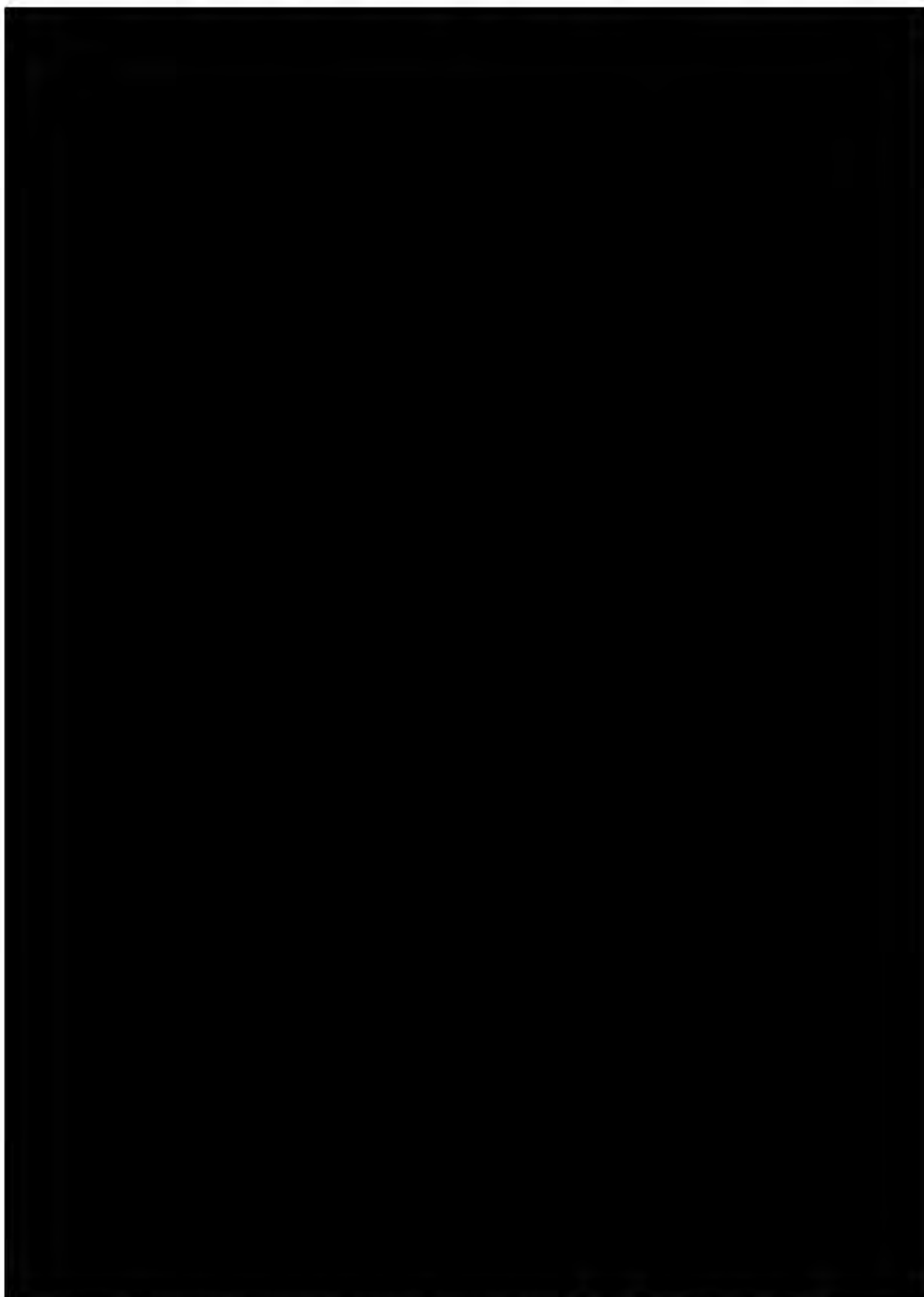




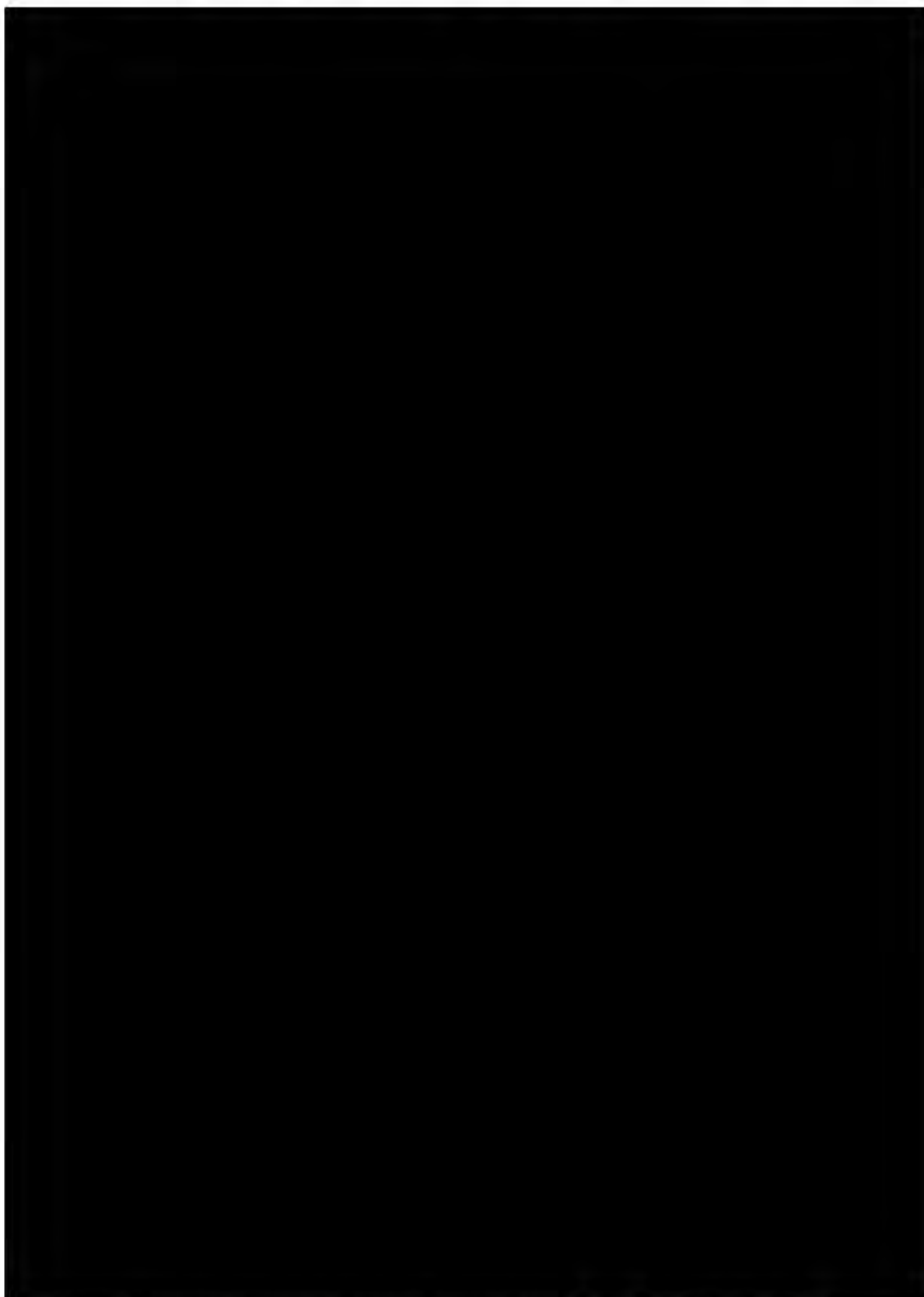
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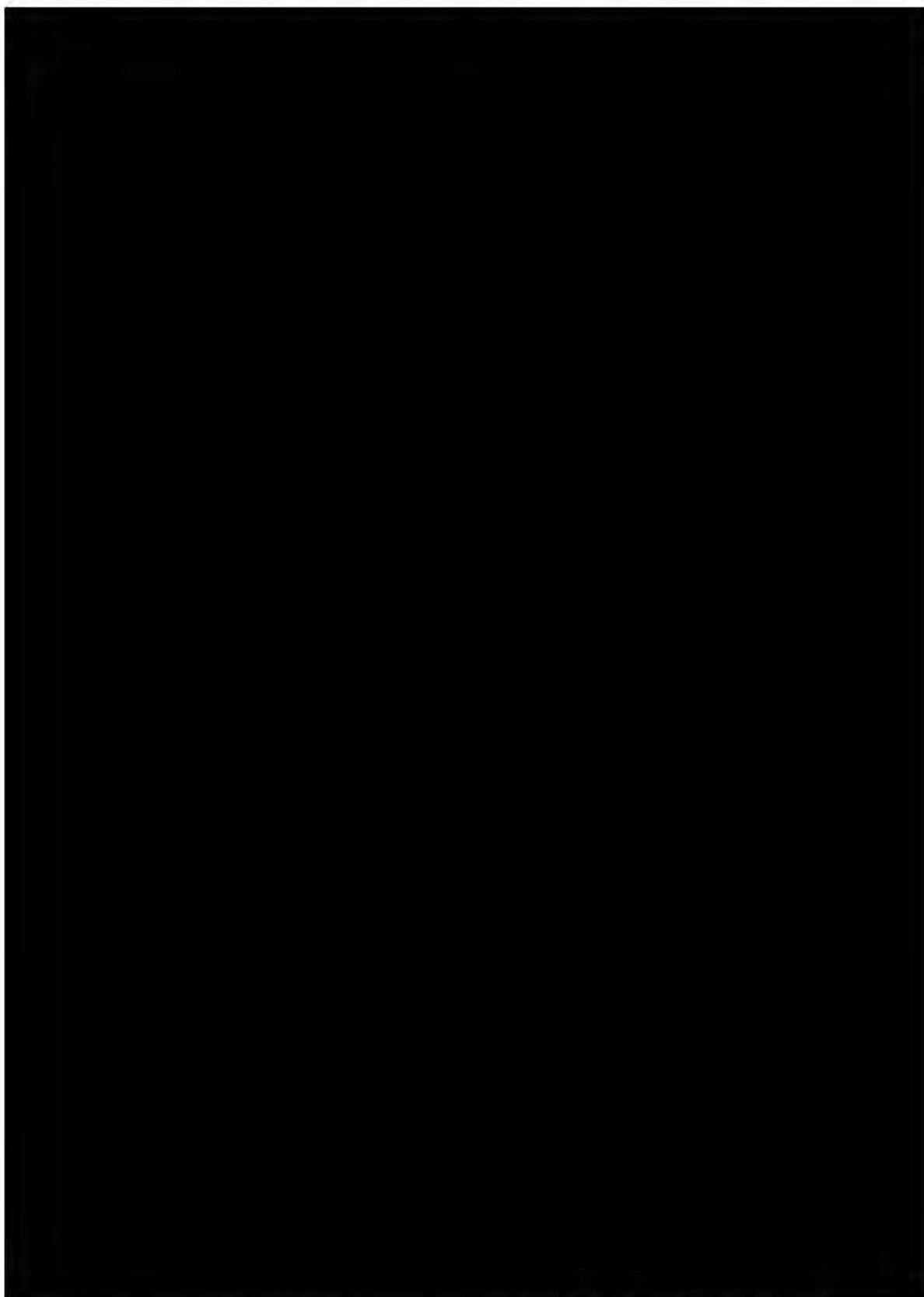
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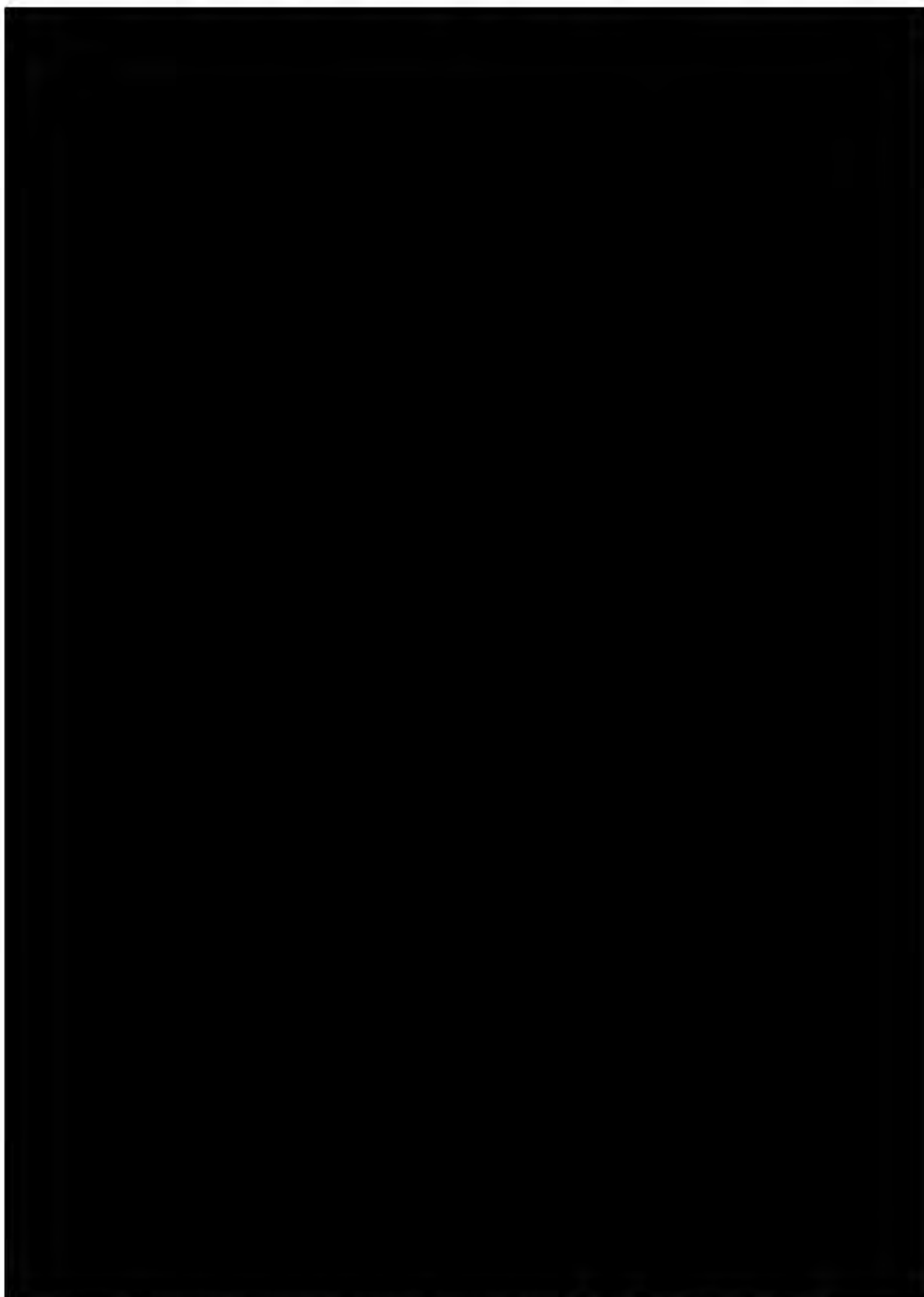


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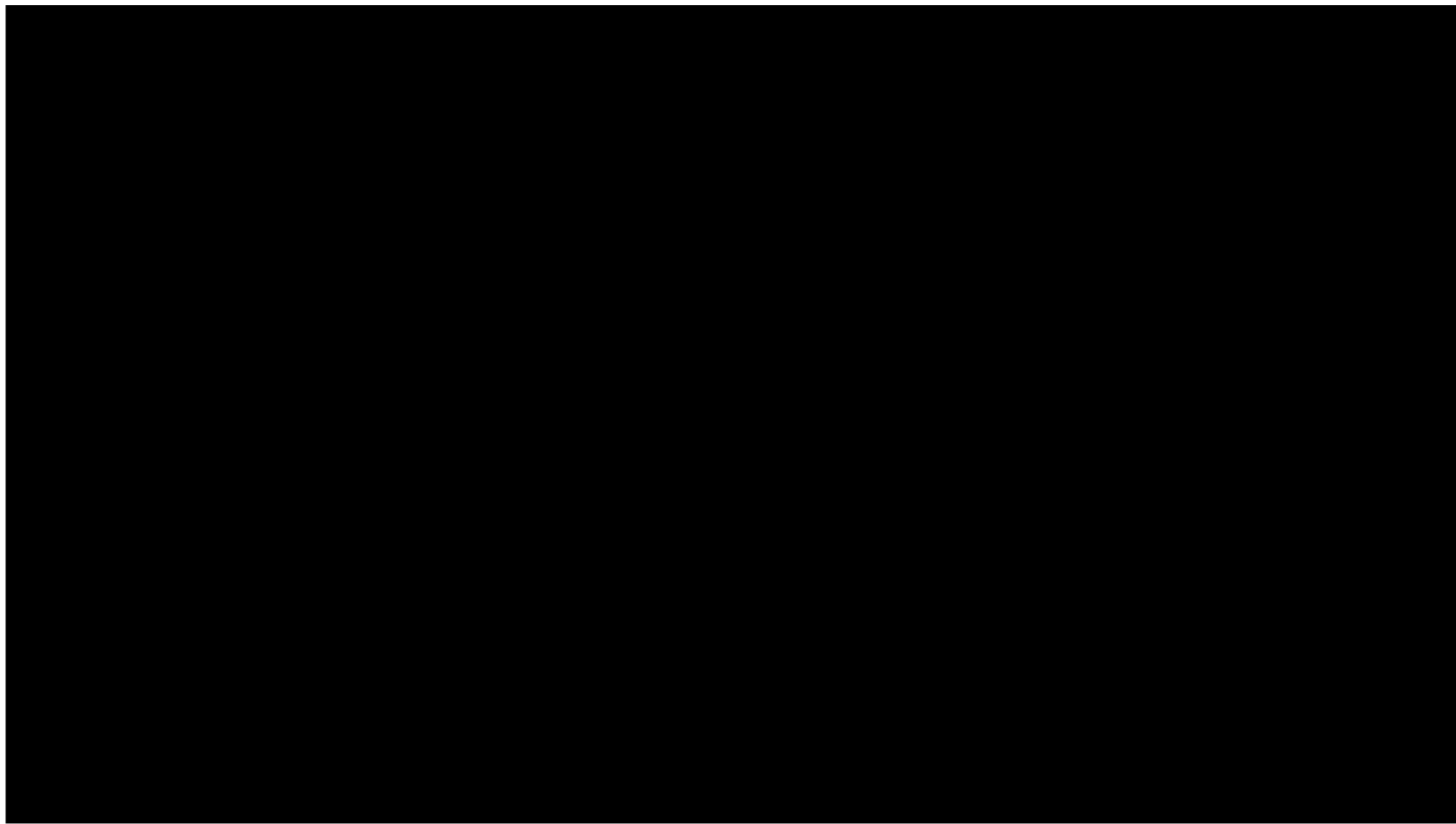


Appendix 12: Study Details Specific to Atezo+BL-8040 Arm (2L Gastric Cancer Cohort)



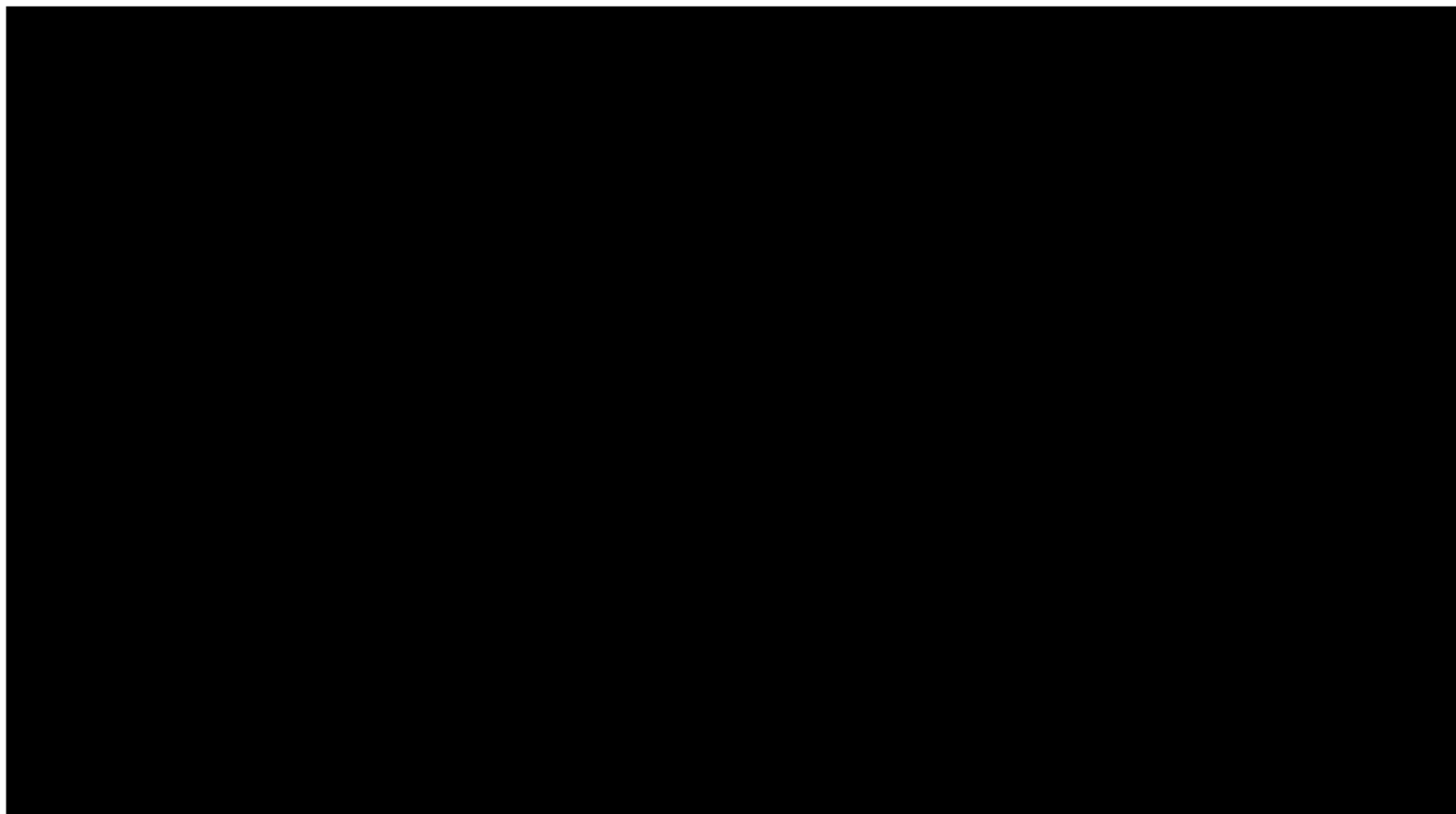


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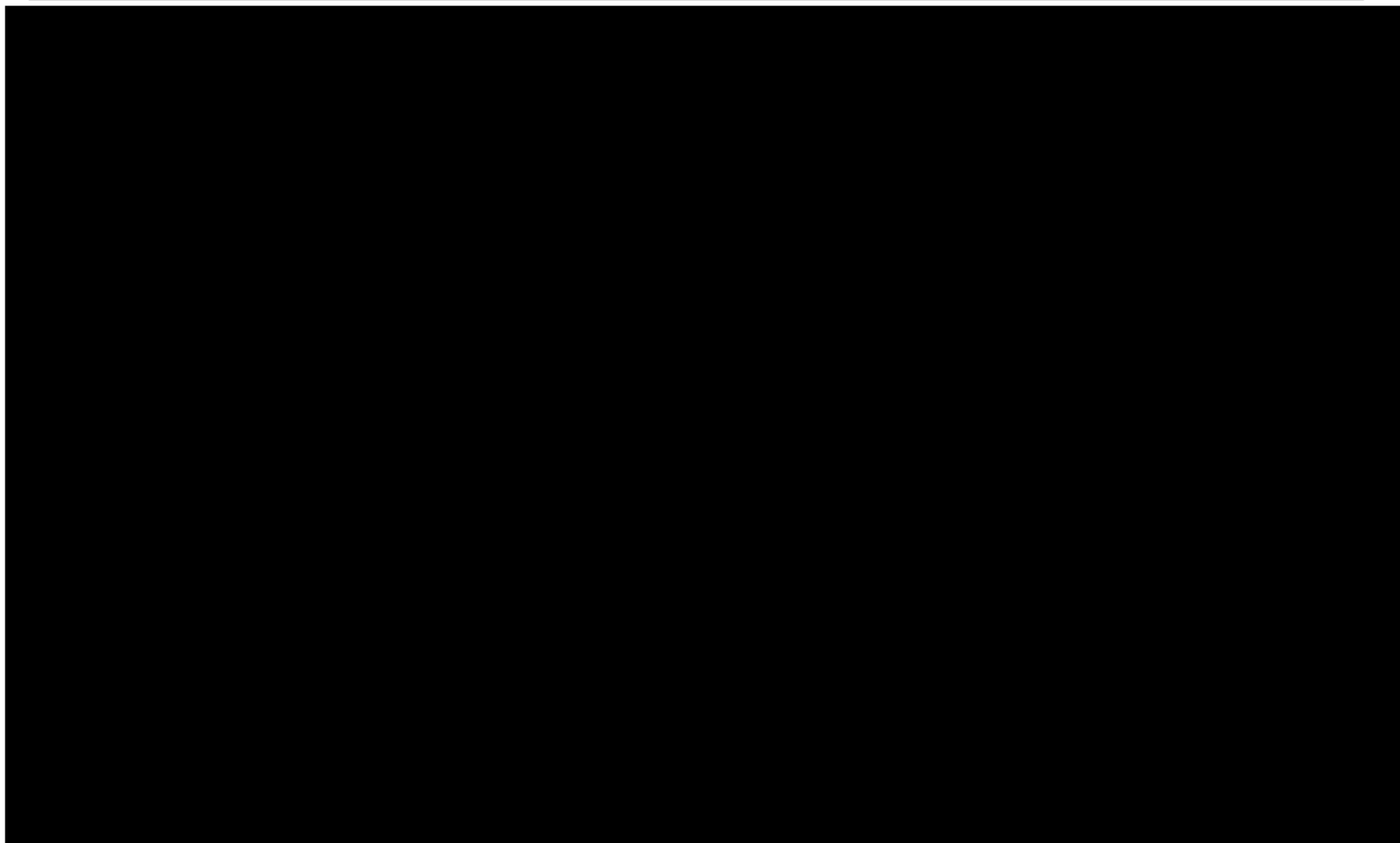


