Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab Plus Tiragolumab in Combination With Paclitaxel and Cisplatin Compared With Paclitaxel and Cisplatin as First-Line Treatment in Patients With Unresectable Locally Advanced, Unresectable Recurrent, or Metastatic Esophageal Squamous Cell Carcinoma

NCT Number: NCT04540211

Document Date: Protocol Amendment Version 7: 22-Nov-2023

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS TIRAGOLUMAB IN COMBINATION WITH PACLITAXEL AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN AS FIRST-LINE TREATMENT IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED, UNRESECTABLE RECURRENT, OR METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA**
PROTOCOL NUMBER:	YO42138
VERSION NUMBER:	7
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
NCT NUMBER:	NCT04540211
TEST PRODUCTS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
7	See electronic date stamp on the final page of this document.
6	8 December 2022
5	21 January 2022
4	20 October 2021
3	16 April 2021
2	15 December 2020
1	15 April 2020

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol YO42138 has been amended primarily to provide additional clarity on the PK and ADA samples collection. Changes to the protocol, along with a rationale for each change, are summarized below:

[redacted]

The following changes have been made to align with the Atezolizumab Investigator's Brochure, Version 20:

- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.3).
- [redacted]
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 10).

The following additional changes and clarifications have been made:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).

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

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS TIRAGOLUMAB IN COMBINATION WITH PACLITAXEL AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN AS FIRST-LINE TREATMENT IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED, UNRESECTABLE RECURRENT, OR METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS TIRAGOLUMAB IN COMBINATION WITH PACLITAXEL AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN AS FIRST-LINE TREATMENT IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED, UNRESECTABLE RECURRENT, OR METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA**
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VERSION NUMBER:	7
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
NCT NUMBER:	NCT04540211
TEST PRODUCTS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
PHASE:	III
INDICATION:	Esophageal squamous cell carcinoma
SPONSOR:	F. Hoffmann-La Roche Ltd

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy and safety of atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin (Atezo + Tira + PC) compared with atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin (Placebo + PC) as first-line treatment in patients with unresectable locally advanced, unresectable recurrent, or metastatic esophageal squamous cell carcinoma (ESCC).

There is no consensus on the optimal regimen for first-line treatment of advanced esophageal cancer globally. For ESCC in particular, there are no data from recent randomized controlled trials, and combination chemotherapy is typically given. However, there continues to be a significant unmet medical need in patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Atezo + Tira + PC compared with Placebo + PC	• OS, defined as the time from randomization to death from any cause • PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1
Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of Atezo + Tira + PC compared with Placebo + PC	• PFS as determined by the investigator according to RECIST v1.1 • Confirmed ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by an IRF according to RECIST v1.1 • Confirmed ORR as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a confirmed objective response to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1 • DOR as determined by the investigator according to RECIST v1.1
• To evaluate the efficacy of Atezo + Tira + PC compared with Placebo + PC	• TTCD in patient-reported physical functioning, role functioning, and GHS/QoL as measured by the respective scales of the EORTC QLQ C30 and defined as the time from randomization to first deterioration (decrease from baseline of ≥10 points) that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks • TTCD in patient-reported dysphagia as measured by the dysphagia scale of the EORTC QLQ OES18 and defined as the time from randomization to first deterioration (increase from baseline of ≥10 points) that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks
Safety Objective	Corresponding Endpoint
• To evaluate the safety of Atezo + Tira + PC compared with Placebo + PC	• Incidence and severity of adverse events Severity for all events will be graded according to NCI CTCAE v5.0, [redacted]

OBJECTIVES AND ENDPOINTS (CONT.)

Pharmacokinetic Objective	Corresponding Endpoint
• To characterize the PK profiles of tiragolumab and atezolizumab when given in combination with paclitaxel and cisplatin	• Serum concentration of tiragolumab and atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to tiragolumab and atezolizumab when given in combination with paclitaxel and cisplatin	• Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study
[redacted]	
Health Status Utility Objectives	**Corresponding Endpoint**
• To evaluate health status utility scores of patients treated with Atezo + Tira + PC compared with Placebo + PC	• Mean change from baseline in the index-based and VAS scores of the EuroQol EQ-5D-5L

[redacted]
Atezo + Tira + PC = atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin; CR = complete response; [redacted] DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS/QoL = global health status and quality of life; IRF = independent review facility; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; [redacted]
PFS = progression-free survival; PR = partial response; PK = pharmacokinetic; Placebo + PC = atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TTCD = time to confirmed deterioration; VAS = Visual Analog Scale.

OVERALL DESIGN AND STUDY POPULATION

This Phase III, randomized, multicenter, double-blind study will evaluate the efficacy and safety of Atezo + Tira + PC compared with Placebo + PC as first-line treatment in patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC.

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

Phase:	Phase III	**Population Type:**	Adult patients

Control Method:	Active Comparator, Placebo	**Population Diagnosis or Condition:**	Unresectable locally advanced, unresectable recurrent, or metastatic esophageal squamous cell carcinoma
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Compound{s}:	atezolizumab and tiragolumab	**Site Distribution:**	Multi-site
Active Comparator:	paclitaxel and cisplatin	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 450

STUDY TREATMENT

Eligible patients will be randomized in a 1:1 ratio to the Atezo + Tira + PC arm or the Placebo + PC arm, and will be stratified by PD-L1 expression as assessed by a central laboratory through use of the [redacted] previous curative treatment consisting of either esophagectomy or chemoradiotherapy (yes vs. no), and Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1). Patients will receive treatment as outlined below:

Treatment Arm	Dose, Route, and Regimen (Drugs Listed in Order of Administration)	
	Induction: Cycles 1–6 (21-Day Cycles)	**Maintenance: Cycles ≥ 7 (21-Day Cycles)**
Atezo + Tira + PC	• Atezolizumab 1200 mg IV on Day 1 • Tiragolumab 600 mg IV on Day 1 • Paclitaxel 175 mg/m^2 IV on Day 1 • Cisplatin 60–80 mg/m^2 IV on Day 1 [a]	• Atezolizumab 1200 mg IV on Day 1 • Tiragolumab 600 mg IV on Day 1
Placebo + PC	• Atezolizumab placebo IV on Day 1 • Tiragolumab placebo IV on Day 1 • Paclitaxel 175 mg/m^2 IV on Day 1 • Cisplatin 60–80 mg/m^2 IV on Day 1 [a]	• Atezolizumab placebo IV on Day 1 • Tiragolumab placebo IV on Day 1

Atezo + Tira + PC = atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin; Placebo + PC = atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin.

[a] Cisplatin dose should be consistent with manufacturer and institutional standards.

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

For management of drug-related toxicities, the dose of paclitaxel and the dose of cisplatin may be reduced by up to 2 times, as outlined in the table below. If the dose of one chemotherapy drug is reduced because of a toxicity considered to be solely related to that drug, there is no need to reduce the dose of the other chemotherapy drug.

Dose Reductions for Paclitaxel and Cisplatin

	Initial Dose	First Dose Reduction	Second Dose Reduction
Paclitaxel	175 mg/m^2	135 mg/m^2	90 mg/m^2

Cisplatin	60–80 mg/m^2	75% of previous dose	75% of previous dose

If further dose reduction is indicated for cisplatin and/or paclitaxel after 2 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. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date. If any chemotherapy agent is held for more than 2 cycles (6 weeks) from the anticipated treatment date, or the dose level-2 is not tolerated, chemotherapy should be permanently discontinued.

Cisplatin dose reductions for renal impairment are provided in the table below.

Cisplatin Dose Reductions for Renal Impairment

	Action to Be Taken
Creatinine Clearance (mL/min)	
>40 to <50	• Continue atezolizumab, tiragolumab, and paclitaxel. • Withhold cisplatin. • If creatinine clearance recovers to baseline or better ≤ 6 weeks after event onset, resume cisplatin with dose reduced by one dose level. [a] If not, permanently discontinue cisplatin. [b]
>30 to ≤ 40	• Continue atezolizumab, tiragolumab, and paclitaxel. • Withhold cisplatin. • If creatinine clearance recovers to baseline or better ≤ 6 weeks after event onset, resume cisplatin with dose reduced by 2 dose levels. [a] If not, permanently discontinue cisplatin. [b]
≤ 30	• Continue atezolizumab, tiragolumab, and paclitaxel. • Permanently discontinue cisplatin. [b]

[a] The dose of paclitaxel and the dose of cisplatin may be reduced by up to 2 times, as outlined in Dose Reductions for Paclitaxel and Cisplatin.

[b] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

DURATION OF PARTICIPATION

Patients will receive study treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with cancer immunotherapy, radiographic progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving study treatment will be permitted to continue treatment if they meet all of the following criteria:

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

Patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0. Laboratory safety assessments will include regular monitoring of hematology and blood chemistry.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee, Independent Data Coordinating Center
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody
[redacted]	[redacted]
[redacted]	[redacted]
Atezo + Tira + PC	atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin
[redacted]	[redacted]
CPS	combined positive score
CR	complete response
CRS	cytokine-release syndrome
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CT	computed tomography
[redacted]	[redacted]
DOR	duration of response
EAE	experimental autoimmune encephalomyelitis
[redacted]	[redacted]
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
[redacted]	[redacted]
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ESCC	esophageal squamous cell carcinoma
FAS	full analysis set
Fc	fragment crystallizable
FFPE	formalin-fixed, paraffin-embedded
GHS/QoL	global health status and quality of life
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio

Abbreviation	Definition
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFN	interferon
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
IxRS	interactive voice or Web-based response system
[redacted]	[redacted]
MDD	minimum detectable difference
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHCPRC	National Health Commission of the People's Republic of China
NK	natural killer (cell)
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
[redacted]	[redacted]
PFS	progression-free survival
PK	pharmacokinetic
Placebo + PC	atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin
PR	partial response
PRO	patient-reported outcome
PVR	poliovirus receptor
[redacted]	[redacted]
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCC	squamous cell carcinoma
SITC	Society for Immunotherapy for Cancer

Abbreviation	Definition
[redacted]	[redacted]
TNF-α	tumor necrosis factor-α
TTCD	time to confirmed deterioration
[redacted]	[redacted]
ULN	upper limit of normal
[redacted]	[redacted]

1. BACKGROUND

1.1 BACKGROUND ON ESOPHAGEAL CARCINOMA

Esophageal cancer is the seventh most common cancer and the sixth most common cause of death from cancer worldwide (Bray et al. 2018). The incidence, prevalence, and histologic type of esophageal cancer varies between geographic regions, particularly between Western countries (United States and Europe) and an area commonly referred to as the "esophageal cancer belt" that stretches across central-eastern Asia from the Caspian region to northern China (Arnold et al. 2015). In 2018, 477,900 of the 572,034 new cases of esophageal cancer were estimated to occur in China. While adenocarcinoma is the predominant histologic type in the United States, 90% of cases in China are squamous cell carcinoma (SCC) (Arnold et al. 2015; Chen et al. 2016). Adenocarcinoma and SCC have differing biologic pathways and are, therefore, treated differently.

Advanced esophageal cancer is a rapidly fatal disease. More than two-thirds of patients diagnosed with esophageal cancer will have advanced or metastatic disease, with a median survival of 8–10 months and an expected 5-year survival rate of $<5\%$ (Drahos et al. 2013; Lin et al. 2016). The impact of esophageal cancer on patients is multi-faceted. Most affected individuals present with physical symptoms, primarily dysphagia (Daly et al. 2000), which can result in unintentional weight loss and loss of appetite; less common symptoms include chest pain, dyspnea, and gastrointestinal reflux. However, patients also frequently report poor emotional well-being, and in particular high rates of anxiety and depression (Bergquist et al. 2007). Each of these has a significant impact on patients' quality of life. These data, combined with the relative lack of highly effective treatments, are indicative of the large unmet medical need in patients diagnosed with advanced esophageal cancer.

1.2 TREATMENT FOR ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA

1.2.1 Chemotherapy

There is no consensus on the optimal regimen for first-line treatment of advanced esophageal cancer globally. For esophageal squamous cell carcinoma (ESCC) in particular, there are no data from recent randomized controlled trials.
However, combination chemotherapy is typically given. Treatment regimens for ESCC commonly consist of cisplatin in combination with paclitaxel or 5-fluorouracil (5-FU) (Lordick and Janjigian 2016; Kitagawa et al. 2019; National Comprehensive Cancer Network [NCCN] 2019; National Health Commission of the People's Republic of China [NHCPRC] 2019); these regimens are associated with objective response rates (ORRs) ranging from 20%–48%, 5-year survival rates of less than 10%, and significant toxicity rates (Grunberger et al. 2007). There are regional preferences for the chemotherapy of choice, which may be based on the toxicity profile of each agent.

1.2.2 Anti–PD-1 Therapy

Currently, anti–PD-L1 therapy is not approved for first-line treatment of advanced esophageal cancer. However, clinical outcome data are available from 2 Phase III studies evaluating anti–PD-1 monotherapy (nivolumab and pembrolizumab) as second-line treatment in patients with advanced esophageal carcinoma.

ATTRACTION-3 demonstrated the survival benefit of nivolumab versus investigator-selected chemotherapy (paclitaxel or docetaxel) in patients with ESCC (Kato et al. 2019). In the intent-to-treat (ITT) population ($n = 419$), overall survival (OS) was statistically significantly prolonged in the nivolumab arm compared with the chemotherapy arm (median OS: 10.9 vs. 8.4 months; hazard ratio [HR]: 0.77; 95% CI: 0.62 to 0.96; $p = 0.019$).

In KEYNOTE-181, patients with advanced esophageal cancer after first-line chemotherapy were treated with pembrolizumab for up to 2 years or investigator-selected chemotherapy (paclitaxel, docetaxel, or irinotecan) for approximately 18 months. Of the 628 patients who were randomized, 401 had ESCC and 222 had tumors that expressed PD-L1 (combined positive score [CPS] ≥ 10). Overall survival was statistically significantly prolonged in the pembrolizumab arm compared with the chemotherapy arm among patients with a CPS of ≥ 10 (median OS: 9.3 vs. 6.7 months; HR: 0.69; 95% CI: 0.52 to 0.93; $p = 0.0074$). There was clinically meaningful improvement in OS with pembrolizumab versus chemotherapy among patients with ESCC, but this was not statistically significant per prespecified boundaries (median OS: 8.2 vs. 7.1 months; HR: 0.78; 95% CI: 0.63 to 0.96; $p = 0.0095$).

Overall, these data indicate that checkpoint inhibitors such as anti–PD-1 demonstrate single-agent activity in esophageal cancer.

1.3 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 fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

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

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

1.4 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds TIGIT, an immune inhibitory receptor that is expressed on the surface of activated T-cell and natural killer (NK)–cell subsets and interacts with high affinity with CD155 (also known as poliovirus receptor [PVR]; Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; 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 tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is combined with other cancer immunotherapy and chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer.

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

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of tiragolumab plus atezolizumab in combination with chemotherapy (paclitaxel and cisplatin) to address a significant unmet medical need in patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC.

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).
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). 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, and myasthenia gravis, have been observed. To date, these events have been manageable with treatment or interruption of atezolizumab treatment. See Appendix 10 of the protocol and Section 6 of the

Atezolizumab Investigator's Brochure for details on the anticipated risks for atezolizumab.

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), which is broadly expressed in solid tumors. TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other immune checkpoint receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). TIGIT is, therefore, 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.

It is hypothesized that adding dual checkpoint inhibition to chemotherapy may result in enhanced and more durable responses than either therapy modality alone. An exploratory study in gastric cancer has shown that after treatment with platinum chemotherapy, patients with a higher percentage of $CD8^{+}TIGIT^{+}$ T cells had increased rates of cancer relapse and shorter disease-free survival (Tang et al. 2019). In another study in esophageal cancer, levels of PVR were increased after chemotherapy (Yoshida et al. 2019). As the TIGIT pathway is associated with immune dysfunction, these findings suggest that TIGIT blockade to restore T-cell function could potentially improve outcomes for patients undergoing chemotherapy. In support of this hypothesis, in vitro studies showed that TIGIT blockade countered the suppression of T-cell proliferation and activation following chemotherapy (Tang et al. 2019).

In a Phase I, dose-escalation and dose-expansion study (GO30103), tiragolumab was administered alone and in combination with atezolizumab to patients with locally advanced, recurrent, or metastatic incurable tumors, including esophageal cancer. [redacted] In a Phase II study (GO40290), tiragolumab plus atezolizumab was compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable or metastatic PD-L1−positive (defined as tumor proportion score $\geq$1%) NSCLC. As of the data cutoff date of 30 June 2019, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%; n=67) than in the placebo plus atezolizumab arm (16.2%; n=68). In addition, investigator-assessed progression-free survival (PFS) was improved in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm (stratified HR=0.57 [95% CI: 0.37 to 0.90]; median PFS, 5.4 vs. 3.6 months, respectively). Detailed efficacy data for these studies are provided in the Tiragolumab Investigator's Brochure.

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. In Study GO40290, serious and high-grade treatment-related adverse events have been balanced between the tiragolumab plus atezolizumab arm and the placebo plus atezolizumab arm, and immune-mediated adverse events have been balanced between the two treatment arms, with the exception of a higher frequency of [redacted] and rash reported in the tiragolumab plus atezolizumab arm. [redacted] Detailed safety data for these studies are provided in the Tiragolumab Investigator's Brochure. Risk mitigation measures for this study are outlined in Section 5.1, and guidelines for managing adverse events associated with study treatment are provided in Appendix 9 and Appendix 10.

Advanced ESCC is an incurable disease with a high unmet need for improved medical intervention. Taking into account the preliminary efficacy and manageable safety profiles of tiragolumab plus atezolizumab and their potentially synergistic mechanisms of action, as well as the potential for improved outcomes when adding dual checkpoint inhibition to chemotherapy, treatment with atezolizumab, tiragolumab, and chemotherapy (paclitaxel and cisplatin) appears to have therapeutic potential in solid tumors such as ESCC.

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

Given the mechanism of action for atezolizumab and tiragolumab, immune-mediated adverse events are potential overlapping toxicities associated with combination use of these two agents.

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

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or

dysregulated immune system defenses (Wykes and Lewin 2018; Schorer et al. 2020). In nonclinical models, PD-L1/PD-1 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 COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection while receiving atezolizumab and/or tiragolumab. At this time, there is insufficient evidence for causal association between atezolizumab or tiragolumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with checkpoint inhibitors and clinical and radiologic features for COVID-19 related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

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

Per recommendations of the NCCN COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 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 cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab and/or 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/or 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.

The 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 4.4.1).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin (Atezo + Tira + PC) compared with atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin (Placebo + PC) as first-line treatment in patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of Atezo + Tira + PC compared with Placebo + PC	• OS, defined as the time from randomization to death from any cause • PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Atezo + Tira + PC compared with Placebo + PC	• PFS as determined by the investigator according to RECIST v1.1 • Confirmed ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by an IRF according to RECIST v1.1 • Confirmed ORR as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a confirmed objective response to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1 • DOR as determined by the investigator according to RECIST v1.1

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of Atezo + Tira + PC compared with Placebo + PC	• TTCD in patient-reported physical functioning, role functioning, and GHS/QoL as measured by the respective scales of the EORTC QLQ-C30 and defined as the time from randomization to first deterioration (decrease from baseline of ≥ 10 points) that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks • TTCD in patient-reported dysphagia as measured by the dysphagia scale of the EORTC QLQ-OES18 and defined as the time from randomization to first deterioration (increase from baseline of ≥ 10 points) that is either maintained for two consecutive assessments or followed by death from any cause within 3 weeks
[redacted]	
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety of Atezo + Tira + PC compared with Placebo + PC	• Incidence and severity of adverse events Severity for all events will be graded according to NCI CTCAE v5.0, [redacted]
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profiles of tiragolumab and atezolizumab when given in combination with paclitaxel and cisplatin	• Serum concentration of tiragolumab and atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to tiragolumab and atezolizumab when given in combination with paclitaxel and cisplatin	• Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

Table 1 Objectives and Corresponding Endpoints (cont.)

[redacted]

Health Status Utility Objectives	Corresponding Endpoint
• To evaluate health status utility scores of patients treated with Atezo + Tira + PC compared with Placebo + PC	• Mean change from baseline in the index-based and VAS scores of the EuroQol EQ-5D-5L

ADA = anti-drug antibody; [redacted]
Atezo + Tira + PC = atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin; CR = complete response; [redacted] DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS/QoL = global health status and quality of life; IRF = Independent Review Facility; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; [redacted] PFS = progression-free survival; PR = partial response; PK = pharmacokinetic; Placebo + PC = atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TTCD = time to confirmed deterioration; [redacted] VAS = Visual Analog Scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, randomized, multicenter, double-blind study designed to evaluate the efficacy and safety of Atezo + Tira + PC compared with Placebo + PC as first-line treatment in patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC.

Patients who do not initially meet all eligibility criteria for participation in this study (screen failure) may qualify for 1 re-screening opportunity (for a total of 2 screenings per patient) at the discretion of the investigator, as described in Section 4.5.1.
The Medical Monitor is available to advise as needed.

This study will enroll approximately 450 patients, who will be randomized in a 1:1 ratio to the Atezo + Tira + PC arm or the Placebo + PC arm, as outlined in Table 2.
Eligible patients will be stratified by PD-L1 expression as assessed by a central laboratory through use of the [redacted] previous curative treatment (consisting of either esophagostomy or chemoradiotherapy) (yes vs. no), and Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1).

