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PROTOCOL AFM24-102

Study Title:	A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of AFM24 in Combination with Atezolizumab in Patients with Selected Advanced/Metastatic *EGFR*-expressing Cancers
Protocol Number:	AFM24-102
Sponsor:	Affimed GmbH Im Neuenheimer Feld 582, 69120 Heidelberg, Germany
Products:	AFM24 *(innate immune cell engaging recombinant antibody against EGFR-expressing solid tumors)* Atezolizumab (*anti-PD-L1 antibody monoclonal IgG1)*
Indication Studied:	Advanced/Metastatic *EGFR*-expressing cancers
Study Phase:	Phase 1/2a
EudraCT Number:	2021-000707-20
IND Number:	143500
Medical Monitor:	[redacted]
Final Version Date:	Version 4.0, 10 May 2023

Sponsor Signatory

This study will be conducted in compliance with International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements, including data privacy laws.

This protocol, V4.0 dated 10 May 2023, has been approved by Affimed GmbH.

Signature: ..... **Date:** .....

[redacted]

Signature: ..... **Date:** .....

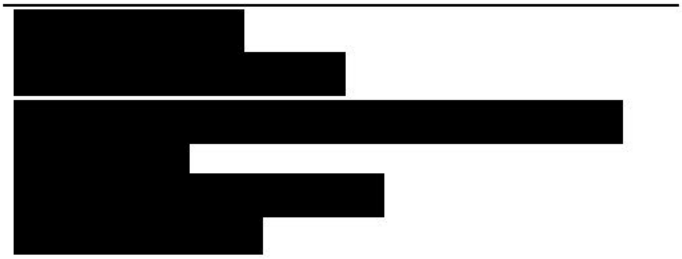
[redacted]

Affimed GmbH
Im Neuenheimer Feld 582
69120 Heidelberg
Germany

[redacted]

Coordinating Investigator

I declare that the protocol contains all the necessary information required for the conduct of the study.



Investigator's Declaration and Approval:

I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described in the current, approved protocol. I verify that I am suitably qualified by education, scientific and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae provided to the Sponsor.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical and clinical experience when available (e.g., in updated editions of the Investigator's Brochure), to all staff involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with the investigational medicinal product and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. I acknowledge that the study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of patients, including data privacy laws. I confirm it is my duty and the duty of my study staff to ensure participating patients are informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. Patients will be informed that they may withdraw from their studies at any time without jeopardizing their future care. I will use only the patient informed consent form approved by the Sponsor and the Ethics Committee/Institutional Review Board for this study. I will supply the Sponsor with any written material prepared by myself or my study staff, e.g., summary of study, which is given to the Ethics Committee/Institutional Review Board in support of the application.

Where applicable, the patient information contained in clinic records, reports and manuscripts will be transcribed to the study case report forms. I (or my delegates as described in my Study File) will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report forms. I agree to the audit and monitoring procedures to verify study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records and from the hospital or institution where the study was conducted (as permitted by the hospital or institution).

I understand that the case report forms and other data pertinent to this study are the property of Affimed GmbH and are confidential. I agree to only supply Affimed GmbH (or their delegates) with patient study data in such a way that the patient cannot be personally identified.

Investigator:	……	……
	Signature	Date
Print Name:	……	
Institution Name:	……	
Institution Address:	……	

OTHER CONTACT INFORMATION

Full contact details for each Investigational site, the Sponsor, the Medical Monitor(s), and key coordinating and operational personnel will be maintained in the Trial Master File and in each site's Study File throughout the course of the study.

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List of Abbreviations

Abbreviation	Definition/Explanation
ADA	anti-drug antibodies
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}168}$	area under the concentration-time curve form time zero to 168 hours
AUC_{tau}	area under the concentration-time curve over the dose interval
BOR	best objective response
C	Cycle
CBR	clinical benefit rate
CD16A	Fcγ receptor IIIA
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CR	complete response
CRA	clinical research associate
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	coefficient of variation
C1D1	Cycle 1 Day 1
D	Day
DDS	dose-determining set
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	epidermal growth factor receptor
EOI	end of infusion
EOT	End of Treatment

Abbreviation	Definition/Explanation
EU-CTR	EU Clinical Trial Regulation
EXP	expansion cohort
Fc	fragment crystallizable
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEJ	gastro-esophageal junction
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IgG	immunoglobulin G
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
i.v.	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	natural killer
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PS	performance status

Abbreviation	Definition/Explanation
PT	prothrombin time
qw	once weekly
q1w	every 1 week
q2w	every 2 weeks
q3w	every 3 weeks
RECIST	Response Evaluate Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
SOC	standard of care
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	time to C_{max}
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
US	United States
WT	wild type

1. STUDY SYNOPSIS

Sponsor	Affimed GmbH.
Study Products	AFM24 (*innate immune cell engaging recombinant antibody against EGFR-expressing solid tumors)* Atezolizumab (*monoclonal IgG1 anti-PD-L1 antibody)*
Title of Study	A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of AFM24 in Combination with Atezolizumab in Patients with Selected Advanced/Metastatic *EGFR*-expressing Cancers
Protocol Number	AFM24-102
Study Design	Open-Label, Multicenter Study
Study Phase	Phase 1/2a
Number of Study Sites	Approximately 20 study centers in United States (US), Europe, and Asia/Pacific
Patient Population	Patients aged 18 years or older with documented histologically or cytologically confirmed select advanced or metastatic epidermal growth factor receptor (*EGFR*)-positive cancers.
Number of Patients	The total number of patients planned for this study is estimated to be approximately 148. Up to 18 patients will be treated in the dose escalation phase (Phase 1) of the study. Up to 130 additional patients will be treated in the expansion phase (Phase 2a) of the study.

Study Objectives and Endpoints

Objectives	Endpoints
Dose Escalation Phase (Phase 1)	
Primary	
• To determine the maximum tolerated dose (MTD) and/or to select one or more recommended phase 2 doses (RP2Ds) of AFM24 in combination with atezolizumab	• Adverse events (AEs) to be assessed by the incidence and severity of dose-limiting toxicity (DLT) within the DLT observation period (Cycle 1)
Secondary	
• To assess the safety and tolerability of AFM24 in combination with atezolizumab • To evaluate the preliminary antitumor activity of AFM24 in combination with atezolizumab in terms of objective response rate (ORR) • To characterize the pharmacokinetic (PK) profile of AFM24 when AFM24 is given in combination with atezolizumab • To assess the immunogenicity of AFM24 when AFM24 is given in combination with atezolizumab	• Incidence of patients with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • ORR using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 determined by Investigator assessment • PK parameters of AFM24: C_{max}, T_{max}, C_{min} and AUC_{tau} • Frequency of patients developing anti-drug antibodies (ADAs) against AFM24
Exploratory	
[redacted]	[redacted]
Phase 2a	
Primary	
• To evaluate the antitumor activity of AFM24 in combination with atezolizumab in terms of	• ORR according to RECIST v1.1 determined by the Investigator assessment