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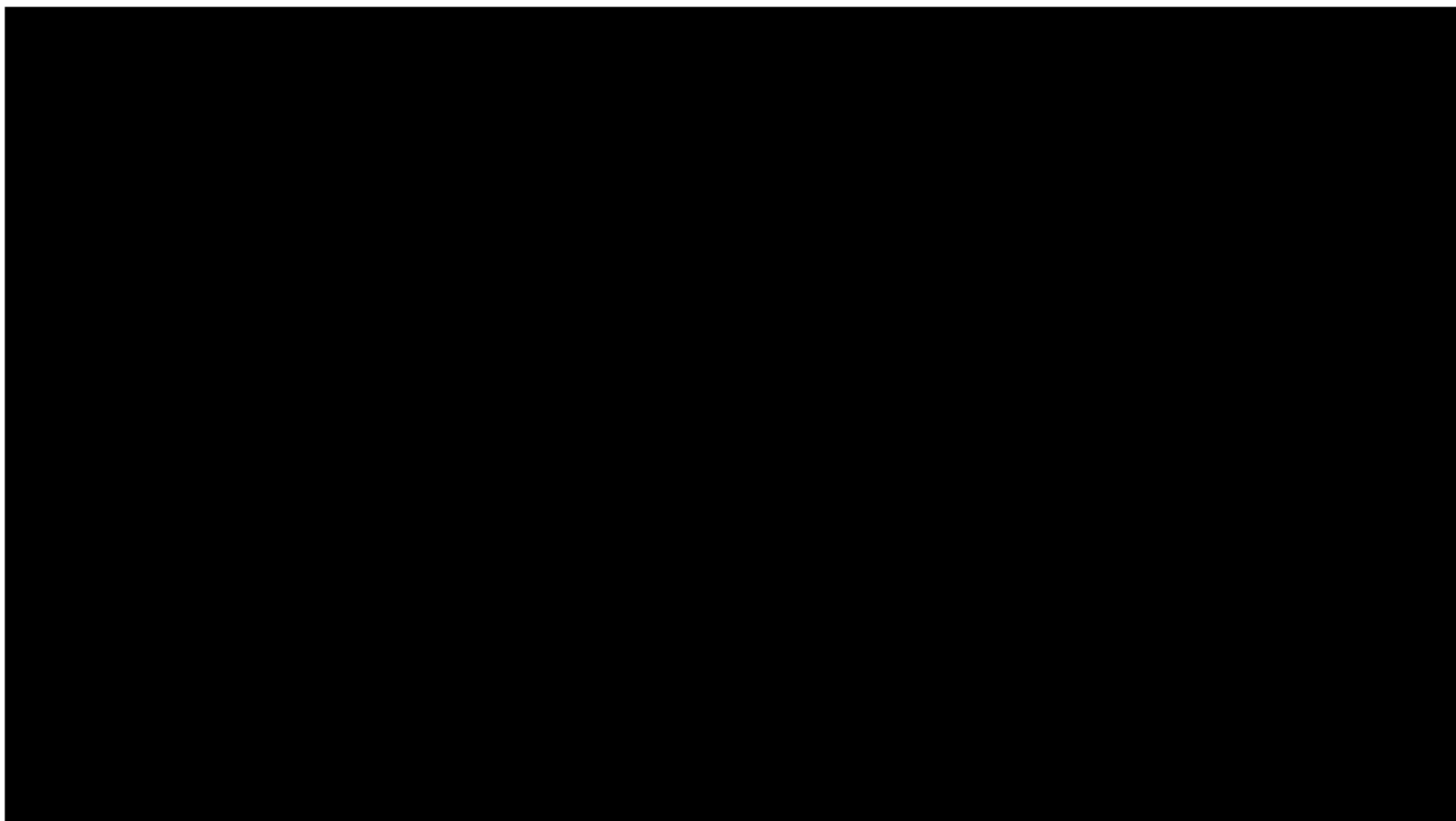
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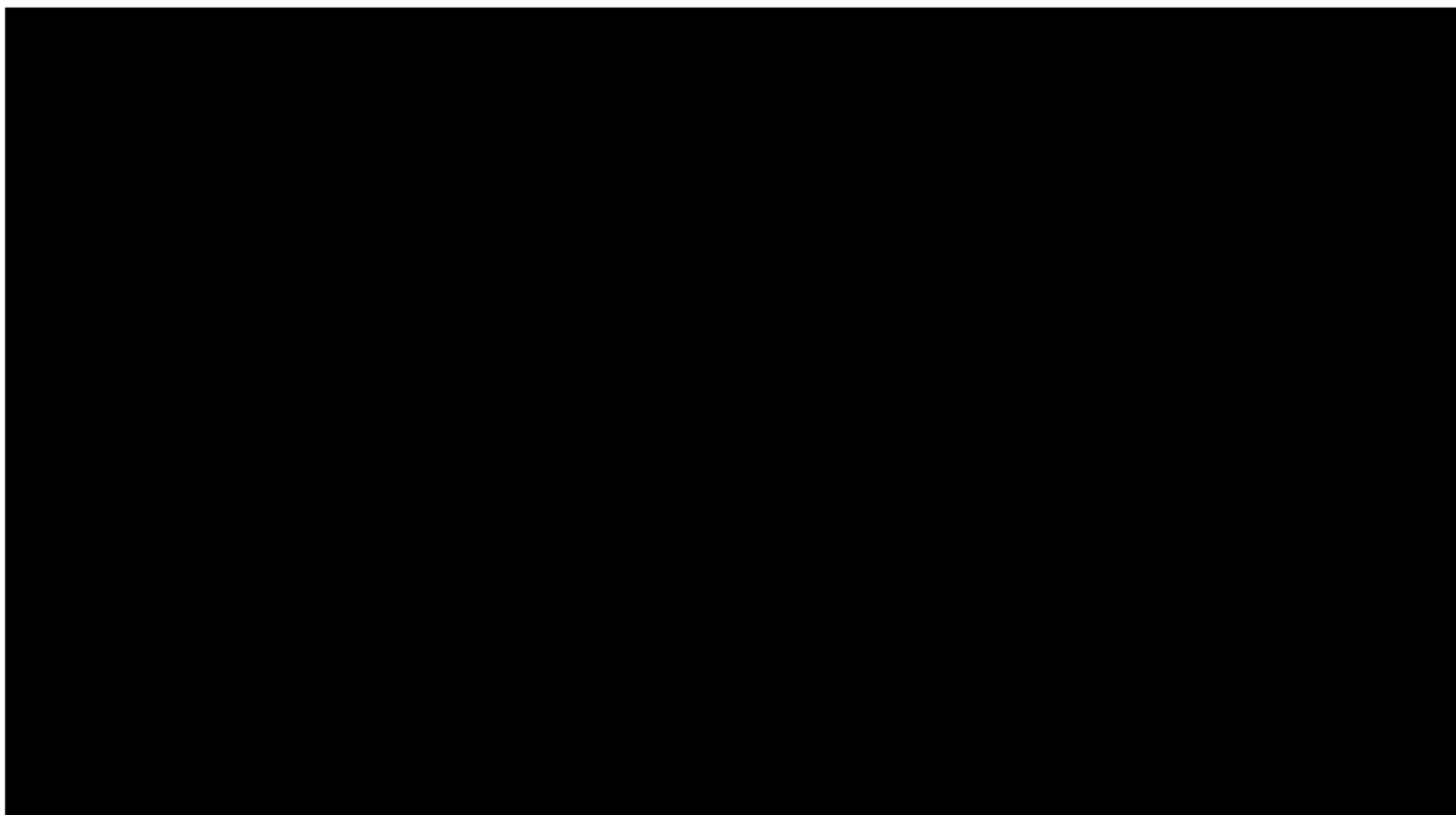
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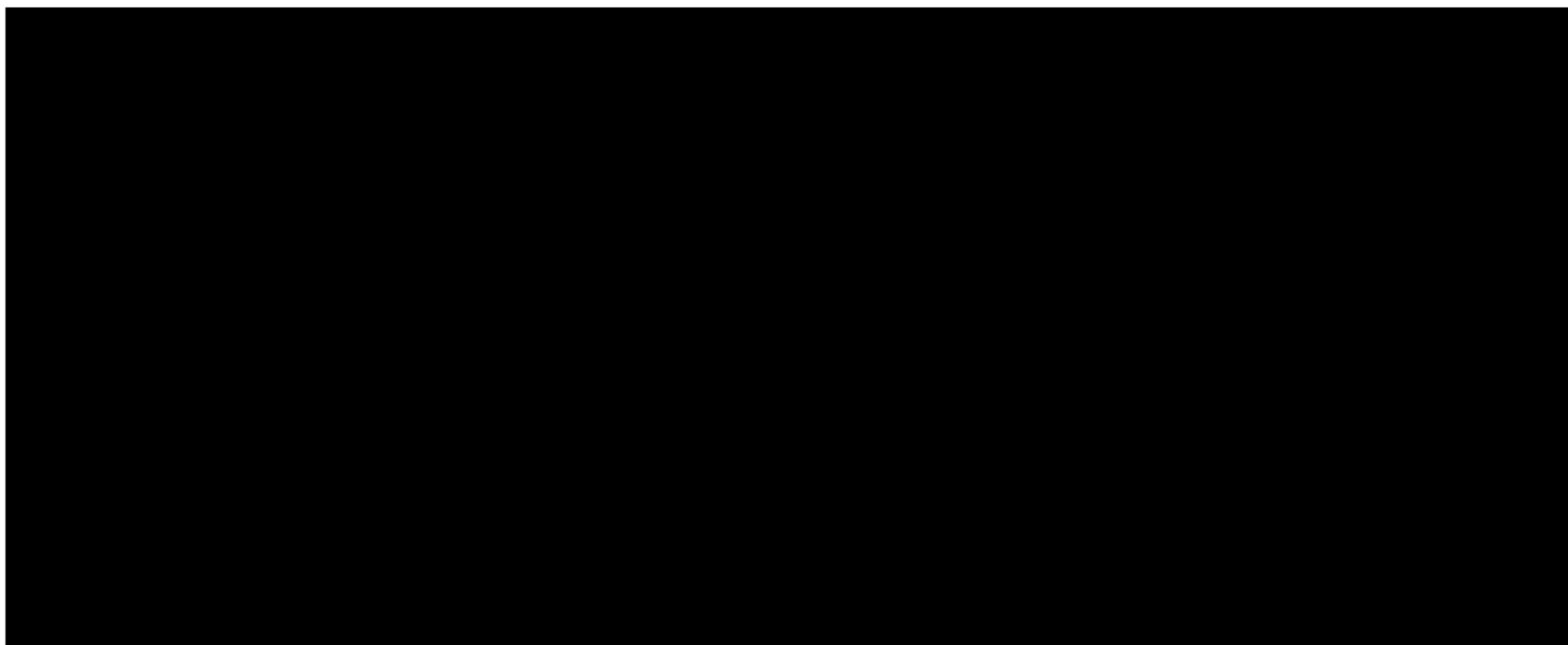
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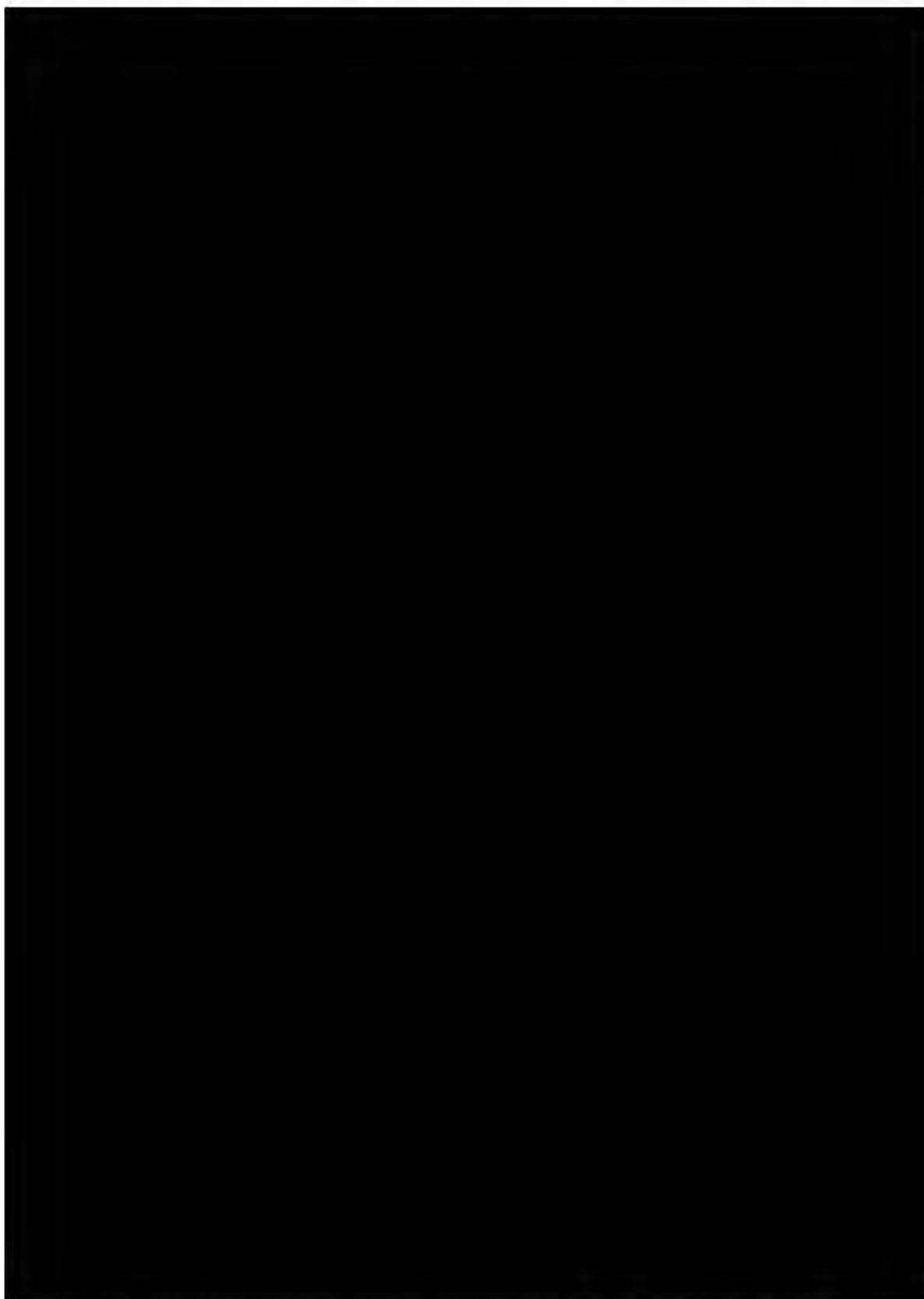
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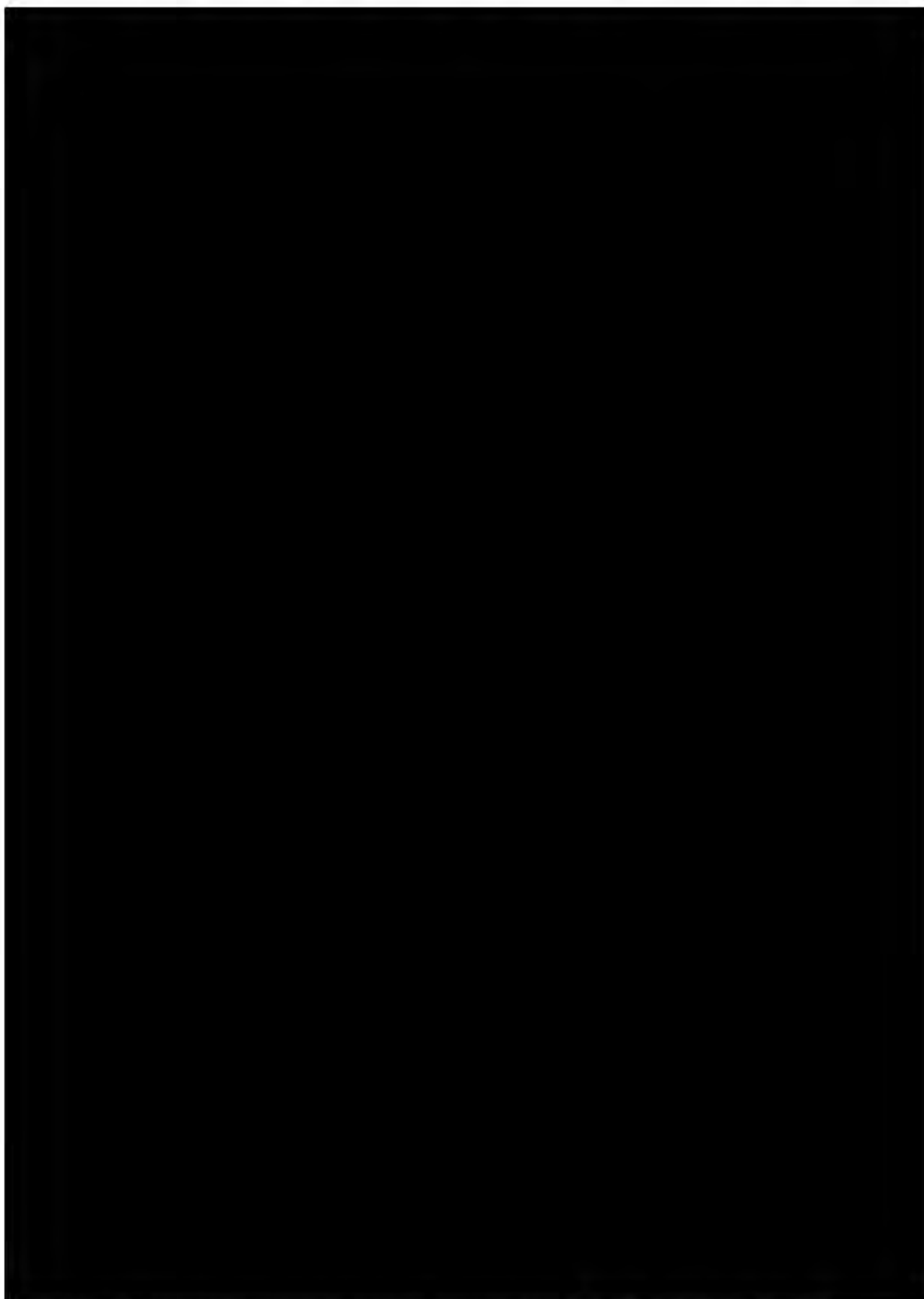
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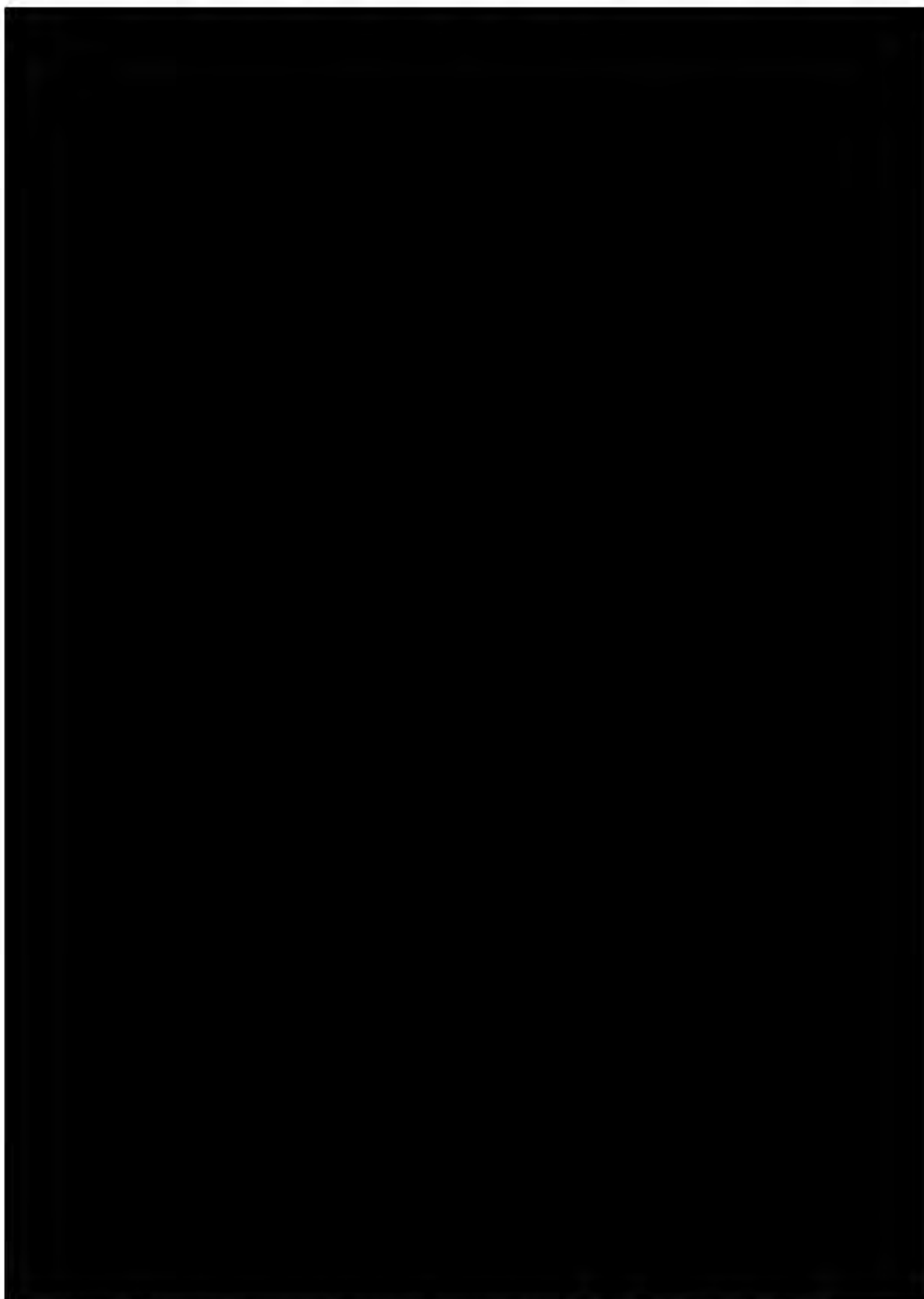
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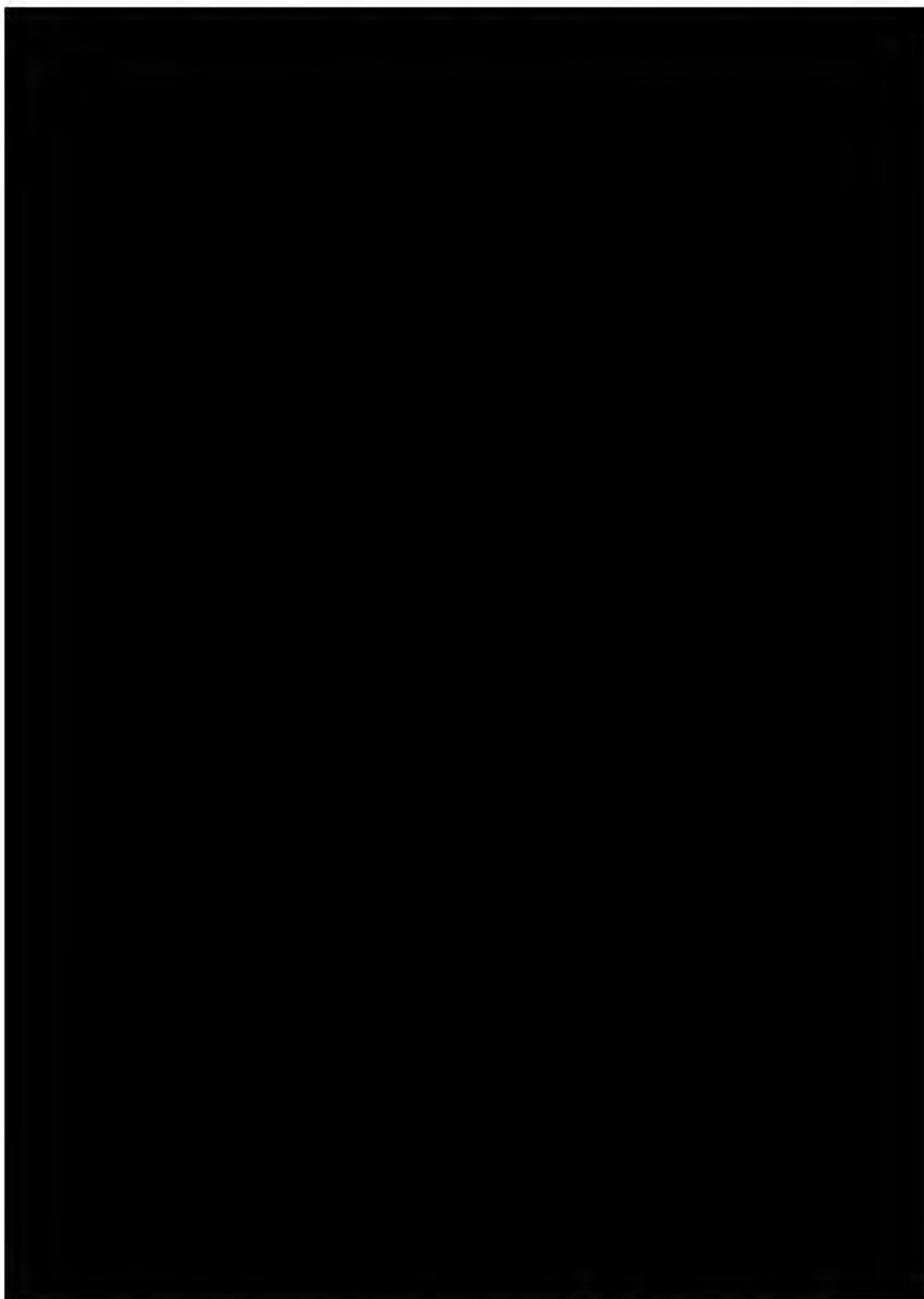
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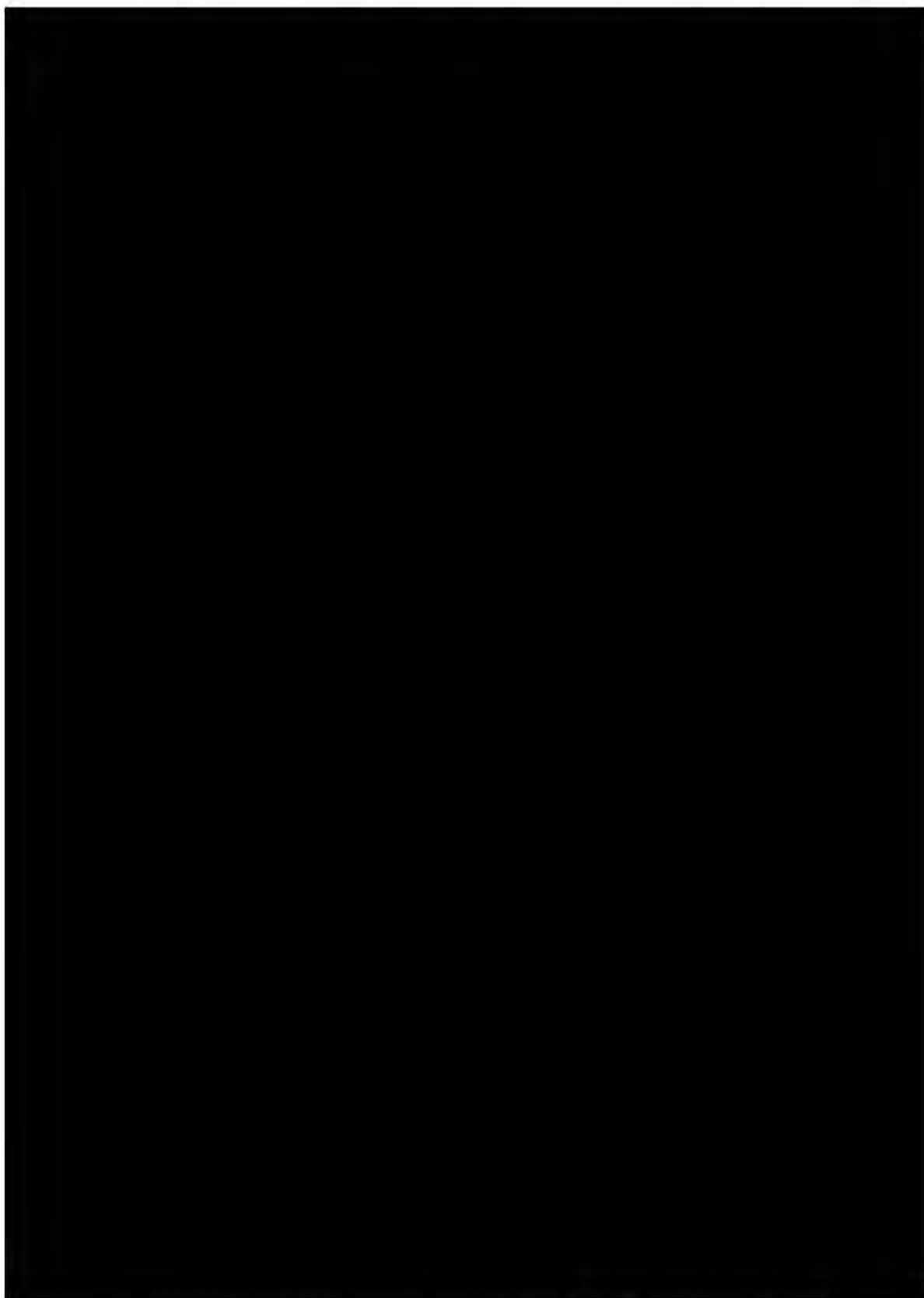
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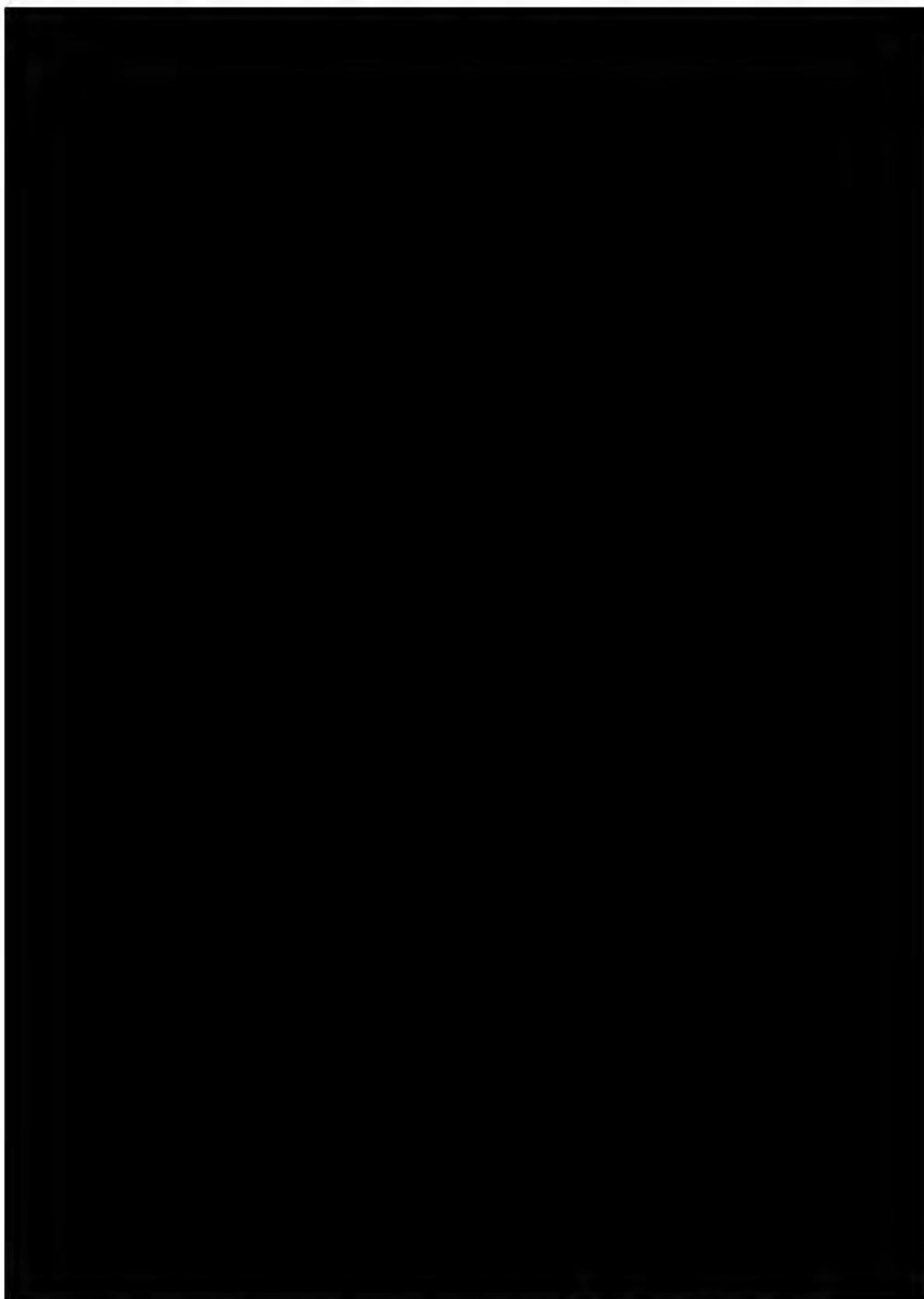
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Appendix 12: Study Details Specific to Atezo+BL-8040 Arm (2L Gastric Cancer Cohort)