Table 2 Treatment Regimens

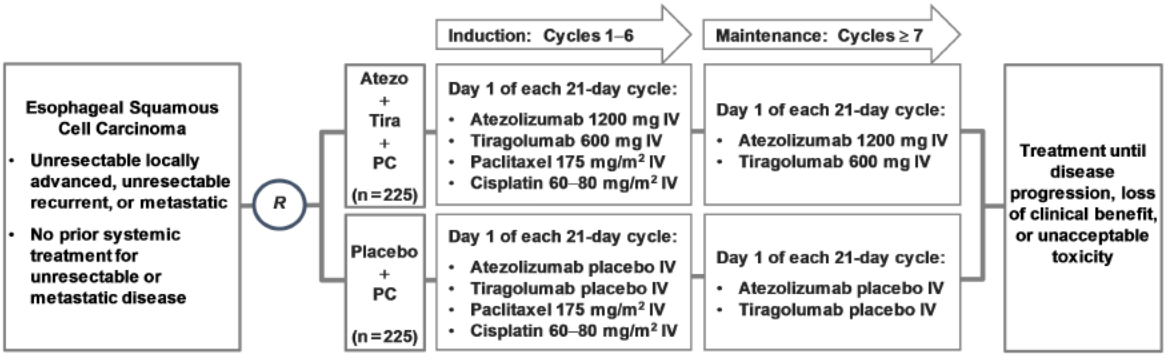
Treatment Arm	Dose, Route, and Regimen (Drugs Listed in Order of Administration)	
	Induction: Cycles 1–6 (21-Day Cycles)	**Maintenance: Cycles ≥7 (21-Day Cycles)**
Atezo + Tira + PC	• Atezolizumab 1200 mg IV on Day 1 • Tiragolumab 600 mg IV on Day 1 • Paclitaxel 175 mg/m^2 IV on Day 1 • Cisplatin 60–80 mg/m^2 IV on Day 1 [a]	• Atezolizumab 1200 mg IV on Day 1 • Tiragolumab 600 mg IV on Day 1
Placebo + PC	• Atezolizumab placebo IV on Day 1 • Tiragolumab placebo IV on Day 1 • Paclitaxel 175 mg/m^2 IV on Day 1 • Cisplatin 60–80 mg/m^2 IV on Day 1 [a]	• Atezolizumab placebo IV on Day 1 • Tiragolumab placebo IV on Day 1

Atezo + Tira + PC = atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin; Placebo + PC = atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin.

[a] Cisplatin dose should be consistent with manufacturer and institutional standards.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



Atezo + Tira + PC = atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin; Placebo + PC = atezolizumab placebo plus tiragolumab placebo in combination with paclitaxel and cisplatin; R = randomization.

Patients will receive study treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with cancer immunotherapy, radiographic progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving study treatment will be permitted to continue treatment if they meet all of the following criteria:

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

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 (NCI CTCAE), Version 5.0. Laboratory safety assessments will include regular monitoring of hematology and blood chemistry.

Patients will undergo tumor assessments every 6–9 weeks, as outlined in the schedule of activities (see Appendix 1). Tumor assessment images will be reviewed by an Independent Review Facility (IRF) and by the investigator.

Patients will undergo patient-reported outcome (PRO) assessments at specified timepoints during treatment and for up to 1 year after treatment discontinuation, as outlined in Appendix 1.

Serum samples will be collected for pharmacokinetic (PK) and immunogenicity analyses. [redacted]

Following treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected until death (unless the patient withdraws consent or the Sponsor terminates the study).

3.2 INDEPENDENT DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (iDMC) will evaluate safety data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed by the iDMC after a minimum of 16 patients have been enrolled and have received 2 cycles of study treatment. Subsequently, the iDMC will review safety data approximately every 6 months until the study is unblinded or the study is terminated by the Sponsor. All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC).

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs)/Ethics Committees (ECs).

3.3 INDEPENDENT REVIEW FACILITY

An IRF will be used to enable centralized, independent reviews of tumor assessment images and other clinical data used for assessment of ESCC (e.g., histopathology, tumor markers). Independent Review Facility reviews will be performed prior to the prespecified efficacy analyses. Independent Review Facility membership and procedures will be detailed in an IRF charter.

3.4 END OF STUDY AND LENGTH OF STUDY

The end of the study will occur when both of the following criteria have been met:

- Required number of deaths for the final OS analysis has been observed (see Section 6.10.1)
- Last patient, last visit has occurred

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

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately [redacted].

3.5 RATIONALE FOR STUDY DESIGN

[redacted]

[redacted]

3.5.3 Rationale for Patient Population

This study will enroll patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC, regardless of PD-L1 expression. Because surgery is not an option for this patient population, first-line treatment commonly includes chemotherapy regimens consisting of cisplatin in combination with paclitaxel or 5-FU (NCCN 2019), which are associated with ORRs ranging from 20%–48%, 5-year survival rates of less than 10%, and significant toxicity rates (Grunberger et al. 2007). Because the efficacy of platinum-containing chemotherapy has plateaued, the outcome of patients with a unresectable locally advanced, unresectable recurrent, or metastatic ESCC has not improved in the past two decades. Thus, there is large unmet medical need in patients diagnosed with ESCC.

Tumor-cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens. Boosting tumor-specific T-cell immunity in this setting by blocking the PD-L1 pathway may result in deeper and more durable responses than

those observed with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

3.5.4 Rationale for Control Group

In general, a combined chemotherapy regimen can achieve a higher ORR than single-agent chemotherapy. As described in Section 1.2.1, NCCN, European Society for Medical Oncology, Japanese, and Chinese Society of Clinical Oncology guidelines all recommend platinum-containing chemotherapy as a first-line treatment option for unresectable advanced recurrent or metastatic ESCC (Lordick and Janjigian 2016; Kitagawa et al. 2019; NCCN 2019; NHCPRC 2019). The combination of paclitaxel and cisplatin is more widely used in China than the combination of cisplatin and 5-FU. Taking into consideration the toxicity of a three-drug chemotherapy regimen and the widespread use of a two-drug regimen in China, the control arm will receive combination chemotherapy consisting of paclitaxel and cisplatin.

3.5.5 Rationale for Progression-Free Survival and Overall Survival as Co-Primary Endpoints

In this study, the co-primary efficacy endpoints will be IRF-assessed PFS and OS. This study will test the hypothesis that treatment with Atezo + Tira + PC will prolong PFS and OS compared with treatment with Placebo + PC.

Progression-free survival as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit–risk profile of the new treatment compared with available therapies (FDA 2007; European Medicines Agency 2012).

Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic esophageal cancer. Recent data also suggest that OS may be a more sensitive endpoint for cancer immunotherapy than PFS.

3.5.6 Rationale for Study Treatment Beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, CR, PR, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed "pseudoprogression" (Hales et al. 2010).
In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed tumor-infiltrating immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow all patients to

continue treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1). 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 for details).

3.5.7 Rationale for Pharmacokinetic Sampling Schedule

Pharmacokinetic samples will be collected from all patients to characterize the pharmacokinetics of tiragolumab and atezolizumab when administered in combination. The exposures of tiragolumab and atezolizumab in this study will be compared with the exposure attained for each agent when administered as a single agent in previous studies, to evaluate whether exposures are altered when administered in combination or in this patient population.

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 450 patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form

- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically confirmed ESCC

  Patients with tumors of mixed histology (i.e., squamous and non-squamous) are eligible if the major histological component appears to be squamous, except if small-cell elements are present.
- Unresectable locally advanced, unresectable recurrent, or metastatic disease (i.e., advanced disease, not suitable for definitive treatment such as radiotherapy, chemoradiotherapy, and/or surgery) that meets the following criteria:
  - [redacted]
  - [redacted]
- 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.
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 expression, as assessed by a central laboratory through use of the [redacted]

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 5–12 slides (12 slides preferred) containing unstained, freshly cut, serial sections (5 slides for determination of PD-L1 expression and 7 slides for [redacted] development) should be submitted along with an associated pathology report prior to enrollment. If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening. A biopsy may also be performed at screening if a patient's archival tissue test results do not meet eligibility criteria. The number of slides provided may also be governed by local regulations (e.g., Human Genetic Resources Administration of China). See Section 4.5.8 for additional information on tumor specimens collected at screening. The remaining tissue samples collected for PD-L1 assessment may be used for [redacted], when the tissue samples collected for [redacted] were insufficient.
- ECOG Performance Status of 0 or 1
- Body mass index ≥ 13 kg/m^2
- Life expectancy ≥ 3 months

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - [redacted]
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- [redacted]
- [redacted]
- [redacted]

[redacted]

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 90 days after the final dose of tiragolumab, for 5 months after the final dose of atezolizumab, and for 6 months after the final dose of paclitaxel or cisplatin. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, 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 final dose of paclitaxel or cisplatin. In the event of chemotherapy discontinuation, men who continue to receive tiragolumab for more than 6 months after the final chemotherapy dose must remain abstinent or use a condom until 90 days after the final dose of tiragolumab. 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 90 days after the final dose of tiragolumab and 6 months after the final dose of paclitaxel or cisplatin 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 adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Palliative radiation treatment for ESCC within 4 weeks prior to initiation of study treatment
- Use of Chinese herbal medicine or Chinese patent medicines to control cancer within 7 days prior to initiation of study treatment
- Higher risk of bleeding or fistula caused by esophageal lesions invading adjacent organs (aorta or trachea)
- Evidence of complete esophageal obstruction not amenable to treatment
- Symptomatic, untreated, or actively progressing CNS metastases

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  –
  –
  –
  –
  –
  –

[redacted]

- Uncontrolled tumor-related pain
  [redacted]
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  [redacted]
- [redacted]
- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, [redacted]
  [redacted]
  [redacted]
  [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  [redacted]

- Severe chronic or active infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Active tuberculosis
- 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
- Any of the following cardiovascular risk factors:
  - [redacted]
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- History of malignancy within 2 years prior to screening, with the exception of the cancer under investigation in this study and 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
- Grade ≥ 2 peripheral neuropathy at screening
- Uncontrolled diabetes or Grade ≥ 2 abnormalities in potassium, sodium, or corrected calcium despite standard medical management within 14 days prior to initiation of study treatment

- Any other disease, medical condition, metabolic dysfunction, alcohol or drug abuse or dependence, physical examination finding, 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
- Poor peripheral venous access
- Prior treatment with CD137 agonists, T-cell co-stimulating, 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, IFN and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - [redacted]
  - [redacted]
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment
- Concurrent participation in another therapeutic clinical trial
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the tiragolumab formulation
- Pregnant or breastfeeding

  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 AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After 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 treatment assignment from the interactive voice or Web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: Atezo + Tira + PC or Placebo + PC. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- PD-L1 expression as assessed by a central laboratory through use of the [redacted]
- Previous curative treatment (yes vs. no)
- ECOG Performance Status (0 vs. 1)

4.2.2 Blinding

Study site personnel, patients, and the IRF will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. Pharmacokinetic samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

The Sponsor will remain blinded to treatment assignment until the primary analysis of PFS has occurred. Investigators and patients will remain blinded to treatment assignment until the final analysis of OS, except in cases where single-patient unblinding is necessary, as outlined below.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken. After emergency unblinding, medical- and study-related questions should be directed to the "Post-Unblinding Medical Monitor" (see Section 5.4.1).

The "Post-Unblinding Medical Monitor" is a qualified medic/physician employed by the Sponsor who can support the investigator after single-subject unblinding and before the primary analysis of PFS occurs. To avoid bias, the "Post-Unblinding Medical Monitor" will not work directly on the study and will have exclusive access to the unblinding mailbox for potentially receiving unblinded patient data. Unblinded patient data or access to the unblinding mailbox will not be shared with blinded individuals on the study team, including, but not limited to the Roche Primary Medical Monitor, Roche Medical Monitor Back-up, or Roche Clinical Scientist.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.
Unblinding may be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate treatment with a proven therapy.
However, unblinding will not be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate treatment with an unproven therapy.
The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS. After unblinding, medical- and study-related questions should be directed to the "Post-Unblinding Medical Monitor" (see Section 5.4.1) to protect the integrity of the data.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab and tiragolumab and their matching placebos. The non-IMPs for this study are paclitaxel and cisplatin.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Atezolizumab and Placebo

The atezolizumab and matching placebo drug product will be supplied by the Sponsor as a [redacted] mL glass vial. The vial contains approximately [redacted] mL of atezolizumab or placebo solution (1200 mg of atezolizumab in the active treatment vial). For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.1.2 Tiragolumab and Placebo

Tiragolumab and matching placebo will be supplied by the Sponsor as a [redacted] mL glass vial. The vial contains approximately [redacted] mL of tiragolumab or placebo solution (600 mg of tiragolumab in the active treatment vial). For information on the tiragolumab formulation, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

4.3.1.3 Paclitaxel and Cisplatin

The commercially available formulations of paclitaxel and cisplatin will be administered in this study. For information on the formulation and packaging of paclitaxel and cisplatin, refer to the local prescribing information for each drug.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1 (see Table 2). Patients will receive study treatment until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1 for details).

Administration of study treatment 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 8. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 9 and Appendix 10.

4.3.2.1 Atezolizumab or Placebo

Atezolizumab 1200 mg or matching placebo (referred to as "atezolizumab" hereafter) will be administered by IV infusion on Day 1 of each 21-day cycle. Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion. • After the infusion of atezolizumab, patients should be observed for at least 60 minutes. • Patient's vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab. • 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, anti-pyretic *medications*, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If clinically indicated, vital signs should be measured during the infusion. • If the patient tolerated the previous infusion of atezolizumab well without an infusion-related reaction, the observation period may be reduced to at least 30 minutes for subsequent infusions. • If the patient experienced an infusion-related reaction in the previous infusion, the observation period should be at least 60 minutes. • If clinically indicated, record the patient's vital signs at 30 (±10) minutes after the infusion.

Guidelines for medical management of IRRs are provided in the Appendix 10.

No dose modification for atezolizumab is allowed.

4.3.2.2 Tiragolumab or Placebo

Tiragolumab 600 mg or matching placebo (referred to as "tiragolumab" hereafter) will be administered by IV infusion on Day 1 of each 21-day cycle. On Day 1 of Cycle 1, tiragolumab will be administered at least [redacted] minutes after completion of the atezolizumab infusion. The interval between subsequent infusions will be [redacted] minutes if the previous atezolizumab infusion was tolerated without an IRR or at least [redacted] minutes if the patient experienced an IRR with the previous atezolizumab infusion. Tiragolumab infusions will be administered per the instructions outlined in Table 4.

Table 4 Administration of First and Subsequent Tiragolumab Infusions

Guidelines for medical management of IRRs for tiragolumab are provided in Appendix 10.

No dose modification for tiragolumab is allowed.

4.3.2.3 Paclitaxel and Cisplatin

On Day 1 of Cycles 1–6 (21-day cycles), patients will receive paclitaxel 175 mg/m^2, administered by IV, followed by cisplatin 60–80 mg/m^2 (dose should be consistent with manufacturer and institutional standards), administered by IV.

The amount of paclitaxel and cisplatin administered will be calculated based on a patient's body surface area. Weight and height should be recorded at baseline and weight should be recorded at every scheduled visit. Height should be re-measured if the investigator thinks it is possible that the patient's height may have changed. The amount paclitaxel and cisplatin to be administered must be recalculated if the patient's body weight has increased or decreased by $>$ 10% from baseline.

If the dose is recalculated because of a $>$ 10% change in weight from baseline, this weight will then be used as the new baseline to calculate the paclitaxel and cisplatin dose in subsequent cycles.

On Day 1 of Cycle 1, paclitaxel will be administered at least 60 minutes after completion of the tiragolumab infusion to allow for observation after tiragolumab administration. The interval between subsequent infusions will be 30 minutes if the previous tiragolumab infusion was tolerated without an IRR or at least 60 minutes if the patient experienced an IRR with the previous tiragolumab infusion.

Patients should receive anti-emetics and IV hydration according to institutional standards and manufacturer's instructions for paclitaxel and cisplatin. Because of the immunomodulatory effects of corticosteroids, premedication with corticosteroids should be minimized to the extent that is clinically feasible.

Any treatment drug (atezolizumab, tiragolumab, paclitaxel, cisplatin, or placebo) that is administered will be counted in number of induction therapy cycles. If one treatment is postponed due to an adverse event, administration for the rest of the treatments are allowed to be completed within 3 days from the first day of the treatment cycle.

The dose of paclitaxel or cisplatin may be modified as outlined in Appendix 9.

4.3.3 Investigational Medicinal Product Handling and Accountability

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

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

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

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from

the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

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

4.3.4 Continued Access to Atezolizumab and Tiragolumab

The Sponsor will offer continued access to Roche IMPs (atezolizumab and tiragolumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

[redacted]

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

[redacted]

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or

respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and 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 (see Appendix 9 and Appendix 10 for details).

4.4.2.2 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 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

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

[redacted]

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should 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 Log

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.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. The screening log form is not required if equivalent screening information is accessible via IxRS. Patients who do not initially meet all eligibility criteria for participation in this study (screen failure) may qualify for 1 re-screening opportunity (for a total of 2 screenings per patient) at the discretion of the investigator. The Medical Monitor is available to advise as needed. Patients must re-sign the Consent Form prior to re-screening. For patients who are re-screened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria outlined in Section 4.1.

4.5.2 Medical History, Baseline Conditions, 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 alcohol use, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment 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

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

As part of the tumor assessment, physical examinations should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (±7 days) for the first 48 weeks following treatment initiation, and every 9 weeks (±7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 as determined by the IRF. 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 anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

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 oral or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm

or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. 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. Subsequent tumor assessments must include CT or MRI scans of the chest, abdomen and pelvis; head CT or MRI is not required except when clinically indicated.

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 evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. 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).

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. In addition, scans will be submitted to an IRF for central review according to RECIST v1.1.

4.5.6 Electrocardiograms

An ECG is required at screening and when clinically indicated. Electrocardiograms for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.7 Clinical Outcome Assessments

To more fully characterize the clinical profile of tiragolumab and atezolizumab, clinical outcome assessment data will be obtained through use of the following PRO instruments: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and its esophageal cancer–specific module (QLQ-OES18) and the EuroQol EQ-5D-5L.

4.5.7.1 Data Collection Methods for Patient-Reported Outcome Assessments

Patient-reported outcome instruments will be completed at specified timepoints during the study (see schedule of activities in Appendix 1). During the treatment period, PROs will be completed on paper at the clinic. For patients who are unable to come into the clinic due to COVID-19 restrictions, PROs may be completed via telephone call; source documentation sufficient to pass an audit should be obtained which includes, among other information, that the questionnaires were administered via phone because of COVID-19. During follow-up, PROs will be completed via telephone call or on paper at the clinic. At the clinic, instruments will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Patient-reported outcome instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the appropriate instruments to be administered in the correct order at each specified timepoint.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 20 minutes at each specified visit
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions, but may read questions verbatim upon request
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.7.2 Description of Patient-Reported Outcome Instruments

EORTC QLQ-C30

The QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 4). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social),

three symptom scales (fatigue, nausea and vomiting, and pain), global health status and quality of life (GHS/QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

EORTC QLQ-OES18

The QLQ-OES18 is a modular supplement to the QLQ-C30, for use in patients with esophageal cancer (Blazeby et al. 2003; see Appendix 5). This module incorporates four multi-item scales (dysphagia, eating, reflux, and pain) and six single items (trouble swallowing saliva, choking when swallowing, dry mouth, trouble with taste, trouble with coughing, and trouble talking) with a recall period of the previous week. The scoring approach is identical in principle to that for the symptom scales and single items of the QLQ-C30. The QLQ-OES18 takes approximately 5 minutes to complete.

EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.8 Laboratory, [redacted] and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if available), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR, and aPTT
- Thyroid function testing: thyroid-stimulating hormone, T3 (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- Carcinoembryonic antigen
- Carbohydrate antigen 19-9

- Pregnancy test

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

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- C-reactive protein

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

- Serum samples for tiragolumab and atezolizumab PK analyses through use of validated assays

  All patients will undergo PK sample collection.
- Serum samples for assessment of ADAs to tiragolumab and atezolizumab through use of validated assays

  All patients will undergo ADA sample collection.
- [redacted]

- Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 expression through use of the [redacted] for patient stratification purposes (see Section 3.1) and for [redacted] development

  A representative FFPE tumor specimen in a paraffin block (preferred) or 5–12 slides (12 slides preferred) containing unstained, freshly cut, serial sections (5 slides for determination of PD-L1 expression and 7 slides for [redacted] development) should be submitted along with an associated pathology report prior to enrollment.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples should 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.

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

[redacted]

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

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

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed.
- [redacted]
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database,

whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

- Remaining tissue samples collected for PD-L1 assessment may be used for [redacted], when the tissue samples collected for [redacted] were insufficient.

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 complexity and exploratory nature of [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 Sponsor policy on study data publication.

4.5.9 Optional Tumor Biopsies

Patients will be given the option of consenting to additional tumor biopsies. Patients who consent to optional biopsies will undergo tumor biopsy sample collection at the time of disease progression per RECIST v1.1 or loss of clinical benefit as determined by the investigator (see Section 3.1 for details), if deemed clinically feasible by the investigator. In addition, patients who consent to optional biopsies may undergo additional on-treatment biopsies at any other time at the investigator's discretion.
Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. The samples may be sent to one or more laboratories for analysis.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for [redacted] as described in Section 4.5.8. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 4.5.8 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from [redacted].

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 determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 3.1 for details)

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 final 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 and PRO assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival status and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 (±1) months until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from the Study

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

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

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

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

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

If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study. The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the 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

The safety plan for patients in this study is based on the prescribing information for paclitaxel and cisplatin and clinical experience with atezolizumab and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1, 5.1.2, 5.1.3, 5.1.4, and 5.1.5). Refer to the Tiragolumab Investigator's Brochure and the Atezolizumab Investigator's Brochure for a complete summary of safety information for each respective study drug.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients, who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 9 and Appendix 10. See Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines. An iDMC will periodically review safety data during the study (see Section 3.2).

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. See Appendix 10 of the protocol and Section 6 of the

Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Tiragolumab

Infusion-related reaction [redacted] identified risks for tiragolumab. [redacted] While clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function.
Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events). Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

5.1.2.1 Infusion-Related Reactions

[redacted]. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Infusion-related reactions have been reported in patients treated with tiragolumab alone or in combination with atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over [redacted] minutes followed by a [redacted]-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well-tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

[redacted]

5.1.2.3 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 encephalomyelitis (EAE). TIGIT–/– and wild-type B6 mice were immunized with suboptimal doses of myelin oligodendrocyte glycoprotein peptide to induce EAE. In contrast to the wild-type B6 mice, the majority of the TIGIT–/– mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may; therefore, be considered a potential risk of tiragolumab.
Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study.
In addition, patients with a history of severe immune-mediated adverse events associated with prior immunotherapy or adverse events that did not resolve to baseline after discontinuation of prior immunotherapy will be excluded from this study (see Section 4.1.2 for details).

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section 5.2.3).

5.1.2.4 Lymphopenia

[redacted]

5.1.2.5 Embryofetal Toxicity

[redacted] No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies

of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

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

5.1.3 Risks Associated with Paclitaxel

Paclitaxel is known to cause bone marrow suppression (e.g., myelosuppression, anemia, thrombocytopenia), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), hepatotoxicity, peripheral neuropathy, hypersensitivity reactions, alopecia, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, and other ECG abnormalities. Patients will be monitored for paclitaxel-related adverse events. For more details regarding the safety profile of paclitaxel, refer to the paclitaxel prescribing information.