ORR	
Secondary	
• To assess preliminary efficacy of AFM24 in combination with atezolizumab using additional measures of clinical benefit • To assess the safety and tolerability of AFM24 in combination with atezolizumab • To characterize the PK profile of AFM24 when AFM24 is given in combination with atezolizumab • To assess the immunogenicity of AFM24 when AFM24 is given in combination with atezolizumab	• Progression-free survival (PFS) according to RECIST v1.1 by Investigator assessment • Duration of response (DOR) according to RECIST v1.1 by Investigator assessment • Clinical benefit rate (CBR) according to RECIST v1.1 by Investigator assessment • Disease control rate (DCR) according to RECIST v1.1 by Investigator assessment • Incidence of patients with TEAEs and SAEs • PK parameters of AFM24: C_{max}, T_{max}, C_{min}, and AUC_{tau} • Frequency of patients developing ADAs against AFM24
Exploratory	
[redacted]	[redacted]

Abbreviations: AUC_{tau}: area under the concentration-time curve over the dose interval; C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration; T_{max}: time to C_{max}

Study Design and Methodology

AFM24-102 is a Phase 1/2a open-label, non-randomized, multicenter, dose escalation, and expansion study evaluating AFM24 in combination with atezolizumab (investigational treatment: AFM24 + atezolizumab) in patients with select *EGFR*-expressing advanced solid malignancies whose disease has progressed after treatment with previous anticancer therapies.

There will be 2 parts in this study: a dose escalation phase (Phase 1) and an expansion phase (Phase 2a). Patients will qualify to receive the investigational treatment (AFM24 + atezolizumab) in the dose escalation phase (Phase 1) or the expansion phase (Phase 2a) only if they are deemed eligible post safety lead-in phase (details provided below).

Pre-screening will be required for patients to determine whether eligibility criteria for EGFR expression (for patients without a positive EGFR test) have been met prior to entering the screening phase (Note: if a positive EGFR test has been performed from a patient's tumor tissue, and the EGFR laboratory report is available, the patient can proceed directly to the screening activities).

Safety Lead-In Phase (for both the dose escalation phase [Phase 1] and the expansion phase [Phase 2a])

Seven days prior to Cycle 1 Day 1 (C1D1) (i.e., at Day -7 [minus 7]), patients will receive a single dose of AFM24 (dose assigned to a given cohort) and will be observed for any AEs for 1 week (from Day -7 through Day -1, the safety lead-in phase). Patients who have any Grade ≥3 cytokine release syndrome (CRS) or infusion-related reaction (IRR) symptoms lasting >6 hrs or any other possibly related Grade ≥3 non-hematological TEAEs or clinically significant hematological Grade ≥3 TEAEs during their safety lead-in phase will be permanently discontinued from the study (please refer to Section 6.7 [redacted]. Patients not proceeding to combination therapy will be replaced.

Patient's eligibility criteria must be re-confirmed on or within 7 days before Day -7, before administration of the first AFM24 infusion; refer to inclusion and exclusion criteria sections (Section 5.1 and Section 5.2, respectively) to see allowed time periods of screening assessments.

Note: Patients are required to receive premedication approximately 1 hour before each dose of AFM24; the list of required pre-medications is provided below in the subsection "Study Treatment, Dose, and Mode of Administration."

Dose Escalation Phase (Phase 1)

The aim of the dose escalation phase (Phase 1) is to determine the MTD/RP2D of AFM24 in combination with atezolizumab.

Dose Escalation Phase (Phase 1) Study Design

Patients will be enrolled sequentially in cohorts of 3 to 6 patients in this phase of the study. AFM24 will be administered at an escalating dose per each cohort as a weekly intravenous (i.v.) infusion (once weekly [qw]) in 4-week cycles. Atezolizumab will be administered at a fixed dose of 840 mg as an i.v. infusion every 2 weeks (q2w) in 4-week cycles. Patients will receive study treatment (AFM24 + atezolizumab) until disease progression, intolerable toxicity, Investigator discretion, or patient withdrawal of consent.

The 160 mg i.v. qw dose was selected as the starting dose for AFM24 in Cohort 1 based on the information from the ongoing AFM24-101 monotherapy study (A first-in-human [FIH] Phase 1/2a open-label, multicenter study to assess the safety, tolerability, pharmacokinetics (PK) and preliminary efficacy of AFM24 in patients with advanced solid cancers). Thereafter, the dose escalations for AFM24 will be based on the data from AFM24-101 in conjunction with the safety and available PK data emerging from this study (as determined by the Safety Review Committee [SRC]) (see Rationale for Dose Selection, Section 2.4).

A 3+3 design will be used to determine the RP2D, with the schematic escalation rules:

Number of patients with DLT at a given dose level will be evaluated as:

- If 0 out of 3
- Escalate to next higher dose level
- If 1 out of 3
- Enter 3 more patients at this dose level:
    - If 0 of these additional patients experience a DLT, proceed to the next higher dose level
    - If 1 or more of these additional patients experience a DLT, the dose escalation will be stopped. Up to 3 additional patients will be entered at the lower dose level if only 3 patients were treated previously at that dose level. Alternatively, up to 6 additional patients could be entered to receive intermediate dose levels, based on the emerging safety, pharmacokinetic, and pharmacodynamic data observed in the FIH AFM24-101 study. If this occurs in Cohort 1, there will be a de-escalation to Cohort -1.
- $\geq$ 2 out of 3
- Dose escalation will be stopped. Up to 3 additional patients will be entered at the lower dose level if only 3 patients were treated previously at that dose level. Alternatively, up to 6 additional patients could be entered to receive intermediate dose levels, based on the emerging safety, pharmacokinetic, and pharmacodynamic data observed in the FIH AFM24-101 study. If this occurs in Cohort 1, there will be a de-escalation to Cohort -1.

MTD definition: The highest dose level below the maximum administered dose where the number of patients with DLT is <2 out of 6 is defined as the MTD. (At least 6 patients evaluable for the safety endpoint must be entered at this dose level and a toxicity rate of less than 0.33 must be observed in order to be confirmed as the MTD).

RP2D definition: An RP2D can be declared at any dose level or schedule where the MTD criteria were not met, yet clinical, PK, pharmacodynamics and/or laboratory data indicate an optimal biologically active dose has been reached (with a toxicity rate of less than 0.33) and at least 6 patients have been treated at that given dose level.

Expansion Phase (Phase 2a)

The dose escalation phase (Phase 1) will be followed by the expansion phase (Phase 2a) once the MTD/RP2D of AFM24 in combination with atezolizumab has been determined. The expansion phase (Phase 2a) of the study is intended to collect preliminary evidence of efficacy and to further confirm the safety of AFM24 in combination with atezolizumab.