Appendix 12: Study Details Specific to Atezo+BL-8040 Arm (2L Gastric Cancer Cohort)



Appendix 13

Study Details Specific to Atezo + Linagliptin Arm (2L Gastric Cancer Cohort)

**NOTE: THE ATEZO + LINAGLIPTIN ARM IS NOT CURRENTLY ENROLLING
NEW PATIENTS AS OF OCTOBER 2019.**

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A13–1 BACKGROUND ON ATEZOLIZUMAB + LINAGLIPTIN ARM

A13–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, 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.

A13–1.2 BACKGROUND ON LINAGLIPTIN

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor developed for the treatment of Type 2 diabetes mellitus. Once a day (QD) linagliptin was approved by the U.S. Food and Drug Administration on 2 May 2011 for the treatment of Type 2 diabetes mellitus.

DPP-4 (also known as CD26) is an X-prolyl dipeptidyl peptidase capable of enzymatically removing the first two N-terminal amino acids from a protein. DPP-4 is enzymatically active as both a membrane-bound protein and a soluble protein and is expressed in several tissues and biological fluids in the body. DPP-4 expression and/or

activity can be affected by inflammation and malignant transformation (Stecca et al. 1997; Kajiyama et al. 2002).

DPP-4 inhibitors are one of the recently developed therapeutic classes for treatment of hyperglycemia in Type 2 diabetes mellitus. The various agents in the class have differing chemical structures, but all act by inhibiting the DPP-4 enzyme, thus prolonging the life of incretin hormones, which in turn raise insulin levels and suppress glucagon secretion in a glucose-dependent manner. As a class, DPP-4 inhibitors have been shown to provide significant improvements in glycosylated hemoglobin, and to have a good safety profile. In addition, the glucose-dependent mechanism of action is associated with a low rate of hypoglycemic events (Richter et al. 2008).

A13-2 RATIONALE FOR ATEZO+LINAGLIPTIN ARM

A13-2.1 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 non-small cell lung cancer, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, breast cancer, and sarcoma (see the 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 on tumor cells in 42%–65% of patients with gastric cancer (Wu et al. 2006; Geng et al. 2015; Kim et al. 2016).

A13–2.2 DPP-4 INHIBITION

In addition to DPP-4 well-studied ability to regulate the activity of incretin hormones, DPP-4 has also been shown to regulate the activity of several pro-inflammatory chemokines such as CXCL9, CXCL10, and CXCL11 (Kim et al. 2014). The two chemokines, CXCL9 and CXCL10, and their CXCR3 receptor mediate the recruitment of tumor-suppressive CXCR3-positive T cells and natural killer (NK) cells into solid cancers (Yang et al. 2006; Gorbachev et al. 2007; Wendel et al. 2008). It has been shown that proteolysis of these chemokines inhibits lymphocyte trafficking, resulting in reduced migration of T cells and NK cells into inflammatory sites such as tumor parenchyma.

Nonclinical experiments have shown that DPP-4 inhibition restores CXCL10 activity and promotes immune cell recruitment in the tumor parenchyma, leading to increased tumor control (Barreira da Silva et al. 2015).

The role of DPP-4 in cancer has been suggested by several studies of hepatic cancer, prostate cancer, colon cancer, and gastric cancer (Stecca et al. 1997; Sun et al. 2008; Pang et al. 2010; Liu et al. 2016; Boccardi et al. 2015). Furthermore, the role of DPP-4 was identified from an unsupervised gene expression analysis of gastric gastrointestinal stromal tumors (Yamaguchi et al. 2008). In this study, expression of DPP-4 protein by immunohistochemistry (IHC) correlated well with gene expression, and disease-free survival and overall survival was worse in DPP-4 IHC-positive patients compared with DPP-4 IHC-negative patients ($p < 0.00001$).

A13–2.3 BENEFIT–RISK ASSESSMENT

Because of the high unmet medical need in metastatic gastric cancer, for which overall survival is between 4 and 12 months, several clinical studies have tested checkpoint inhibitors in this setting. A number of studies have indicated a role for PD-L1 in gastric carcinogenesis. In case studies, PD-L1 was expressed on tumor cells in 42%–65% of patients with gastric cancer (Wu et al. 2006; Geng et al. 2015; Kim et al. 2016).

KEYNOTE-012 was a Phase Ib, multicenter, open-label trial that included cohorts of patients with PD-L1–positive recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction. Although from one perspective, the results look promising as 22% of the patients showed a partial response with median duration of response of 40 weeks (Muro et al. 2016), most of the treated gastric cancers results indicate disease that is refractory to checkpoint inhibitors.

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

One potential mechanism for converting otherwise resistant cancers is to recruit immune cells to the tumor sites so that an anti-PD-L1 agent can be effective in activating the local immune system against the cancer cells. Inhibition of DPP-4 activity is one strategy to promote lymphocyte recruitment in tumors, acting by re-establishing functional chemokine gradients. This strategy has achieved proof of concept in nonclinical models in which DPP-4 inhibition improved the anti-tumorigenic activity of anti-PD-L1 (Barreira da Silva et al. 2015). Specifically, it was demonstrated that DPP-4 inhibitors, used in combination with checkpoint inhibitors, resulted in 100% cure of tumor-bearing mice (harboring CT-26 colon carcinoma), rejecting their tumor by Day 21, whereas checkpoint inhibition alone cured 42% of the mice during the same period of time. DPP-4 inhibition, by regulating lymphocytes trafficking, can be used to enhance the response to current tumor immunotherapy regimens.

Considering the safety profile of linagliptin for patients with Type 2 diabetes, no major risk is anticipated by combining atezolizumab and linagliptin.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment, please refer to Section 1.6.

A13-3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+LINAGLIPTIN ARM

[REDACTED]

A13-3.2 RATIONALE FOR LINAGLIPTIN DOSE AND SCHEDULE

The dose of 5 mg once daily (QD), the current approved regimen for patients with Type 2 diabetes (Tradjenta® U.S. Package Insert), was selected on the basis of PK and pharmacodynamic modeling and nonclinical results. Linagliptin was tested at single or multiple oral doses of 1–10 mg in healthy volunteers (Graefe-Mody et al. 2012). At steady state, ≥80% inhibition of plasma DPP-4 activity was achieved with 5-mg and 10-mg QD dosing. The 10-mg QD dosage led only to a modest increase in inhibition of DPP-4 compared with the 5-mg dosage.

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

Evidence correlating 80% DPP-4 inhibition in the plasma with increased immune cell infiltration into tumors comes from nonclinical experiments performed in mice (unpublished), and direct evidence of tissue penetration of the drug comes from rats intravenously dosed with linagliptin (Fuchs et al. 2009). Evidence of effective tissue penetration has also been observed in mice receiving a single dose of linagliptin by oral gavage (unpublished data).

A13-3.3 RATIONALE FOR DPP-4 ACTIVITY AS A BIOMARKER

Nonclinical experiments testing with increasing doses of linagliptin in tumor-bearing mice have showed a positive correlation between the percentage of DPP-4 inhibition in plasma and intra-tumoral lymphocyte infiltration, with 80% plasma inhibition being required to modulate lymphocyte trafficking (unpublished data). To confirm that this inhibition target is indeed achieved, DPP-4 inhibition will be monitored retrospectively in plasma using an enzymatic activity assay (Matheeußen et al. 2012).

Plasma samples will also be used for testing other [REDACTED], including, but not limited to, NH₂-truncated forms of CXCL10 (Decalf et al. 2016). Pretreatment tumor samples will be also tested retrospectively by IHC to identify biomarkers that are predictive of clinical benefit with Atezo+Linagliptin combination treatment.

A13-4 MATERIALS AND METHODS SPECIFIC TO ATEZO+LINAGLIPTIN ARM

A13-4.1 TREATMENT IN ATEZO+LINAGLIPTIN ARM

A13-4.1.1 Formulation, Packaging, and Handling

A13-4.1.1.1 Atezolizumab

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

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

A13-4.1.1.2 Linagliptin

For information on the formulation, packaging and handling of linagliptin, refer to the local label.

A13-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo+Linagliptin arm will receive treatment as outlined in [Table A13-1](#) 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

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A13-1 Treatment Regimen for Atezo+Linagliptin Arm

Cycle Length	Dose, Route, and Regimen (Drugs Listed in Order of Administration)
21 days	• Atezolizumab 1200 mg administered by IV infusion on Day 1 of each cycle • Linagliptin 5 mg orally QD

Atezo=atezolizumab; QD=once a day.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under "special situations" as explained in Section 5.3.5.12. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available.

A13-4.1.2.1 Linagliptin

Patients will take linagliptin at a dose of 5 mg (one tablet) orally once daily (on Days 1–21 of each 21-day cycle). This is the current dosage approved for linagliptin for the treatment of Type 2 diabetes.

Refer to the local prescribing information for guidelines on treatment interruption or discontinuation.

A13-4.1.2.2 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A13-2.

Table A13-2 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, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. - Atezolizumab should be infused over 60 ($\pm$ 15) minutes. - If clinically indicated, vital signs should be recorded every 15 ($\pm$ 5) minutes during the infusion and at 30 ($\pm$ 10) minutes after the infusion. - Patients should be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms.	- If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, 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 ($\pm$ 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. - If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 ($\pm$ 10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in [Section A13–5.1.4.2](#). 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.

A13–4.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit, as determined by the investigator (as described in [Section 3.1.1](#)), will be given the option of receiving a different treatment combination during Stage 2 of the study, as outlined in [Table A13-3](#), provided they meet eligibility criteria (see [Section 4.1](#)) and the Stage 2 arm is open for enrollment. Patients who experience unacceptable toxicity not related to atezolizumab may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

benefit or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A13-3 Stage 2 Treatment Regimen Available for the Atezo+Linagliptin Arm

Study Treatment	Appendix
No Stage 2 treatment currently available	—

Atezo=atezolizumab.

A13-4.2 CONCOMITANT THERAPY FOR ATEZO+LINAGLIPTIN ARM

Concomitant therapy 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 10 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.

A13-4.2.1 Permitted Therapy for Atezo+Linagliptin Arm

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)
 - Live, attenuated vaccines are not permitted (see Section [A13-4.2.3](#))
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids and mineralocorticoids (e.g., fludrocortisone) administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

- 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 linagliptin 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.

- Anticonvulsant 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 with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-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 5](#)).

At this time there is insufficient experience with COVID-19 vaccines to support concrete recommendations concerning the use of COVID-19 vaccines in patients receiving linagliptin. Based on the data available to date, a potential for overlapping toxicities with linagliptin is not expected due to the mechanism of action of linagliptin. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to

a patient should be made on an individual basis by the investigator in consultation with the patient.

A13-4.2.2 Cautionary Therapy for Atezo+Linagliptin Arm

A13-4.2.2.1 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 6](#) for details).

A13-4.2.2.2 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 4.4) may be used during the study at the discretion of the investigator.

A13-4.2.2.3 Medications Given with Precaution due to Effects Related to P-Glycoprotein and CYP3A4

Concomitant use of strong inducers of P-glycoprotein and CYP3A4 (e.g., rifampicin) should be avoided during linagliptin treatment because exposure will be decreased in presence of these agents and reduce linagliptin activity. Therefore, use of alternative treatments is strongly recommended during linagliptin treatment.

A13-4.2.2.4 Medications Known to Cause Hypoglycemia

Concomitant use of insulin or insulin-secretagogue drugs are allowed but should be used with caution owing to an increased risk of hypoglycemia. An initial dose decrease in the insulin or insulin-secretagogue drugs should be considered to prevent hypoglycemic events.

A13-4.2.3 Prohibited Therapy for Atezo+Linagliptin 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, is prohibited for

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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 above in the section on permitted therapy.

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, 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.

A13-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+LINAGLIPTIN ARM

Contraception requirements for the Atezo+Linagliptin arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, 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 last dose of study treatment. Women must refrain from donating eggs during this same period.

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

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male 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 acceptable methods of contraception.

A13–5 ASSESSMENT OF SAFETY FOR ATEZO+LINAGLIPTIN ARM

A13–5.1 SAFETY PLAN FOR ATEZO+LINAGLIPTIN ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and linagliptin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A13–5.1.1](#), [A13–5.1.2](#), and [A13–5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A13–5.1.4](#).

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 atezolizumab 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](#). An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections [3.1.6](#) and [3.1.7](#).

A13–5.1.1 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 palsy, 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). Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A13–5.1.2 Risks Associated with Linagliptin

Linagliptin is known to cause acute pancreatitis, hypoglycemia, hypersensitivity, arthralgia, bullous pemphigoid, nasopharyngitis, and cough in patients with Type 2 diabetes mellitus. When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycemia was increased over that of placebo. Linagliptin alone showed a comparable incidence of hypoglycemia to placebo.

For more details regarding the safety profile of linagliptin, refer to the local prescribing information.

A13–5.1.3 Risks Associated with Combination Use of Atezolizumab+Linagliptin

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and linagliptin: acute pancreatitis.

A13–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo+Linagliptin Arm

A13–5.1.4.1 Dose Modifications

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

A13–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A13-4](#)). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day of oral prednisone 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 for 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 (or an appropriate delegate). The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended 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.

Linagliptin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If linagliptin has been withheld for > 21 days because of toxicity, the patient may be discontinued from linagliptin.

If atezolizumab is discontinued, linagliptin should also be discontinued. If linagliptin is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to [Section A13–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A13–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events related to linagliptin are provided in the linagliptin prescribing information.

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General guidelines for management of patients who experience adverse events in this arm are provided in [Table A13-4](#).

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Pancreatic events	
Amylase and/or lipase elevation, Grade 1	• Continue atezolizumab and linagliptin. • Monitor amylase and lipase prior to dosing.
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab and withhold linagliptin. • Monitor amylase and lipase weekly. • If event resolves to Grade 1 or better within 21 days, resume linagliptin at the current dose. If not linagliptin may be permanently discontinued. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab and linagliptin. • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.^{a, b} • Permanently discontinue atezolizumab and contact the Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.^{a, b, c} • For recurrent events, permanently discontinue atezolizumab and linagliptin and contact the Medical Monitor.^c • If event resolves to Grade 1 or better within 21 days, resume linagliptin at the current dose. If not, linagliptin may be permanently discontinued.

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

^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Pancreatic events (cont.)	
Pancreatitis, Grade 2 or 3	• Withhold atezolizumab. • Permanently discontinue linagliptin. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. ^{a, b} • Permanently discontinue atezolizumab and contact the Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. ^{a, b, c} • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. ^c
Pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. ^c • Permanently discontinue linagliptin. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Linagliptin-related toxicities not described above	
Grade 1 or 2	Continue linagliptin and atezolizumab.
Grade 3	- Withhold linagliptin treatment. Continue atezolizumab. - If event resolves to Grade 2 within 21 days, resume linagliptin. - If event resolves to Grade 1 or better within 21 days, resume linagliptin. - If event does not resolve to Grade 2 or better within 21 days, linagliptin may be permanently discontinued.
Grade 4	- Withhold linagliptin and atezolizumab. - If event resolves to Grade 2 or better within 21 days, resume linagliptin. If not, linagliptin may be permanently discontinued. - If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	- Follow guidelines for atezolizumab in Appendix 6. - Continue linagliptin.
Grade 3	- Follow guidelines for atezolizumab in Appendix 6. - Withhold linagliptin treatment. - If event resolves to Grade 2 within 21 days, resume linagliptin. - If event resolves to Grade 1 or better within 21 days, resume linagliptin. - If event does not resolve to Grade 2 or better within 21 days, linagliptin may be permanently discontinued.
Grade 4	- Follow guidelines for atezolizumab in Appendix 6. - Withhold linagliptin treatment. - If event resolves to Grade 2 or better within 21 days, resume linagliptin. If not, linagliptin may be permanently discontinued.

- ^a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

**A13–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR
ATEZO+LINAGLIPTIN ARM (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 the Atezo+Linagliptin arm include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10\times$ upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Grade ≥ 3 hypoglycemia
- Myelitis
- Facial paresis

A13–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO+LINAGLIPTIN ARM

A13–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A 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/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.

A13–5.3.2 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.

A13–5.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/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).

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A13-6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+LINAGLIPTIN ARM

Table A13-5 Schedule of Activities for Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

Assessment/Procedure	Stage 1 Screening (see Appendix 7)	Treatment Cycles (21-Day Cycles) ^a			Stage 2 Screening (see Appendix 7) ^c or Treat. Discon. ^d	Follow-Up ^d Every 3 Months
		Cycle 1 ^b		Cycles ≥ 2		
		Days –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	
Informed consent	See Appendix 7 .		x ^{ee}			
Molecular profile of gastric cancer (if available)			Whenever updated information becomes available			
Vital signs ^g			x	x	x	
Weight ^{dd}			x		x	
Complete physical examination ^f					x	
Limited physical examination ^{g, dd}			x	x		
ECOG Performance Status ^{dd}			x		x	
ECG ^{h, dd}			Perform as clinically indicated.			
Hematology ⁱ			x ^{i, k}	x ^j	x ^j	x
Chemistry ^l			x ^{i, k}	x ^j	x ^j	x
TSH, free T3 (or total T3), and free T4 ^m			x ^{j, k, m}			x
Viral serology (if applicable) ⁿ					x ⁿ	x ⁿ
CA19-9			x		x	
Pregnancy test ^o			x ^{i, k}		x ^j	x ^o
Urinalysis ^p			Perform as clinically indicated. ^j			

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Assessment/Procedure	Stage 1 Screening (see Appendix 7)	Treatment Cycles (21-Day Cycles) ^a			Stage 2 Screening (see Appendix 7) ^c or Treat. Discon. ^d	Follow-Up ^d
		Cycle 1 ^b		Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months
Serum autoantibody sample ^q	See Appendix 7 .	Perform if a patient experiences a suspected immune-mediated adverse event.				
PK samples		Refer to Table A13-6 .				
ADA samples		Refer to Table A13-6 .				
Biomarker samples		Refer to Table A13-6 .				
Blood sample for RBR (optional) ^r		X				
Tumor biopsy		X ^s				
Tumor biopsy (optional)		X ^t				
Tumor response assessments		X ^{u, v, w}				
Concomitant medications ^x		X	X	X	X	
Adverse events ^y		X	X	X	X ^y	X ^y
Atezolizumab administration ^{z, aa}		X		X		
Dispense linagliptin ^{aa, bb}		X		X		
Survival follow-up and anti-cancer treatment						X ^{cc}

2L = second-line; ADA = anti-drug antibody; App. = Appendix; Atezo = atezolizumab; CT = computed tomography; Discon. = Discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Treat. = Treatment; TSH = thyroid-stimulating hormone.