5.1.4 Risks Associated with Cisplatin

Cisplatin is known to cause bone marrow suppression (e.g., myelosuppression, anemia, thrombocytopenia), 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, refer to the cisplatin prescribing information.

5.1.5 Risks Associated with Combination Use of Atezolizumab, Tiragolumab, Paclitaxel, and Cisplatin

Immune-mediated adverse events are potential overlapping toxicities associated with combination use of 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. The risk of overlapping toxicities between the cancer immunotherapy agents (tiragolumab and atezolizumab) and the chemotherapy agents (paclitaxel and cisplatin) is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., [redacted]) may be ambiguous when the agents are administered together. It is theoretically possible that hypersensitivity reactions or inflammatory adverse events associated with paclitaxel and cisplatin (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of tiragolumab and/or atezolizumab.

On the basis of 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 to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study,

with some exceptions (e.g., autoimmune hypothyroidism managed with thyroid-replacement hormone or Type 1 diabetes mellitus managed with insulin; see Section 4.1.2). 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 Section 1.5), patients with active infection (including, but not limited to, [redacted], or tuberculosis) and/or recent severe infections will be excluded from this study (see Sections 4.1.1 and 4.1.2). [redacted]

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can; therefore, be any of the following:

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/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).

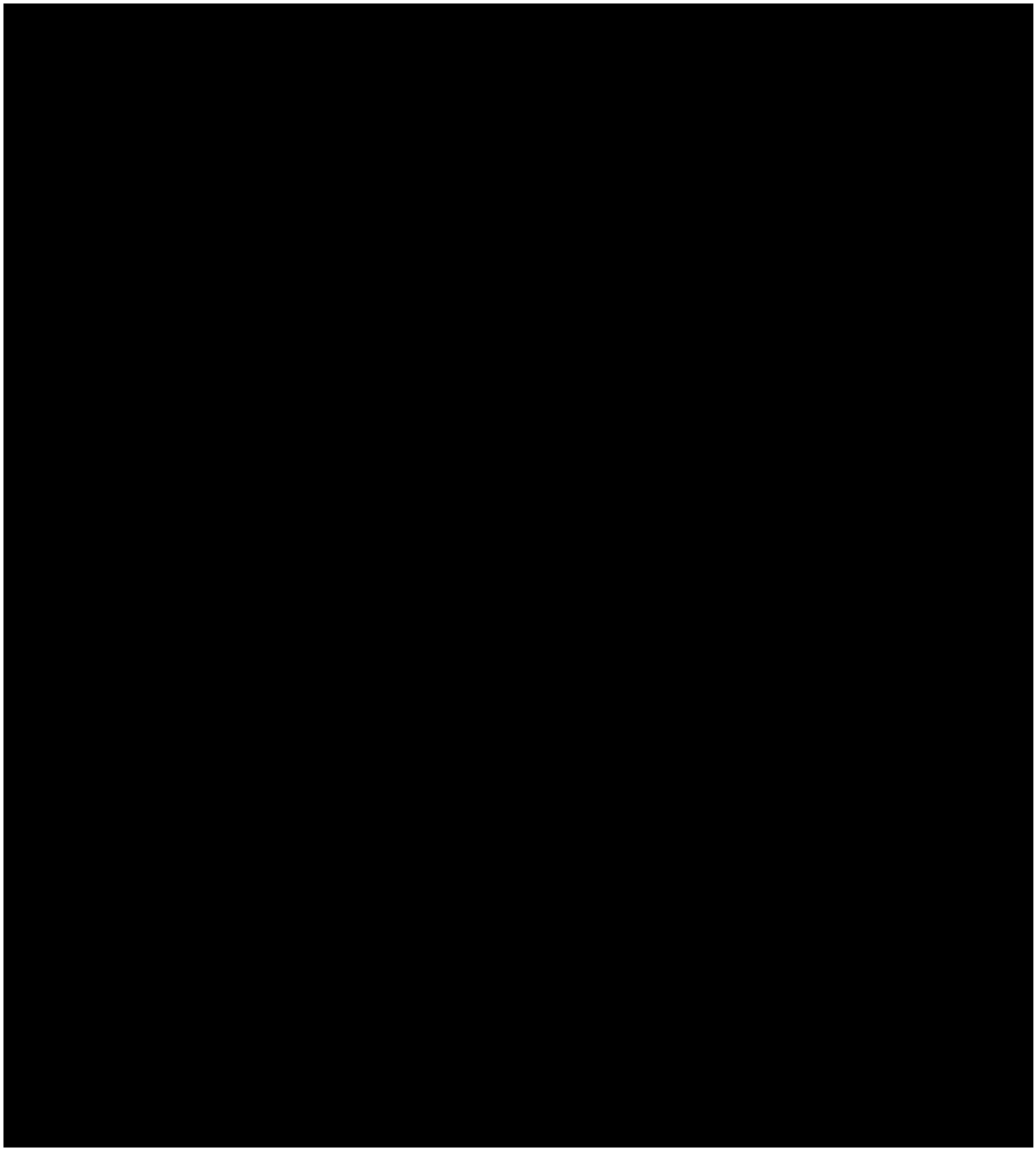
Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- [redacted]



5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, [redacted]

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://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]

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- 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 7 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

Only 1 adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and [redacted]

There may be significant overlap in signs and symptoms of 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 should be captured as a diagnosis (e.g., "infusion-related reaction" or [redacted]) on the Adverse Event eCRF. 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 or [redacted], as appropriate.

If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or [redacted].

[redacted]

Guidelines for medical management of IRRs and CRS are provided in Table A10-7 and Table A10-8, respectively, of Appendix 10.

5.3.5.2 Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all 3 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., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ 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 ESCC 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). An independent monitoring committee will monitor the frequency of deaths from all causes.

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 Esophageal Squamous Cell Carcinoma

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 Accidental Overdose or Medication Error

Accidental overdose and medication error (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
- 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.

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 or tiragolumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- 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.

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- 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.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track

all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur Prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur After Study Treatment Initiation

[redacted] 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 e-mailing the form using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or 6 months after the final dose of paclitaxel or cisplatin. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or 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.

5.4.3.2 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 while receiving chemotherapy or within 90 days after the final dose of tiragolumab or 6 months after the final dose of chemotherapy. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or 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 with additional information on the pregnant partner and the course and outcome of the pregnancy as it 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 treating physician and/or obstetrician.

5.4.3.3 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.

5.4.3.4 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).

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, e-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 reporting period for serious adverse events and adverse events of special interest (as defined in Section 5.3.1), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

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

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

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, randomized, multicenter, double-blind study designed to evaluate the efficacy and safety of Atezo + Tira + PC compared with Placebo + PC as first-line treatment in approximately 450 patients with unresectable locally advanced, unresectable recurrent, or metastatic ESCC.

The statistical considerations and analysis plan are summarized below. Further details on the statistical considerations and analysis plan will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to test the hypothesis that Atezo + Tira + PC prolongs the duration of OS and/or PFS relative to Placebo + PC in the full analysis set (FAS), defined

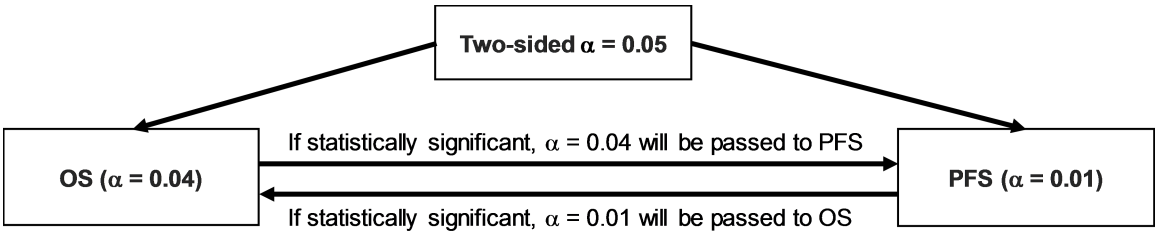
as all randomized patients regardless of whether they receive any study treatment. Approximately 450 patients in total will be randomized in a 1:1 ratio to the two arms.

6.1.1 Type I Error Control

The type I error (α) for this study is 0.05 (two-sided) and will be controlled for the co-primary efficacy endpoints of OS and IRF-assessed PFS between treatment arms in the FAS.

To control the overall type I error rate at 0.05, a group sequential weighted Holm procedure (Ye et al. 2013) will be used wherein the two-sided α of 0.04 and 0.01 will be allocated to the primary endpoints of OS and PFS, respectively. If OS in the FAS is statistically significant at the two-sided α of 0.04, the α of 0.04 will be recycled to PFS in the FAS, which will then be tested at a two-sided α of 0.05. Additionally, if PFS in the FAS is statistically significant at the two-sided α of 0.01, the α of 0.01 will be recycled to OS in the FAS, which will then be tested at a two-sided α of 0.05. The study will be considered positive if statistical significance is achieved for either of the two co-primary endpoints. An overview of the type I error rate control strategy is shown in Figure 2.

Figure 2 Overview of the Type I Error Control for Co-Primary Endpoints



OS = overall survival; PFS = progression-free survival.

6.1.2 Co-Primary Endpoint: Overall Survival

The sample size of the study was determined on the basis of the number of deaths (OS events) required in the FAS to demonstrate efficacy in terms of OS. To detect an improvement in OS through use of a log-rank test at a two-sided significance level of 0.04, approximately [redacted] OS events ([redacted] patients) will be required at the final OS analysis to achieve an overall [redacted] power, assuming a target HR of [redacted]. The minimum detectable difference (MDD) is an OS HR of [redacted] (median OS improvement of [redacted] months, from [redacted] months in the Placebo + PC arm to [redacted] months in the Atezo + Tira + PC arm). The final analysis of OS is expected to occur at approximately [redacted] months after the first patient is randomized. The calculation of sample size and estimates of the OS analysis timeline are based on the following assumptions:

- Patient randomization in a [redacted] ratio to the Atezo + Tira + PC arm or the Placebo + PC arm
- One-piece exponential distribution for OS in each arm

- Median OS of [redacted] months in the Placebo + PC arm and [redacted] months in the Atezo + Tira + PC arm (increase of [redacted] months, corresponding to a target HR of [redacted])
- Annual dropout rate of [redacted] for OS in each arm
- [redacted] planned OS interim analysis at approximately [redacted] of the information fraction, using the O'Brien–Fleming stopping boundaries approximated by the Lan–DeMets α-spending function
- Recruitment of [redacted] patients will take place over approximately [redacted] months

6.1.3 Co-Primary Endpoint: Progression-Free Survival

The primary analysis of IRF-assessed PFS will take place when approximately [redacted] PFS events ([redacted] patients) or approximately [redacted] OS events ([redacted] patients) have been observed in the FAS, whichever occurs later. The [redacted] PFS events provides an overall [redacted] power to detect a target HR of [redacted] for PFS using a log-rank test at a two-sided significance level of [redacted]. The MDD based on [redacted] PFS events is a PFS HR of [redacted] (median PFS improvement of [redacted] months, from [redacted] months in the Placebo + PC arm to [redacted] months in the Atezo + Tira + PC arm). The primary analysis of PFS is expected to occur at approximately [redacted] months after the first patient is randomized. The estimates are based on the following assumptions:

- Patient randomization in a [redacted] ratio to the Atezo + Tira + PC arm or the Placebo + PC arm
- One-piece exponential distribution for PFS in each arm
- Median PFS of [redacted] months in the Placebo + PC arm and [redacted] months in the Atezo + Tira + PC arm (increase of [redacted] months, corresponding to a target HR of [redacted])
- Annual dropout rate of [redacted] for PFS in each arm
- Recruitment of [redacted] patients will take place over approximately [redacted] months

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, duration of survival follow-up, study drug administration, reasons for study drug discontinuation, and reasons for discontinuation from the study will be summarized by treatment arm. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographics (including age, sex, race) and baseline characteristics (e.g., PD-L1 expression, previous curative treatment, and ECOG Performance Status) will be summarized overall and by treatment arm. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data, as appropriate.

Baseline measurements are defined as the last available measurement obtained prior to the patient receiving the first dose of any component of study treatment, or prior to randomization for patients who were not treated, unless otherwise noted.

6.4 EFFICACY ANALYSES

Unless otherwise specified, efficacy analyses will be performed in the FAS. Patients will be grouped according to the treatment assigned at randomization.

6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints for this study are OS and IRF-assessed PFS, as defined in Section 2.

6.4.1.1 Overall Survival

Overall survival is defined as the time from randomization to death from any cause. Patients who are not reported as having died at the time of analysis will be censored at the last date they were known to be alive. Patients with no postbaseline survival information will be censored at the date of randomization.

The two-sided log-rank test, stratified by PD-L1 expression [redacted] see definition in Section 3.1), previous curative treatment (yes vs. no), and ECOG Performance Status (0 vs. 1), will be used as the primary analysis to compare OS between the two treatment arms. The results from the unstratified log-rank test will also be provided as a sensitivity analysis to check the robustness of the results of the stratified log-rank test.

The stratified Cox proportional-hazards model will be used to estimate the HR and its 95% CI. The stratification factors will be the same as those used for the primary stratified log-rank test. The unstratified HR will also be provided.

Kaplan–Meier methodology will be used to estimate the median OS for each treatment arm, and a Kaplan–Meier curve will be constructed to provide a visual description of the difference between treatment arms. The Brookmeyer–Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm.

A group sequential design will be used for testing OS to account for the interim analysis. The type I error control plan is presented in Section 6.1.1, and the timing and stopping boundaries of the interim and final OS analyses are provided in Section 6.10.1. On the basis of emerging external data, the testing strategy may be modified to improve the efficiency of the design. Should this occur, modifications to the testing strategy will be made prior to any unblinding of the data.

Sensitivity analyses may be conducted to assess the robustness of the analysis of the co-primary efficacy endpoint of OS. For example, a sensitivity analysis may be conducted to evaluate the impact of non-protocol anti-cancer therapy on OS benefit, by applying the rank-preserving structural failure time model.

In order to assess the homogeneity of the treatment effect with respect to the co-primary efficacy endpoint of OS across important subgroups, forest plots (including the estimated HRs) will be provided.

6.4.1.2 IRF-Assessed Progression-Free Survival

Independent Review Facility-assessed PFS is defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by an IRF according to RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

Methods for the IRF-assessed PFS analysis are similar to those described for OS. The type I error control plan and the analysis timing for PFS are presented in Section 6.1.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Investigator-Assessed Progression-Free Survival

Investigator-assessed PFS is 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. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

Methods for the investigator-assessed PFS analysis will be similar to those described for OS.

6.4.2.2 Objective Response Rate

IRF-Assessed Objective Response Rate

An objective response per IRF is defined as a CR or PR as determined by an IRF according to RECIST v1.1. Patients not meeting these criteria, including patients without any postbaseline tumor assessment, will be considered non-responders. Confirmed ORR is defined as the proportion of patients who achieved an objective response on two consecutive occasions ≥4 weeks apart. Patients must have measurable disease at baseline to be included in the analysis.

The two-sided Cochran–Mantel–Haenszel test, stratified by PD-L1 expression [redacted] see definition in Section 3.1), previous curative treatment (yes vs. no), and ECOG Performance Status (0 vs. 1), will be used to compare ORR between the two treatment arms. Objective response rate will be calculated for each treatment arm, and the difference in ORR between treatment arms will be computed. The 95% CI for ORR for each arm will be derived through use of the

Wilson score method. The 95% CI for difference in ORR will be computed using the Newcombe method.

Investigator-Assessed Objective Response Rate

Objective response rate analyses will be performed separately on the basis of investigator-assessed tumor response according to RECIST v1.1. The analysis methods will be similar to those described for IRF-assessed ORR.

6.4.2.3 Duration of Response

IRF-Assessed Duration of Response

Duration of response (DOR) per IRF will be assessed in patients who achieved a confirmed objective response, as determined by an IRF according to RECIST v1.1. Duration of response is defined as the time from the first occurrence of a confirmed objective response (CR or PR, whichever status is recorded first) to the first occurrence of disease progression or death from any cause, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the date of the last tumor assessment. The analysis of DOR is based on a non-randomized subset of patients (specifically, patients who achieved a confirmed objective response); therefore, comparisons between treatment arms will be made for descriptive purposes only.

The analysis methods will be similar to those described for OS.

Investigator-Assessed Duration of Response

Duration of response analyses will be performed separately on the basis of investigator-assessed tumor response according to RECIST v1.1. The analysis methods will be similar to those described for OS.

6.4.2.4 Time to Confirmed Deterioration

Time to confirmed deterioration (TTCD) in patient-reported physical functioning, role functioning, and GHS/QoL, as measured by the respective scales of the QLQ-C30, will be defined as the time from randomization to first deterioration (decrease from baseline of $\geq$10 points) that is maintained for two consecutive assessments or followed by death from any cause within 3 weeks.

Time to confirmed deterioration in patient-reported dysphagia, as measured by the dysphagia scale of the QLQ-OES18, will be defined as the time from randomization to first deterioration (increase from baseline of $\geq$10 points) that is maintained for two consecutive assessments or followed by death from any cause within 3 weeks.

The analysis methods will be similar to those described for OS.

[redacted]

6.5 SAFETY ANALYSES

Safety analyses will be conducted in the safety-evaluable analysis set, which includes all randomized patients who receive any amount of study treatment, with patients grouped according to the actual treatment received. Specifically, a patient will be included in the Atezo + Tira + PC arm in the safety analyses if the patient receives any amount of tiragolumab and/or atezolizumab, regardless of the initial treatment assignment at randomization.

Study treatment exposure, including treatment duration, number of cycles, and dose intensity, will be summarized for each treatment arm with descriptive statistics.

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms. Severity for all events will be graded by the investigator according to NCI CTCAE v5.0, and [redacted] All adverse events will be summarized by treatment arm and NCI CTCAE [redacted]. In addition, serious adverse events, adverse events of special interest, adverse events leading to study treatment discontinuation, and adverse events leading to study treatment interruption or dose modification will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum grade.

All deaths and causes of deaths will be summarized by treatment arm.

Laboratory data with values outside the normal ranges will be identified. Additionally, selected laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized by treatment arm with shift tables from baseline to worst postbaseline value. Changes in vital signs will be summarized.

Additional analyses may be performed as indicated.

6.6 PHARMACOKINETIC ANALYSES

Pharmacokinetic samples of tiragolumab and atezolizumab will be collected in this study as outlined in Appendix 2.

Pharmacokinetic samples will be collected from all patients enrolled in the study. In these patients, tiragolumab and atezolizumab serum concentration data (minimum serum concentration [C_{min}] and maximum serum concentration [C_{max}]) will be tabulated and summarized. Descriptive statistics will include mean, median, range, and standard deviation, as appropriate.

Additional PK analyses will be conducted, as appropriate, based on the availability of data.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ADA assessments, with patients grouped according to treatment received.

The numbers and proportions of treatment-emergent ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods for both tiragolumab and atezolizumab will be summarized by treatment arm.

[redacted]

[redacted]

6.9 HEALTH STATUS UTILITY ANALYSES

Health utility data from the EQ-5D-5L will be evaluated in pharmacoeconomic models. Results from health economic data analyses will be reported separately from the CSR.

[redacted]

[redacted]

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.

Electronic Case Report Forms 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.

Patient-reported outcome data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms 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. Electronic Case Report Forms 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. Electronic Case Report Forms 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 that must be kept with the study records. Acknowledgement of receipt of the data 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 into 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, PROs, 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, paper PRO data, 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 applicable 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 Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it 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.

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

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in

each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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 Sponsor policy on study data publication (see Section 9.6).

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

Study data, which may include [redacted], 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 CSRs and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.4).

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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 40 sites globally will participate to randomize approximately 450 patients. 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]), as specified in Sections 4.5.8 and 4.5.9. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will monitor and evaluate patient safety throughout the study. All summaries and analyses for the iDMC review will be prepared by an iDCC.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted CSRs 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 CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	Screening [a]		Induction (21-Day Cycles)				Maintenance (21-Day Cycles)	Treatment Discon. [d]	
			Cycle 1		Cycles 2–6 [b]		Cycles ≥7 [b, c]		
	Days –28 to –1	Days –14 to –1	Day 1 [e]	Day 8 (±3 d)	Day 1 (±3 d)	Day 8 (±3 d)	Day 1 (±3 d)	≤30 Days after Final Dose	Follow-Up [f]
Informed consent [g]	x								
Baseline tumor tissue sample [h]	x								
Demographic data	x								
Medical history and baseline conditions	x								
PRO assessments [i]			x [j]		x [j]		Every other cycle (Cycles 7, 9, etc.) [j]	x	x [k]
Complete physical examination [l, m]	x							x	
Limited physical examination [m, n]			x [j]		x [j]		x [j]		
ECOG Performance Status	x		x [j]		x [j]		x [j]	x	
Vital signs [o]	x		x	x	x	x	x	x	
Weight	x		x		x		x	x	
Height	x								
12-lead ECG [p]	x		Perform as clinically indicated					x	
[redacted]									
Hematology [s]		x	x [t]	x	x [t]	x	x [t]	x	
Chemistry [u]		x	x [t]	x	x [t]	x	x [t]	x	
Coagulation (aPTT, INR)		x	x [t]		x [t]		x [t]	x	

Appendix 1: Schedule of Activities

	Screening [a]		Induction (21-Day Cycles)				Maintenance (21-Day Cycles)	Treatment Discon. [d]	
			Cycle 1		Cycles 2–6 [b]		Cycles ≥7 [b, c]		
	Days –28 to –1	Days –14 to –1	Day 1 [e]	Day 8 (±3 d)	Day 1 (±3 d)	Day 8 (±3 d)	Day 1 (±3 d)	≤30 Days after Final Dose	Follow-Up [f]
TSH, free T3 (or total T3), free T4 [v]	x		x [v]					x	
CA19-9 and CEA			x [j]		x [j]		x [j]	x	
C-reactive protein			x [j]						
Pregnancy test [w]		x	x [t]		x [t]		x [t]	x	x [w]
Urinalysis [x]	x		Perform as clinically indicated						
[redacted]									
Tumor biopsy (optional)			x [y]						
Tumor response assessments [m]	x [z]		x [aa, bb]						
Concomitant medications [cc]		x [cc]	x	x	x	x	x	x	
Adverse events [dd]	x [dd]	x [dd]	x [dd]	x	x	x	x	x	x [dd]
Study treatment administration [ee]			x [ff]		x [ff]		x [gg]		
Survival and anti-cancer therapy follow-up									x

Appendix 1: Schedule of Activities

[redacted] CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; d = day; discon. = discontinuation; EBNA = Epstein-Barr nuclear antigen; [redacted] ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; [redacted] IRF = independent review facility; MRI = magnetic resonance imaging; [redacted] PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; [redacted]

[a] Patients who do not initially meet all eligibility criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of 2 screenings per patient) at the discretion of the investigator, as described in Section 4.5.1. The Medical Monitor is available to advise as needed. Results of standard of care tests or examinations performed prior to obtaining informed consent and within the protocol-specified window may be used; such tests do not need to be repeated for screening.