Expansion Phase (Phase 2a) Study Design

During the expansion phase (Phase 2a), up to 130 patients will receive weekly infusions of AFM24 at the RP2D in combination with every 2-weekly infusion of atezolizumab at a fixed dose of 840 mg in 4-week cycles in the following 3 expansion phase cohorts based on tumor types:

- Expansion Cohort (EXP)-1 will enroll patients with advanced or metastatic *EGFR*-wild type (*EGFR*-WT) expressing non-small cell lung cancer (NSCLC);
- EXP-2 will enroll patients with locally advanced, unresectable, or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma;
- EXP-3 will enroll patients with advanced or metastatic hepatocellular carcinoma (other than fibrolamellar and sarcomatoid subtype, Barcelona Clinic Liver Cancer Stage C disease or Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy), hepatobiliary-, or pancreatic adenocarcinoma.
- **EXP**-4: will enroll patients with advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation.

Based on results from dose escalation phase (Phase 1), additional treatment schedules of AFM24 administration (i.e., q2w) may be explored as part of the expansion phase (Phase 2a) within or across cohorts.

Patients will receive the investigational treatment (AFM24 + atezolizumab) as long as they continue to show clinical benefit as judged by Investigator until disease progression, intolerable toxicity, Investigator discretion, or patient withdrawal of consent.

An Independent Data Monitoring Committee (IDMC), consisting of clinical experts who are not directly involved in this clinical study, will be established for Phase 2a of the study. The IDMC will review all safety data generated throughout the dose expansion phase (Phase 2a) of the study on a regular basis. Based on the outcome of their review, the IDMC will provide recommendations to the Sponsor with regard to study conduct or study procedures. The set-up and operational process for this IDMC will be described in a separate IDMC charter.

The following stopping rules for the expansion phase (Phase 2a) part of the study apply:

- ≥ 3 patients report the same AE occurring within 30 days of starting study treatment meeting the DLT criteria in the same expansion cohort or
- ≥ 3 patients report the same SAE with at least possible relationship to the study treatment occurring within 30 days of starting study treatment within the same expansion cohort, or
- any death with at least possible relationship to the study treatment occurring within 30 days of starting study treatment, or
- ≥ 30% patients experiencing the same SAE with at least possible relationship to the study treatment occurring within 30 days of starting study treatment across expansion cohorts.

If at least 1 of the stopping rules is met, patient recruitment will be paused. Patients who are already receiving study treatment and are deriving clinical benefit may continue study treatment at the discretion of the Investigator. The ICF will be updated with the new safety information and the patients will be reconsented once the ICF is approved and available. Following the stop of patient enrollment, a thorough investigation will be done jointly by the Sponsor and the IDMC. The study will continue only if the IDMC confirms a positive benefit/risk assessment of the study treatment. Following a positive assessment by the IDMC, a substantial amendment will be submitted to the regulatory authority, and enrolment can be restarted only after approval by the regulatory authority.

In addition, all study treatments must be paused in any patient who experiences a TEAE meeting the DLT criteria regardless of when it occurs pending further evaluation by the Investigator and/or IDMC.

Study Assessments and Procedures

Please see [redacted] for a schematic study design [redacted] and Schedule of Assessment Tables [redacted] for dosing regimen with AFM24 administered qw and atezolizumab infusion administered q2w throughout the study (i.e., in dose escalation phase [Phase 1] and expansion phase [Phase 2a]).

Please see [redacted] for a schematic study design () for dosing regimen with AFM24 administered qw and atezolizumab infusion administered q2w in the dose escalation phase (Phase 1) and both AFM24 and atezolizumab administered q2w in expansion phase (Phase 2a) and Schedule of Assessment Tables [redacted], and [redacted] for dosing regimen of both AFM24 and atezolizumab administered q2w in expansion phase (Phase 2a).

Safety Assessments

During the safety lead-in phase, dose escalation phase (Phase 1), and expansion phase (Phase 2a), safety will be assessed by monitoring and recording of all AEs graded by the National Cancer Institute (NCI)- Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Laboratory assessments (complete blood count, clinical chemistry, coagulation and urinalysis), vitals, physical exams, and electrocardiograms (ECGs) findings will also be used in determining safety.

DLT Analysis

The MTD and/or RP2D dose of AFM24 in combination with atezolizumab as determined during the DLT evaluation period in the dose escalation phase (Phase 1), will be used in the expansion phase (Phase 2a). All events meeting the DLT criteria will be summarized descriptively throughout the study.

[redacted]

Pharmacokinetic Assessments

During the dose escalation phase (Phase 1) and expansion phase (Phase 2a), to evaluate the PK profile of AFM24 when it is administered in combination with atezolizumab, AFM24 levels will be measured in samples collected at the time points as indicated in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments [redacted]. PK samples may be used to evaluate the level of atezolizumab in serum if deemed appropriate.

Immunogenicity

During the dose escalation phase (Phase 1) and expansion phase (Phase 2a), to assess the immunogenicity of AFM24 when AFM24 is administered in combination with atezolizumab, ADAs will be measured as indicated in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments [redacted]

[redacted]

Criteria for Study Inclusion

Patients will be considered eligible to be enrolled in the study if ALL the inclusion criteria and NONE of the exclusion criteria are met as defined below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Please note that based on various guidelines (e.g., *NCCN Guidelines: Cancer and COVID-19 Vaccination* [NCCN 2023] and *MHRA Guidance on Coronavirus [COVID-19])* [MHRA 2022], COVID-19 vaccination should be prioritized for patients with cancer with the understanding that there are limited safety and efficacy data in this patient group. These guidelines also state:

- "Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T cell and B cell immunity can be considered."
- "Systemic corticosteroids and targeted agents are expected to blunt immune responses to vaccination."

This study utilizes a mandatory premedication regimen that contains corticosteroids for at least the duration of the first cycle (i.e., Cycle 1). Therefore, every effort should be made to vaccinate patients prior to being considered for this study based on the Investigator's risk/benefit analysis for each patient. If a patient receives the COVID-19 vaccination prior to study participation, the vaccine should be administered at least 2 weeks prior to Day -7 or at least 4 weeks prior to Day -7 for live attenuated vaccines. For patients whose opportunity for COVID-19 vaccination arrives during the conduct of the study **(i.e., ongoing patients in the study)**, see instructions for COVID-19 vaccination provided in Section 6.8.1.1.