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

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- ^a If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.
- ^b It is recommended that treatment be initiated no later than 7 days after randomization.
- ^c Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) and patients who experience unacceptable toxicity to linagliptin will be given the option of receiving a different treatment combination in Stage 2 of the study (provided Stage 2 is open for enrollment; see Section A13-4.1.3) and will undergo screening assessments to determine eligibility (see Appendix 7). Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Written informed consent must be obtained before performing screening evaluations for Stage 2, except as noted in footnote "w" below.
- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments after completing the treatment discontinuation visit.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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 ($\pm$ 5) minutes during and 30 ($\pm$ 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 ($\pm$ 10) minutes after the infusion.
- ^f Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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. 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 carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, pre-albumin, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.
- ^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 fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

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- ⁿ Patients with a positive quantitative HBV DNA at screening will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (± 7 days), and at 3, 6, 9, and 12 months (± 14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥ 500 IU/mL, consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended. The Medical Monitor is available to advise as needed.
- ^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 treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^p Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. If urinary protein is $> 1+$ on dipstick and there is no explanation for the positive dipstick result (e.g., menses), a 24-hour urine collection is required to check total urinary protein.
- ^q Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.
- ^r Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.
- ^s 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 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have granted approval for mandatory serial biopsies (see Section 3.1.1.2) will also undergo tumor biopsy sample collection at 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible by the investigator). See Section 4.5.6 for tissue sample requirements.
- ^t Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible by the investigator, and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.
- ^u Patients will undergo tumor assessments at baseline, every 8 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 8 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

- ^v 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 CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ^w For patients who undergo screening for Stage 2: 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 loss of clinical benefit or unacceptable toxicity 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.
- ^x 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.
- ^y After initiation of study treatment, all adverse events will be reported until 30 days after the last 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 135 days after the last dose of study treatment or until initiation of 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.
- ^z Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg. The initial dose of atezolizumab will be delivered over 60 ($\pm$ 15) minutes. Subsequent infusions will be delivered over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^{aa} Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^{bb} Patients will take linagliptin at a dose of 5 mg (one tablet) orally once daily. On clinic visit days, patients should take their tablets in the clinic.

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).
- ^{dd} Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^{ee} If a patient decides to continue treatment beyond progression, an additional written consent form from the patient is required at the time of initial disease progression to acknowledge deferring other treatment options in favor of continuing study treatment.

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

Table A13-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Linagliptin Arm (2L Gastric Cancer Cohort): Preliminary and Expansion Phases

Visit	Time	Sample Type(s)
Day 1 of Cycle 1	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma, serum, and PBMC)
	30 ($\pm$ 10) minutes after atezolizumab infusion	Atezolizumab PK (serum)
	2 hours after linagliptin dose	- Linagliptin PK (plasma) - Biomarker (plasma and serum)
Day 15 of Cycle 1	Prior to study treatment ^a	- Linagliptin PK (plasma) - Biomarker (plasma and serum)
Day 1 of Cycle 2	Prior to study treatment ^a	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Linagliptin PK (plasma) - Biomarker (plasma, serum, and PBMC)
Day 1 of Cycle 3	Prior to study treatment ^a	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Linagliptin PK (plasma)
Day 1 of Cycle 4	Prior to study treatment ^a	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Linagliptin PK (plasma) - Biomarker (plasma and serum)
Day 1 of Cycle 8	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum)

2L = second-line; ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

^a On Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 4, patients should take their linagliptin tablet in the clinic after the PK, ADA, and biomarker samples have been obtained.

^b Perform only for patients who do not enter Stage 2.

Appendix 13: Study Details Specific to Atezo+Linagliptin Arm (2L Gastric Cancer Cohort)

Table A13-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Linagliptin Arm (2L Gastric Cancer Cohort): Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type(s)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
120 (± 30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum)^b • Atezolizumab ADA (serum)^b

2L = second-line; ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

^a On Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 4, patients should take their linagliptin tablet in the clinic after the PK, ADA, and biomarker samples have been obtained.

^b Perform only for patients who do not enter Stage 2.

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Appendix 14

Placeholder for Future Arm

The mFOLFOX6 plus atezolizumab plus cobimetinib arm has been removed as all randomized patients have completed treatment and follow-up. The content of Appendix 14 (previously Appendix 13, entitled "Study Details Specific to mFOLFOX6 + Atezo + Cobi Arm [1L Gastric Cancer Cohort]") has been deleted. Appendix 14 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 15

Placeholder for Future Arm

The mFOLFOX6 plus atezolizumab arm has been removed, with no patients enrolled in that arm, and the content of Appendix 15 (previously Appendix 14, entitled "Study Details Specific to mFOLFOX6 + Atezo Arm [1L Gastric Cancer Cohort]") has been deleted. Appendix 15 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 16

Placeholder for Future Arm

The atezolizumab plus selicrelumab plus bevacizumab arm has been removed, with no patients enrolled in that arm, and the content of Appendix 16 (previously Appendix 15, entitled "Study Details Specific to Atezo + Seli + Bev Arm [2L Gastric Cohort]") has been deleted. Appendix 16 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 17

Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

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**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

**A17-1 BACKGROUND ON ATEZO + TIRAGOLUMAB + CISPLATIN +
5-FU ARM**

A17-1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) 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.

A17-1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human immunoglobulin G1 (IgG1)/kappa mAb derived in Open Monoclonal Technology rats that binds T-cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif [ITIM] domains (TIGIT) and prevents its interaction with the poliovirus receptor (PVR). The recombinant antibody is produced in Chinese hamster ovary cells and consists of two heavy chains [REDACTED] and two light chains [REDACTED].

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The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. TIGIT is an immunoglobulin (Ig) super family member expressed on subsets of activated T cells and natural killer (NK) cells, and found highly expressed in tumor tissue and in tumor-infiltrating immune cells in many human cancers, including, but not limited to NSCLC, breast cancer, multiple myeloma (MM), and non-Hodgkin lymphoma (NHL). In multiple tumor types, TIGIT is coordinately expressed with PD-1 (Yu et al. 2009; Johnston et al. 2014; Manieri et al. 2017). Genetic ablation or antibody blockade of TIGIT has been shown to enhance NK cell killing, CD4+ and CD8+ T-cell activation, and effector function in vitro and in vivo in nonclinical models (Yu et al. 2009; Johnston et al. 2014; Stanietsky et al. 2009; Joller et al. 2011). In the nonclinical tumor models, TIGIT interacted with high affinity to CD155 (also known as PVR), which also has an activating counter-receptor CD226. Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells (Yu et al. 2009; Stanietsky et al. 2009; Johnston et al. 2014).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the 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 studies.

A17-2 RATIONALE FOR ATEZO+TIRAGOLUMAB+CISPLATIN+ 5-FU ARM

A17-2.1 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

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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, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Several studies have reported PD-L1 expression in esophageal cancer and revealed that higher expression of PD-L1 predicted poorer survival in patients (Ohigashi et al. 2005; Chen et al. 2014; Dhupar et al. 2017; Zhao et al. 2018). These data suggest that PD-L1 status as a predictor of prognosis for patients with esophageal cancer and provide the rationale for developing novel immunotherapies of targeting PD-L1 pathway. There is an ongoing study of atezolizumab monotherapy in Chinese patients with locally advanced or metastatic solid tumors who had exhausted all available standard treatment options (NCT02825940).

[REDACTED]

A17-2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). 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 checkpoint immune-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).

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TIGIT is expressed in a wide variety of human tumors, including most solid tumors, such as NSCLC, breast cancer and melanoma, and hematological tumors, such as MM and NHL, 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; Yang 2016; Guilleroy et al. 2018). TIGIT expression ranged from 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's 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 genetically deficient mice and blocking antibodies, have revealed a key role for TIGIT in regulating T-cell responses in cancer. Together these data support the hypothesis that anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A17-2.3 COMBINED INHIBITION OF THE PD-L1/PD-1 PATHWAY WITH CHEMOTHERAPY

In nonclinical immune competent mouse tumor models, chemotherapy treatment with multiple classes of chemotherapeutic agents resulted in activation or increase of tumor infiltrating CD8+ T cells, whereas there was a depletion of peripheral immune cells, including CD8+ T cells (Belvin et al. 2016). Combination of anti-PD-L1 with several chemotherapeutic agents showed combination efficacy, correlating with the increased activation of tumor infiltrating CD8+ T cells (Belvin et al. 2016). Depending on the immune context of the nonclinical model tested, chemotherapeutic agents showed different mechanisms of activating CD8+ T cells, including increased IFN- γ production, increased Granzyme B levels, and decreased markers of exhaustion (Belvin et al. 2016). Tumor cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

Indeed, the addition of PD-L1 and PD-1 checkpoint inhibitors to standard platinum-based chemotherapy demonstrated encouraging anti-tumor activity and acceptable safety in early Phase I and II studies (Giaccone et al. 2015; Langer et al. 2016; Rizvi et al. 2016). In multiple large randomized Phase III trials in different advanced solid tumors, the addition of PD-L1 and PD-1 checkpoint inhibitors to standard chemotherapy led to significantly longer overall survival and progression-free survival for patients compared with chemotherapy alone (Gandhi et al. 2018; Paz-Ares et al. 2018; Horn et al. 2018;

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Schmid P et al. 2018). As a result of these trials, PD-1/PD-L1 checkpoint inhibitors in combination with chemotherapies have been approved by some health authorities, including the FDA, for patients with advanced cancer.

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 IFN- γ production by CD8+ tumor-infiltrating lymphocytes was observed (Vincent et al. 2010). In addition, in nonclinical models, oxaliplatin has been shown to enhance immune responses by decreasing T-regulatory cells and myeloid-derived suppressor cells in tumor microenvironment (Sato et al. 2005; Gonzalez-Aparicio et al. 2011), suggesting potential synergy with immunotherapy induced by PD-L1 blockade. Based on this nonclinical and clinical data, these regimens may enhance the efficacy of atezolizumab in patients with esophageal cancer.

A17-2.4 COMBINED INHIBITION OF THE PD-L1/PD-1 AND TIGIT PATHWAYS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. 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 suppressed the effector function of chronically stimulated CD8+ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, respectively targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab in patients may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types.

A17-2.5 COMBINED INHIBITION OF THE PD-L1/PD-1 AND TIGIT PATHWAYS WITH CHEMOTHERAPY

Because of the established benefit to patients of adding PD-1 and PD-L1 checkpoint inhibitors to chemotherapy in many solid tumors, and the nonclinical finding that concomitant blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over single-agent PD-L1/PD-1 blockade, it is hypothesized that the combination of TIGIT and PD-L1/PD-1 blockade with chemotherapy may result in even deeper and more durable responses compared with standard chemotherapy alone or even single agent PD-L1/PD-1 blockade and chemotherapy. Evaluating the safety and efficacy of tiragolumab and atezolizumab with chemotherapy in patients with locally advanced/metastatic esophageal cancer in this study will enable future tests of this hypothesis.

A17-2.6 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290) and one ongoing clinical study in patients with hematological malignancies (Study GO40136).

A17-2.6.1 Clinical Study of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors.

As of the data cutoff date of 3 December 2018, 42 patients have been enrolled in the Phase Ia portion of the study of tiragolumab monotherapy evaluating dose levels from 2 mg to 1200 mg, and 164 patients have been enrolled in Phase Ib portion evaluating dose levels of tiragolumab from 2 mg to 600 mg, in combination with 1200-mg atezolizumab. [REDACTED]

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence or severity of adverse events in the Phase Ia

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or Phase Ib portions of Study GO30103 in solid tumors have been determined for tiragolumab as a single agent and in combination with atezolizumab. [REDACTED]

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile is observed to be consistent across different solid tumor indications.

A17-2.6.2 Clinical Study of Tiragolumab in Combination with Atezolizumab in PD-L1–Selected Patients with NSCLC

Study GO40290 is a global, multicenter, randomized, blinded, placebo-controlled Phase II study designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable, or metastatic PD-L1–selected NSCLC.

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS $\geq 1\%$ were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). Of the enrolled patients, 43.0% of patients had a TPS $\geq 50\%$ relative to 57.0% of patients with a TPS 1%–49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

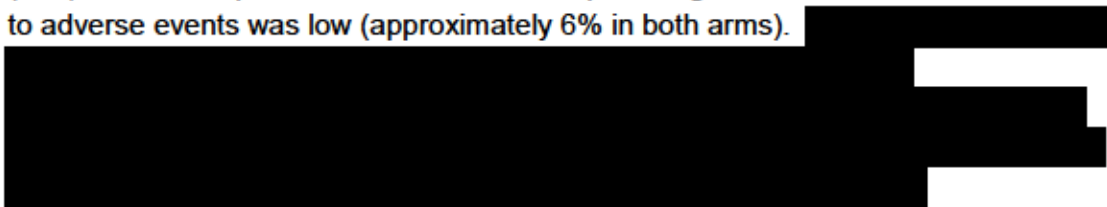
In the ITT population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%). In the subgroup of patients with TPS $\geq 50\%$, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n=29; 55.2% [95% CI: 35.4%, 75.0%]) than the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8%, 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 progression-free survival (PFS) was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (stratified HR=0.57 [95% CI: 0.37, 0.90]; median PFS 5.4 vs.

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3.6 months, respectively). In the subgroup of patients with TPS $\geq 50\%$, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified HR=0.33 [95% CI: 0.15, 0.72]; median PFS not estimable vs. 3.9 months, respectively) (Roche unpublished data on file).

To 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. Immune-mediated adverse events were 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. Discontinuation due to adverse events was low (approximately 6% in both arms).



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

A17-2.7 CLINICAL STUDY OF ATEZOLIZUMAB IN COMBINATION WITH CISPLATIN AND 5-FU

Study GO30140 is an ongoing Phase I study that included an arm evaluating the combination of atezolizumab with cisplatin and 5-FU in patients with metastatic esophageal cancer.

As of January 2019, adverse events that have been reported were consistent with the known risks of atezolizumab, 5-FU, and cisplatin. Atezolizumab in combination with chemotherapy has not been associated with additive, severe toxicities (i.e., Grade ≥ 3), indicating that atezolizumab can be safely combined with standard chemotherapy.



A17-2.8 BENEFIT-RISK ASSESSMENT

Taking into account the potentially synergistic mechanisms of action for tiragolumab and atezolizumab, as well as the preliminary efficacy data and manageable safety profiles for each of the combinations described in Sections [A17-2.6](#) and [A17-2.7](#), treatment with

atezolizumab plus tiragolumab plus chemotherapy (cisplatin and 5-FU) may have promising therapeutic potential for patients with advanced, metastatic esophageal cancer.

A17-3 **RATIONALE FOR DOSE AND SCHEDULE FOR**
ATEZO+TIRAGOLUMAB+CISPLATIN+5-FU ARM

[REDACTED]

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Refer to the Tiragolumab Investigator's Brochure for additional details.

A17-4 MATERIALS AND METHODS SPECIFIC TO ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM

A17-4.1 TREATMENT IN ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM

A17-4.1.1 Formulation, Packaging, and Handling

A17-4.1.1.1 Atezolizumab

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

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

A17-4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied in [REDACTED]-mL glass vials. The vials contain [REDACTED] mL of tiragolumab drug product and are buffered in histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI. The approximate concentration of tiragolumab antibody in the vials is [REDACTED] mg/mL.

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

A17-4.1.1.3 Cisplatin

For information on the formulation, packaging, and handling of cisplatin, refer to the local prescribing information.

A17-4.1.1.4 5-Fluorouracil

For information on the formulation, packaging, and handling of 5-FU, refer to the local prescribing information.

A17-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Tiragolumab + Cisplatin + 5-FU arm will receive treatment as outlined in [Table A17-1](#) 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). [REDACTED]

**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

Table A17-1 Treatment Regimen for Atezo + Tiragolumab + Cisplatin + 5-FU Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle • Cisplatin 80 mg/m² IV on Day 1 of each cycle ^{a, b} • 5-FU 800 mg/m²/24 hours IV (continuous) on Days 1–5 of each cycle ^b

5-FU = 5-fluorouracil; Atezo = atezolizumab.

^a Cisplatin treatment will be capped after 6 doses. Initial cisplatin dose should take into consideration patient's creatinine clearance levels (see [Table A17-5](#)).

^b Infusion times for cisplatin and 5-FU may be adapted in accordance with local standard practice.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under "special situations" as explained in Section 5.3.5.12. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or tiragolumab are available.

A17-4.1.2.1 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 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A17-2](#).

**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

Table A17-2 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, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. - Atezolizumab should be infused over 60 ($\pm$ 15) minutes. - After the infusion of atezolizumab, the patient begins a 30-minute observation period. - If clinically indicated, vital signs should be recorded every 15 ($\pm$ 5) minutes during the infusion and at 30 ($\pm$ 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 infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, 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 ($\pm$ 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. - If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 ($\pm$ 10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in [Appendix 6](#).

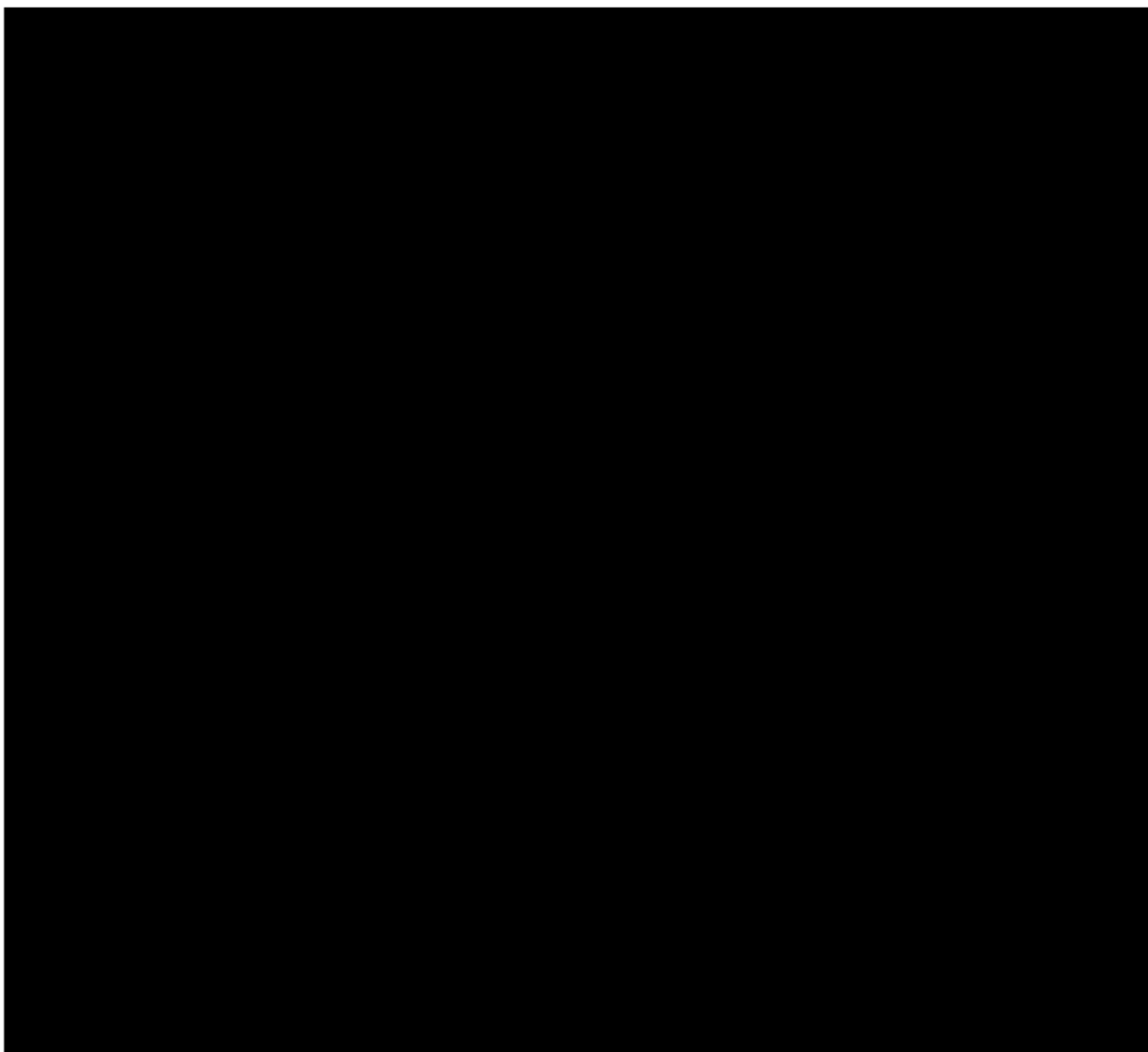
No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in [Section A17-5.1.6.3](#). Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment 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.

A17-4.1.2.2 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 A17-3](#).

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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 5](#). Tiragolumab infusions will be administered per the instructions outlined in [Table A17-3](#).



Guidelines for medical management of IRRs for tiragolumab are provided in [Appendix 6](#).

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section [A17–5.1.6.3](#). 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

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A17-4.1.2.3 Cisplatin and 5-Fluorouracil

Cisplatin will be administered by IV infusion over 120 minutes at a dose of 80 mg/m² on Day 1 of each 21-day cycle and capped at 6 doses. 5-FU will be administered by continuous IV infusion over Days 1–5 (120 hours) at a dose of 800 mg/m²/24 hours starting on Day 1 of each 21-day cycle.

Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Cisplatin treatment will continue for a total of 6 cycles, unless unacceptable toxicity occurs or the patient is withdrawn from study treatment for any reason. Treatment with 5-FU may be continued as long as patients experience clinical benefit in the opinion of the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression) after an integrated assessment of radiographic data, tissue biopsy results (if available), and clinical status.

Guidelines for cisplatin and 5-FU dose modification, treatment interruption, and discontinuation because of toxicities are provided in Section [A17-5.1.6](#).

Cisplatin and 5-FU 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.

A17-4.2 CONCOMITANT THERAPY FOR ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU 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 10 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.

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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 5](#)).

A17-4.2.2 Cautionary Therapy for Atezo + Tiragolumab + Cisplatin + 5-FU Arm

A17-4.2.2.1 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 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 tiragolumab therapy (refer to [Appendix 6](#) for details).

A17-4.2.2.2 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 [A17-4.2.3](#)) may be used during the study at the discretion of the investigator.

A17-4.2.2.3 Cautionary Therapy Related to Cisplatin

Caution should be used when co-administering nephrotoxic (e.g., cephalosporins, aminoglycosides, or amphotericin B or contrast media) or ototoxic (e.g., aminoglycosides, loop diuretics) medicinal products that will potentiate the toxic effect of cisplatin on the kidneys and auditory function. Starting a new anti-convulsant treatment with phenytoin is strictly contraindicated during cisplatin therapy.

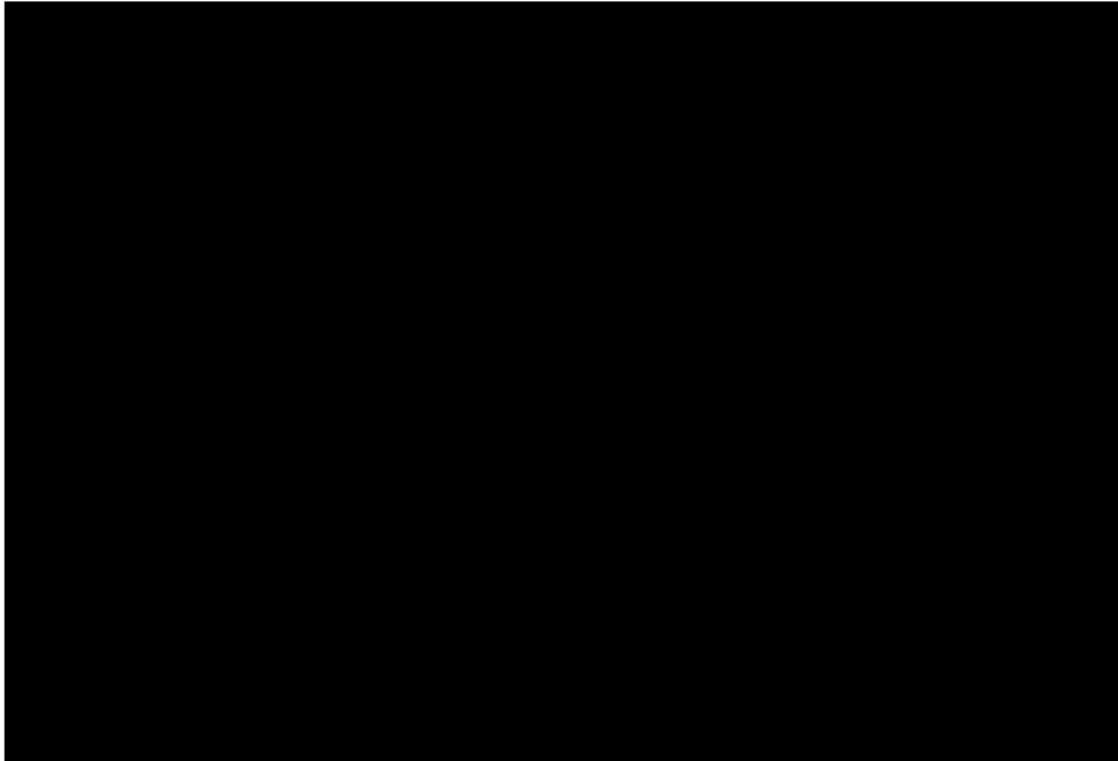
A17-4.2.2.4 Cautionary Therapy Related to 5-Fluorouracil

Elevated coagulation times, as evidenced by increases above baseline international normalization ratio (INR), have been reported in patients taking warfarin concomitantly with 5-FU. Patients receiving warfarin with 5-FU should be monitored closely with frequent INR.