[b] If a visit is precluded because of a holiday, weekend, or other circumstance, it can be postponed to the soonest following date. If treatment was postponed > 3 days, subsequent visits should be adjusted to maintain a 21-day treatment cycle.

[c] During maintenance treatment, one out of every 3 cycles can be delayed by 1 week (28-day cycle rather than 21-day cycle) to allow for a vacation or holiday. Two consecutive 28-day cycles are not permitted.

[d] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after their final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[e] The first dosing date (Day 1 of Cycle 1) should occur within 7 days after randomization, with one exception: dosing may be postponed for patients who experience an adverse event.

[f] After treatment discontinuation, information on survival 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 (±1) 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.

[g] 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.

[h] If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. See Section 4.5.8 for tissue sample requirements.

[i] PRO instruments (EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L) will be completed before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. In scenarios where laboratory assessments (e.g., blood draws) are done at a different location than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs, as long as results have not been discussed with patients. PRO instruments are to be completed as outlined in Section 4.5.7.

[j] PRO assessments, limited physical examination, CA19-9, CEA, C-reactive protein, and ECOG Performance Status may be performed within 96 hours prior to administration of study treatment.

[k] During follow-up, patients will complete the PRO instruments at the clinic or via telephone call approximately every 3 months for 1 year.

[l] A complete physical examination should include evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[m] As part of the tumor assessment, physical examinations should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[n] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated.

[o] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. For the first infusion of atezolizumab/placebo, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and at 30 (±10) minutes after the infusion; for subsequent infusions, 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 at 30 (±10) minutes after the infusion. For the first infusion of tiragolumab/placebo, vital signs should be measured within [redacted] minutes prior to the infusion and every [redacted] minutes during and at [redacted] minutes after the infusion; for subsequent infusions, 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 at [redacted] minutes after the infusion.

[p] Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[redacted]

Appendix 1: Schedule of Activities

[redacted]

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

[t] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated. During the study treatment period, test results of the assessments scheduled on the days of study treatment infusions should be reviewed prior to administration of study treatment unless otherwise noted.

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

[v] 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 4 cycles thereafter (i.e., Cycles 5, 9, 13, etc.). If the screening test was performed within 96 hours prior to Day 1 of Cycle 1, it does not have to be repeated.

[w] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests will be performed at specified subsequent visits during treatment, at the treatment discontinuation visit, and at 3 months and 6 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[x] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[y] Patients who consent to optional biopsies will undergo tumor biopsy sample collection at the time of disease progression per RECIST v1.1 or loss of clinical benefit as determined by the investigator (see Section 3.1 for details), if deemed clinically feasible, and may undergo additional on-treatment biopsies at any time at the investigator's discretion.

[z] 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 oral or IV contrast) or MRI scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head 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.

[aa] Prior to the final PFS analysis, patients will undergo tumor assessments at baseline, every 6 weeks (± 7 days) for the first 48 weeks following treatment initiation, and every 9 weeks (± 7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 as determined by the IRF. After the final PFS analysis, the IRF will discontinue the review of tumor assessment data. However, tumor assessments should be conducted until radiographic disease progression per RECIST v1.1 as determined by the investigator. 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 anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

[bb] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Tumor assessments must include CT or MRI scans of the chest, abdomen and pelvis. Head CT or MRI is not required except when clinically indicated.

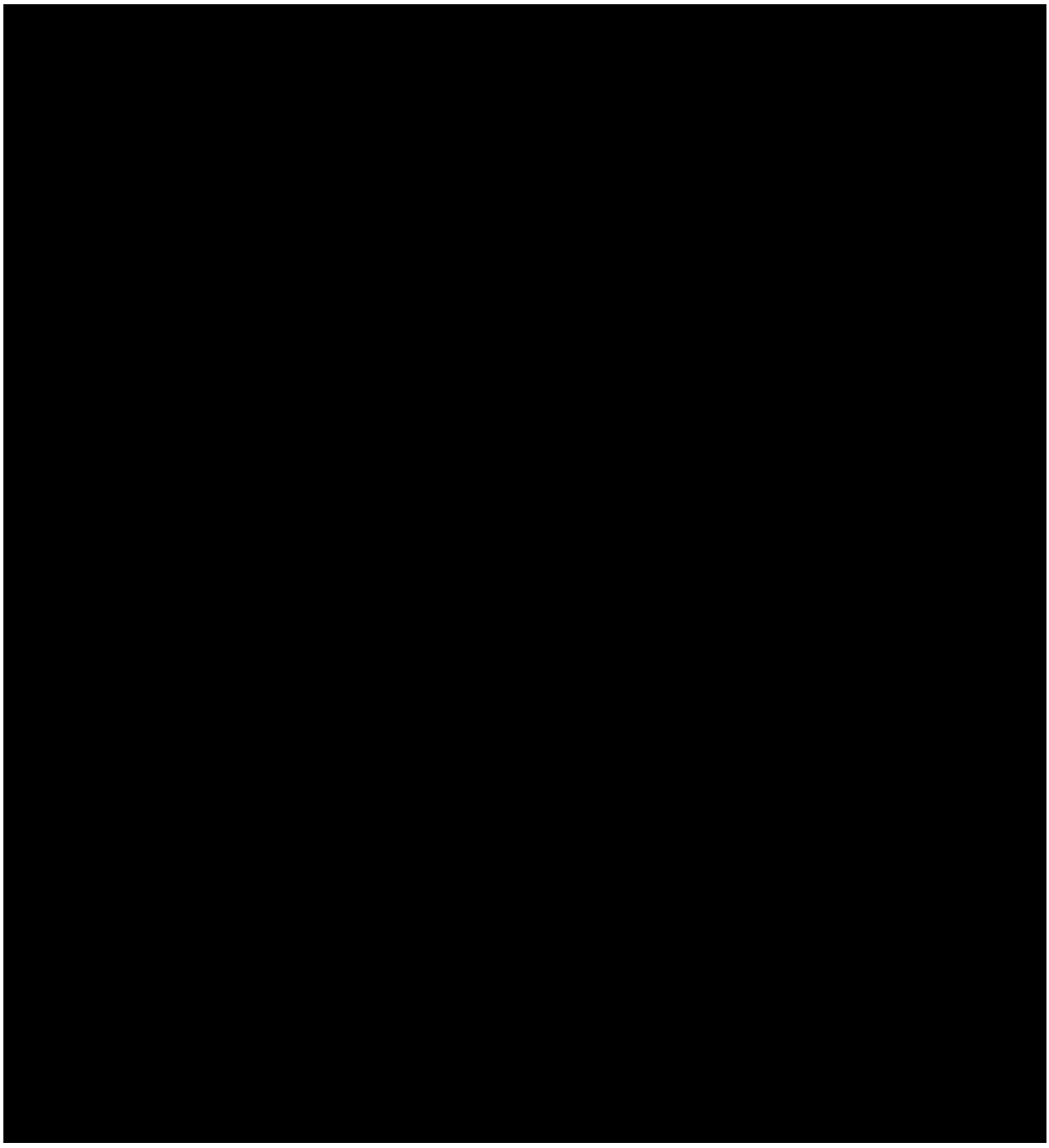
[cc] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[dd] 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. [redacted] 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.

[ee] The initial infusion of atezolizumab/placebo and the initial infusion of tiragolumab/placebo 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.

[ff] During induction, the infusions will be given in the following order: atezolizumab/placebo, tiragolumab/placebo, paclitaxel, cisplatin. See Sections 4.3.2.2 and 4.3.2.3 for information on intervals between infusions. Patients should receive anti-emetics and IV hydration according to institutional standards and manufacturer's instructions for paclitaxel and cisplatin.

[gg] During maintenance, the infusions will be given in the following order: atezolizumab/placebo, tiragolumab/placebo.



Appendix 3
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 ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

Computed tomography 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. Magnetic resonance imaging is also acceptable.

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

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

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

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

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-progressive disease: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease: 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 (e.g., 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 A3-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A3-1 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 progressive disease. 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 progressive disease status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A3-1.

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 4
European Organisation for Research and Treatment of Cancer QLQ-C30

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5
European Organisation for Research and Treatment of Cancer QLQ-OES18

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ENGLISH

EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Could you eat solid food?	1	2	3	4
32.	Could you eat liquidised or soft food?	1	2	3	4
33.	Could you drink liquids?	1	2	3	4
34.	Have you had trouble with swallowing your saliva?	1	2	3	4
35.	Have you choked when swallowing?	1	2	3	4
36.	Have you had trouble enjoying your meals?	1	2	3	4
37.	Have you felt full up too quickly?	1	2	3	4
38.	Have you had trouble with eating?	1	2	3	4
39.	Have you had trouble with eating in front of other people?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Did food and drink taste different from usual?	1	2	3	4
42	Have you had trouble with coughing?	1	2	3	4
43.	Have you had trouble with talking?	1	2	3	4
44.	Have you had acid indigestion or heartburn?	1	2	3	4
45.	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46.	Have you had pain when you eat?	1	2	3	4
47.	Have you had pain in your chest?	1	2	3	4
48.	Have you had pain in your stomach?	1	2	3	4

Appendix 6
EuroQol EQ-5D-5L

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

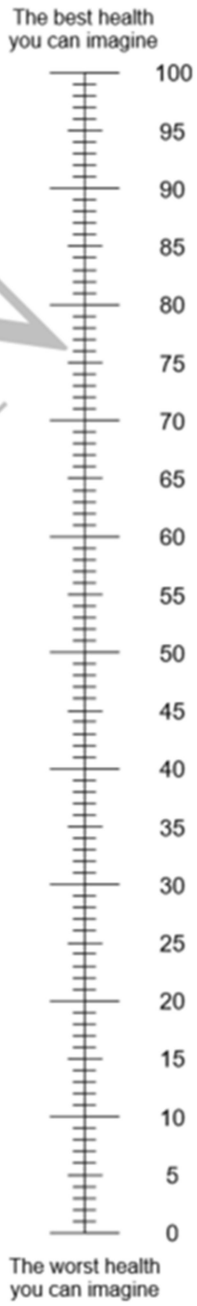
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 7
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Appendix 6: EuroQol EQ-5D-5L

Appendix 8
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

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

Appendix 9
Overall Guidelines for Management of Patients Who Experience Adverse Events

This appendix provides guidelines for management of patients who experience adverse events associated with atezolizumab or matching placebo (referred to as "atezolizumab" hereafter), tiragolumab or matching placebo (referred to as "tiragolumab" hereafter), paclitaxel, and cisplatin.

DOSE MODIFICATIONS

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

For management of drug-related toxicities, the dose of paclitaxel and the dose of cisplatin may be reduced by up to 2 times, as outlined in Table A9-1 . If the dose of one chemotherapy drug is reduced because of a toxicity considered to be solely related to that drug, there is no need to reduce the dose of the other chemotherapy drug.

Table A9-1 Dose Reductions for Paclitaxel and Cisplatin

	Initial Dose	First Dose Reduction	Second Dose Reduction
Paclitaxel	175 mg/m^2	135 mg/m^2	90 mg/m^2
Cisplatin	60–80 mg/m^2	75% of previous dose	75% of previous dose

If further dose reduction is indicated for cisplatin and/or paclitaxel after 2 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. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date. If any chemotherapy agent is held for more than 2 cycles (6 weeks) from the anticipated treatment date, or the dose level-2 is not tolerated, chemotherapy should be permanently discontinued.

Cisplatin dose reductions for renal impairment are provided in Table A9-2 .

Table A9-2 Cisplatin Dose Reductions for Renal Impairment

	Action to Be Taken
Creatinine Clearance (mL/min)	
>40 to <50	• Continue atezolizumab, tiragolumab, and paclitaxel. • Withhold cisplatin. • If creatinine clearance recovers to baseline or better ≤6 weeks after event onset, resume cisplatin with dose reduced by one dose level. [a] If not, permanently discontinue cisplatin. [b]
>30 to ≤40	• Continue atezolizumab, tiragolumab, and paclitaxel. • Withhold cisplatin. • If creatinine clearance recovers to baseline or better ≤6 weeks after event onset, resume cisplatin with dose reduced by 2 dose levels. [a] If not, permanently discontinue cisplatin. [b]
≤30	• Continue atezolizumab, tiragolumab, and paclitaxel. • Permanently discontinue cisplatin. [b]

[a] The dose of paclitaxel and the dose of cisplatin may be reduced by up to 2 times, as outlined in Table A9-1.

[b] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

TREATMENT INTERRUPTION

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. [redacted] 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.

Paclitaxel and/or cisplatin treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table A9-3). If paclitaxel or cisplatin have been withheld for >6 weeks because of toxicity, the patient should be discontinued from both chemotherapy agents. However, paclitaxel or cisplatin can be resumed after being withheld for >6 weeks if the patient is likely to derive clinical benefit as determined by the investigator. The Medical Monitor is available to advise as needed.

If one or more study treatments is interrupted, subsequent cycles should be restarted such that the study treatment infusions remain synchronized.

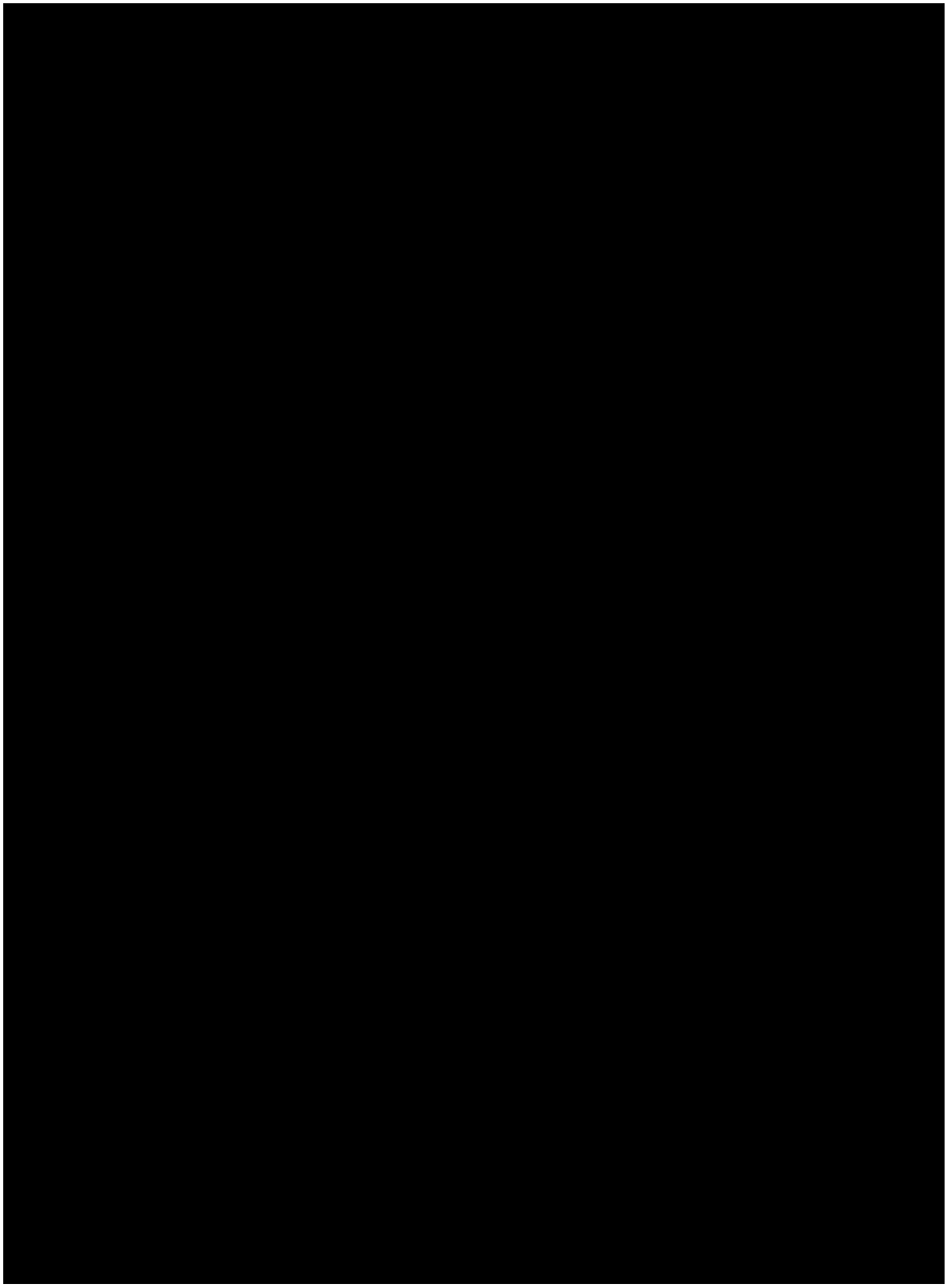
[redacted]

MANAGEMENT GUIDELINES

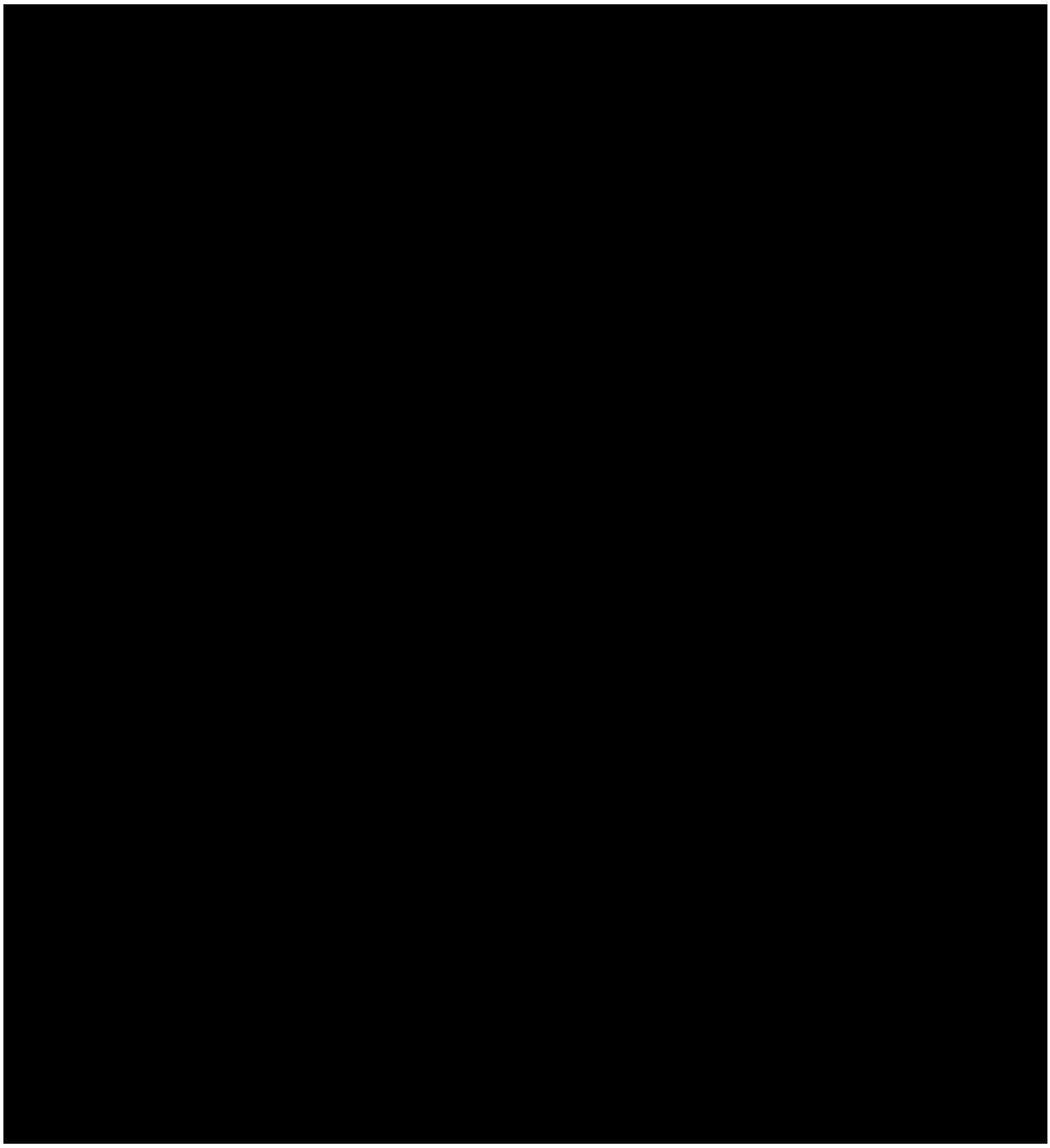
Guidelines for management of patients who experience specific adverse events are provided in Table A9-3. If several toxicities of different severity grades occur at the same time, the patient should be managed according to guidelines for the most severe

toxicity. The investigator may use discretion in adhering to the guidelines 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.

For adverse events associated with paclitaxel or cisplatin that are not listed in Table A9-3, refer to guidelines in the applicable local prescribing information (if available) or Summary of Product Characteristics. For cases in which management guidelines are not covered in the protocol or prescribing information, patients should be managed as deemed appropriate by the investigator according to best medical judgment.