Inclusion Criteria (Phase 1 and Phase 2a):

Patients will be considered eligible to be enrolled in the study if ALL the following inclusion criteria are satisfied unless otherwise specified:

1) Voluntary provision and understanding of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, or analysis.
2) Patients must be aged ≥18 years on the day of signing informed consent (or of an acceptable age according to local regulations, whichever is older).
3) Patients must have documented radiological progression during or after their latest therapy for all phases.
4) Patients have documented histologically or cytologically confirmed advanced or metastatic EGFR-positive (positive staining for EGFR in ≥1% of tumor cells determined by a locally validated immunohistochemistry assay) select cancer types, except for NSCLC patients (cohorts EXP-1 and EXP-4); and meet the following criteria:

   Dose Escalation Phase (Phase 1):

   Dose Escalation Cohorts: Patients who meet the criteria specified for the expansion cohorts.

   Expansion phase (Phase 2a):

   - **EXP-1**: patients with advanced or metastatic, *EGFR*-WT expressing NSCLC whose disease has progressed after having received ≥1 prior lines of therapy for advanced disease. Patients must have received at least a platinum-based doublet in combination with an anti-programmed cell death protein 1 (PD1)/programmed death-ligand 1 (PD-L1) antibody or must have received an anti-PD1/PD-L1 antibody prior to or after a platinum-based doublet. Patients with a known actionable driver mutation (other than EGFR mutation) must have received an approved targeted treatment for the respective mutation. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the standard of care (SOC) is not appropriate.
   - **EXP-2**: patients with locally advanced, unresectable, or metastatic gastric or GEJ adenocarcinoma refractory to or, intolerant of, standard therapy. Patients must have received ≥1 prior chemotherapy regimen including a platinum and fluoropyrimidine doublet. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate,
   - **EXP-3**: patients with advanced or metastatic hepatocellular carcinoma (other than fibrolamellar and sarcomatoid subtype; Barcelona Clinic Liver Cancer Stage C disease or Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy), hepatobiliary-, or pancreatic adenocarcinoma. Patients must have been treated with at least 1 previous line of an approved, SOC therapy for the respective disease type or, in the opinion of the Investigator, available SOC is not appropriate. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate.
   - **EXP-4**: patients with advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation and whose disease has progressed on or after having received ≥1 prior lines of therapy

for advanced disease including ≥1 prior TKI approved for EGFR mutated NSCLC, such as gefitinib, erlotinib, afatinib, dacomitinib or osimertinib. Subjects who were treated with a 1st or 2nd generation TKI in 1st line and developed a documented T790M mutation must have received a TKI targeting this mutation such as osimertinib or lazertinib to be eligible. Subjects must have documentation of EGFR mutated NSCLC as assessed by an approved test using genomic sequencing of tumor or circulating free tumor DNA. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate.

[redacted]

5) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1

6) [redacted]

9) Patients must have evaluable or measurable disease per RECIST v1.1 for the dose escalation phase (Phase 1). For the expansion phase (Phase 2a), patients must have measurable disease by RECIST

v1.1. Measurable disease per RECIST v1.1 is defined as at least 1 measurable lesion ≥10 mm by computed tomography (CT) scan or magnetic resonance imaging (MRI) or ≥20 mm by chest X-ray; malignant lymph nodes are considered measurable if short axis is ≥15 mm as assessed by CT scan. The last imaging must have been performed within 28 days prior to the first dose of AFM24 (i.e., Day -7).

10) Female patients of childbearing potential must have a negative urine or serum pregnancy test at Screening and prior to first AFM24 infusion (i.e., Day -7) to be eligible in this study. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible. Non-childbearing potential is defined as:
    a. Postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b. Surgically sterile. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
11) Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of study drug through 5 months after the last dose of study drug. Acceptable highly effective birth control methods include:
    a. Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
    b. Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
    c. Intrauterine device;
    d. Intrauterine hormone-releasing system;
    e. Bilateral tubal occlusion;
    f. Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and
    g. Sexual abstinence. In the context of this study sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of study drug up to 5 months after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
12) Males who have female partners of childbearing potential must agree to use a highly effective method of contraception as described in Inclusion Criterion 11) starting with the first dose of study therapy through 5 months after the last dose of study drug.

Exclusion Criteria:

Patients who fulfill ANY of the following criteria will not be enrolled into the study:

1) Currently receiving active treatment in any other clinical study, or administration of other investigational agent.

[redacted]

[redacted]

4) Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day -7 or anticipation of need for a major surgical procedure during the course of the study. Note: Procedures that are considered to be minimally invasive (e.g., peripherally inserted central catheters lines and/or port placements) will be exceptions.

[redacted]

6) Patients with toxicities (because of prior anticancer therapy) which have not recovered to baseline or CTCAE v5.0 ≤ Grade 1, except for AEs not considered a likely safety risk (e.g., alopecia, neuropathy, specific laboratory abnormalities).

[redacted]

8) History of any other invasive malignancy, unless previously treated with curative intent and the patient has been disease free for 3 years or longer.

[redacted]

9) Untreated or symptomatic central nervous system metastases including leptomeningeal disease or spinal cord compression.

[redacted]

[redacted]

16) Patient's unwillingness to comply with the protocol [redacted] or inability to appreciate the nature, meaning, and consequences of the study and to formulate his/her own wishes correspondingly.

17) Known hypersensitivity to monoclonal antibodies or any components used [redacted]

18) Uncontrolled intercurrent illness including, [redacted]

19) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate.

Study Treatment, Dose, and Mode of Administration

[redacted]

Study Treatment

Safety Lead-in Phase

- Patients will receive a single dose of AFM24 i.v. on Day – 7 at the dose assigned

Dose Escalation Phase (Phase 1)

- Cohort 1: 160 mg AFM24 i.v. qw + atezolizumab 840 mg i.v. q2w
- Cohort 2: AFM24 i.v. qw (at dose to be based on the data from AFM24-101 in conjunction with the safety and available PK data emerging from this study, as determined by the SRC) + atezolizumab 840 mg i.v. q2w
- Cohort 3: AFM24 i.v. qw (at dose to be based on the data from AFM24-101 in conjunction with the safety and available PK data emerging from this study, as determined by the SRC) + atezolizumab 840 mg i.v. q2w

Expansion Phase (Phase 2a)

- EXP-1 (*EGFR*-WT NSCLC): AFM24 i.v. qw or q2w at RP2D dose + atezolizumab 840 mg i.v. q2w
- EXP-2 (gastric or GEJ adenocarcinoma): AFM24 i.v. qw or q2w at RP2D dose + atezolizumab 840 mg i.v. q2w
- EXP-3 (Hepatocellular Carcinoma, Hepatobiliary-, or Pancreatic Adenocarcinoma): RP2D AFM24 i.v. qw or q2w at RP2D dose + atezolizumab 840 mg i.v. q2w
- EXP-4 (EGFRmut NSCLC): RP2D AFM24 i.v. qw or q2w at RP2D dose + atezolizumab 840 mg i.v. q2w

If AFM24 is given on a q2w schedule, the daily dose of AFM24 will not be higher than the highest daily dose that was tested in the Phase 1 part of the study and was considered safe.