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(Esophageal Cancer Cohort)**

A17-4.2.3 Prohibited Therapy for Atezo + Tiragolumab + Cisplatin + 5-FU Arm

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

- 
-
-
-
-

**A17-4.3 CONTRACEPTION REQUIREMENTS FOR
ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM**

Contraception requirements for men and women in the
Atezo + Tiragolumab + Cisplatin + 5-FU 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, for 90 days after the final dose of tiragolumab, for 6 months after the final dose of cisplatin, and for 6 months after the final dose of 5-FU.

A woman is considered to be of childbearing potential if she is postmenarcheal, 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.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable 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 90 days after the final dose of tiragolumab, for 6 months after the final dose of cisplatin, and for 6 months after the final dose of 5-FU 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 acceptable 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.

A17-5 ASSESSMENT OF SAFETY FOR ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM

A17-5.1 SAFETY PLAN FOR ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, tiragolumab, cisplatin, and 5-FU in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A17-5.1.1](#), [A17-5.1.2](#), [A17-5.1.3](#), [A17-5.1.4](#), and [A17-5.1.5](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A17-5.1.6](#).

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 atezolizumab, tiragolumab, cisplatin, and 5-FU 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 [5.2-5.6](#). An Internal

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Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections 3.1.6 and 3.1.7.

A17–5.1.1 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 HLH. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A17–5.1.2 Risks Associated with Tiragolumab

Although 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 immune-mediated adverse events).

Refer to [Appendix 6](#) of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

A17–5.1.2.1 Infusion-Related Reactions

Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

The majority of events were mild to moderate and manageable.

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

Refer to Section [A17-4.1.2.2](#) for detailed guidance on administration of tiragolumab in this study. Refer to [Appendix 5](#) for guidance on anaphylaxis precautions and [Appendix 6](#) for guidance on management of IRRs.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

[REDACTED]

[REDACTED]

[REDACTED]

A17–5.1.2.4 Immune-Mediated Adverse Events

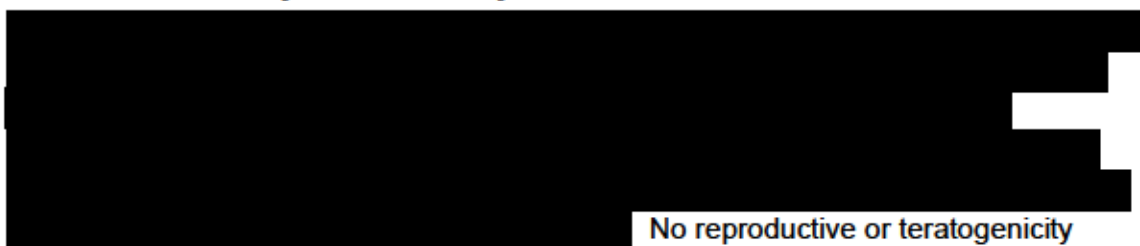
Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT^{-/-}), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT^{-/-} and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT^{-/-} mice developed severe EAE (Joller et al. 2011).

[REDACTED]

Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.4).

Management guidelines for individual suspected immune-mediated adverse events are provided in Section A17–5.1.6.

A17–5.1.2.5 Embryofetal Toxicity



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.

A17–5.1.3 Risks Associated with Cisplatin

Cisplatin is known to cause myelosuppression, ototoxicity, and nephrotoxicity. Cisplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for cisplatin-related adverse events.

For more details regarding the safety profile of cisplatin, see the prescribing information for cisplatin.

A17–5.1.4 Risks Associated with 5-Fluorouracil

5-FU is known to cause diarrhea, nausea, vomiting, stomatitis, cardiotoxicity, hepatotoxicity, hand–foot syndrome, and hematologic toxicity.

Patients must have adequate liver function, as manifested by measurements of serum levels of total bilirubin, hepatic transaminases, and alkaline phosphatase, to be eligible for this study. Patients with diseases that affect liver function, such as viral hepatitis, will be excluded. Hepatic parameters will be assessed prior to each treatment cycle.

Patients will be monitored for other 5-FU–associated adverse events as described above.

For more details regarding the safety profile of 5-FU, refer to the 5-FU prescribing information.

A17–5.1.5 Risks Associated with Combination Use of Atezolizumab, Tiragolumab, Cisplatin, and 5-Fluorouracil

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab plus tiragolumab plus cisplatin plus 5-FU:



**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

A17-5.1.6 Management of Patient Who Experience Specific Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm

A17-5.1.6.1 Dose Modifications

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

For management of drug-related toxicities, the dose of cisplatin may be reduced by 20 mg/m² (one dose level) up to two times and the dose of 5-FU may be reduced by 200 mg/m² (one dose level) up to two times, as outlined below:

Table A17-4 Cisplatin and 5-FU Dose Adjustment

	Initial Dose	First Dose Reduction	Second Dose Reduction
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²
5-FU	800 mg/m ² /24 hours	600 mg/m ² /24 hours	400 mg/m ² /24 hours

5-FU = 5-fluorouracil.

Table A17-5 Cisplatin Dose Adjustment for Creatinine Clearance

Creatinine Clearance (mL/min)				
	≥ 60	> 50 to < 60	> 40 to ≤ 50	≤ 40
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²	Permanently discontinue

Creatinine clearance (CrCl) is calculated by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} (\times 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

If further dose reduction is indicated for cisplatin and/or 5-FU after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient may continue other study treatments at the investigator's discretion. All dose reductions for cisplatin and 5-FU are permanent.

A17-5.1.6.2 Treatment Interruption for Toxicities

[REDACTED]

The Medical Monitor is available to advise as needed.

Atezolizumab and tiragolumab treatment may be suspended 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.

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

[REDACTED]

Cisplatin and/or 5-FU treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A17-6](#)). If cisplatin or 5-FU have been withheld for >6 weeks because of toxicity, the patient should be discontinued from the chemotherapy agent. However, cisplatin or 5-FU can be resumed after being withheld for >6 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with cisplatin or 5-FU should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

In the absence of disease progression, cisplatin or 5-FU may be discontinued for toxicity independent of atezolizumab and tiragolumab. Additionally, in the absence of disease progression, [REDACTED] for toxicity independent of cisplatin or 5-FU. Chemotherapy alone or both tiragolumab and atezolizumab in combination together without chemotherapy may be continued as therapy if the patient is likely to derive clinical benefit. The decision to continue these study treatments should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Refer to Section [A17–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A17–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A17-6](#) and [Appendix 6](#).

The investigator may use discretion in adhering to the guidelines for cisplatin and 5-FU described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice, must be followed.

Appendix 17: Study Details Specific to Atezo+Tiragolumab+Cisplatin+5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tiragolumab+Cisplatin+5-FU Arm

Event	Action to Be Taken
Gastrointestinal toxicity	

Appendix 17: Study Details Specific to Atezo+Tiragolumab+Cisplatin+5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tiragolumab+Cisplatin+5-FU Arm (cont.)

[illegible]

Appendix 17: Study Details Specific to Atezo+Tiragolumab+Cisplatin+5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tiragolumab+Cisplatin+5-FU Arm (cont.)

[illegible]

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Hepatic events	

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken

Appendix 17: Study Details Specific to Atezo+Tiragolumab+Cisplatin+5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tiragolumab+Cisplatin+5-FU Arm (cont.)

[illegible]

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity (life-threatening)	
Endocrine events	

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Immune-mediated myocarditis	
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
Dermatologic events	
[REDACTED]	[REDACTED]
[REDACTED]	

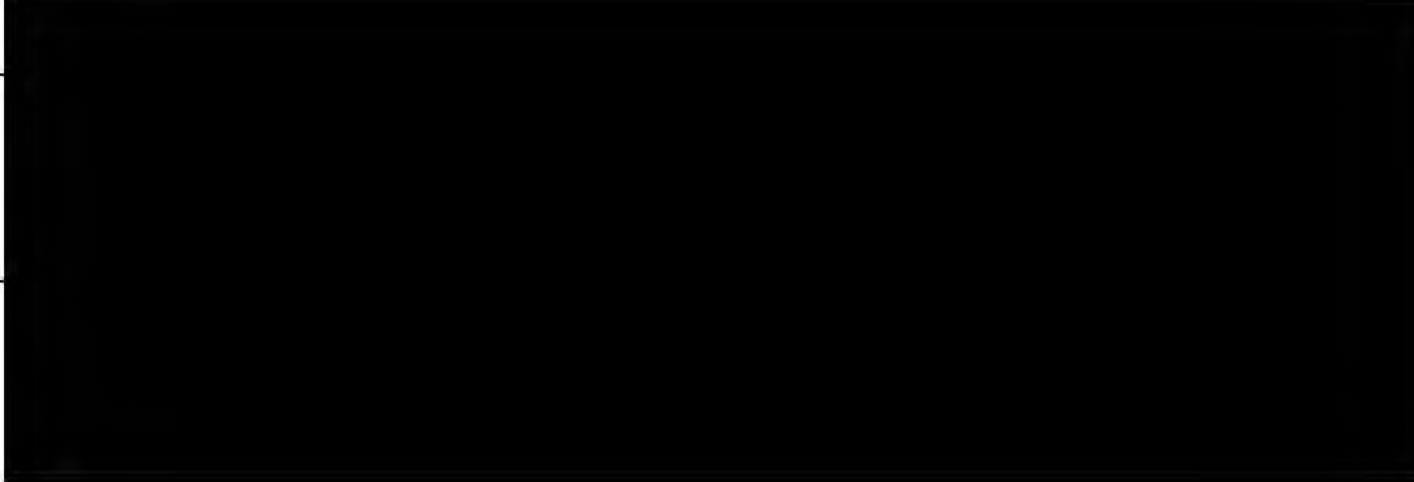
Appendix 17: Study Details Specific to Atezo+Tiragolumab+Cisplatin+5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tiragolumab+Cisplatin+5-FU Arm (cont.)

Event	Action to Be Taken
[REDACTED]	
[REDACTED]	
[REDACTED]	

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
	
Neurologic disorders	
	
	
	

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
Renal events	[REDACTED]
[REDACTED]	
[REDACTED]	

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
	• • • • • • •
Atezolizumab and tiragolumab-related toxicities not described above	
	• • • • • • • •

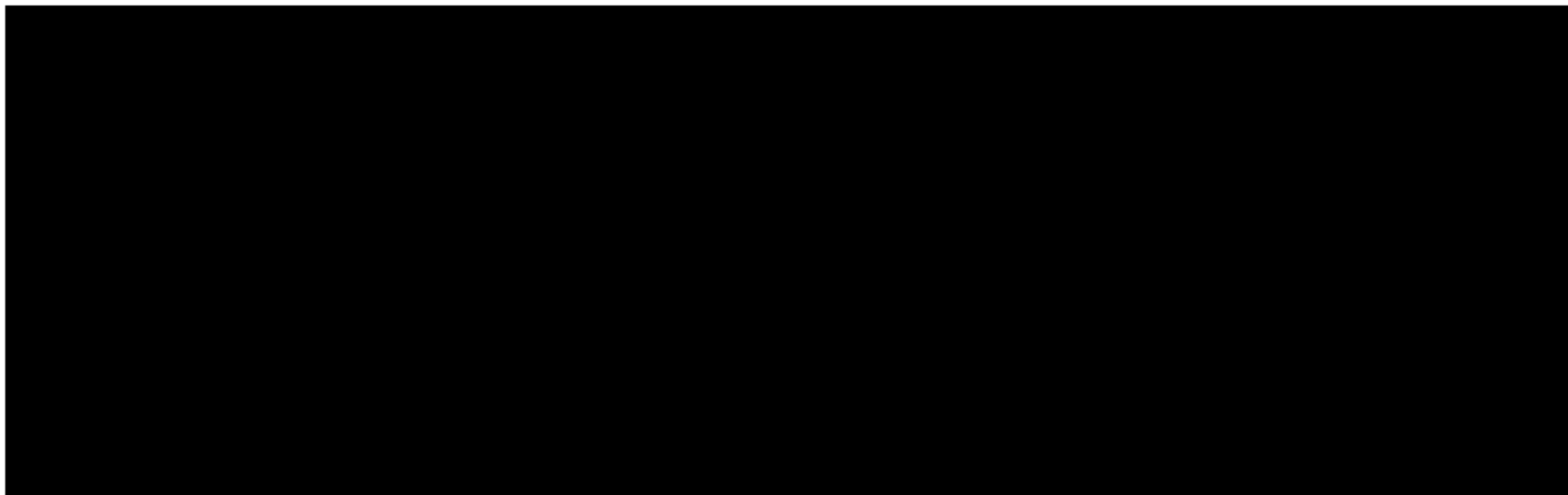
Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
[REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]	[REDACTED]
Chemotherapy-related toxicities not described above	
[REDACTED] • [REDACTED]	[REDACTED]
[REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]	[REDACTED]
[REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]	[REDACTED]

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)



**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

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**A17-5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE
ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM**

A17-5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, within 90 days after the final dose of tiragolumab, within 6 months after the final dose of cisplatin, or within 6 months after the final dose of 5-FU. 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 e-mailing the form using the fax number or e-mail 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/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.

A17-5.3.2 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 90 days after the last dose of tiragolumab, 6 months after the final dose of cisplatin, and 6 months after the final dose of 5-FU. 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 e-mailing the form using the fax number or e-mail 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 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 when updated information on the course and outcome of the pregnancy becomes available. 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 investigator and/or obstetrician.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

A17–5.3.3 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.

A17–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/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).

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

**A17-6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR
ATEZO + TIRAGOLUMAB + CISPLATIN + 5-FU ARM**

Table A17-7 Schedule of Activities for Atezo + Tiragolumab + Cisplatin + 5-FU Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^c
	Days –28 to –1	Cycles 1 ^b			Cycles ≥ 2		Every 3 Months
		Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)		
Informed consent	See Appendix 7.	X ^{ee}					
Molecular profile of esophageal cancer (if available)		Whenever updated information becomes available					
Vital signs ^d		X	X	X	X	X	
Weight ^{dd}		X	X	X	X	X	
Complete physical examination ^e						X	
Limited physical examination ^{f, dd}		X	X	X	X		
ECOG Performance Status ^{dd}		X			X	X	
ECG ^{g, d, dd}		Perform as clinically indicated.					
Hematology ^h		X ^{i, j}	X ⁱ	X ⁱ	X ⁱ	X	
Chemistry ^k		X ^{i, j}	X ⁱ	X ⁱ	X ⁱ	X	
Creatinine clearance ^l		X			X		
C-reactive protein		X ^{i, j}			X ⁱ		
TSH, free T3 (or total T3), and free T4 ^m		X ^{i, j, m}				X	
Pregnancy test ^o		X ^{i, j}			X ⁱ	X	X ^o

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-7 Schedule of Activities for Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^c
		Cycles 1 ^b			Cycles ≥2		
	Days –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months
Urinalysis ^p		Perform as clinically indicated ⁱ					
Serum autoantibody sample ^q		Perform if a patient experiences a suspected immune-mediated adverse event					
Blood sample for RBR (optional) ^r	See Appendix 7.	x					
Tumor biopsy		x ^s					
Tumor response assessments		x ^{t,u}					
Concomitant medications ^v		x	x	x	x	x	
Adverse events ^w		x	x	x	x	x ^w	x ^w
Atezolizumab administration ^{x,y}		x			x		
Tiragolumab administration ^{y,z}		x			x		
Cisplatin administration ^{y,aa}		x			x		
5-FU administration ^{y,bb}		x			x		
Survival follow-up and anti-cancer treatment							x ^{cc}

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-7 Schedule of Activities for Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

5-FU = 5-fluorouracil; [REDACTED] Atezo = atezolizumab; CT = computed tomography; Discon. = Discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = Treatment; TSH = thyroid-stimulating hormone.

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 will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments.
- ^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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 ($\pm$ 5) minutes during and 30 ($\pm$ 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 ($\pm$ 10) minutes after the infusion. For the first infusion of tiragolumab, vital signs should be measured within [REDACTED] minutes prior to the infusion and every [REDACTED] minutes during and [REDACTED] minutes after the infusion. For subsequent infusions of tiragolumab, vital signs should be measured within [REDACTED] minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and [REDACTED] minutes after the infusion.
- ^e Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^h Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ⁱ Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.
- ^j If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^k Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-7 Schedule of Activities for Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

^l Creatinine clearance is calculated by the method of Cockcroft and Gault (1976) (see [Table A17-5](#)).

^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.)

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 treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

^p Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

^q Autoantibody testing includes anti-nuclear antibody, anti-double-stranded DNA antibody, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional timepoints may be considered.

^r Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

^s 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 3.1.1](#) for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. In addition, patients enrolled during the expansion phase will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible), unless on-treatment tissue samples have already been collected, and determined to be evaluable. See [Section 4.5.6](#) for tissue sample requirements.

^t Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 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 3.1.1](#) for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-7 Schedule of Activities for Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

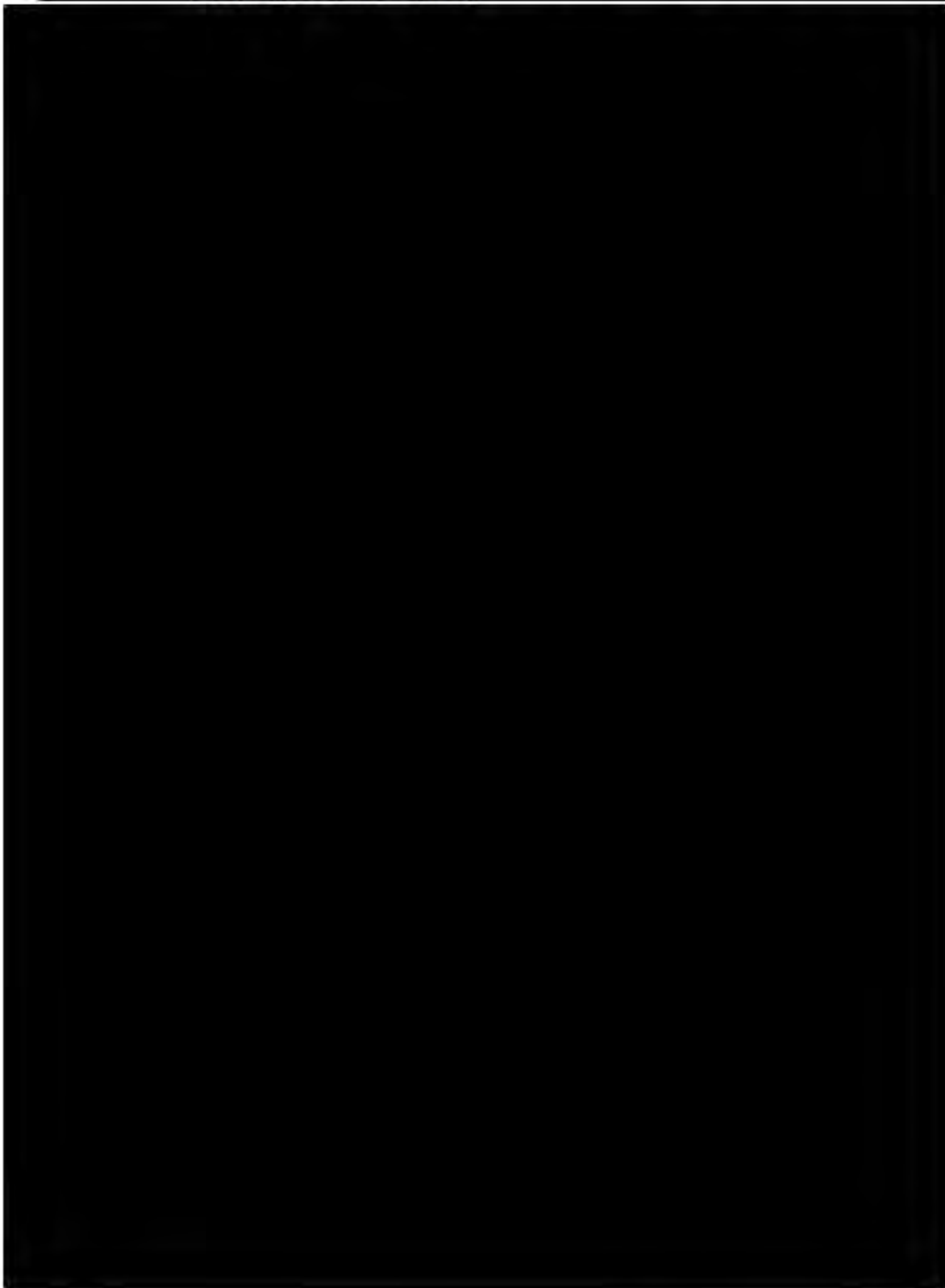
- ^u All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ^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 10 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 last 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 135 days after the last dose of study treatment or until initiation of 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 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 ($\pm$ 15) minutes. Subsequent infusions will be delivered over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^y Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^z 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 [REDACTED] minutes. Subsequent infusions will be delivered over [REDACTED] minutes if the previous infusion was tolerated without infusion-associated adverse events, or [REDACTED] minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^{aa} Cisplatin will be administered by IV infusion at a dose of 80 mg/m² over 120 minutes on Day 1 of the first six 21-day cycles. Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.
- ^{bb} 5-FU will be administered by continuous IV infusion at a dose of 800 mg/m²/24 hours over Days 1–5 (120 hours) on Day 1 of each 21-day cycle. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A17-7 Schedule of Activities for Atezo + Tiragolumab + Cisplatin + 5-FU Arm (cont.)

- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).
- ^{dd} Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^{ee} If a patient decides to continue treatment beyond progression, an additional written consent form from the patient is required at the time of initial disease progression to acknowledge deferring other treatment options in favor of continuing study treatment.

**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**



**Appendix 17: Study Details Specific to Atezo + Tiragolumab + Cisplatin + 5-FU Arm
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Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

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A18–1 BACKGROUND ON ATEZO+CISPLATIN+5-FU ARM

A18–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) 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.

A18–2 RATIONALE FOR ATEZO+CISPLATIN+5-FU ARM

A18–2.1 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

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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, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Several studies have reported PD-L1 expression in esophageal cancer and revealed that higher expression of PD-L1 predicted poorer survival in patients (Ohigashi et al. 2005; Chen et al. 2014; Dhupar et al. 2017; Zhao et al. 2018). These data suggest that PD-L1 status as a predictor of prognosis for patients with esophageal cancer and provide the rationale for developing novel immunotherapies of targeting PD-L1 pathway. There is an ongoing study of atezolizumab monotherapy in Chinese patients with locally advanced or metastatic solid tumors who had exhausted all available standard treatment options (NCT02825940).



A18-2.2 COMBINED INHIBITION OF THE PD-L1/PD-1 PATHWAY WITH CHEMOTHERAPY

In nonclinical immune competent mouse tumor models, chemotherapy treatment with multiple classes of chemotherapeutic agents resulted in activation or increase of tumor infiltrating CD8+ T cells, whereas there was a depletion of peripheral immune cells, including CD8+ T cells (Belvin et al. 2016). Combination of anti-PD-L1 with several chemotherapeutic agents showed combination efficacy, correlating with the increased activation of tumor infiltrating CD8+ T cells (Belvin et al. 2016). Depending on the immune context of the nonclinical model tested, chemotherapeutic agents showed different mechanisms of activating CD8+ T cells, including increased IFN- γ production, increased Granzyme B levels, and decreased markers of exhaustion (Belvin et al. 2016). Tumor cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses

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compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

Indeed, the addition of PD-L1 and PD-1 checkpoint inhibitors to standard platinum-based chemotherapy demonstrated encouraging anti-tumor activity and acceptable safety in early Phase I and II studies (Giaccone et al. 2015; Langer et al. 2016; Rizvi et al. 2016). In multiple large randomized Phase III trials in different advanced solid tumors, the addition of PD-L1 and PD-1 checkpoint inhibitors to standard chemotherapy led to significantly longer overall survival and progression-free survival for patients compared with chemotherapy alone (Gandhi et al. 2018; Paz-Ares L et al. 2018; Horn L et al. 2018; Schmid P et al. 2018). As a result of these trials, PD-1/PD-L1 checkpoint inhibitors in combination with chemotherapies have been approved by some health authorities, including the FDA, for patients with advanced cancer.

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 IFN- γ production by CD8+ tumor-infiltrating lymphocytes was observed (Vincent et al. 2010). In addition in nonclinical models, oxaliplatin has been shown to enhance immune responses by decreasing T-regulatory cells and myeloid-derived suppressor cells in tumor microenvironment (Sato et al. 2005; Gonzalez-Aparicio et al. 2011), suggesting potential synergy with immunotherapy induced by PD-L1 blockade. Based on this nonclinical and clinical data, these regimens may enhance the efficacy of atezolizumab in patients with esophageal cancer.

A18-2.3 CLINICAL STUDY OF ATEZOLIZUMAB IN COMBINATION WITH CISPLATIN AND 5-FU

Study GO30140 is an ongoing Phase I study that included an arm evaluating the combination of atezolizumab with cisplatin and 5-FU in patients with metastatic esophageal cancer.

As of January 2019, adverse events that have been reported were consistent with the known risks of atezolizumab, 5-FU, and cisplatin. Atezolizumab in combination with chemotherapy has not been associated with additive, severe toxicities (i.e., Grade ≥ 3), indicating that atezolizumab can be safely combined with standard chemotherapy. Efficacy data showed a confirmed ORR in 3 out of 7 patients (42%) (Roche unpublished data on file).

A18-2.4 BENEFIT-RISK ASSESSMENT

The combination of 5-FU and cisplatin is one of the Category 1 recommended regimens by the NCCN for the first-line treatment of advanced or metastatic esophageal cancer. Based on the potential synergistic mechanisms of action of chemotherapy with atezolizumab and the manageable safety and efficacy profile from Study GO30140

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

evaluating atezolizumab in combination with 5-FU and cisplatin, this combination appears to have a favorable benefit–risk profile in advanced/metastatic esophageal cancer patients.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.6.