Appendix 9: Overall Guidelines for Management of Patients Who Experience Adverse Events



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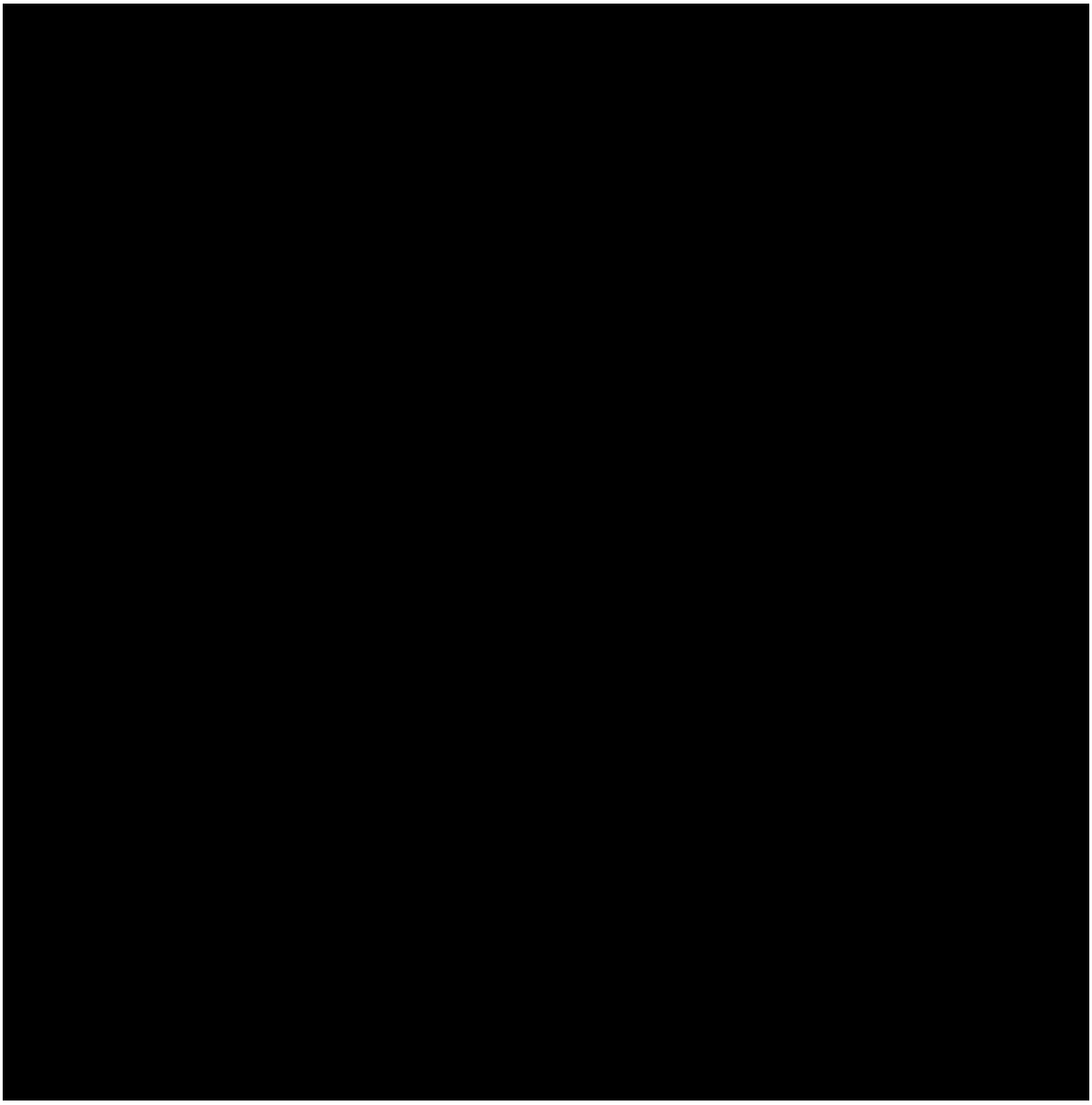

Appendix 9: Overall Guidelines for Management of Patients Who Experience Adverse Events

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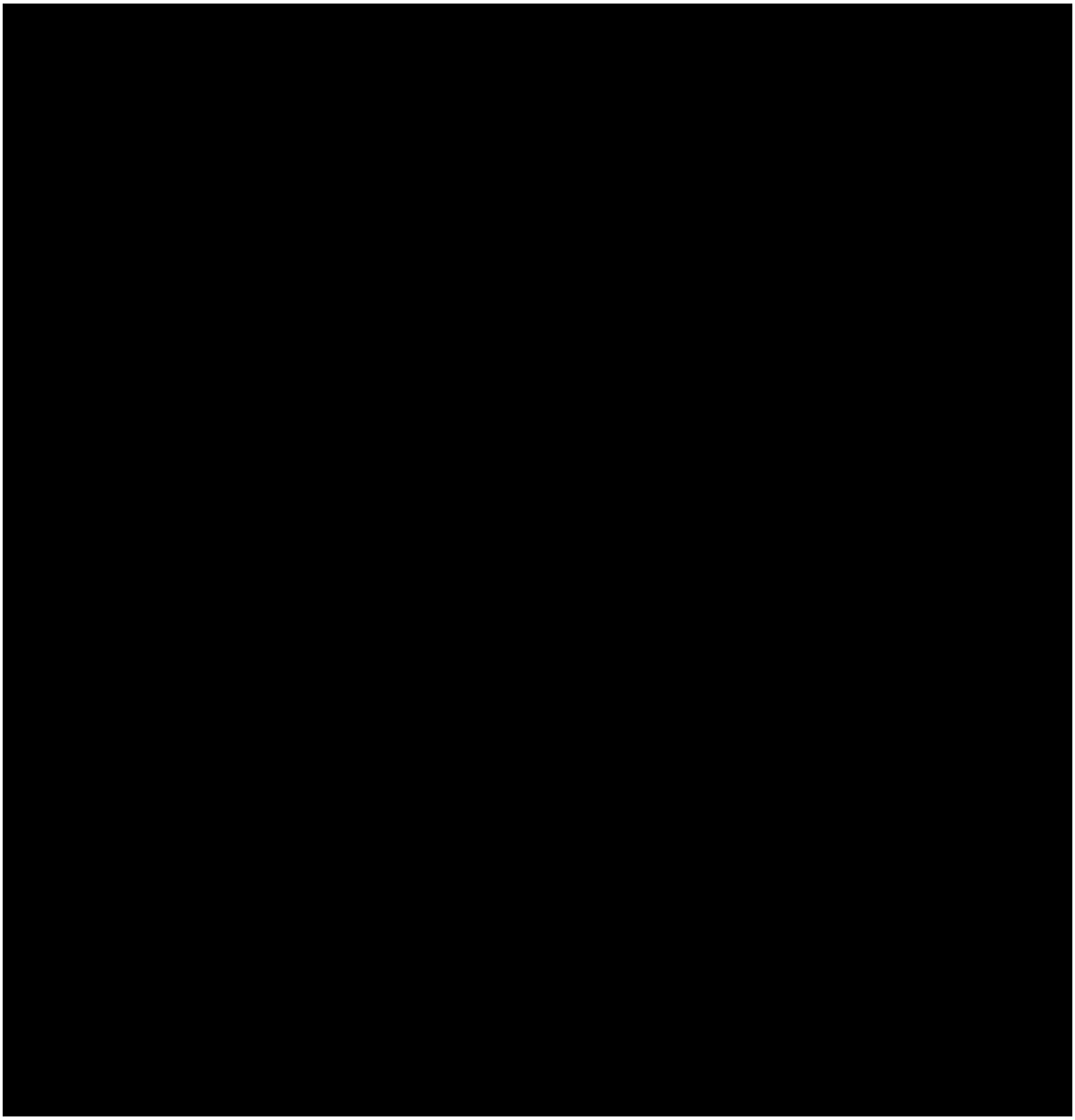

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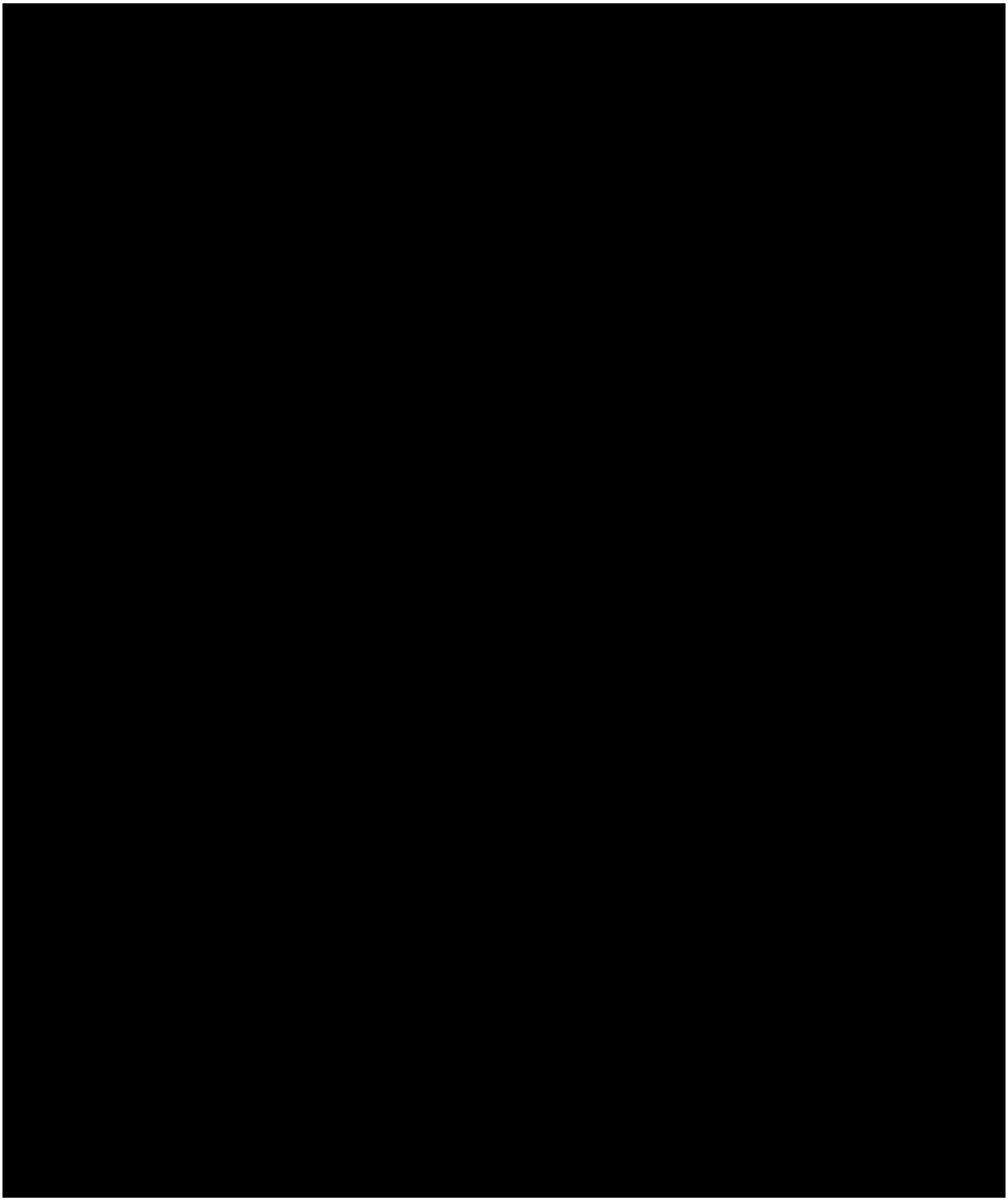

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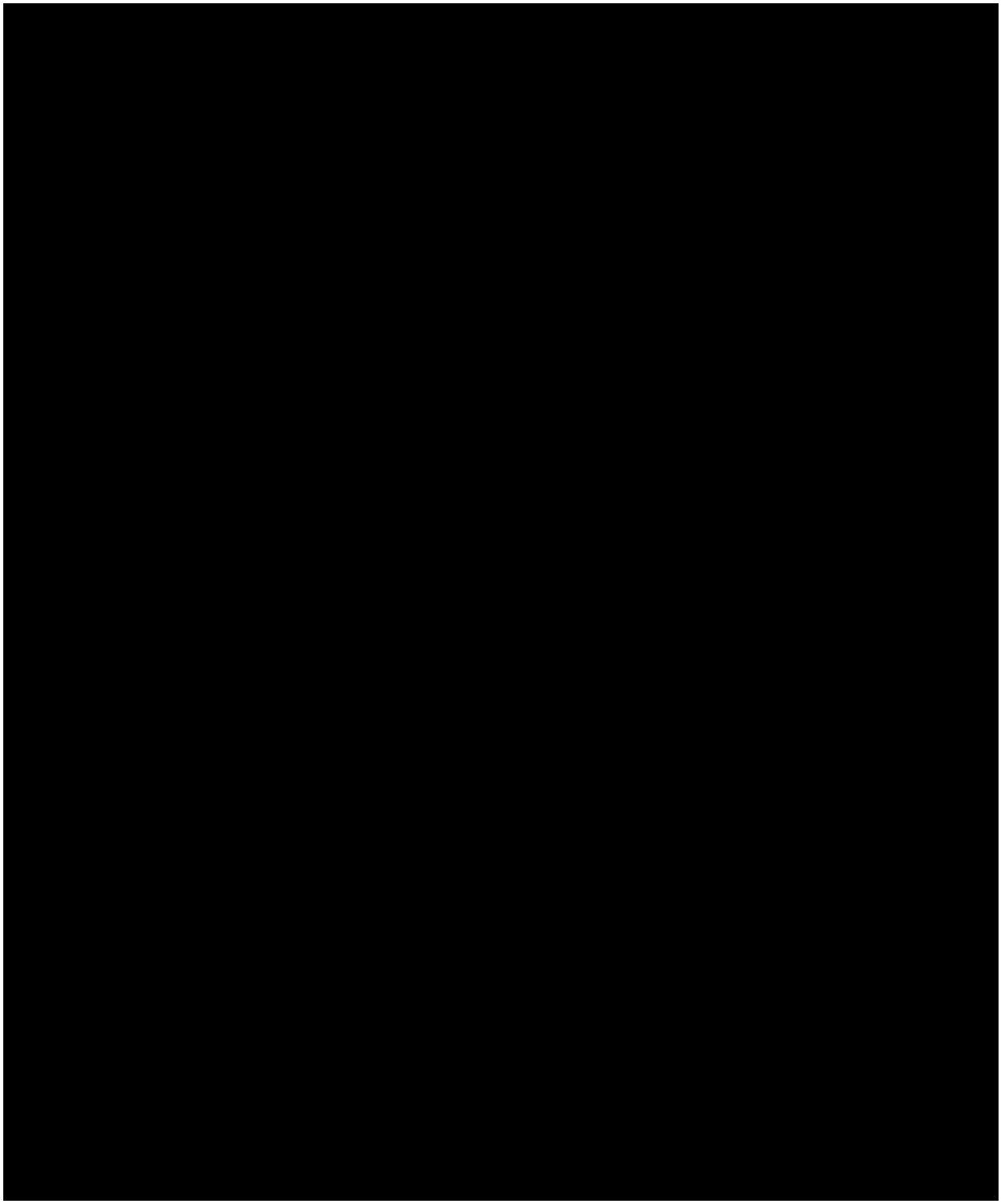

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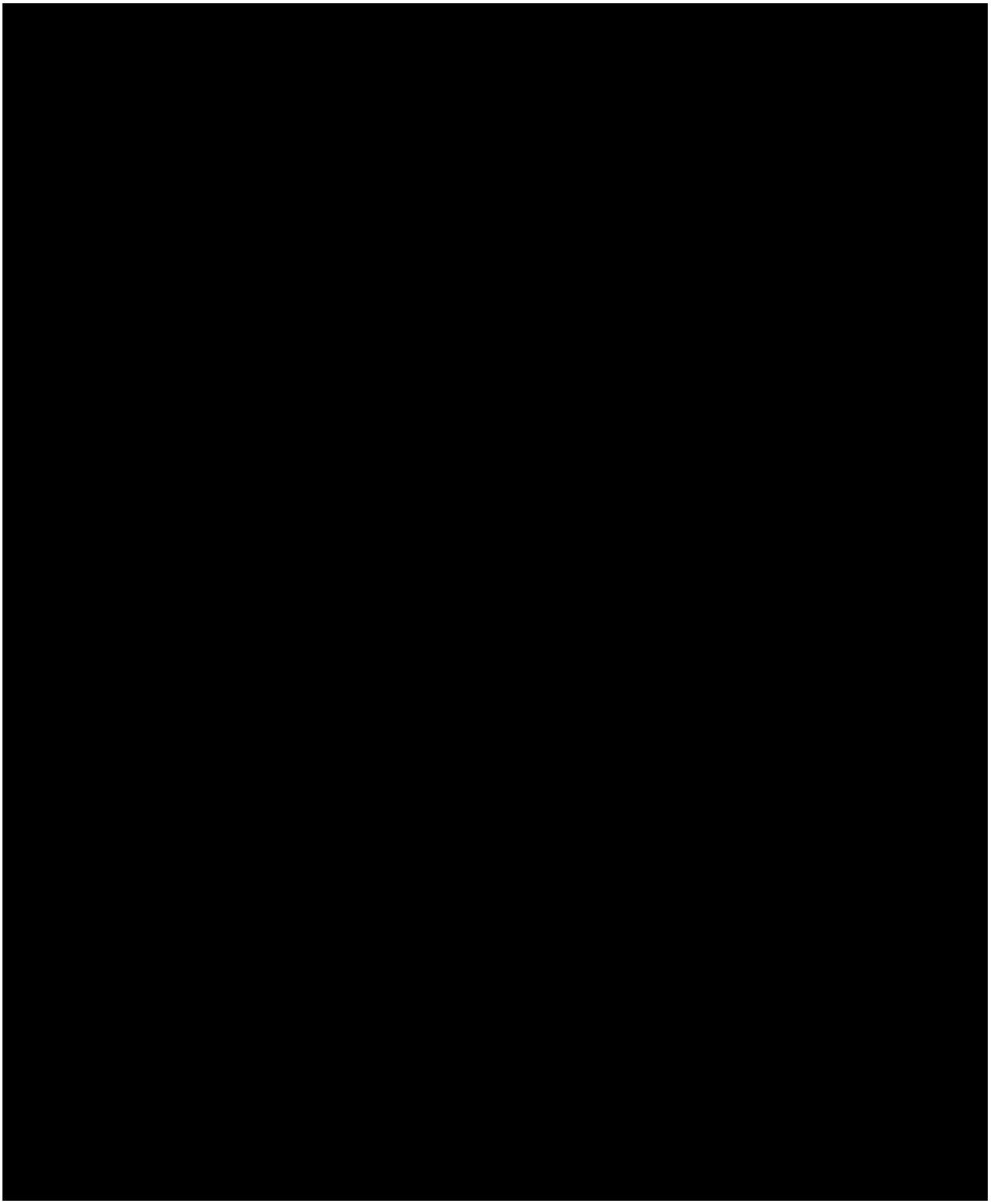

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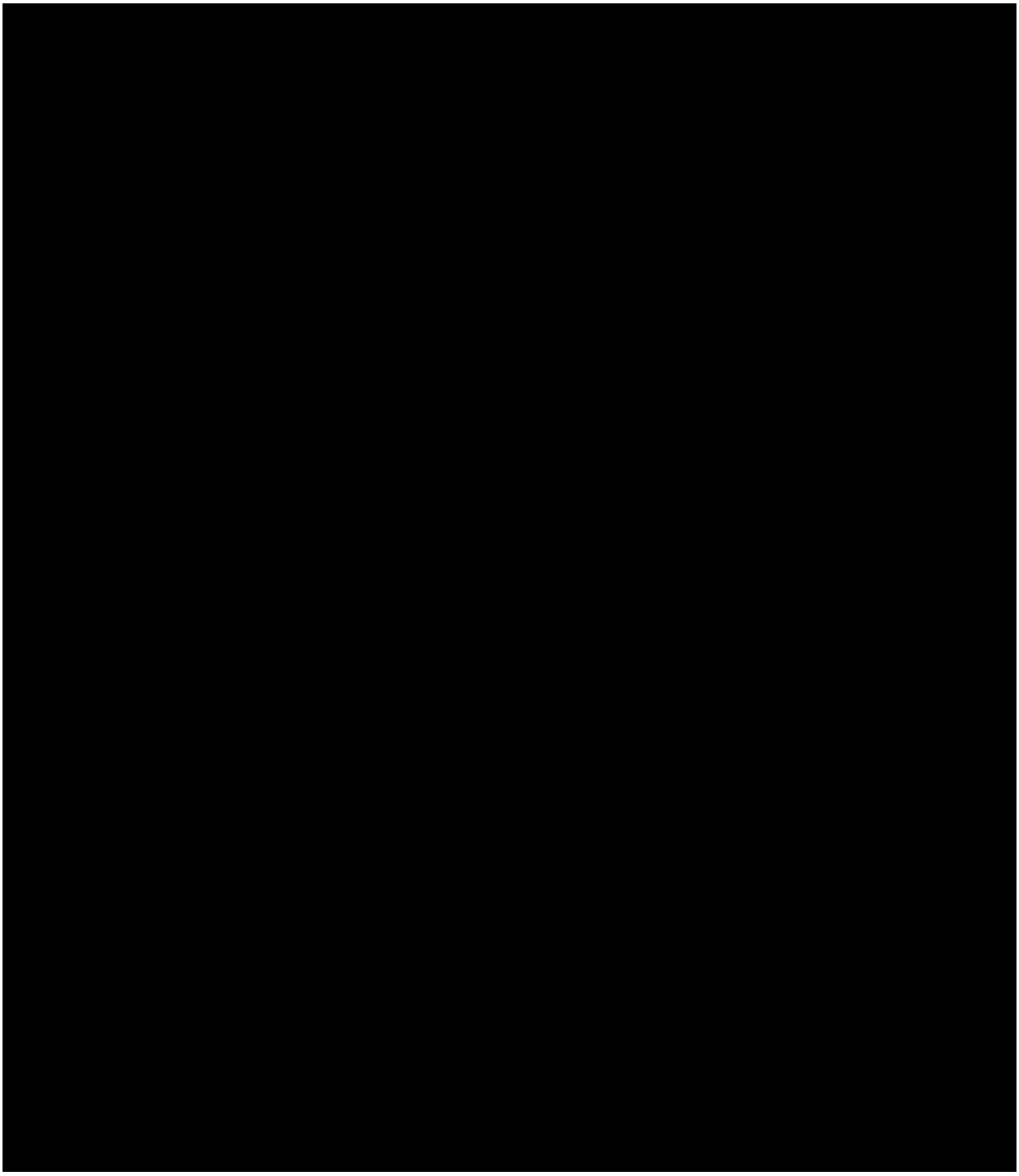