Order of Study Treatment Administration for Dose Escalation Phase (Phase 1) and Expansion Phase (Phase 2a)

Atezolizumab will be administered first over approximately 60 minutes, followed by an observation period of 1 hour. After the end of the atezolizumab infusion, the premedication regimen required prior to AFM24 infusion will be administered. The first 2 consecutive AFM24 administrations (i.e., D-7 and C1D1) should not take less than approximately 4 hours (-10 minutes). Please refer to the pharmacy manual for detailed information. It should also be noted that as the dose escalation continues into the higher dosing cohorts, the baseline infusion time may increase to longer than 4 hours and may take as long as over 2 days (i.e., split day dosing) based on a given patient's tolerability as detailed in the Pharmacy Manual for each cohort. For infusion times that span over 2 days (i.e., split day dosing), time points for different assessment may be affected and the Schedule of Assessment (SoA) should be referenced for details [redacted] SoA tables for weekly and q2w dosing schedules, respectively). If the first two consecutive AFM24 infusions are well tolerated (defined as no IRR/CRS Grade >2), then the infusion time may be decreased to < 4 hours to a minimum of 1 hour starting with the third subsequent infusion (i.e., C1D8 for weekly dosing regimen and C1D15 for q2w dosing regimen) at the discretion of the Investigator along with a potential reduction of post infusion observation period to a minimum of 2 hours and a taper of corticosteroid premedication. Investigators should only make 1 modification per infusion (i.e., either reduction of infusion time, reduction of the observation period, or tapering of corticosteroid premedication on a given day of study drug administration, starting with the third infusion). ([redacted] for details regarding treatment management for symptoms of IRR/CRS due to study treatment). Refer to the Pharmacy Manual for full details regarding study drug administration.

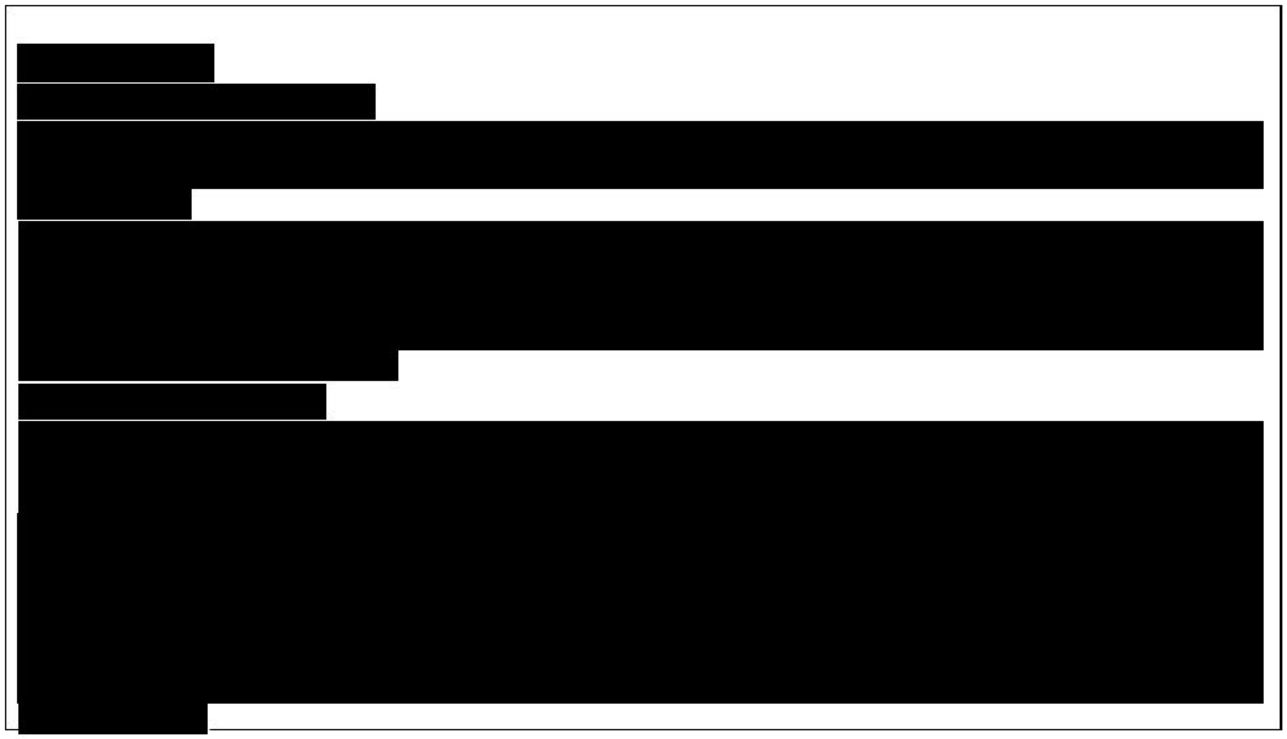
Statistical Considerations

Dose escalation phase (Phase 1)

A 3+3 dose finding design will be implemented. The number of patients dosed within each cohort is based on safety. The objective is to expose the lowest possible number of patients to the investigational drug, while still being able to assess safety where the estimated MTD is the highest dose level with the observed toxicity rate less than or equal to 0.33.

Expansion phase (Phase 2a)

[redacted]



2. INTRODUCTION

AFM24 is a first-in-class, tetravalent, bispecific, fragment crystallizable (Fc)-silenced antibody designed to target epidermal growth factor receptor-expressing ($EGFR^+$) solid tumors. Of its 4 binding sites, 2 binding sites are specific for EGFR; the other 2 binding sites are specific for CD16A, which is the Fcγ receptor expressed by natural killer (NK) cells and macrophages.

AFM24 is designed to utilize the cytotoxic potential of NK cells and macrophages for the elimination of $EGFR^+$ cancer cells, offering a novel therapeutic approach to target $EGFR^+$ tumors with active immunotherapy. This bispecific innate immune cell recruiting antibody binds to both $EGFR^+$ cancer cells and $CD16A^+$ NK cells and macrophages with strong avidity, thus creating an immunological synapse. This results in antibody-dependent cellular cytotoxicity (ADCC; induced by NK cells) and antibody-dependent cellular phagocytosis (ADCP; induced by macrophages) of $EGFR^+$ tumor cells, thereby activating a potent anti-tumor immune response. At high concentrations, AFM24 can also down-modulate ligand-induced EGFR signaling.

Due to its ADCC- and ADCP-related mode of actions, it is anticipated that AFM24 would be active in patients who harbor $EGFR^+$ cancers, potentially also including cancers that have intrinsic or acquired resistance to EGFR targeting monoclonal antibodies and tyrosine kinase inhibitors (TKIs). Therefore, AFM24 has the potential to overcome the limitations of EGFR-targeting standard of care (SOC) monoclonal antibodies and TKIs. In addition, it is anticipated that AFM24 would have an improved safety profile compared with these SOC agents.