A18–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + CISPLATIN + 5-FU ARM

[REDACTED]

A18–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + CISPLATIN + 5-FU ARM

A18–4.1 TREATMENT IN ATEZO + CISPLATIN + 5-FU ARM

A18–4.1.1 Formulation, Packaging, and Handling

A18–4.1.1.1 Atezolizumab

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

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

A18–4.1.1.2 Cisplatin

For information on the formulation, packaging, and handling of cisplatin, refer to the local prescribing information.

A18–4.1.1.3 5-Fluorouracil

For information on the formulation, packaging, and handling of 5-FU, refer to the local prescribing information.

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(Esophageal Cancer Cohort)**

A18–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Cisplatin + 5-FU arm will receive treatment as outlined in [Table A18-1](#) 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). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A18-1 Treatment Regimen for Atezo + Cisplatin + 5-FU Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Cisplatin 80 mg/m² IV on Day 1 of each cycle ^{a, b} • 5-FU 800 mg/m²/24 hours IV (continuous) on Days 1–5 of each cycle ^b

5-FU = 5-fluorouracil; Atezo = atezolizumab.

^a Cisplatin treatment will be capped after 6 doses. Initial cisplatin dose should take into consideration patient's creatinine clearance levels (see [Table A18-4](#)).

^b Infusion times for cisplatin and 5-FU may be adapted in accordance with local standard practice.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under "special situations" as explained in Section 5.3.5.12. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available.

A18–4.1.2.1 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 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A18-2](#).

Table A18-2 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, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. - Atezolizumab should be infused over 60 ($\pm$ 15) minutes. - After the infusion of atezolizumab, the patient begins a 30-minute observation period. - If clinically indicated, vital signs should be recorded every 15 ($\pm$ 5) minutes during the infusion and at 30 ($\pm$ 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 infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, 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 ($\pm$ 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. - If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 ($\pm$ 10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in [Appendix 6](#).

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in [Section A18–5.1.5.3](#). 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.

A18–4.1.2.2 Cisplatin and 5-Fluorouracil

Cisplatin will be administered by IV infusion over 120 minutes at a dose of 80 mg/m² on Day 1 of each 21-day cycle and capped at 6 doses. 5-FU will be administered by continuous IV infusion over Days 1–5 (120 hours) at a dose of 800 mg/m²/24 hours starting on Day 1 of each 21-day cycle.

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Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Cisplatin treatment will continue for a total of 6 cycles, unless unacceptable toxicity occurs or the patient is withdrawn from study treatment for any reason. Treatment with 5-FU may be continued as long as patients experience clinical benefit in the opinion of the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression) after an integrated assessment of radiographic data, tissue biopsy results (if available), and clinical status.

Guidelines for cisplatin and 5-FU dose modification, treatment interruption, and discontinuation because of toxicities are provided in Section [A18-5.1.5](#).

Cisplatin and 5-FU 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.

A18-4.2 CONCOMITANT THERAPY FOR ATEZO + CISPLATIN + 5-FU 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 10 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.

A18-4.2.1 Permitted Therapy for Atezo + Cisplatin + 5-FU Arm

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

- Oral contraceptives with a failure rate of < 1% per year (see Section [4.1.3](#))
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)
 - Live, attenuated vaccines are not permitted (see Section [A18-4.2.3](#))
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)

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- 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 may be continued during palliative radiotherapy. Chemotherapy should be interrupted as per institutional standard of care.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, 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 therapies other than those defined as cautionary or prohibited therapies (see Sections [A18-4.2.2](#) and [A18-4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-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 5](#)).

A18-4.2.2 Cautionary Therapy for Atezo + Cisplatin + 5-FU Arm

A18-4.2.2.1 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.

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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 6](#) for details).

A18–4.2.2.2 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 [A18–4.2.3](#)) may be used during the study at the discretion of the investigator.

A18–4.2.2.3 Cautionary Therapy Related to Cisplatin

Caution should be used when co-administering nephrotoxic (e.g., cephalosporins, aminoglycosides, or amphotericin B or contrast media) or ototoxic (e.g., aminoglycosides, loop diuretics) medicinal products that will potentiate the toxic effect of cisplatin on the kidneys and auditory function. Starting a new anti-convulsant treatment with phenytoin is strictly contraindicated during cisplatin therapy.

A18–4.2.2.4 Cautionary Therapy Related to 5-Fluorouracil

Elevated coagulation times, as evidenced by increases above baseline international normalization ratio (INR), have been reported in patients taking warfarin concomitantly with 5-FU. Patients receiving warfarin with 5-FU should be monitored closely with frequent INR.

A18–4.2.3 Prohibited Therapy for Atezo + Cisplatin + 5-FU 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, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section [4.1.4](#), 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 above in Section [A18–4.2.1](#).
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the final dose of atezolizumab.

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- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (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.

A18-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+CISPLATIN+5-FU ARM

Contraception requirements for men and women in the Atezo + Cisplatin + 5-FU 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, for 6 months after the final dose of cisplatin, and for 6 months after the final dose of 5-FU.

A woman is considered to be of childbearing potential if she is postmenarcheal, 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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable 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 6 months after the final dose of cisplatin and for 6 months after the final dose of 5-FU to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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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 acceptable 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.

A18–5 ASSESSMENT OF SAFETY FOR ATEZO+CISPLATIN+5-FU ARM

A18–5.1 SAFETY PLAN FOR ATEZO+CISPLATIN+5-FU ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab, cisplatin, and 5-FU in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A18–5.1.1](#), [A18–5.1.2](#), [A18–5.1.3](#), and [A18–5.1.4](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A18–5.1.5](#).

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 atezolizumab, cisplatin, and 5-FU 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 [5.2–5.6](#). An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections [3.1.6](#) and [3.1.7](#).

A18–5.1.1 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 palsy, 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). Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A18–5.1.2 Risks Associated with Cisplatin

Cisplatin is known to cause myelosuppression, ototoxicity, and nephrotoxicity. Cisplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for cisplatin-related adverse events.

For more details regarding the safety profile of cisplatin, see the prescribing information for cisplatin.

**Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

A18–5.1.3 Risks Associated with 5-Fluorouracil

5-FU is known to cause diarrhea, nausea, vomiting, stomatitis, cardiotoxicity, hepatotoxicity, hand–foot syndrome, and hematologic toxicity.

Patients must have adequate liver function, as manifested by measurements of serum levels of total bilirubin, hepatic transaminases, and alkaline phosphatase, to be eligible for this study. Patients with diseases that affect liver function, such as viral hepatitis, will be excluded. Hepatic parameters will be assessed prior to each treatment cycle.

Patients will be monitored for other 5-FU–associated adverse events as described above.

For more details regarding the safety profile of 5-FU, refer to the 5-FU prescribing information.

A18–5.1.4 Risks Associated with Combination Use of Atezolizumab, Cisplatin, and 5-Fluorouracil

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab plus cisplatin plus 5-FU: immune-mediated toxicities, including HLH (see [Appendix 6](#) for complete list), gastrointestinal toxicities, hepatotoxicity, hematologic toxicity, renal toxicity, cardiac toxicities, and skin toxicities.

A18–5.1.5 Management of Patient Who Experience Specific Adverse Events in the Atezo + Cisplatin + 5-FU Arm

A18–5.1.5.1 Dose Modifications

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

For management of drug-related toxicities, the dose of cisplatin may be reduced by 20 mg/m² (one dose level) up to two times and the dose of 5-FU may be reduced by 200 mg/m²/24 hours (one dose level) up to two times, as outlined below:

Table A18-3 Cisplatin and 5-FU Dose Adjustment

	Initial Dose	First Dose Reduction	Second Dose Reduction
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²
5-FU	800 mg/m ² /24 hours	600 mg/m ² /24 hours	400 mg/m ² /24 hours

5-FU = 5-fluorouracil.

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(Esophageal Cancer Cohort)**

Table A18-4 Cisplatin Dose Adjustment for Creatinine Clearance

Creatinine Clearance (mL/min)				
	≥ 60	> 50 to < 60	> 40 to ≤ 50	≤ 40
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²	Permanently discontinue

Creatinine clearance (CrCl) is calculated by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} (\times 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

If further dose reduction is indicated for cisplatin and/or 5-FU after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient may continue other study treatments at the investigator's discretion. All dose reductions for cisplatin and 5-FU are permanent.

A18-5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab 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 the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed. If study treatment is withheld for > 12 weeks, the patient will be discontinued from study treatment. However, study treatment may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Study treatment 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 study treatment should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended 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.

Cisplatin and/or 5-FU treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A18-4](#)). If cisplatin or

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

5-FU have been withheld for >6 weeks because of toxicity, the patient should be discontinued from the chemotherapy agent. However, cisplatin or 5-FU can be resumed after being withheld for >6 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with cisplatin or 5-FU should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

In the absence of disease progression, cisplatin or 5-FU may be discontinued for toxicity independent of atezolizumab. Additionally, in the absence of disease progression, atezolizumab may be discontinued for toxicity independent of cisplatin or 5-FU. Chemotherapy alone or atezolizumab without chemotherapy may be continued as therapy if the patient is likely to derive clinical benefit. The decision to continue chemotherapy alone or atezolizumab without chemotherapy should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Refer to Section [A18-4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A18-5.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A18-5](#) and [Appendix 6](#).

The investigator may use discretion in adhering to the guidelines for cisplatin and 5-FU described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice, must be followed.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	- Guidelines for management of IRRs and CRS for atezolizumab are provided in Appendix 6. - Guidelines for management of IRRs for cisplatin and 5-FU should be consistent with local clinical practice. - For anaphylaxis precautions, see Appendix 5. - For severe hypersensitivity reactions, permanently discontinue the causative agent.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	- Continue atezolizumab, cisplatin, and 5-FU. - Initiate symptomatic treatment. - Endoscopy is recommended if symptoms persist for > 7 days. - Monitor closely.
Diarrhea or colitis, Grade 2	- Continue 5-FU. Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin for up to 6 weeks after event onset.^a - Initiate symptomatic treatment. - Patient referral to GI specialist is recommended. - For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab.^b If not, permanently discontinue atezolizumab and contact the Medical Monitor.^c <u>First occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin at full dose level with prophylaxis (if possible). If not, permanently discontinue cisplatin. <u>Second occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level with prophylaxis (if possible).^d If not, permanently discontinue cisplatin. <u>Third occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level with prophylaxis (if possible).^d If not, permanently discontinue cisplatin. <u>Fourth occurrence</u>: Permanently discontinue cisplatin.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Diarrhea or colitis, Grade 3	- Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin and 5-FU for up to 6 weeks after event onset. ^a - Refer patient to GI specialist for evaluation and confirmatory biopsy. - Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. ^b If not, permanently discontinue atezolizumab and contact the Medical Monitor. ^c - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level with prophylaxis (if possible). ^d If not, permanently discontinue 5-FU. <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level with prophylaxis (if possible). ^d If not, permanently discontinue cisplatin. <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level with prophylaxis (if possible). ^d If not, permanently discontinue cisplatin. <u>Third occurrence:</u> Permanently discontinue cisplatin.
Diarrhea or colitis, Grade 4	- Withhold 5-FU for up to 6 weeks after event onset. Permanently discontinue atezolizumab and cisplatin and contact the Medical Monitor. ^{c, e} - Refer patient to GI specialist for evaluation and confirmation biopsy. - Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level with prophylaxis (if possible). ^d If not, permanently discontinue 5-FU.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Nausea or vomiting, Grade 3	- Continue atezolizumab. Withhold cisplatin and 5-FU for up to 6 weeks after event onset. - Administer 5-HT3 serotonin receptor antagonist, olanzapine 10mg orally on Days 1–4 chemotherapy, and aprepitant for prophylaxis for future cycles of chemotherapy. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU. <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Third occurrence:</u> Permanently discontinue cisplatin.
Nausea or vomiting, Grade 4	- Withhold cisplatin and 5-FU for up to 6 weeks after event onset. Permanently discontinue atezolizumab and contact the Medical Monitor.^c - Administer 5-HT3 serotonin receptor antagonist, olanzapine 10mg orally on Days 1–4 chemotherapy, and aprepitant for prophylaxis for future cycles of chemotherapy. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU. <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Second occurrence:</u> Permanently discontinue cisplatin.
Stomatitis, Grade 3	- Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin and 5-FU for up to 6 weeks after event onset. - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor. <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin and 5-FU, resume cisplatin and 5-FU reduced by one dose level with prophylaxis (if possible).^d If not, permanently discontinue cisplatin and 5-FU. <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin and 5-FU, resume cisplatin and 5-FU reduced by one dose level with prophylaxis (if possible).^d If not, permanently discontinue cisplatin and 5-FU. <u>Third occurrence:</u> Permanently discontinue cisplatin and 5-FU.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Stomatitis, Grade 4	- Withhold atezolizumab for up to 12 weeks after event onset and withhold 5-FU for up to 6 weeks after event onset. Permanently discontinue cisplatin. ^e - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by two dose levels. ^d If not, permanently discontinue 5-FU.
Hepatic events	
Hepatic event, Grade 1	- Continue atezolizumab, cisplatin, and 5-FU. - Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	- Continue atezolizumab, cisplatin, and 5-FU. - Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: - Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin and 5-FU for up to 6 weeks after event onset. ^a - Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. ^b If not, permanently discontinue atezolizumab and contact the Medical Monitor. ^c - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level. ^d If not, permanently discontinue 5-FU. <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin at full dose level. If not, permanently discontinue cisplatin. <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level. ^d If not, permanently discontinue cisplatin. <u>Third occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level. ^d If not, permanently discontinue cisplatin. <u>Fourth occurrence:</u> Permanently discontinue cisplatin.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Hepatic event, Grade 3	- Withhold cisplatin and 5-FU for up to 6 weeks after event onset. Permanently discontinue atezolizumab and contact the Medical Monitor.^c - Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. - Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU. <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Third occurrence:</u> Permanently discontinue cisplatin.
Hepatic event, Grade 4	- Permanently discontinue atezolizumab, cisplatin, and 5-FU and contact the Medical Monitor.^{c, e} - Manage as per Grade 3 guidelines.
Hematologic toxicity (excluding febrile neutropenia)	
ANC $\geq 1.0 \times 10^9/L$ (1000/ μL) <u>and</u> platelet count to $\geq 75 \times 10^9/L$ (75,000/ μL)	Continue cisplatin, 5-FU, and atezolizumab.
ANC $\geq 1.0 \times 10^9/L$ (1000/ μL) <u>and</u> platelet count to $< 75 \times 10^9/L$ (75,000/ μL)	- Continue atezolizumab. - Cisplatin and 5-FU can be continued with a reduction by one dose level. OR - Withhold cisplatin and 5-FU and assess ANC and platelet counts weekly. - If ANC $\geq 1.0 \times 10^9/L$ (1000/μL) and platelet count improves to $\geq 75 \times 10^9/L$ (75,000/μL) ≤ 6 weeks after event onset, resume cisplatin and 5-FU at full dose level. If not, permanently discontinue cisplatin and 5-FU.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
ANC $< 1.0 \times 10^9/L$ (1000/ μL) and platelet count to $\geq 75 \times 10^9/L$ (75,000/ μL)	- Continue atezolizumab. - Withhold cisplatin and 5-FU and assess ANC and platelet counts weekly. - If ANC improves to $\geq 1.5 \times 10^9/L$ (1500/μL) and platelet count $\geq 75 \times 10^9/L$ (75,000/μL) ≤ 6 weeks after event onset, resume cisplatin and 5-FU. If ANC is 1.0–$1.5 \times 10^9/L$, resume cisplatin and 5-FU reduced by one dose level. ^d If ANC $< 1.0 \times 10^9/L$ (1000/μL), permanently discontinue 5-FU and cisplatin.
ANC $< 1.0 \times 10^9/L$ (1000/ μL) and platelet count to $< 75 \times 10^9/L$ (75,000/ μL)	- Continue atezolizumab. - Withhold cisplatin and 5-FU and assess ANC and platelet counts weekly. - If ANC improves to $\geq 1.5 \times 10^9/L$ (1500/μL) and platelet count $\geq 75 \times 10^9/L$ (75,000/μL) ≤ 6 weeks after event onset, resume cisplatin and 5-FU. If ANC is 1.0–$1.5 \times 10^9/L$ and platelet count $\geq 75 \times 10^9/L$ (75,000/μL), resume cisplatin and 5-FU reduced by one dose level. ^d If ANC $< 1.0 \times 10^9/L$ (1000/μL) and platelet count is $< 75 \times 10^9/L$ (75,000/μL), permanently discontinue 5-FU and cisplatin.
Hematologic toxicity (life-threatening)	
Febrile neutropenia, Grade 3	- Withhold cisplatin, 5-FU, and atezolizumab. - If fever resolves and ANC improves to $\geq 1.0 \times 10^9/L$ (1000/μL) ≤ 6 weeks after event onset, resume cisplatin and 5-FU reduced by one dose level and provide GCSF support. ^d If not, permanently discontinue cisplatin and 5-FU. - If fever resolves and ANC improves to $\geq 1.0 \times 10^9/L$ (1000/μL) ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab.
Febrile neutropenia, Grade 4	- Withhold cisplatin, 5-FU, and atezolizumab. - If fever resolves and ANC improves to $\geq 1.0 \times 10^9/L$ (1000/μL) ≤ 6 weeks after event onset, resume cisplatin and 5-FU reduced by two dose levels and provide GCSF support. ^d If not, permanently discontinue cisplatin and 5-FU. - If fever resolves and ANC improves to $\geq 1.0 \times 10^9/L$ (1000/μL) ≤ 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab.
Endocrine events	
Asymptomatic hypothyroidism	- Continue atezolizumab, cisplatin, and 5-FU. - Initiate treatment with thyroid replacement hormone. - Monitor TSH closely.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Symptomatic hypothyroidism	• Withhold atezolizumab, cisplatin, and 5-FU. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab, cisplatin, and 5-FU when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: • Continue atezolizumab, cisplatin, and 5-FU. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.
Symptomatic hyperthyroidism	• Withhold atezolizumab, cisplatin, and 5-FU. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab, cisplatin, and 5-FU when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab, cisplatin, and 5-FU and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism.^e

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Immune-mediated myocarditis	
Immune-mediated myocarditis, Grade 2	• Continue cisplatin. Permanently discontinue atezolizumab and contact the Medical Monitor. ^c Permanently discontinue 5-FU. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Immune-mediated myocarditis, Grade 3 or 4	• Permanently discontinue atezolizumab, cisplatin, and 5-FU. ^{c, e} • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Dermatologic events	
Dermatologic event, Grade 1	• Continue atezolizumab, cisplatin, and 5-FU. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab, cisplatin, and 5-FU. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin and 5-FU for up to 6 weeks after event onset. ^a • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. ^b If not, permanently discontinue atezolizumab and contact the Medical Monitor. ^c • If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by two dose levels. ^d If not, permanently discontinue 5-FU. • <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level. ^d If not, permanently discontinue cisplatin. • <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level. ^d If not, permanently discontinue cisplatin. • <u>Third occurrence:</u> Permanently discontinue cisplatin.
Dermatologic event, Grade 4	• Withhold 5-FU and contact the Medical Monitor. Permanently discontinue atezolizumab and cisplatin. ^{c, e} • If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by two dose levels. ^d If not, permanently discontinue 5-FU.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab, cisplatin, and 5-FU for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. Contact the Medical Monitor. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above for the management of Grade 3 dermatologic events, pending recommendations from consulted specialist(s). • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab, cisplatin, and 5-FU.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Neurologic disorders	
Immune-mediated neuropathy, Grade 1	- Continue atezolizumab, cisplatin, and 5-FU. - Investigate etiology.
Immune-mediated neuropathy, Grade 2	- Continue 5-FU. Permanently discontinue cisplatin. Withhold atezolizumab for up to 12 weeks after event onset.^a - Investigate etiology. - Initiate treatment as per institutional guidelines and refer patient to neurologist. - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab.^b If not, permanently discontinue atezolizumab and contact the Medical Monitor.^c
Immune-mediated neuropathy, Grade 3	- Withhold 5-FU. Permanently discontinue atezolizumab and cisplatin and contact the Medical Monitor.^c - Refer patient to neurologist. - Initiate treatment as per institutional guidelines. - If event resolves to Grade 2 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU.
Immune-mediated neuropathy, Grade 4	- Permanently discontinue atezolizumab, cisplatin, and 5-FU and contact the Medical Monitor.^c - Refer patient to neurologist. - Initiate treatment as per institutional guidelines.
Cisplatin-related neurotoxicity, Grade 2	Continue atezolizumab and 5-FU. Permanently discontinue cisplatin.
Cisplatin-related neurotoxicity, Grade 3 or 4	- Withhold atezolizumab for up to 12 weeks after event onset and withhold 5-FU for up to 6 weeks after event onset. Permanently discontinue cisplatin. - If event resolves to Grade 2 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab and contact the Medical Monitor. - If event resolves to Grade 2 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU.
Cisplatin-related ototoxicity	Continue atezolizumab and 5-FU. Permanently discontinue cisplatin.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Renal events	
Renal event, Grade 1	- Continue atezolizumab and 5-FU. If CrCl $\geq$ 60 mL/min, continue cisplatin at full dose. If CrCl < 60 mL/min, adjust dose of cisplatin as shown in Table A18-4. - Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	- Continue 5-FU. Withhold atezolizumab for up to 12 weeks after event onset and withhold cisplatin for up to 6 weeks after event onset.^a - Refer patient to renal specialist. - Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. - If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab.^b If not, permanently discontinue atezolizumab and contact the Medical Monitor.^c - If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin based on guidelines for CrCl in Table A18-4. If event does not resolve while withholding cisplatin, permanently discontinue cisplatin.
Renal event, Grade 3 and 4	- Withhold atezolizumab for up to 12 weeks after event onset. Withhold 5-FU and cisplatin for up to 6 weeks after event onset. - Refer patient to renal specialist and consider renal biopsy. - Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month. Atezolizumab should be continued based on the investigator's judgement. Otherwise, permanently discontinue atezolizumab. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU. - If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin based on guidelines for CrCl in Table A18-4. If event does not resolve while withholding cisplatin, permanently discontinue cisplatin.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	- Follow guidelines for atezolizumab in Appendix 6. - Continue cisplatin and 5-FU.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Grade 3	- Follow guidelines for atezolizumab in Appendix 6. - Withhold 5-FU and cisplatin for up to 6 weeks after event onset. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU. <u>First occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Second occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Third occurrence</u>: Permanently discontinue cisplatin.
Grade 4	- Follow guidelines for atezolizumab in Appendix 6. - Permanently discontinue 5-FU. Withhold cisplatin for up to 6 weeks after event onset. <u>First occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Second occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Third occurrence</u>: Permanently discontinue cisplatin.
Chemotherapy-related toxicities not described above	
Grade 1 or 2	Continue atezolizumab, cisplatin, and 5-FU.
Grade 3	- Continue atezolizumab. Withhold 5-FU and cisplatin for up to 6 weeks after event onset. - If event resolves to Grade 1 or better while withholding 5-FU, resume 5-FU reduced by one dose level.^d If not, permanently discontinue 5-FU. <u>First occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Second occurrence</u>: If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. <u>Third occurrence</u>: Permanently discontinue cisplatin.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-5 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Cisplatin + 5-FU Arm (cont.)

Event	Action to Be Taken
Grade 4	• Withhold atezolizumab and cisplatin. Permanently discontinue 5-FU. • If event resolves to Grade 1 or better while withholding atezolizumab, resume atezolizumab. If not, permanently discontinue atezolizumab. • <u>First occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. • <u>Second occurrence:</u> If event resolves to Grade 1 or better while withholding cisplatin, resume cisplatin reduced by one dose level.^d If not, permanently discontinue cisplatin. • <u>Third occurrence:</u> Permanently discontinue cisplatin.

5-FU = 5-fluorouracil; CrCl = creatinine clearance; CRS = cytokine release syndrome; ECMO = extracorporeal membrane oxygenation; IRR = infusion-related reaction; TSH = thyroid-stimulating hormone; VAD = ventricular assist device.

- ^a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- ^b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.
- ^c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.
- ^d All dose reductions for cisplatin and 5-FU are permanent. If further dose reduction is indicated for cisplatin and/or 5-FU after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient may continue other study treatments at the investigator's discretion.
- ^e At first occurrence of Grade 4 event, cisplatin may be withheld for 6 weeks. If event resolves to Grade 1 or better while withholding cisplatin, retreat at a reduced dose of two levels of original dose with prophylaxis (if possible). If not, permanently discontinue cisplatin. At second occurrence of Grade 4 event, permanently discontinue cisplatin.

**A18-5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE
ATEZO + CISPLATIN + 5-FU ARM (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 the Atezo + Cisplatin + 5-FU arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.4.2)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10\times$ upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, or toxic epidermal necrolysis)

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

- Myelitis
- Facial paresis

A18–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO + CISPLATIN + 5-FU ARM

A18–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab, within 6 months after the final dose of cisplatin, or within 6 months after the final dose of 5-FU. 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 e-mailing the form using the fax number or e-mail 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/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.

A18–5.3.2 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 6 months after the final dose of cisplatin or within 6 months after the final dose of 5-FU. 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 e-mailing the form using the fax number or e-mail 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 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 when updated information on the course and outcome of the pregnancy becomes available. 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 investigator and/or obstetrician.

A18–5.3.3 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.

A18–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/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).