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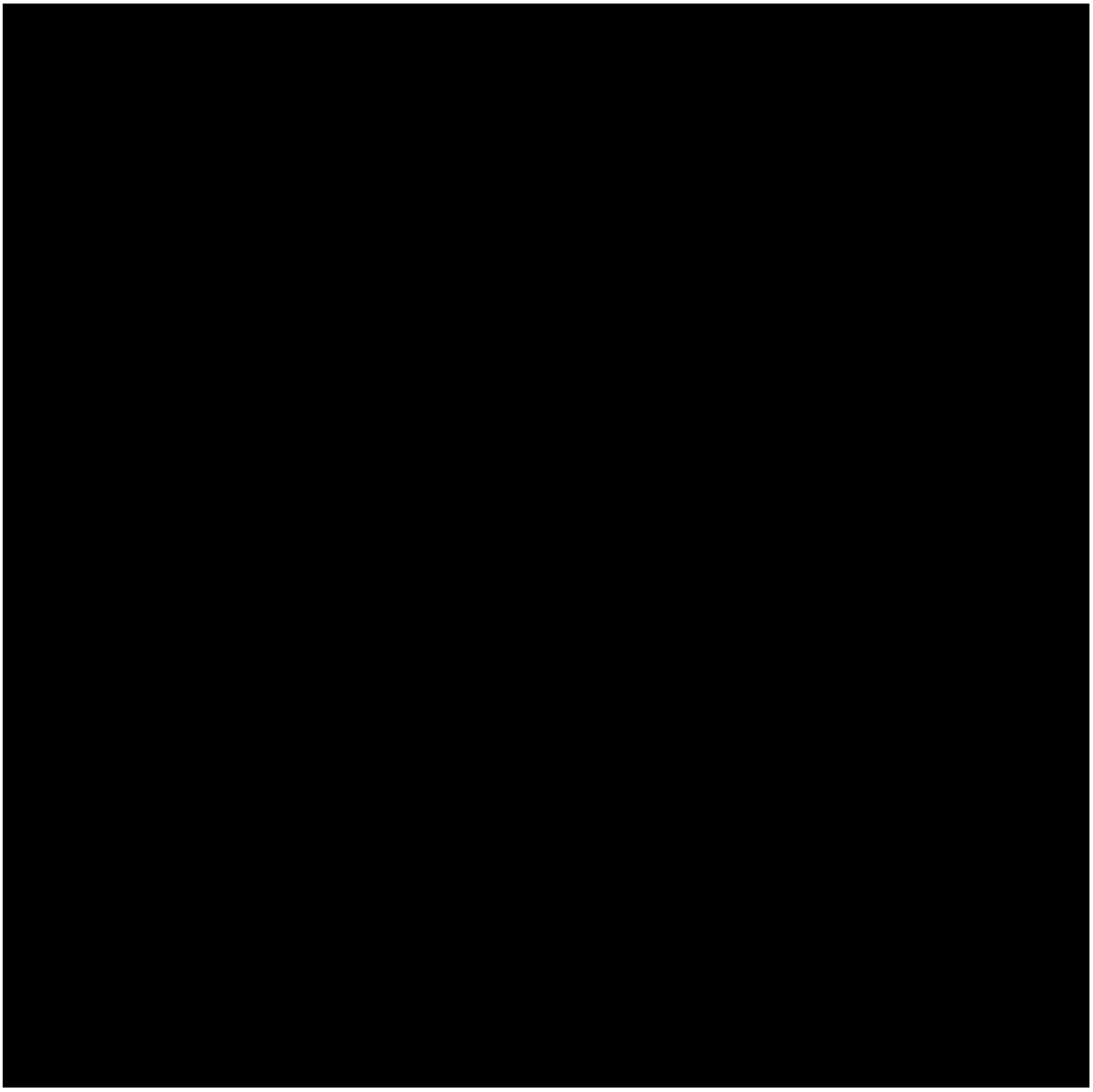

Appendix 10
Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

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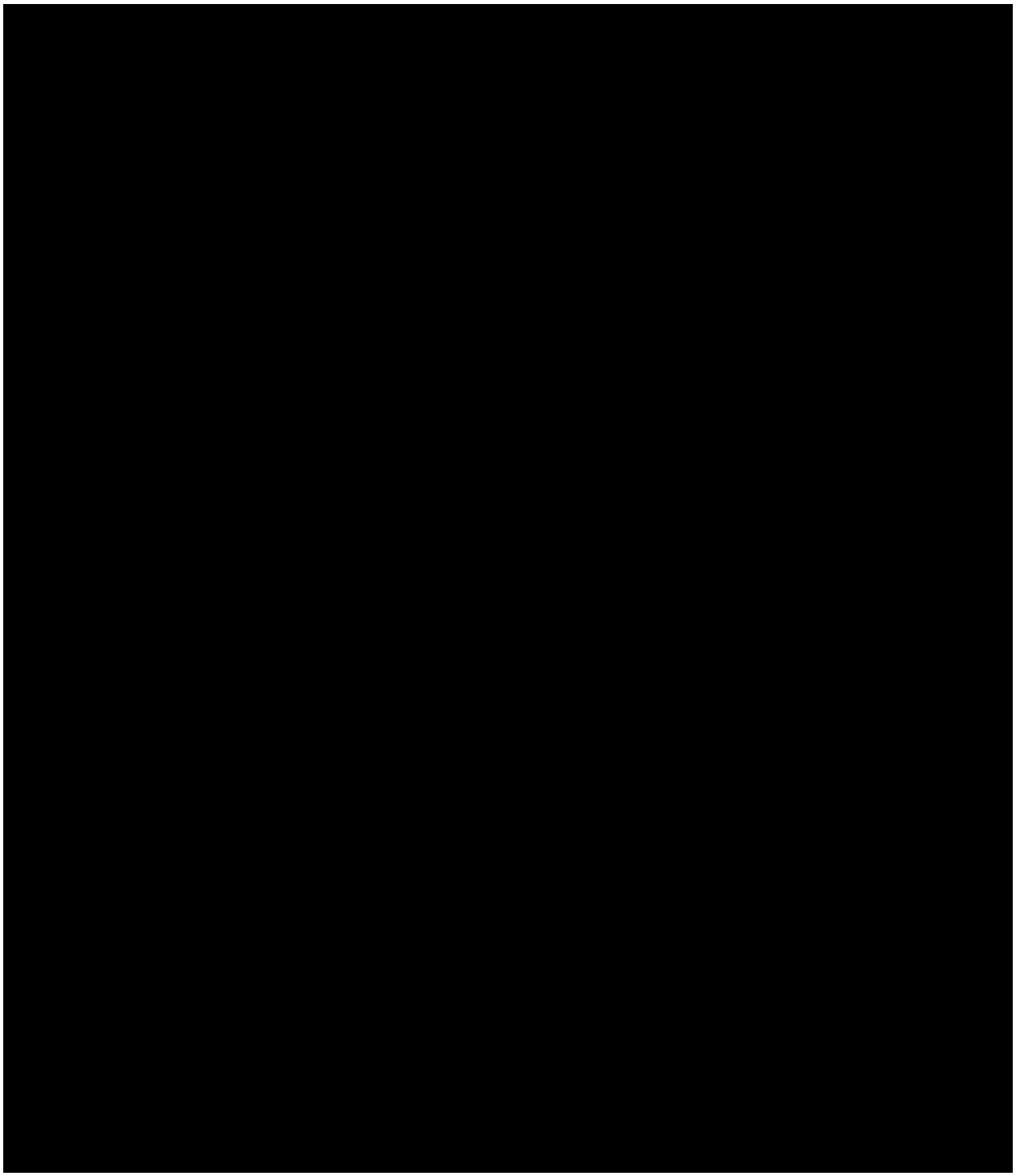

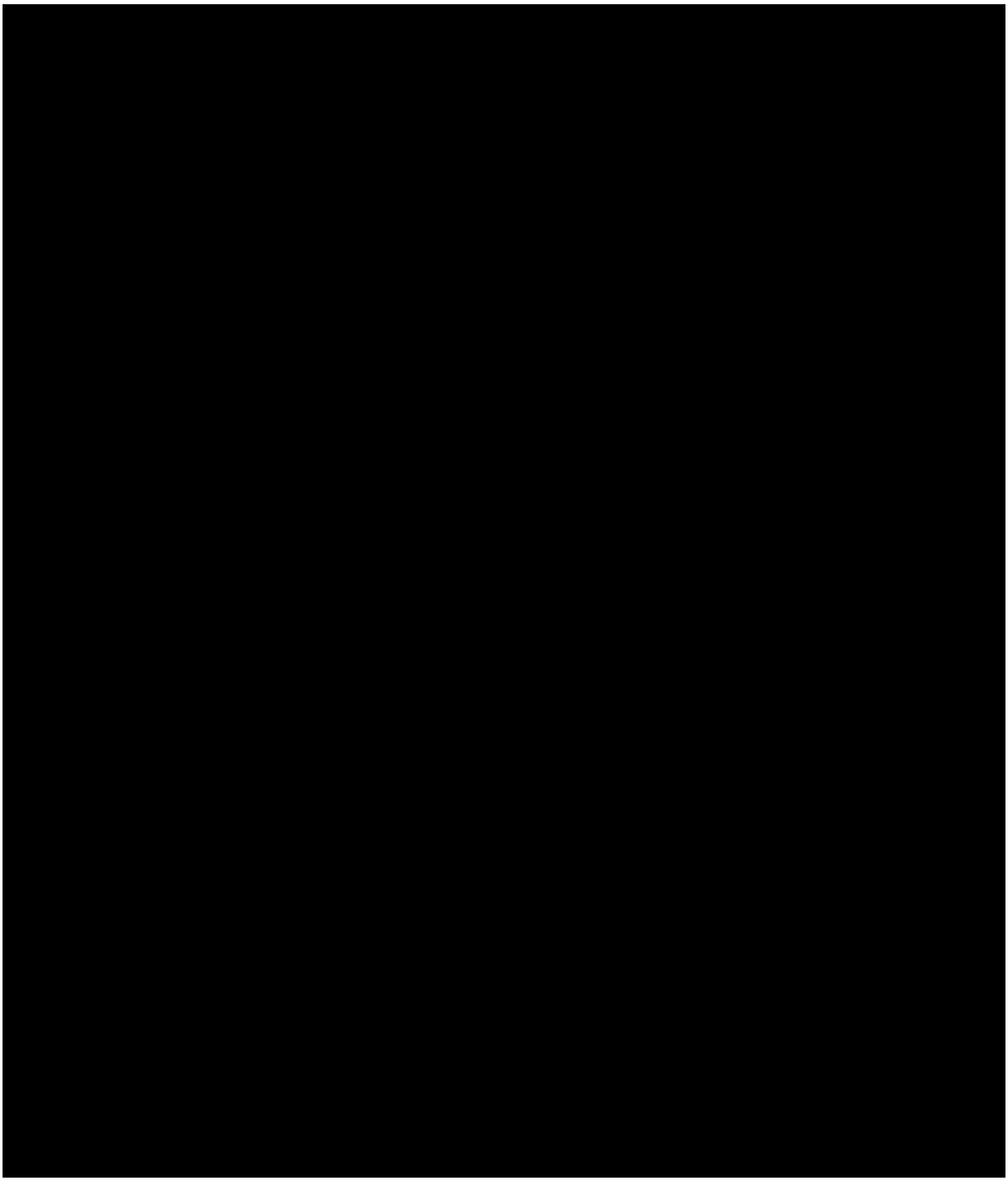

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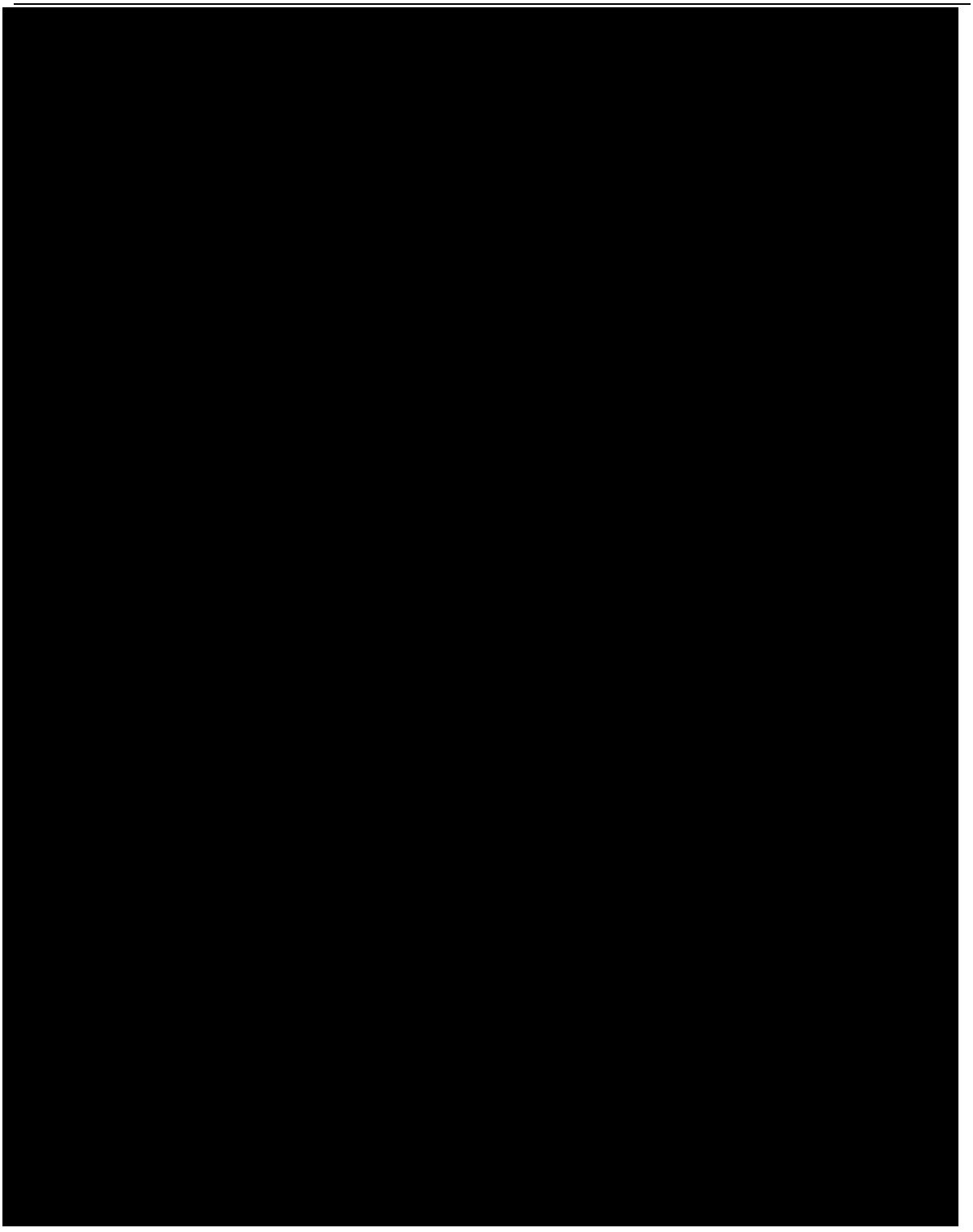

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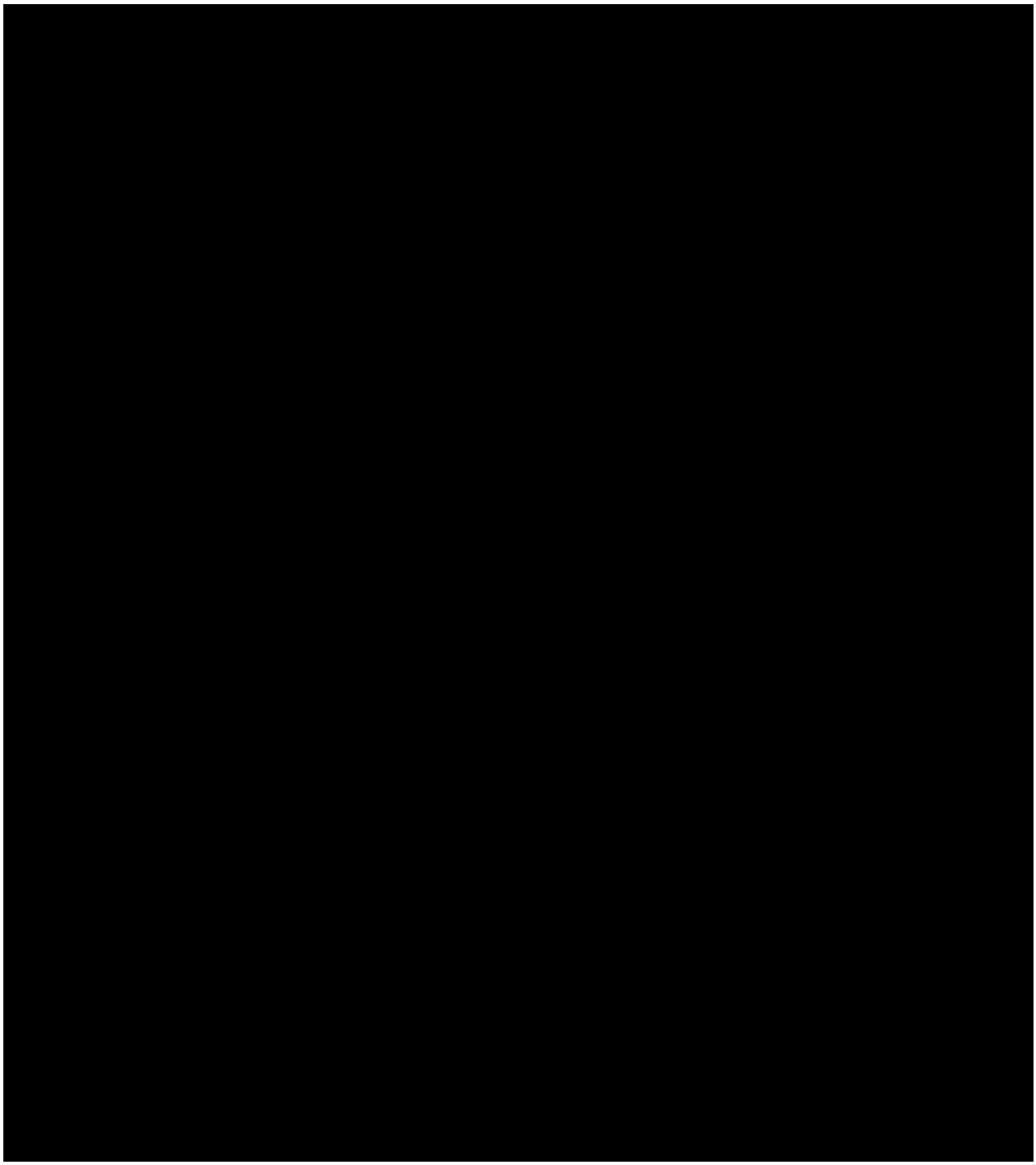