Patients with previously treated advanced or metastatic solid tumor malignancies that express EGFR represent a high unmet medical need due to the associated poor prognosis and limited number of effective treatment options available. NK cells and macrophages have an intrinsic ability to eliminate tumor cells; however, innate immunity is often suppressed in cancer patients. By utilizing AFM24 to redirect and activate such immune cells it may be possible to release the anti-tumor potential of patients' own innate immunity to effectively control their cancers.

Intact and effective immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades and requires a coordinated effort between the innate and adaptive component (Diss 2010). Limited response rates of T cell-based checkpoint immunotherapies against cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) indicate that additional checkpoint pathways exist to suppress efficient adaptive tumor immunity (Sharma 2015; Zou 2018). Tumors usually escape T cell immune surveillance by downregulating the expression of primary histocompatibility complex class I. Therefore, this compromises the tumor antigen presentation pathway (Keenan 2019; Bi 2017), making these tumors challenging to be recognized by T cells. Nevertheless, these tumors are highly susceptible to NK cell elimination via the "missing-self" recognition (Lanier 2005; Ljunggren 1990).

The helper effects of NK cells are essential in the context of T cell-based checkpoint immunotherapy. Although anti-PD-1 immunotherapy mainly targets T cells, intratumoral NK cells' frequency correlates with patient responsiveness to PD-1 blockade immunotherapy and increased overall survival (Barry 2018). These intratumoral NK cells form clusters with intratumoral stimulatory dendritic cells and play a role in stimulating anti-tumor T cell activity (Barry 2018). In line with this, data from mouse models showed that the depletion of NK cells

abrogated the efficacy of PD-L1 blockade immunotherapy (Zhang 2018). The presence of NK cells prevented the formation of an exhausted status of tumor-infiltrating CD8+ T cells even under conditions of PD-L1 blockade, as evidenced by decreased expression of degranulation marker CD107a, and effector cytokines, tumor necrosis factor (TNF)-α and interferon (IFN)-γ, and increased expression of exhaustion marker PD-1 by CD8+ T cells, after NK cell depletion (Zhang 2018). Therefore, by facilitating an efficient anti-tumor T cell response, NK cells contribute to the PD-1/PD-L1 checkpoint immunotherapy. Also, higher levels of intra-tumoral NK cells might serve as a biomarker to predict better clinical response to PD-1/PD-L1 checkpoint immunotherapy.

Immune checkpoint inhibition targeting PD-L1 or PD-1 has become an important approach in treating multiple human cancers, as PD-L1 expression on tumor cells and tumor-infiltrating immune cells can inhibit anticancer immune responses (Chen 2013). Atezolizumab, a humanized, engineered monoclonal immunoglobulin (Ig) G1 antibody, selectively targets PD-L1 to block interactions with its receptors to promote T-cell activation and reinvigorate and enhance the anticancer activity while leaving the interaction between PD-L2 and PD-1 intact (Chen 2012; Herbst 2014). Atezolizumab is approved to treat certain types of locally advanced or metastatic non-small cell lung cancer (NSCLC) and urothelial carcinoma in the United States (US), Europe, and elsewhere, extensive stage small cell lung cancer (SCLC), alveolar soft part sarcoma and melanoma in the United States (TECENTRIQ PI, 2022).

Based on the above-described high unmet need in patients with relapsed/refractory EGFR expressing cancers and the potential for AFM24 and atezolizumab to synergistically target *EGFR* -expressing tumor cells, the current study (AFM24-102) is planned.

2.1. EGFR and Description of Disease

EGFR is a member of the human epidermal growth factor receptor family of receptor tyrosine kinases and is typically activated through ligand binding and homo- or heterodimerization resulting in intracellular tyrosine phosphorylation and signal transduction. It is expressed in a variety of different cell types (Huang & Harari, 1999) and is involved in the regulation of cellular differentiation and proliferation (Salomon et al., 1995). EGFR is known to be overexpressed in multiple tumor types (e.g., colorectal cancer, NSCLC, head and neck squamous cell carcinoma, glioblastoma multiforme, and prostate, kidney, cervical, bladder, ovarian, and triple-negative breast cancers) (Bast et al., 1993; Ishikawa et al., 1990; Itakura et al., 1994; Kim et al., 1996; Rikimaru et al., 1992; Robertson 1996; Sargent et al., 1989). In many cases, aberrant EGFR activation, mediated primarily through changes in gene amplification, gene mutations, and autocrine ligand stimulation, is an important factor in tumorigenesis.

2.2. AFM24

2.2.1. Mechanism of Action

AFM24 is a first-in-class tetravalent bispecific IgG1-scFv fusion antibody with a silenced IgG1 Fc functionality, which binds specifically to the EGFR and CD16A. The product is being investigated for the treatment of patients with advanced or metastatic cancers that express EGFR. Through binding to EGFR on target cells and to CD16A on NK cells and macrophages, AFM24 mediates specific, potent, and efficient lysis of EGFR-positive human tumor cell lines via NK cell-mediated ADCC and macrophage-mediated ADCP. In contrast to other EGFR-targeting antibodies, like cetuximab, AFM24 shows a substantially reduced inhibition of EGFR signaling,

which potentially could be associated with an improved safety profile, particularly regarding skin toxicity. Nevertheless, residual inhibition of EGFR signaling and complement activation may both augment the ADCC and ADCP mechanisms of action and contribute to the anti-tumor activity of AFM24.

2.2.2. Nonclinical Studies

AFM24 has been characterized extensively in non-clinical studies and an overview of these results are provided below. Further details are provided in the AFM24 Investigator's Brochure.

AFM24 is highly specific for EGFR and does not cross-react with other members of the EGFR family. In addition, AFM24 binds exclusively to CD16A and does not cross-react with other human Fcγ receptors, except for the neonatal Fc receptor, via its silenced Fc moiety.

In co-cultures of human peripheral blood mononuclear cells or purified human NK cells with a variety of different EGFR-positive tumor cells, AFM24 induced substantial ADCC. For all tested EGFR-positive target cells, mean half maximal effective concentration (EC_{50}) values for inducing ADCC by AFM24 were in the lower picomolar range. Importantly, RAS-mutated human tumor cell lines were also efficiently killed by effector cells activated by AFM24 due to its mode of action (ADCC and/or ADCP). AFM24 did not induce ADCC by NK cells against EGFR-negative cells.

AFM24 also induced ADCP of human EGFR-positive tumor target cells by macrophages, while leaving EGFR-negative cells unaffected.