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

A18-6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + CISPLATIN + 5-FU ARM

Table A18-6 Schedule of Activities for Atezo + Cisplatin + 5-FU Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^c
		Cycles 1 ^b			Cycles ≥ 2		
	Days -28 to -1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months
Informed consent	See Appendix 7.	X ^{dd}					
Molecular profile of esophageal cancer (if available)		Whenever updated information becomes available					
Vital signs ^d		X	X	X	X	X	
Weight ^{ee}		X	X	X	X	X	
Complete physical examination ^e						X	
Limited physical examination ^{f, ee}		X	X	X	X		
ECOG Performance Status ^{ee}		X			X	X	
ECG ^{g, ee}		Perform as clinically indicated.					
Hematology ^h		X ^{i, j}	X ⁱ	X ⁱ	X ⁱ	X	
Chemistry ^k		X ^{i, j}	X ⁱ	X ⁱ	X ⁱ	X	
Creatinine clearance ^l		X			X		
C-reactive protein		X ^{i, j}			X ⁱ		
TSH, free T3 (or total T3), and free T4 ^m		X ^{i, j, m}				X	
Viral serology (if applicable) ⁿ					X ⁿ	X ⁿ	X ⁿ
Pregnancy test ^o		X ^{i, j}			X ⁱ	X	X ^o
Urinalysis ^p		Perform as clinically indicated. ⁱ					
Serum autoantibody sample ^q		Perform if a patient experiences a suspected immune-mediated adverse event.					

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)
Table A18-6 Schedule of Activities for Atezo + Cisplatin + 5-FU Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^c Every 3 Months
		Cycles 1 ^b			Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		
PK samples	See Appendix 7.	Refer to Table A18-7.					
ADA samples		Refer to Table A18-7.					
Biomarker samples		Refer to Table A18-7.					
Blood sample for RBR (optional) ^r		x					
Tumor biopsy		x ^s					
Tumor response assessments		x ^{t,u}					
Concomitant medications ^v		x	x	x	x	x	
Adverse events ^w		x	x	x	x	x ^w	x ^w
Atezolizumab administration ^{x,y}		x			x		
Cisplatin administration ^{y,z}		x			x		
5-FU administration ^{y,aa}		x			x		
Survival follow-up and anti-cancer treatment							x ^{bb}

5-FU = 5-fluorouracil; ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; Discon. = Discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = Treatment; TSH = thyroid-stimulating hormone.

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 It is recommended that treatment be initiated no later than 7 days after randomization.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-6 Schedule of Activities for Atezo + Cisplatin + 5-FU Arm (cont.)

- ^c Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments.
- ^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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 Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^h Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ⁱ Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.
- ^j If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^k Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.
- ^l Creatinine clearance is calculated by the method of Cockcroft and Gault (1976) (see [Table A18-4](#)).
- ^m TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ⁿ Patients with a positive quantitative HBV DNA at screening (must be < 500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests every 3 months (± 7 days) during treatment, at treatment discontinuation (± 7 days), and at 3, 6, 9, and 12 months (± 14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥ 500 IU/mL, consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended. The Medical Monitor is available to advise as needed.
- ^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 treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^p Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-6 Schedule of Activities for Atezo + Cisplatin + 5-FU Arm (cont.)

- ^q Autoantibody testing includes anti-nuclear antibody, anti-double-stranded DNA antibody, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional timepoints may be considered.
- ^r Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.
- ^s 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 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. In addition, patients enrolled during the expansion phase will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.6 for tissue sample requirements.
- ^t Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 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 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or 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 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 CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ^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 10 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 last 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 135 days after the last dose of study treatment or until initiation of 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.

Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm (Esophageal Cancer Cohort)

Table A18-6 Schedule of Activities for Atezo + Cisplatin + 5-FU Arm (cont.)

- ^x 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 ($\pm$ 15) minutes. Subsequent infusions will be delivered over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^y Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^z Cisplatin will be administered by IV infusion at a dose of 80 mg/m² over 120 minutes on Day 1 of the first six 21-day cycles. Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.
- ^{aa} 5-FU will be administered by continuous IV infusion at a dose of 800 mg/m²/24 hours over Days 1–5 (120 hours) on Day 1 of each 21-day cycle. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.
- ^{bb} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).
- ^{cc} Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^{dd} If a patient decides to continue treatment beyond progression, an additional written consent form from the patient is required at the time of initial disease progression to acknowledge deferring other treatment options in favor of continuing study treatment.

**Appendix 18: Study Details Specific to Atezo + Cisplatin + 5-FU Arm
(Esophageal Cancer Cohort)**

Table A18-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Cisplatin + 5-FU Arm: Preliminary and Expansion Phase

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma, serum, PBMC)^a
	30 minutes after the end of atezolizumab infusion	Atezolizumab PK (serum)
Day 15 of Cycle 1	At visit	Biomarker (plasma, serum)^a
Day 1 of Cycle 2	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma, serum, PBMC)^a
Day 1 of Cycle 3	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma, serum)^a
Day 1 of Cycle 8	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma, serum)^a
Day 1 of Cycle 12	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum)
Day 1 of Cycle 16 and every fourth cycle thereafter	Prior to study treatment	- Atezolizumab PK (serum) - Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	- Atezolizumab PK (serum) - Atezolizumab ADA (serum) - Biomarker (plasma, serum)^a

ADA=anti-drug antibody; Atezo = atezolizumab; PK=pharmacokinetic.

Note: On the basis of emerging PK or biomarker data, the number of PK or biomarker samples may be reduced and/or the timing of those samples may be modified.

^a Biomarker collections are applicable only after approval from local regulatory authorities.

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(Esophageal Cancer Cohort)**

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(Esophageal Cancer Cohort)**

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Appendix 19

Study Details Specific to Cisplatin+5-FU Control Arm (Esophageal Cancer Cohort)

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A19-1 MATERIALS AND METHODS SPECIFIC TO CISPLATIN+5-FU CONTROL ARM**A19-1.1 TREATMENT IN CISPLATIN+5-FU CONTROL ARM****A19-1.1.1 Formulation, Packaging, and Handling****A19-1.1.1.1 Cisplatin**

For information on the formulation, packaging, and handling of cisplatin, refer to the local prescribing information.

A19-1.1.1.2 5-Fluorouracil

For information on the formulation, packaging, and handling of 5-FU, refer to the local prescribing information.

A19-1.1.2 Dosage, Administration, and Compliance

Patients in the Cisplatin+5-FU control arm will receive treatment as outlined in [Table A19-1](#) until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A19-1 Treatment Regimen for Cisplatin+5-FU Control Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Cisplatin 80 mg/m² IV on Day 1 of the first six cycles ^{a, b} • 5-FU 800 mg/m²/24 hours IV (continuous) on Days 1–5 of each cycle ^b

5-FU=5-fluorouracil.

^a Cisplatin treatment will be capped after 6 doses. Initial cisplatin dose should take into consideration patient's creatinine clearance levels (see [Table A19-4](#)).

^b Infusion times for cisplatin and 5-FU may be adapted in accordance with local standard practice.

Treatment will be administered according to institutional standards in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under "special situations" as explained in [Section 5.3.5.12](#). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

A19–1.1.2.1 Cisplatin and 5-Fluorouracil

Cisplatin will be administered by IV infusion over 120 minutes at a dose of 80 mg/m² on Day 1 of the first six 21-day cycles. 5-FU will be administered by continuous IV infusion over Days 1–5 (120 hours) at a dose of 800 mg/m²/24 hours starting on Day 1 of each 21-day cycle.

Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Premedication with steroids should be limited when clinically feasible, because of their immunosuppressant effects. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Cisplatin treatment will continue for a total of 6 cycles, unless unacceptable toxicity occurs or the patient is withdrawn from study treatment for any reason.

Guidelines for cisplatin and 5-FU dose modification, treatment interruption, and discontinuation because of toxicities are provided in [Section A19–2.1.2](#).

Cisplatin and 5-FU 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.

A19–1.1.3 Stage 2 Treatment

Patients who experience disease progression per RECIST v1.1 will be given the option of receiving a different treatment combination during Stage 2 of the study, as outlined in [Table A19-2](#), provided they meet eligibility criteria (see [Section 4.1](#)) and the Stage 2 arm is open for enrollment. Patients who experience unacceptable toxicity may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of disease progression or unacceptable toxicity 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 (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table A19-2 Stage 2 Treatment Regimen Available for the Cisplatin+5-FU Control Arm

Study Treatment	Appendix
Atezo+ Tiragolumab	Appendix 20

Atezo= atezolizumab.

A19–1.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR CISPLATIN+5-FU CONTROL 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 10 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.

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for the control agents, refer to the local label for each agent.

A19–1.3 CONTRACEPTION REQUIREMENTS FOR CISPLATIN+5-FU CONTROL ARM

Contraception requirements for men and women in the Cisplatin+5-FU control 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 6 months after the final dose of cisplatin and for 6 months after the final dose of 5-FU.

A woman is considered to be of childbearing potential if she is postmenarcheal, 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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable 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 6 months after the final dose of cisplatin and for 6 months after the final dose of 5-FU 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 acceptable 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.

A19-2 ASSESSMENT OF SAFETY FOR CISPLATIN+5-FU CONTROL ARM

A19-2.1 SAFETY PLAN FOR CISPLATIN+5-FU CONTROL ARM

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 cisplatin and 5-FU 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 5.2–5.6. An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections 3.1.6 and 3.1.7.

A19-2.1.1 Risks Associated with Cisplatin or 5-Fluorouracil

Risks associated with cisplatin or with 5-FU are described in the local prescribing information for each agent.

A19-2.1.2 Management of Patient Who Experience Specific Adverse Events in the Cisplatin+5-FU Control Arm

Dose modification guidelines are for the management of chemotherapy-specific toxicities. The treating physician may use discretion in modifying the dose modification guidelines described below, depending on the severity of toxicity and an assessment of

Appendix 19: Cisplatin+ 5-FU Control Arm (Esophageal Cancer Cohort)

the benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care.

A19-2.1.2.1 Dose Modifications

For management of drug-related toxicities, the dose of cisplatin may be reduced by 20 mg/m² (one dose level) up to two times and the dose of 5-FU may be reduced by 200 mg/m²/24 hours (one dose level) up to two times, as outlined below:

Table A19-3 Cisplatin and 5-FU Dose Adjustment

	Initial Dose	First Dose Reduction	Second Dose Reduction
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²
5-FU	800 mg/m ² /24 hours	600 mg/m ² /24 hours	400 mg/m ² /24 hours

5-FU = 5-fluorouracil.

Table A19-4 Cisplatin Dose Adjustment for Creatinine Clearance

Creatinine Clearance (mL/min)				
	≥ 60	> 50 to < 60	> 40 to ≤ 50	≤ 40
Cisplatin	80 mg/m ²	60 mg/m ²	40 mg/m ²	Permanently discontinue

Creatinine clearance (CrCl) is calculated by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} \quad (\times 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

If further dose reduction is indicated for cisplatin and/or 5-FU after two dose reductions, that drug (or both drugs, if applicable) should be discontinued, but the patient may continue other study treatments at the investigator's discretion. All dose reductions for cisplatin and 5-FU are permanent.

A19-2.1.2.2 Treatment Interruption for Toxicities

Cisplatin and/or 5-FU treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see [Table A19-3](#)). If cisplatin or

5-FU have been withheld for >6 weeks because of toxicity, the patient should be discontinued from the chemotherapy agent.

A19–2.1.2.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events can be found in the local prescribing information for cisplatin and 5-FU.

A19–2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR CISPLATIN + 5-FU CONTROL ARM (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 the control arm include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A19–2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE CISPLATIN+5-FU ARM

A19–2.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the final dose of cisplatin or within 6 months after the final dose of 5-FU. 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 e-mailing the form using the fax number or e-mail 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/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.

A19-2.3.2 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 6 months after the final dose of cisplatin or within 6 months after the final dose of 5-FU. 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 e-mailing the form using the fax number or e-mail 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 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 when updated information on the course and outcome of the pregnancy becomes available. 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 investigator and/or obstetrician.

A19-2.3.3 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.

A19-2.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/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).

Appendix 19: Cisplatin+5-FU Control Arm (Esophageal Cancer Cohort)

A19-3 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR CISPLATIN + 5-FU ARM

Table A19-5 Schedule of Activities for Cisplatin+5-FU Control Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Stage 2 Screening (see Appendix 7) ^e or Treat. Discon. ^d	Follow-Up ^d
	Days –28 to –1	Cycles 1 ^b			Cycles ≥2		Every 3 Months
		Day 1	Day 8 (± 3 days)	Day 15 (±3 days)	Day 1 (±3 days)		
Molecular profile of esophageal cancer (if available)	See Appendix 7.	Whenever updated information becomes available					
Vital signs ^e		x	x	x	x	x	
Weight ^{dd}		x	x	x	x	x	
Complete physical examination ^f						x	
Limited physical examination ^{g, dd}		x	x	x	x		
ECOG Performance Status ^{dd}		x			x	x	
ECG ^{h, dd}		Perform as clinically indicated.					
Hematology ⁱ		x ^{j, k}	x ^j	x ^j	x ^j	x	
Chemistry ^l		x ^{j, k}	x ^j	x ^j	x ^j	x	
Creatinine clearance ^m		x			x		
C-reactive protein		x ^{j, k}			x ^j		
TSH, free T3 (or total T3), and free T4 ⁿ		x ^{j, k, n}				x	
Viral serology (if applicable) ^o						x ^o	
Pregnancy test ^p		x ^{j, k}			x ^j	x	x ^p
Urinalysis ^q		Perform as clinically indicated. ⁱ					
Plasma, serum, and PBMC sample for biomarkers ^r		x		x	x ^r	x	

Appendix 19: Cisplatin +5-FU Control Arm (Esophageal Cancer Cohort)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) ^a				Stage 2 Screening (see Appendix 7) ^c or Treat. Discon. ^d	Follow-Up ^d Every 3 Months
		Cycles 1 ^b			Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)		
Blood sample for RBR (optional) ^s	See Appendix 7.	x					
Tumor biopsy		x ^t					
Tumor response assessments		x ^{u, v, w}					
Concomitant medications ^x		x	x	x	x	x	
Adverse events ^y		x	x	x	x	x ^y	x ^y
Cisplatin administration ^{z, aa}		x			x		
5-FU administration ^{aa, bb}		x			x		
Survival follow-up and anti-cancer treatment							x ^{cc}

5-FU=5-fluorouracil; ADA=anti-drug antibody; CT=computed tomography; Discon.=Discontinuation; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; HBV=hepatitis B virus; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen=screening; T3=triiodothyronine; T4=thyroxine; Treat.=Treatment; TSH=thyroid-stimulating hormone.

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 It is recommended that treatment be initiated no later than 7 days after randomization.

^c Patients who experience disease progression per RECIST v1.1 and patients who experience unacceptable toxicity will be given the option of receiving a different treatment combination during Stage 2 of the study (provided Stage 2 is open for enrollment; see Section A19–1.1.3) and will undergo screening assessments to determine eligibility (see Appendix 7). Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible. Study-specific details for the Stage 2 treatment regimen are provided in Appendix 20. Written informed consent must be obtained before performing screening evaluations for Stage 2, except as noted in footnote "w" below.

Appendix 19: Cisplatin +5-FU Control Arm (Esophageal Cancer Cohort)

- ^d Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which disease progression is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments after completing the treatment discontinuation visit.
- ^e Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Vital signs should be measured within 60 minutes prior to the infusion. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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. 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 carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.
- ^m Creatinine clearance is calculated by the method of Cockcroft and Gault (1976) (see Section 4.1.3.1).
- ⁿ TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).
- ^o Assessment to be performed only for patients undergoing Stage 2 screening.
- ^p 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 treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^q Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^r PBMC samples should only be collected at the Day 1 visit of Cycles 1 and 2. After Cycle 1, biomarker samples (plasma and serum) should only be collected on Day 1 of Cycles 2, 4, and 8 only.
- ^s Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.
- ^t Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or disease progression per RECIST v1.1, if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.

Appendix 19: Cisplatin + 5-FU Control Arm (Esophageal Cancer Cohort)

- ^u Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ^v 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 CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ^w For patients who undergo screening for Stage 2: 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 disease progression per RECIST v1.1 or unacceptable toxicity 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.
- ^x 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.
- ^y After initiation of study treatment, all adverse events will be reported until 30 days after the last 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 135 days after the last dose of study treatment or until initiation of 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.
- ^z Cisplatin will be administered by IV infusion at a dose of 80 mg/m² over 120 minutes on Day 1 of the first six 21-day cycles. Prior to treatment with cisplatin, patients must receive appropriate pretreatment hydration. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.
- ^{aa} Treatment will continue until unacceptable toxicity or disease progression per RECIST v1.1.
- ^{bb} 5-FU will be administered by continuous IV infusion at a dose of 800 mg/m²/24 hours over Days 1–5 (120 hours) on Day 1 of each 21-day cycle. Prophylactic anti-emetics (e.g., 5-HT₃ receptor antagonists) may be administered per local practice. All medications must be recorded on the appropriate Concomitant Medications eCRF.

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- ^{cc} After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).
- ^{dd} Assessment may be performed within 24 hours prior to dosing during the treatment period.

A19-4 REFERENCES

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine.
Nephron 1976;16:31–41.

Appendix 20

Study Details Specific to Atezo+Tiragolumab Arm (Esophageal Cancer Cohort)

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A20–1 BACKGROUND ON ATEZO+TIRAGOLUMAB ARM

A20–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to 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 has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, myasthenia gravis, myocarditis, and nephritis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab (Tecentriq®) 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.

A20–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human immunoglobulin G1 (IgG1)/kappa mAb derived in Open Monoclonal Technology rats that binds T-cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif [ITIM] domains (TIGIT) and prevents its interaction with the poliovirus receptor (PVR). The recombinant antibody is produced in Chinese hamster ovary cells and consists of two heavy chains [REDACTED] and two light chains [REDACTED].

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. TIGIT is an immunoglobulin (Ig) super family member

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expressed on subsets of activated T cells and natural killer (NK) cells, and found highly expressed in tumor tissue and in tumor-infiltrating immune cells in many human cancers, including, but not limited to NSCLC, breast cancer, multiple myeloma (MM), and non-Hodgkin lymphoma (NHL). In multiple tumor types, TIGIT is coordinately expressed with PD-1 (Yu et al. 2009; Johnston et al. 2014; Manieri et al. 2017). Genetic ablation or antibody blockade of TIGIT has been shown to enhance NK cell killing, CD4+ and CD8+ T-cell activation, and effector function in vitro and in vivo in nonclinical models (Yu et al. 2009; Johnston et al. 2014; Stanietsky et al. 2009; Joller et al. 2011). In the nonclinical tumor models, TIGIT interacted with high affinity to CD155 (also known as PVR), which also has an activating counter-receptor CD226. Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells (Yu et al. 2009; Stanietsky et al. 2009; Johnston et al. 2014).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the 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 studies.

A20-2 RATIONALE FOR ATEZO+TIRAGOLUMAB ARM

A20-2.1 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;

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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, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Several studies have reported PD-L1 expression in esophageal cancer and revealed that higher expression of PD-L1 predicted poorer survival in patients (Ohigashi et al. 2005; Chen et al. 2014; Dhupar et al. 2017; Zhao et al. 2018). These data suggest that PD-L1 status as a predictor of prognosis for patients with esophageal cancer and provide the rationale for developing novel immunotherapies of targeting PD-L1 pathway. There is an ongoing study of atezolizumab monotherapy in Chinese patients with locally advanced or metastatic solid tumors who had exhausted all available standard treatment options (NCT02825940).

[REDACTED]

A20-2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin super family (Yu et al. 2009). 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 checkpoint immune-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 and melanoma, and hematological tumors, such as MM and NHL, and fluorescence activated cell sorting analysis of T cells isolated from fresh tumor

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samples revealed that TIGIT and PD-1 are also co-expressed on tumor infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey et al. 2018). TIGIT expression ranged from 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's 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 genetically deficient mice and blocking antibodies, have revealed a key role for TIGIT in regulating T-cell responses in cancer. Together these data support the hypothesis that anti-TIGIT may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A20–2.3 COMBINED INHIBITION OF THE PD-L1/PD-1 AND TIGIT PATHWAYS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. 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 suppressed the effector function of chronically stimulated CD8+ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, respectively targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab in patients, may enhance the efficacy of PD1/PDL1 blockade across different cancer types.

A20–2.4 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290) and one ongoing clinical study in patients with hematological malignancies (Study GO40136).

A20–2.4.1 Clinical Study of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors.

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As of the data cutoff date of 3 December 2018, 42 patients have been enrolled in the Phase Ia portion of the study of tiragolumab monotherapy evaluating dose levels from 2 mg to 1200 mg, and 164 patients have been enrolled in Phase Ib portion evaluating dose levels of tiragolumab from 2 mg to 600 mg, in combination with 1200-mg atezolizumab.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence or severity of adverse events in the Phase Ia or Phase Ib portions of Study GO30103 in solid tumors have been determined for tiragolumab as a single agent and in combination with atezolizumab.

[REDACTED]

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile is observed to be consistent across different solid tumor indications.

A20-2.4.2 Clinical Study of Tiragolumab in Combination with Atezolizumab in PD-L1–Selected Patients with NSCLC

Study GO40290 is a global, multicenter, randomized, blinded, placebo-controlled Phase II study designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable, or metastatic PD-L1–selected NSCLC.

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS $\geq 1\%$ were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). Of the enrolled patients, 43.0% of patients had a TPS $\geq 50\%$ relative to 57.0% of patients with a TPS 1%–49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

In the ITT population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in 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%, 75.0%]) than the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8%, 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 group over the placebo plus atezolizumab group (stratified HR=0.57 [95% CI: 0.37, 0.90]; median PFS 5.4 vs. 3.6 months, respectively). In the subgroup of patients with TPS $\geq 50\%$, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified HR=0.33 [95% CI: 0.15, 0.72]; median PFS not estimable vs. 3.9 months, respectively) (Roche unpublished data on file).

To 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. Immune-mediated adverse events were balanced between

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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. Discontinuation due to adverse events was low (approximately 6% in both arms).

[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

A20-2.5 BENEFIT-RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications support a favorable benefit-risk profile for tiragolumab. This favorable benefit-risk profile, the potential for TIGIT as a target for therapeutic intervention in esophageal cancer, and the significant unmet medical need in this indication are key reasons for the current study.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment, please refer to Section 1.6.

A20-3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+TIRAGOLUMAB ARM

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Appendix 20: Study Details Specific to Atezo + Tiragolumab Arm (Esophageal Cancer Cohort)



Refer to the Tiragolumab Investigator's Brochure for additional details.

A20-4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRAGOLUMAB ARM

A20-4.1 TREATMENT IN ATEZO + TIRAGOLUMAB ARM

A20-4.1.1 Formulation, Packaging, and Handling

A20-4.1.1.1 Atezolizumab

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

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

A20-4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied in [REDACTED]-mL glass vials. The vials contain [REDACTED] mL of tiragolumab drug product and are buffered in histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI. The approximate concentration of tiragolumab antibody in the vials is [REDACTED] mg/mL.

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

Appendix 20: Study Details Specific to Atezo + Tiragolumab Arm (Esophageal Cancer Cohort)

A20-4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Tiragolumab arm will receive treatment as outlined in [Table A20-1](#) 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). Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1 or unacceptable toxicity in Stage 1. However, it is recommended that patients begin Stage 2 treatment as soon as possible.

Table A20-1 Treatment Regimen for Atezo + Tiragolumab Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle

Atezo = atezolizumab.

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

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under “special situations” as explained in [Section 5.3.5.12](#). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or tiragolumab are available.

A20-4.1.2.1 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 5](#). Atezolizumab infusions will be administered per the instructions outlined in [Table A20-2](#).

Table A20-2 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, pulse oximetry, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. - Atezolizumab should be infused over 60 ($\pm$ 15) minutes. - After the infusion of atezolizumab, the patient begins a 30-minute observation period. - If clinically indicated, vital signs should be recorded every 15 ($\pm$ 5) minutes during the infusion and at 30 ($\pm$ 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 infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, 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 ($\pm$ 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. - If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 ($\pm$ 10) minutes after the infusion.

Guidelines for medical management of IRRs for atezolizumab are provided in [Appendix 6](#).

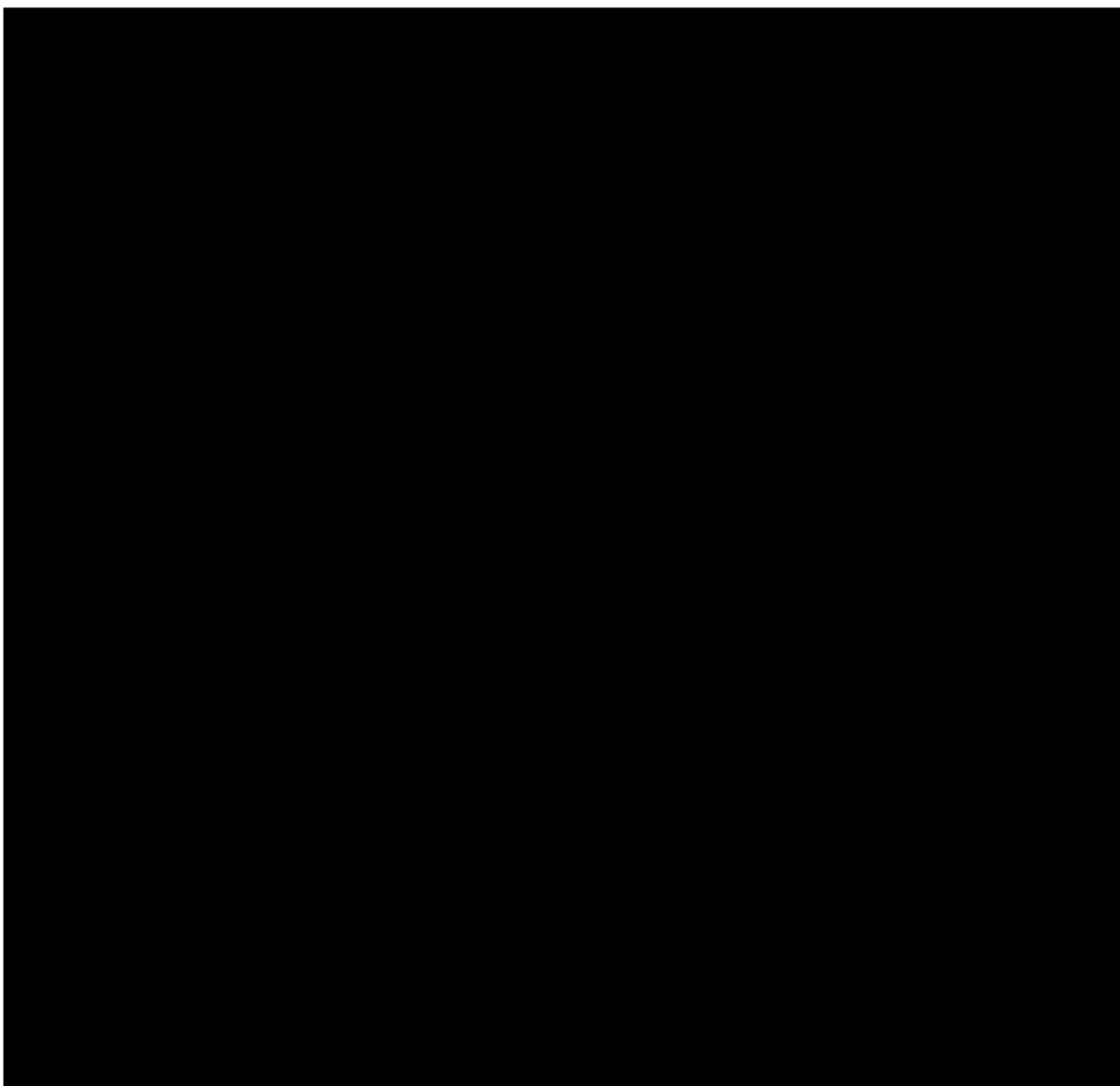
No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in [Section A20–5.1.4.2](#). Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment 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.