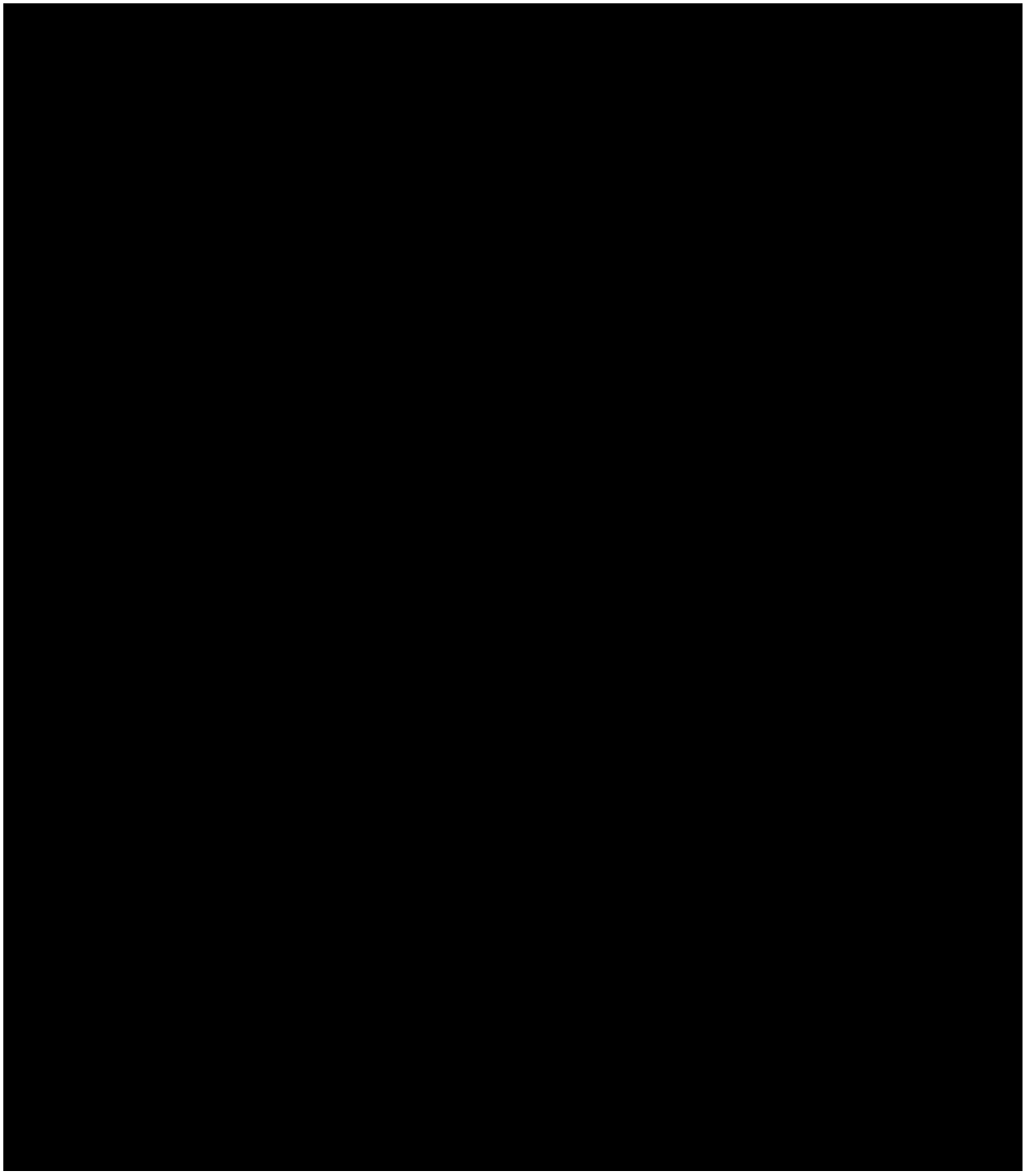

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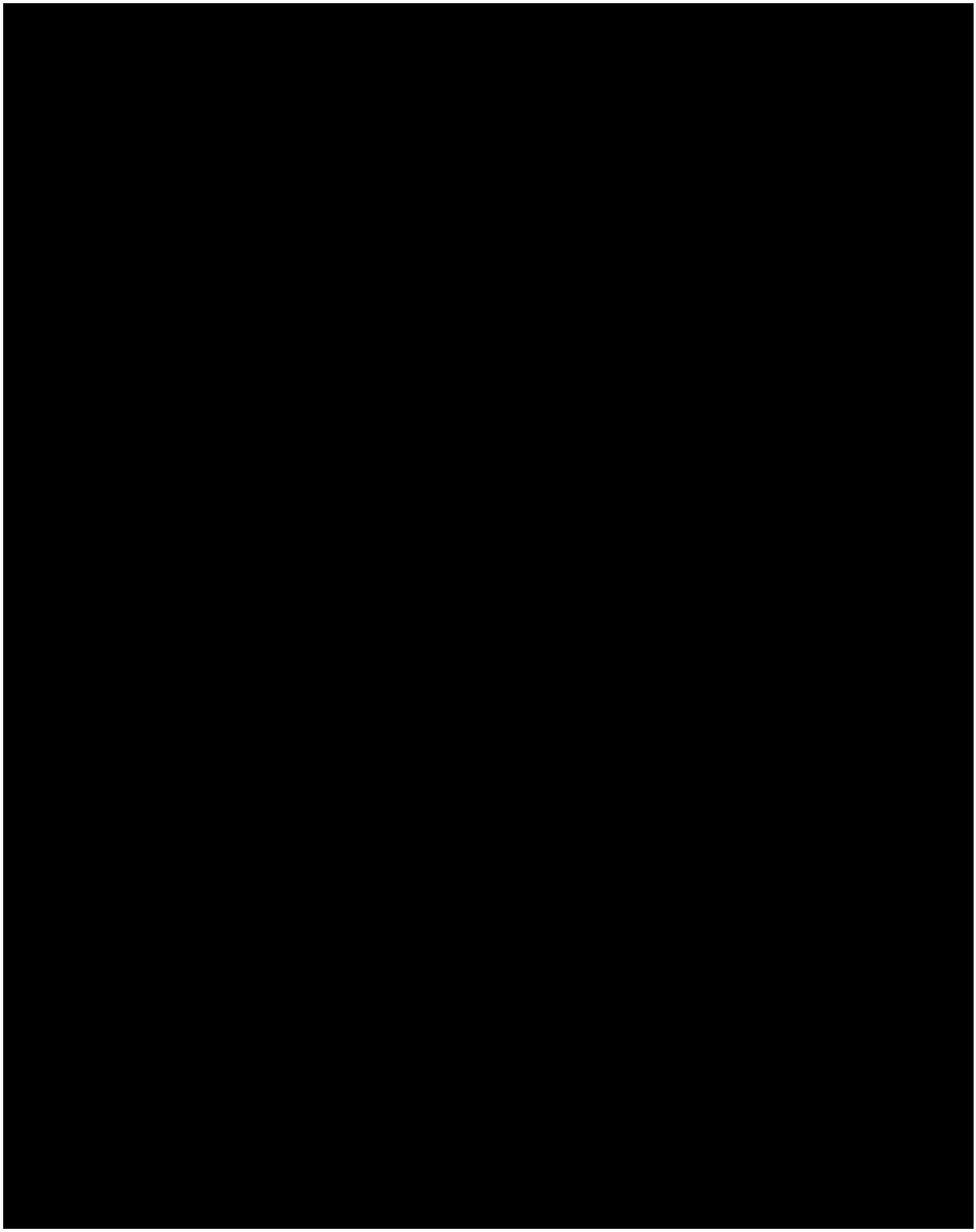

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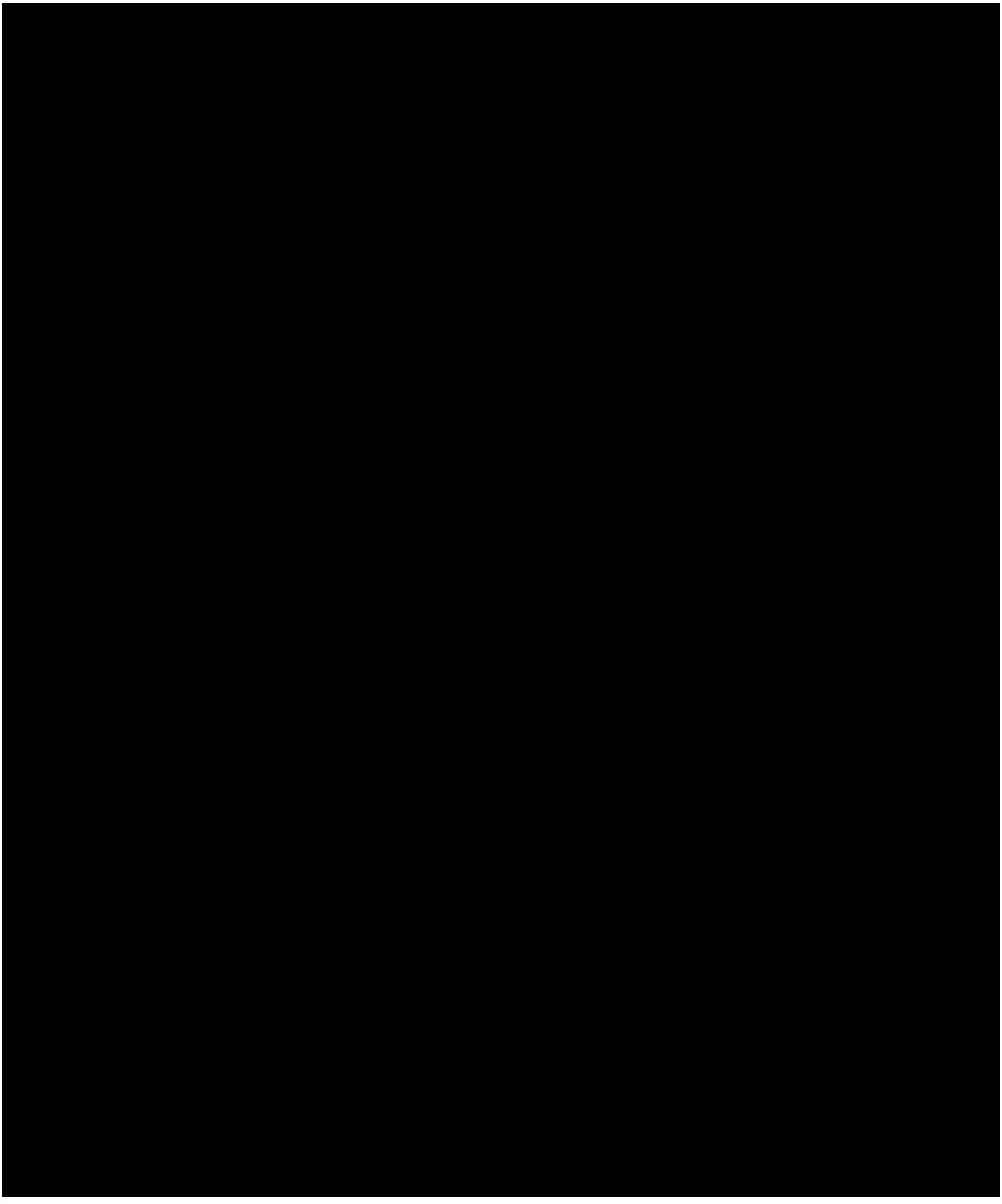

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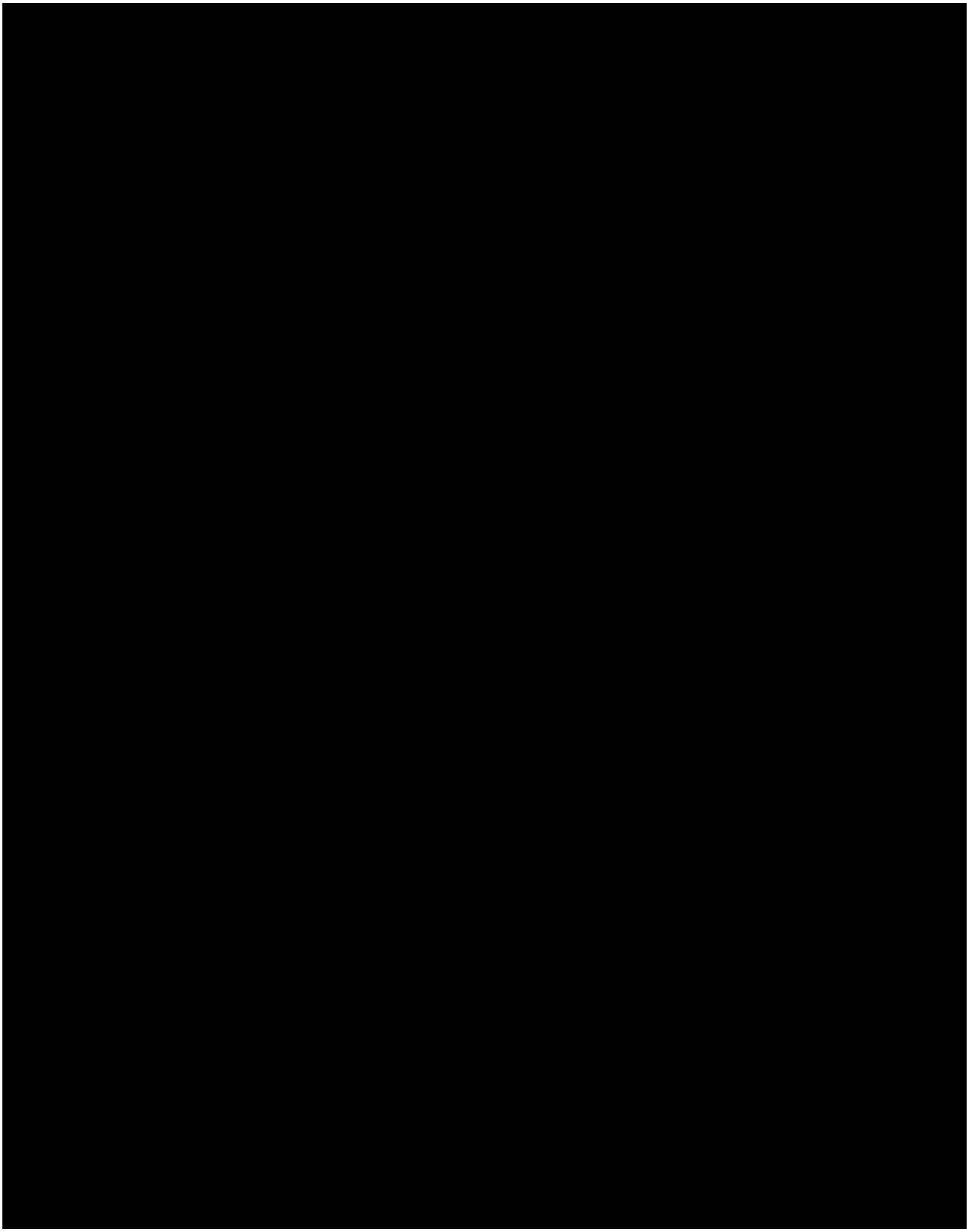

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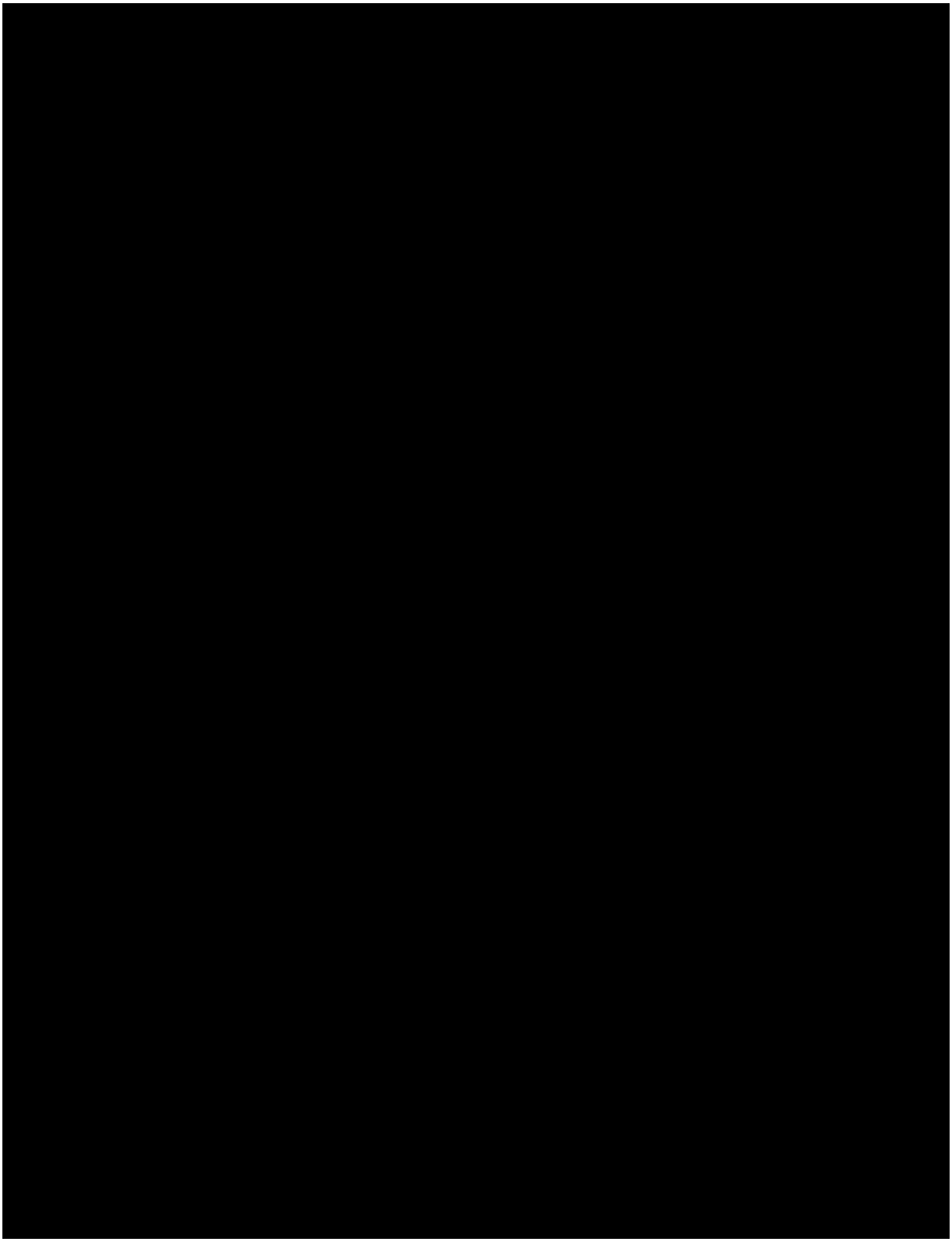

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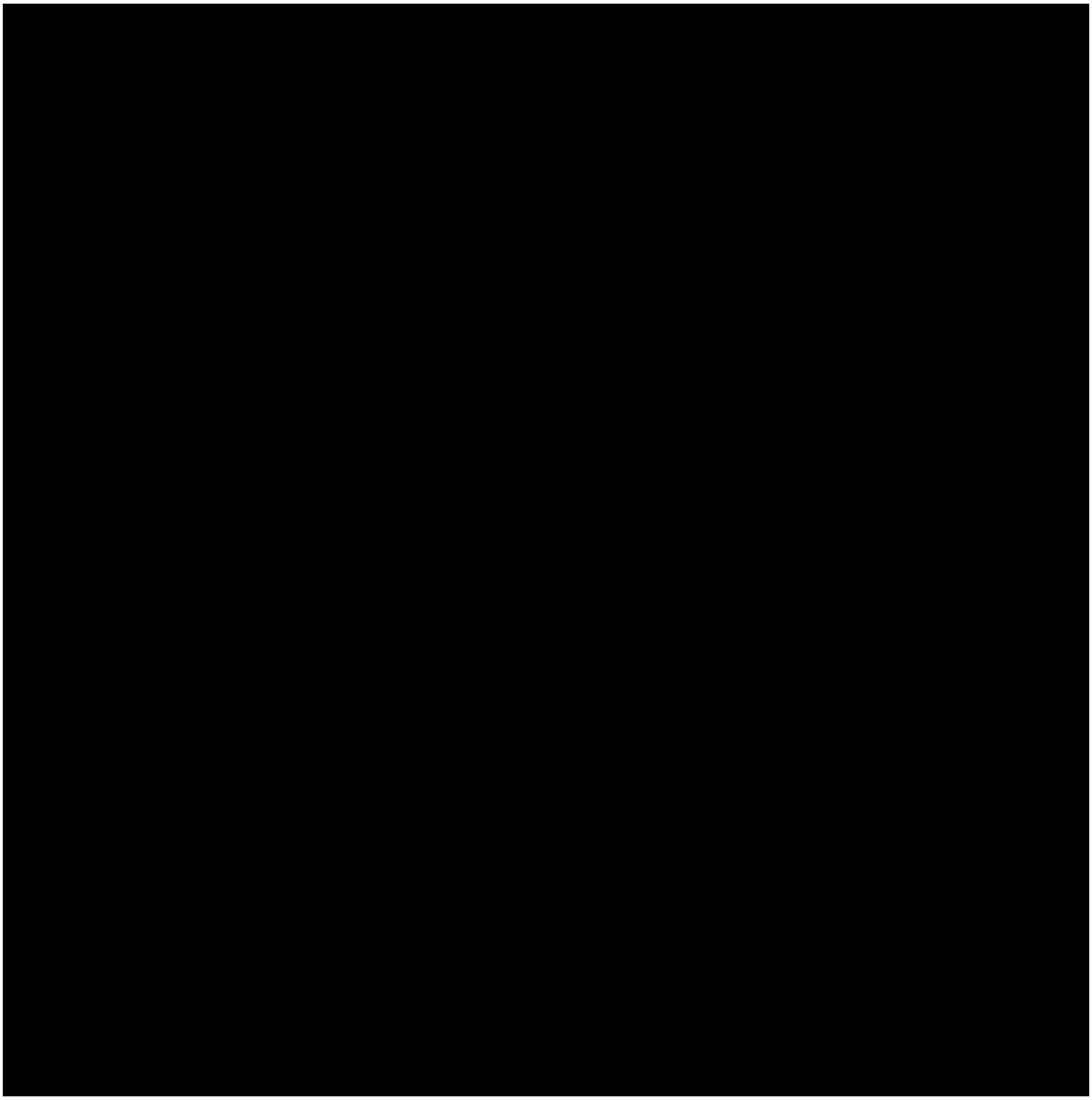

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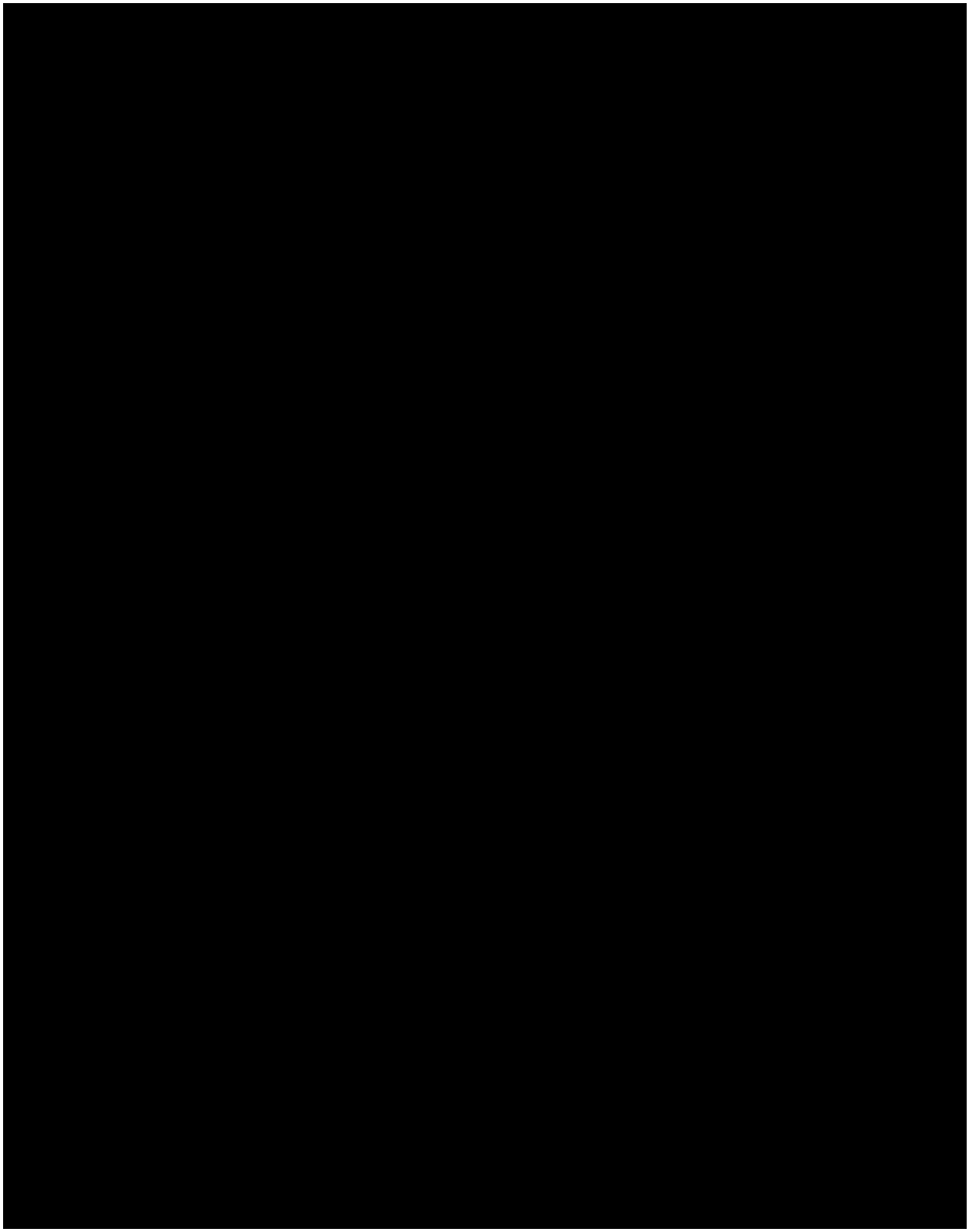