In vivo efficacy was assessed using a humanized mouse model bearing xeno-transplanted human EGFR-positive tumors. In the prophylactic treatment setting a trend of reduced tumor growth by AFM24 treatment was observed at 5 mg/kg and significant inhibition of tumor growth was observed at 10 mg/kg and higher. In the therapeutic setting significant inhibition of tumor growth by AFM24 treatment was also seen at a dose level of 10 mg/kg and higher.

AFM24 induced cytokine release from human peripheral blood mononuclear cells in a concentration-dependent manner, but only when cultured in the presence of EGFR-positive target cells. The most dominant cytokine was interleukin-6, which was measured in co-cultures in substantial amounts after 24 h of stimulation.

Safety pharmacology, and toxicology was assessed in cynomolgus monkeys which was validated as the only relevant and fully cross-reactive species. Animals showed no signs of behavioral alteration or neurotoxicity, no alteration of cardiovascular and respiratory parameters. No effect of AFM24 on coagulation and on ophthalmic examinations up to the highest dose level of 75 mg/kg was observed.

Vomiting was observed in 2 of the 5 males on Day 1 of the dosing phase. This finding was only noted for the high dose; as such, it was considered AFM24-related. No other signs of gastrointestinal or renal effects were observed.

The first dose of AFM24 caused a transient elevation of circulating interleukin -6 levels and transient, non-dose-dependent reductions in absolute peripheral NK cells. All observed immunological changes appear to be in line with the anticipated mode of action of AFM24 and are therefore not considered to be manifestations of immunotoxicity.

Half-life of AFM24 ranged from 30 hours to more than 140 hours in cynomolgus monkeys. AFM24 exposures increased with the increase in dose level (mean maximum plasma concentration

[C_{max}] and area under the concentration-time curve form time zero to 168 hours [AUC_{0-168}] values). There was no sex-related difference in exposure. Increases in mean C_{max} and AUC_{0-168} values were dose proportional from 8 to 75 mg/kg. The calculated apparent volume of distribution of AFM24 was similar to or up to 3-fold greater than total plasma volume in the cynomolgus monkey, indicating only limited distribution of AFM24 into tissues. No accumulation of AFM24 was observed after 5 once-weekly doses in monkeys.

Treatment-induced anti-drug antibodies (ADAs) were detected in 10/26 monkeys included in the Good Laboratory Practice study. In the majority of cases, the positive ADA analysis results were sporadic and/or associated with low electrochemiluminescence values, and AFM24 exposure was similar to that of ADA-negative animals. However, 2 animals in the intermediate dose group (24 mg/kg) gave consistent ADA-positive results, with notably higher and increasing electrochemiluminescence values, during the recovery phase. The exposure of AFM24 in these animals was notably lower than that of the other 2 animals in the dose group. These observations are consistent with ADA-mediated clearance of AFM24.

2.2.3. AFM24 Clinical Experience

A first-in-human (FIH) Phase 1/2a open-label, multicenter study to assess the safety, tolerability, pharmacokinetic (PK) and preliminary efficacy of AFM24 in patients with advanced solid cancers (AFM24-101) is currently ongoing. The recommended phase 2 dose (RP2D) of AFM24 as a monotherapy is 480 mg.

Preliminary data from the ongoing study AFM24-101 indicate that AFM24 has an apparent half-life estimated to be 11.2 days at doses ≥320 mg. Please refer to the latest version of the Investigator's Brochure for further information.

The most common treatment-emergent adverse events (TEAEs) for the study that were reported as related to AFM24 are infusion-related reactions (IRR).

Data from the NSCLC EGFRmut cohort showed initial signs of activity, some cases of partial response and stable disease were observed.

For details on the currently ongoing studies with AFM24, please refer to the most recent AFM24 Investigator's Brochure.

2.3. Background Information Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, SCLC, hepatocellular carcinoma, alveolar soft part sarcoma, and melanoma. To date, atezolizumab has received approval for one or more of these indications in over 90 countries worldwide.

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

2.3.1. Pharmacokinetics

Atezolizumab is administered intravenously (i.v.). Exposure to atezolizumab increases in a dose-proportional manner over a range of 1 mg/kg to 20 mg/kg, including the recommended fixed dose of 1200 mg. In clinical studies, clearance was 0.2 L/day (coefficient of variation [CV], 29%) and volume of distribution at steady-state was 6.9 L. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV) from baseline value of approximately 17.1% (CV%, 41%); however, this was not considered statistically relevant. The terminal half-life was 27 days, with steady-state reached after 6 to 9 weeks following multiple doses. In clinical studies, the systemic accumulation in area under the concentration-time curve (AUC), C_{max}, and trough concentration (C_{min}) was 1.91, 1.46, and 2.75-fold, respectively, following i.v. administration of 1200 mg atezolizumab every 3 weeks (q3w). The systemic accumulation ratio for atezolizumab was 3.3-fold when administered every 2 weeks (q2w) and 1.9-fold when administered q3w.

Atezolizumab is not expected to show PK interactions with other drugs and is therefore not expected to interact with other drugs through protein binding, effects on cytochrome P450 activity, renal excretion or competition for common drug transporter proteins.

2.3.2. Atezolizumab Clinical Experience

Atezolizumab in combination with chemotherapy and other therapeutic agents has demonstrated to have benefit in the settings of SCLC and NSCLC. Efficacy of atezolizumab has been evaluated in combination with other therapeutic agents and demonstrated anti-tumor activity across a range of tumor types, across lines of therapy, and across PD-L1 expression subgroups (TECENTRIQ PI, 2022).

[redacted]

2.6. Benefit/Risk Assessment

This Phase 1/2a study will evaluate AFM24 in combination with atezolizumab in patients with advanced solid malignancies that express the EGFR. As mentioned in Section 2.4, the selected patient populations have advanced or metastatic disease that has progressed during or after treatment with SOC therapies and represent a high unmet need. New therapies with novel mechanisms of action are urgently needed for the patient population to be enrolled in this study.

AFM24 has been investigated in nonclinical toxicity studies and currently in an ongoing FIH Phase 1 clinical study described above (AFM24-101). The safety profile and adverse drug reactions observed in patients treated with AFM24 monotherapy are summarized above and the most observed adverse reaction to date are IRRs that have been manageable with SOC therapies.

Additionally, AFM13, a tetravalent bispecific recombinant antibody being evaluated for the indication treatment of HL and other CD30-positive malignancies, which shares the structural similarity to AFM24 was evaluated in combination with anti-PD-1 agent (pembrolizumab) in a Phase 1 dose escalation and expansion study AFM13-103 in 30 patients. AFM13 was administered at increasing dose levels in combination with 200 mg pembrolizumab q3w. The efficacy analysis included the best response from 28 of 30 patients who were evaluable for efficacy and had at least one postbaseline disease assessment. The objective response rate (ORR) and complete response (CR) rate for patients treated at the dose and schedule chosen for expansion (N=24; Cohort 3 and Extension Cohort [both receiving AFM13 dose of 3 mg/kg × 3 at Week 2 and 3 and then 7.0 mg/kg up to Week 25]) were 88% and 42%, respectively by investigator-confirmed assessment. Independent assessment resulted in an ORR of 88% and CR rate of 46% for these patients. Both AFM13 and pembrolizumab were administered at dose levels that are planned for these treatments when administered as monotherapy, and the combination of these treatments did not reveal any signs of overlapping toxicity. The reported side effects were similar to those observed in monotherapy studies.