A20–4.1.2.2 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 A20-3](#).

Appendix 20: Study Details Specific to Atezo+Tiragolumab Arm (Esophageal Cancer Cohort)

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 5](#). Tiragolumab infusions will be administered per the instructions outlined in [Table A20-3](#).



Guidelines for medical management of IRRs for tiragolumab are provided in [Appendix 6](#).

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in [Section A20–5.1.4.2](#). 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.

A20-4.2 CONCOMITANT THERAPY FOR ATEZO+TIRAGOLUMAB 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 10 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.

A20-4.2.1 Permitted Therapy for Atezo+Tiragolumab Arm

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

-

Appendix 20: Study Details Specific to Atezo+Tiragolumab Arm (Esophageal Cancer Cohort)

Premedication with antihistamines, antipyretics, 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 therapies other than those defined as cautionary or prohibited therapies (see Sections [A20-4.2.2](#) and [A20-4.2.3](#)) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-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 5](#)).

A20-4.2.2 Cautionary Therapy for Atezo+Tiragolumab Arm

A20-4.2.2.1 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 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.

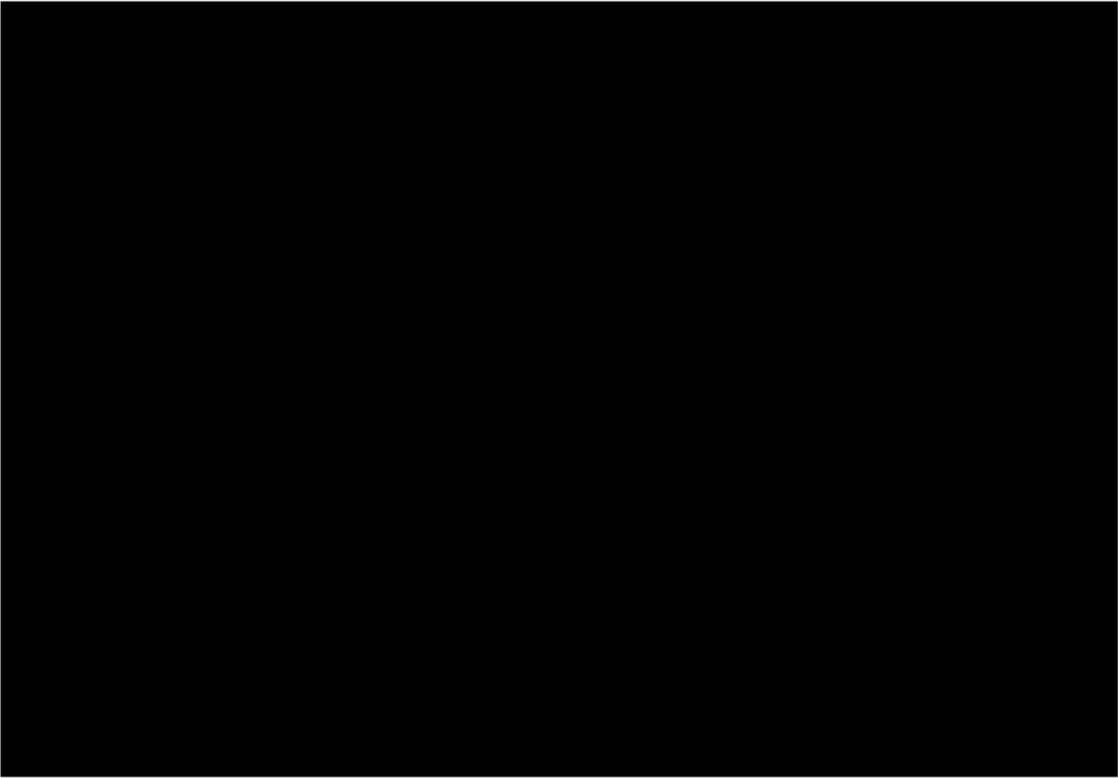
Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and tiragolumab therapy (refer to [Appendix 6](#) for details).

A20-4.2.2.2 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 [A20-4.2.3](#)) may be used during the study at the discretion of the investigator.

A20-4.2.3 Prohibited Therapy for Atezo+Tiragolumab Arm

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

- 
-
-
-
-

A20-4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+TIRAGOLUMAB ARM

Contraception requirements for men and women in the Atezo+Tiragolumab 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 and for 90 days after the final dose of tiragolumab.

A woman is considered to be of childbearing potential if she is postmenarcheal, 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.

Appendix 20: Study Details Specific to Atezo + Tiragolumab Arm (Esophageal Cancer Cohort)

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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable 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 90 days after the final dose of tiragolumab. 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 acceptable 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.

A20-5 ASSESSMENT OF SAFETY FOR ATEZO+TIRAGOLUMAB ARM

A20-5.1 SAFETY PLAN FOR ATEZO+TIRAGOLUMAB ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections [A20-5.1.1](#), [A20-5.1.2](#), and [A20-5.1.3](#)). Guidelines for management of patients who experience specific adverse events are provided in Section [A20-5.1.4](#).

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 atezolizumab and tiragolumab 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 [5.2-5.6](#). An Internal Monitoring Committee and Scientific Oversight Committee will review safety data throughout the study as described in Sections [3.1.6](#) and [3.1.7](#).

A20–5.1.1 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 HLH. Refer to [Appendix 6](#) of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A20–5.1.2 Risks Associated with Tiragolumab

[REDACTED]

[REDACTED]. Although 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 immune-mediated adverse events).

Refer to [Appendix 6](#) of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

A20–5.1.2.1 Infusion-Related Reactions

[REDACTED]

[REDACTED] Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

[REDACTED]

[REDACTED] The majority of events were mild to moderate and manageable.

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

Refer to Section [A20–4.1.2.2](#) for detailed guidance on administration of tiragolumab in this study. Refer to [Appendix 5](#) for guidance on anaphylaxis precautions and [Appendix 6](#) for guidance on management of IRRs.

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[REDACTED]

[REDACTED]

[REDACTED]

A20–5.1.2.4 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT^{-/-}), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT^{-/-} and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT^{-/-} mice developed severe EAE (Joller et al. 2011).

[REDACTED]

Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.4).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 6.

A20–5.1.2.5 Embryofetal Toxicity

[REDACTED] (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. 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.

A20–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

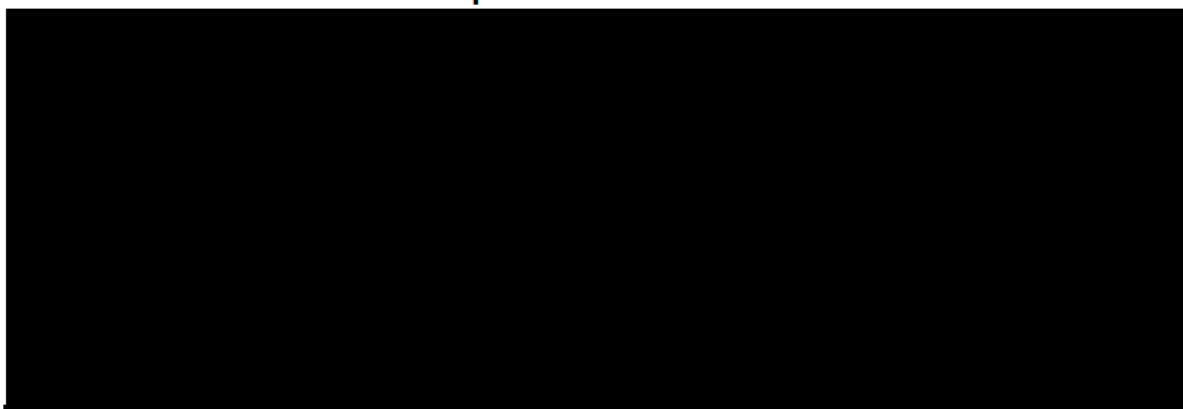
Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see [A20–5.1](#)) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section [4.1.4](#)). Patients previously treated with approved or experimental cancer immunotherapy will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see [A20–2.4.2](#)), patients with active infection (including, but not limited to, HIV, hepatitis B virus, hepatitis C virus, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Section [4.1.4](#)).

A20–5.1.4 Management of Patient Who Experience Specific Adverse Events in the Atezo + Tiragolumab Arm

A20–5.1.4.1 Dose Modifications

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

A20–5.1.4.2 Treatment Interruption for Toxicities



The Medical Monitor is available to advise as needed.

Atezolizumab and tiragolumab treatment may be suspended 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.

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



Refer to Section [A20–4.1.2](#) for information on dose interruptions for reasons other than toxicity.

A20–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in [Table A20-4](#) and [Appendix 6](#).

Appendix 20: Study Details Specific to Atezo+Tiragolumab Arm (Esophageal Cancer Cohort)

For cases in which management guidelines are not covered in [Appendix 6](#), patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A20-4 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tiragolumab Arm

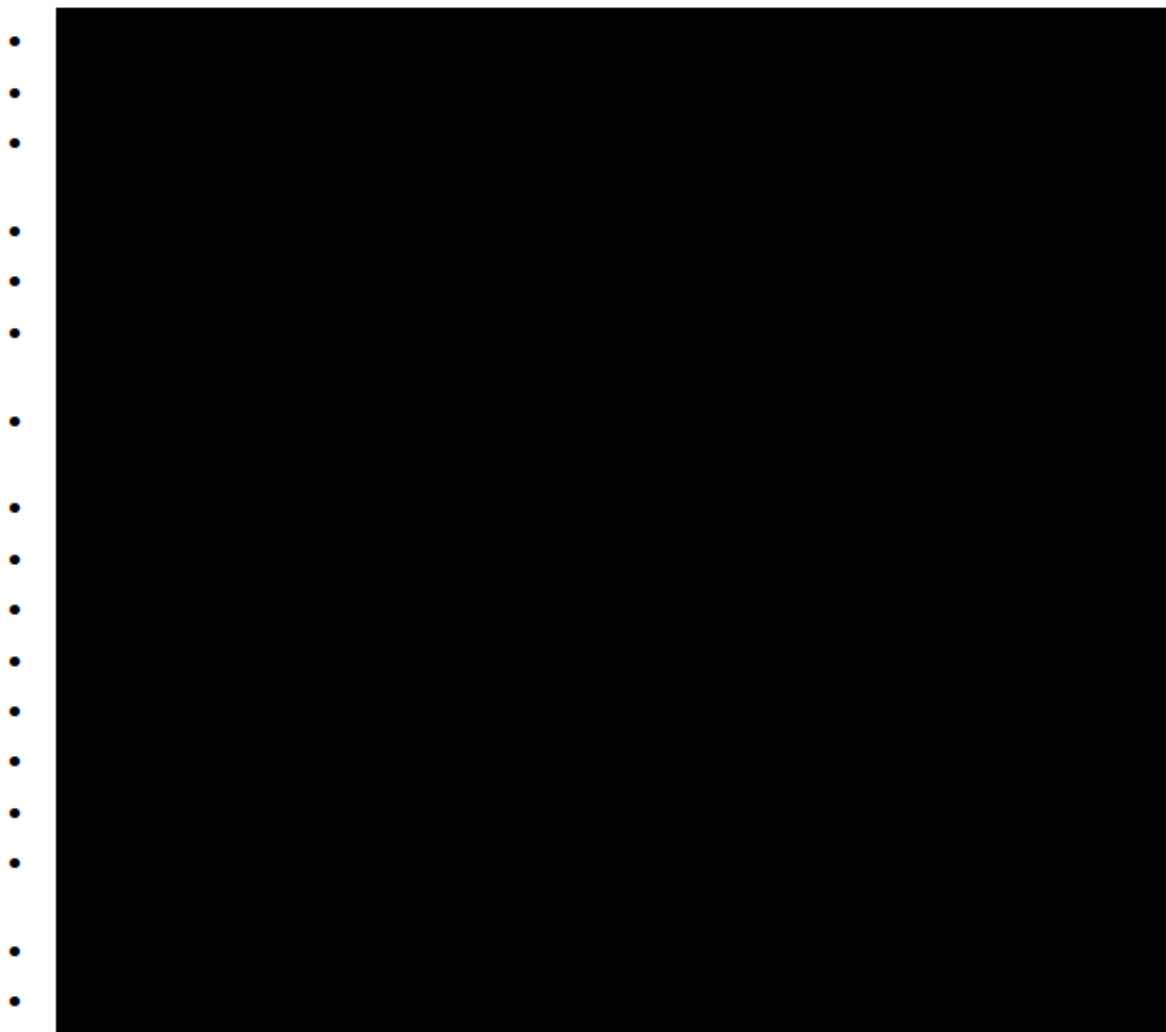
Event	Action to Be Taken
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

A20-5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO+TIRAGOLUMAB ARM (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 the Atezo+Tiragolumab arm are as follows:

- [REDACTED]
- [REDACTED]

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A20–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO+TIRAGOLUMAB ARM

A20–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab. 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 e-mailing the form using the fax number or e-mail 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/birth defect in the

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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.

A20–5.3.2 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 90 days after the last dose of tiragolumab. 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 e-mailing the form using the fax number or e-mail 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 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 when updated information on the course and outcome of the pregnancy becomes available. 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 investigator and/or obstetrician.

A20–5.3.3 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.

A20–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/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

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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](#)).

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A20–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+TIRAGOLUMAB ARM

Table A20-5 Schedule of Activities for Atezo+Tiragolumab Arm

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^c
	Days –28 to –1	Cycles 1 ^b			Cycles ≥ 2		Every 3 Months
		Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		
Informed consent	See Appendix 7.	X ^{aa}					
Molecular profile of esophageal cancer (if available)		Whenever updated information becomes available					
Vital signs ^d		X	X	X	X	X	
Weight ^z		X	X	X	X	X	
Complete physical examination ^e						X	
Limited physical examination ^{f, z}		X	X	X	X		
ECOG Performance Status ^z		X			X	X	
ECG ^{g, z}		Perform as clinically indicated.					
Hematology ^h		X ^{i, j}	X ⁱ	X ⁱ	X ⁱ	X	
Chemistry ^k		X ^{i, j}	X ⁱ	X ⁱ	X ⁱ	X	
C-reactive protein		X ^{i, j}			X ⁱ		
TSH, free T3 (or total T3), and free T4 ^l		X ^{i, j, l}				X	
Pregnancy test ⁿ		X ^{i, j}			X ⁱ	X	X ⁿ
Urinalysis ^o		Perform as clinically indicated. ⁱ					

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Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) ^a				Treat. Discon. ^c	Follow-Up ^c
	Days –28 to –1	Cycles 1 ^b			Cycles ≥2		Every 3 Months
		Day 1	Day 8 (± 3 days)	Day 15 (±3 days)	Day 1 (±3 days)		
Serum autoantibody sample ^p		Perform if a patient experiences a suspected immune-mediated adverse event					
Blood sample for RBR (optional) ^q	See Appendix 7.	x					
Tumor response assessments		x ^{r, s}					
Concomitant medications ^t		x	x	x	x	x	
Adverse events ^u		x	x	x	x	x ^u	x ^u
Atezolizumab administration ^{v, w}		x			x		
Tiragolumab administration ^{w, x}		x			x		
Survival follow-up and anti-cancer treatment							x ^y

Atezo = atezolizumab; CT = computed tomography; Discon. = Discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = Treatment; TSH = thyroid-stimulating hormone.

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 Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1 or unacceptable toxicity in Stage 1. However, it is recommended that patients begin Stage 2 treatment as soon as possible.

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- ^c Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the treatment discontinuation visit. Patients will then undergo follow-up assessments.
- ^d Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, 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 ($\pm$ 5) minutes during and 30 ($\pm$ 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 ($\pm$ 10) minutes after the infusion. For the first infusion of tiragolumab, vital signs should be measured within [REDACTED] minutes prior to the infusion and every [REDACTED] minutes during and [REDACTED] minutes after the infusion. For subsequent infusions of tiragolumab, vital signs should be measured within [REDACTED] minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and [REDACTED] minutes after the infusion.
- ^e Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^g It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^h Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).
- ⁱ Laboratory tests must be performed within 96 hours prior to dosing during the treatment period.
- ^j If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.
- ^k Chemistry panel (serum or plasma) includes bicarbonate or carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.
- ^l TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.)
- ^m [REDACTED]
- ⁿ 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 treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

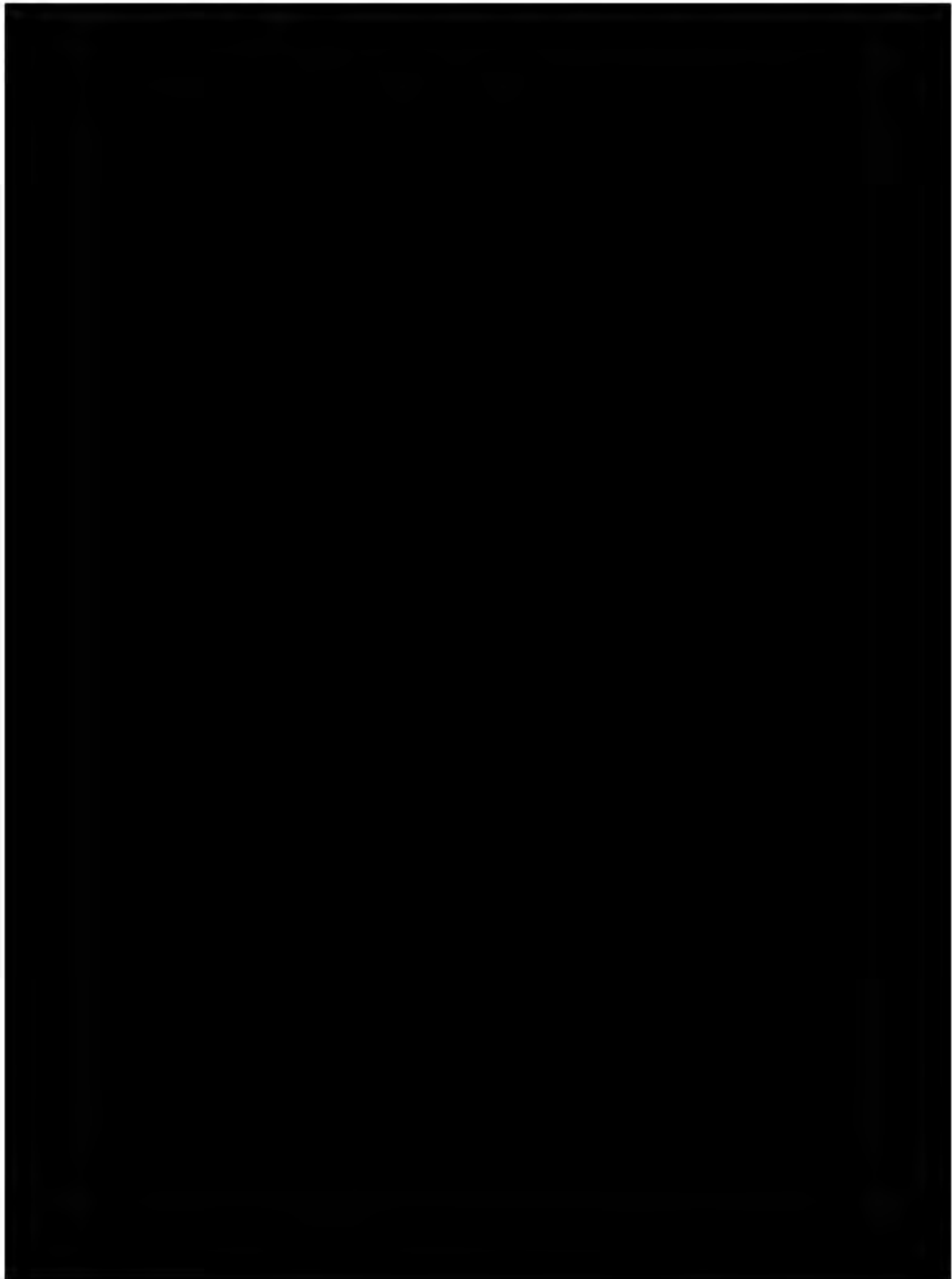
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- ° Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ° Autoantibody testing includes anti-nuclear antibody, anti-double-stranded DNA antibody, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional timepoints may be considered.
- ° Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.
- ° Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 12 months following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 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 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non-protocol-specified anti-cancer therapy.
- ° 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 CT 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). At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. 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. Refer to Section 4.5.5 for further details on tumor assessments.
- ° 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.
- ° After initiation of study treatment, all adverse events will be reported until 30 days after the last 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 135 days after the last dose of study treatment or until initiation of 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.

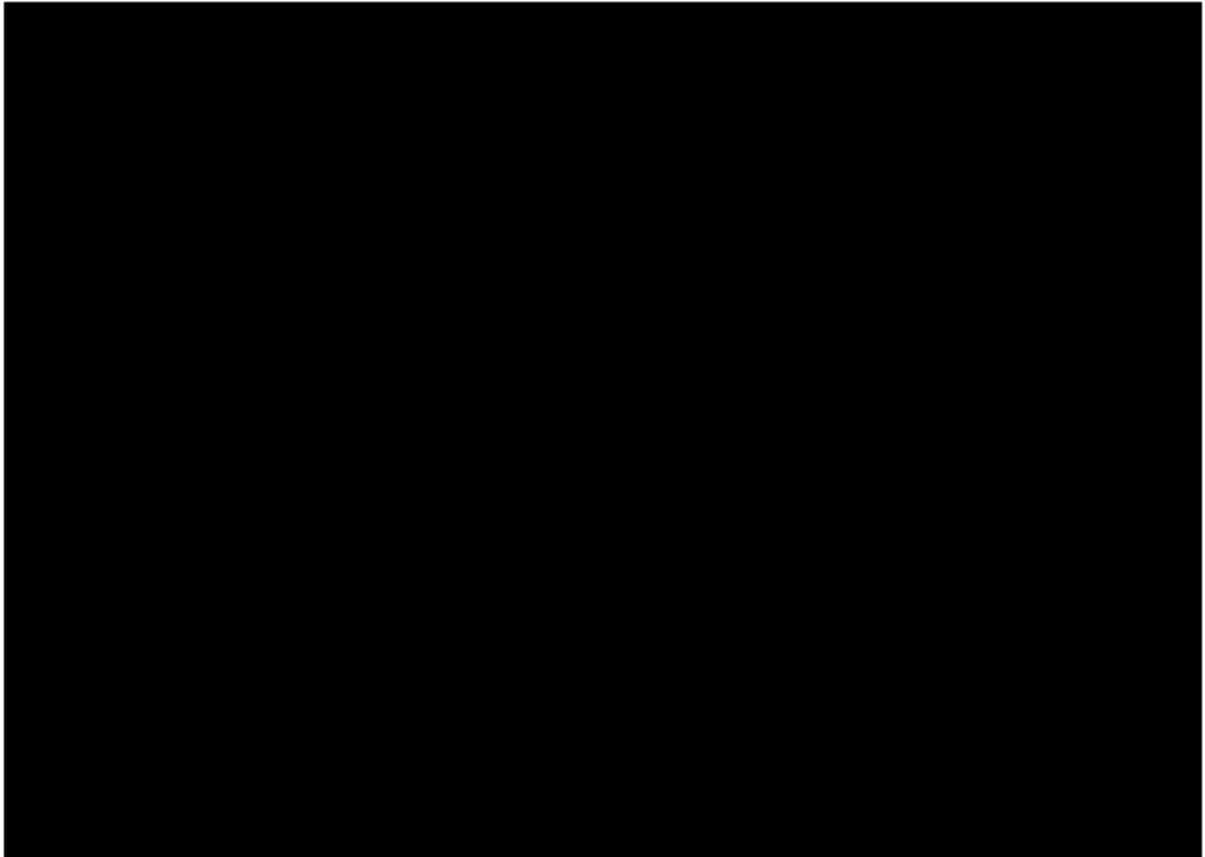
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- ^v Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 ($\pm$ 15) minutes. Subsequent infusions will be delivered over 30 ($\pm$ 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 ($\pm$ 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^w Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).
- ^x 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 [REDACTED] minutes. Subsequent infusions will be delivered over [REDACTED] minutes if the previous infusion was tolerated without infusion-associated adverse events, or [REDACTED] minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
- ^y After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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. The Sponsor may conclude treatment arms in which all patients have discontinued treatment and completed safety follow-up and/or treatment arms in which approximately 80% of patients have discontinued the study (with the remaining ~20% of patients to be discontinued from the study).
- ^z Assessment may be performed within 24 hours prior to dosing during the treatment period.
- ^{aa} If a patient decides to continue treatment beyond progression, an additional written consent form from the patient is required at the time of initial disease progression to acknowledge deferring other treatment options in favor of continuing study treatment.

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Approval Task	 Company Signatory 27-Sep-2023 14:44:02 GMT+0000
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