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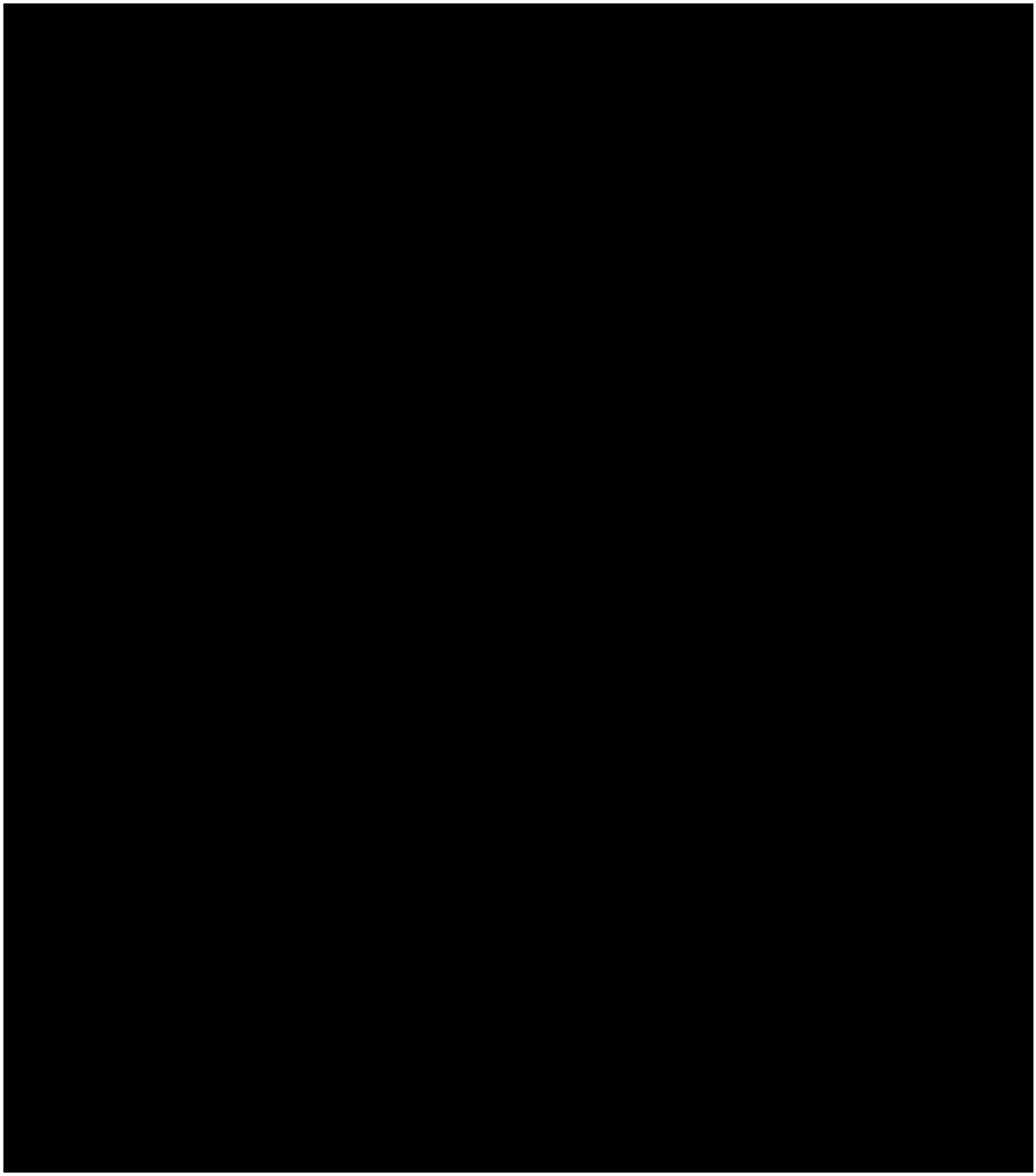

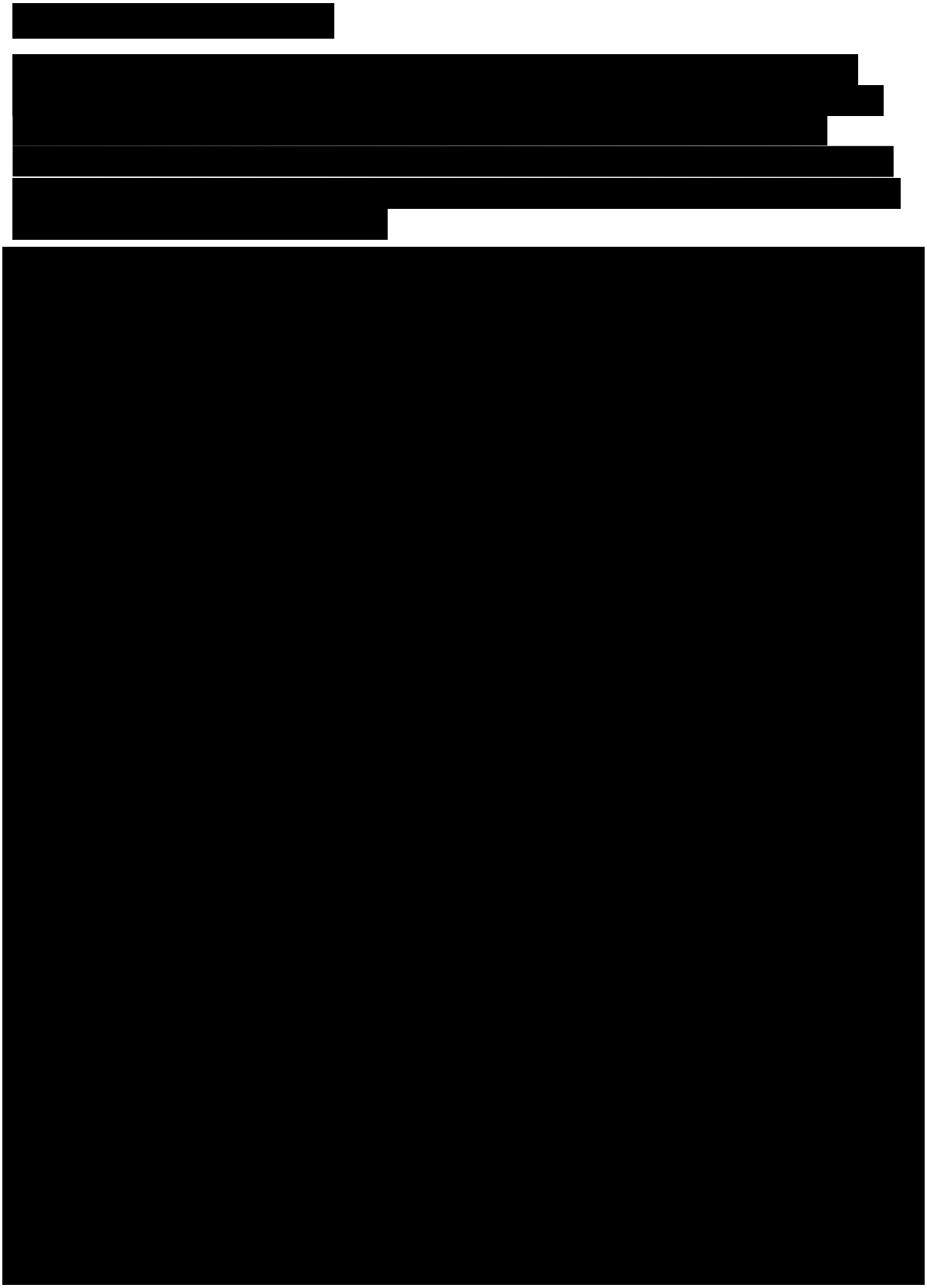

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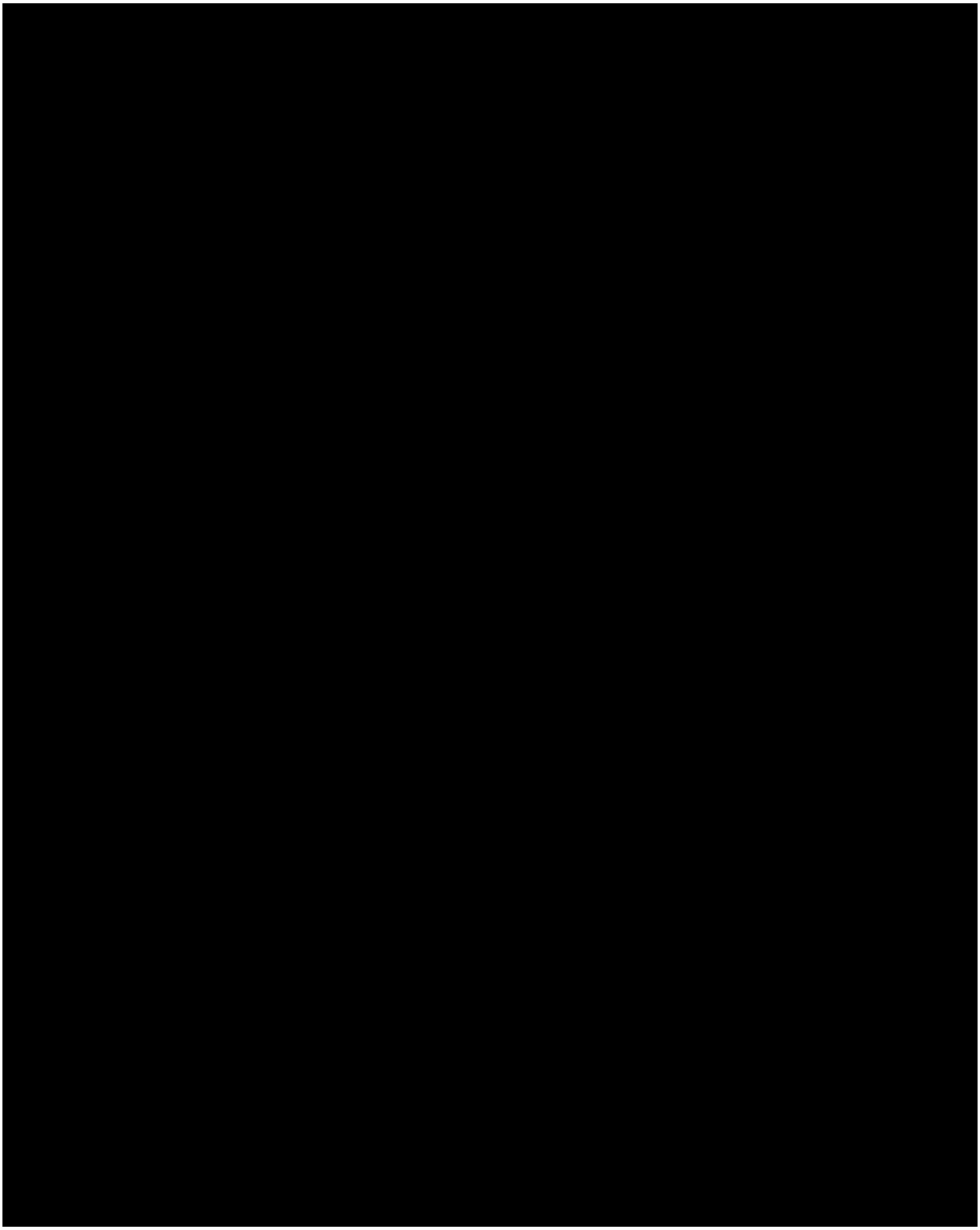

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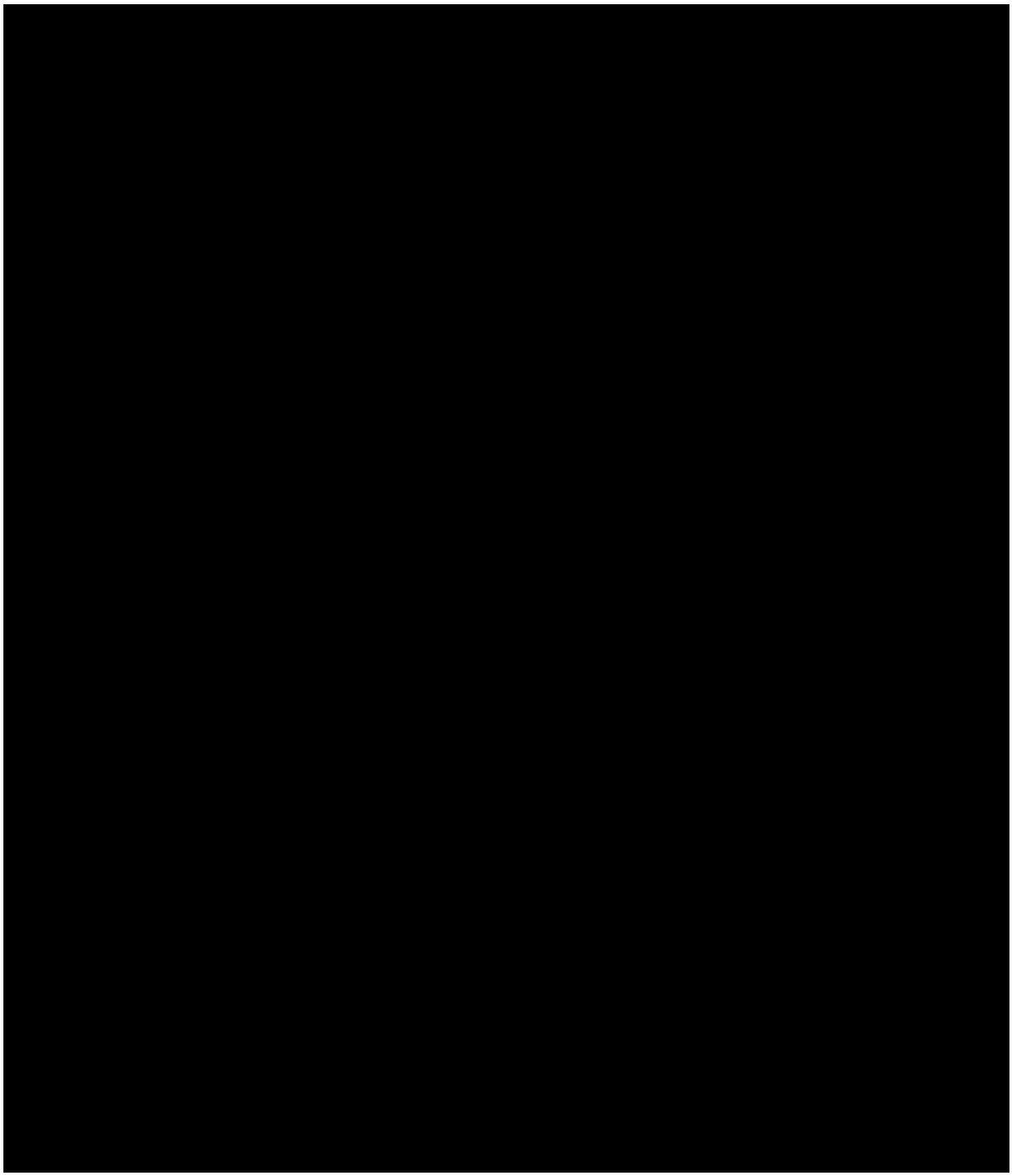

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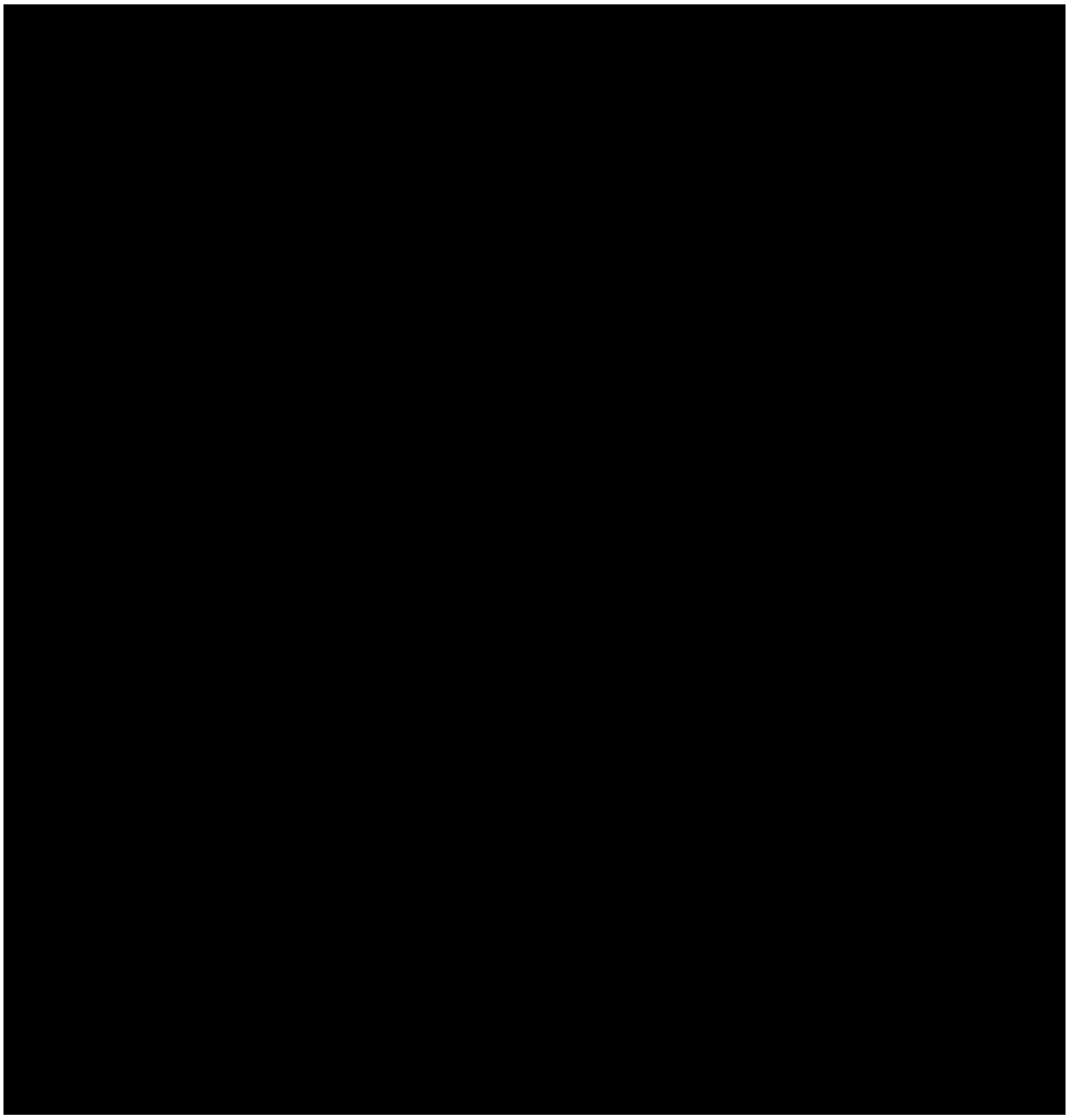

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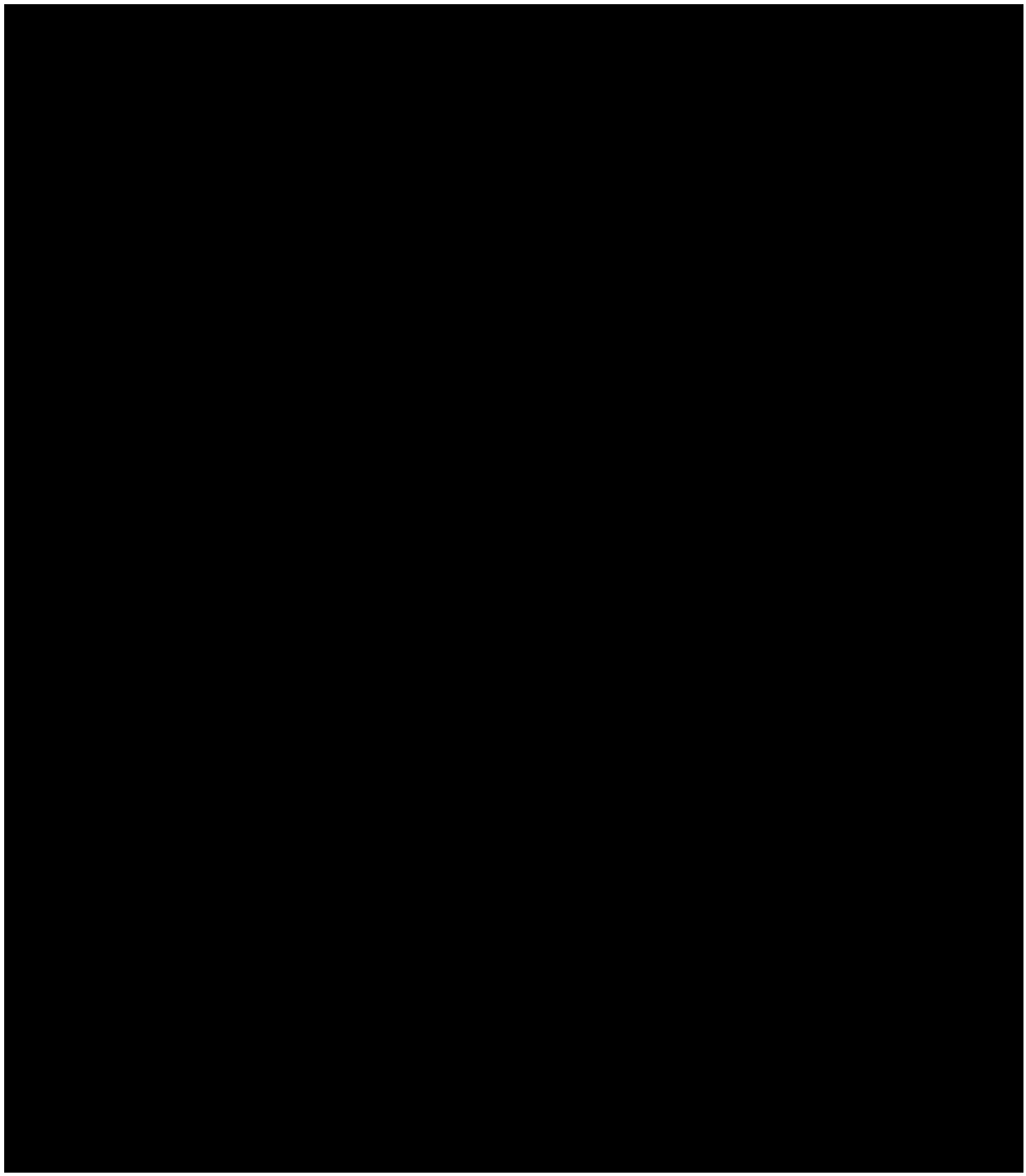

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