Available data from clinical trials of atezolizumab have demonstrated favorable efficacy in patients with advanced solid tumors (liver cancer, NSCLC, Melanoma, Bladder cancer) previously treated with 2 or more prior chemotherapy regimens (Inman 2017, Socinski 2018, Tie 2019). Available data has also indicated that combined treatment of chemotherapy and anti-PD1/PDL1 antibodies has a manageable safety profile (Horn 2018, West 2019).

Considering the high unmet needs, and the currently known safety profiles of AFM24 and atezolizumab, the potential benefit outweighs the risks identified in association with the investigational treatment for this study (AFM24 + atezolizumab).

2.7. Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), and according to Good Clinical Practice (GCP) guidelines. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and IRB except where it may be necessary to eliminate an immediate hazard to a research patient. In such case, the deviation will be reported to the Sponsor and IRB as soon as possible.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Dose Escalation Phase (Phase 1)	
Primary	
• To determine the MTD and/or to select one or more RP2Ds of AFM24 in combination with atezolizumab	• Adverse events (AEs) to be assessed by the incidence and severity of dose-limiting toxicity (DLT) within the DLT observation period (Cycle 1)
Secondary	
• To assess the safety and tolerability of AFM24 in combination with atezolizumab • To evaluate the preliminary antitumor activity of AFM24 in combination with atezolizumab in terms of ORR • To characterize the pharmacokinetic (PK) profile of AFM24 when AFM24 is given in combination with atezolizumab • To assess the immunogenicity of AFM24 when AFM24 is given in combination with atezolizumab	• Incidence of patients with TEAEs and serious adverse events (SAEs) • ORR using RECIST v1.1 determined by Investigator assessment • PK parameters of AFM24: C_{max}, T_{max}, C_{min} and AUC_{tau} • Frequency of patients developing ADAs against AFM24
Exploratory	
[redacted]	[redacted]

Phase 2a	
Primary	
• To evaluate the antitumor activity of AFM24 in combination with atezolizumab in terms of ORR	• ORR according to RECIST v1.1 determined by the Investigator assessment
Secondary	
• To assess preliminary efficacy of AFM24 in combination with atezolizumab using additional measures of clinical benefit • To assess the safety and tolerability of AFM24 in combination with atezolizumab • To characterize the PK profile of AFM24 when AFM24 is given in combination with atezolizumab • To assess the immunogenicity of AFM24 when AFM24 is given in combination with atezolizumab	• Progression-free survival (PFS) according to RECIST v1.1 by Investigator assessment • Duration of response (DOR) according to RECIST v1.1 by Investigator assessment • Clinical benefit rate (CBR) according to RECIST v1.1 by Investigator assessment • Disease control rate (DCR) according to RECIST v1.1 by Investigator assessment • Incidence of patients with TEAEs and SAEs • PK parameters of AFM24: C_{max}, T_{max}, C_{min}, and AUC_{tau} • Frequency of patients developing ADAs against AFM24
Exploratory	
[redacted]	[redacted]

Abbreviations: AUC_{tau}: area under the concentration-time curve over the dose interval; C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration; T_{max}: time to C_{max}

4. STUDY DESIGN

4.1. Overall Study Design

AFM24-102 is a Phase 1/2a open-label, non-randomized, multicenter, dose escalation and expansion study evaluating AFM24 in combination with atezolizumab (investigational treatment: AFM24 + atezolizumab) in patients with select *EGFR*-expressing advanced solid malignancies whose disease has progressed after treatment with previous anticancer therapies.

There will be 2 parts in this study: a dose escalation phase (Phase 1) and an expansion phase (Phase 2a). Patients will qualify to receive the investigational treatment (AFM24 + atezolizumab) in the dose escalation phase (Phase 1) or in the expansion phase (Phase 2a) only if they are deemed eligible post the safety lead-in phase where they will receive a single i.v. AFM24 infusion (see Section 4.2.2). Patients who qualify the safety-lead in phase will receive AFM24 i.v. infusion, qw, in 4-week cycles and atezolizumab i.v. infusion, q2w, in 4-week cycles.

Overall, the study will consist of following periods:

- Pre-Screening period
- Screening period (≤ 21 days prior to Day -7)
- Safety lead-in phase (Day -7 through Day -1) to evaluate patient's hypersensitivity to AFM24 *only* infusion

Note: Some of the screening assessments will be allowed during the safety lead-in phase as well. Please review the Inclusion Criteria (Section 5.1) and Exclusion Criteria (Section 5.2) to see allowed time periods of screening assessments.

- Treatment Period (AFM24 + atezolizumab)
    - Dose Escalation Phase (Phase 1)
    - Expansion Phase (Phase 2a)

Note: Patients will receive the investigational treatment (AFM24 + atezolizumab) until disease progression, intolerable toxicity, Investigator discretion, or patient withdrawal of consent.

- Follow-Up
    - End of Treatment (EOT) Visit (14 days [±2 days] after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner)
    - Safety Follow-Up Visit (30 days [±5 days] after the last administration of study treatment or before start of any new anti-cancer treatment whichever is sooner)
    - Long-term follow-up (patients will be contacted every 3 months [±2 weeks] to collect data on their subsequent therapies and disease status.

    Note: Patients who are permanently discontinued from the study during the safety lead-in phase should complete the EOT visit and the Safety follow-up visit but will not be required to complete the long-term follow up.

4.2. Overall Study Periods

4.2.1. Pre-Screening and Screening

Pre-Screening:

Pre-Screening is required for all patients planned to be enrolled in this trial. EGFR expression is to be assessed for EXP-2 and EXP-3 cohorts as per Inclusion Criterion #4 before the patient enters the screening phase. Archived paraffin embedded tumor tissue is acceptable for EGFR determination otherwise, a fresh tumor biopsy must be performed. EGFR assessment by a locally validated immunohistochemistry assay test is acceptable.

Patients will sign a Pre-screening informed consent form (ICF) allowing the testing of EGFR expression to determine whether eligibility criteria for EGFR expression have been met prior to entering Screening (**Note**: if a positive EGFR test has been performed from a patient's tumor tissue, and the EGFR laboratory report is available, the patient does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities).

The Screening phase starts only after the patient has met the eligibility criterion for EGFR expression for EXP-2 and EXP-3 cohorts, and has signed the main ICF for all cohorts.

Screening:

The screening period lasts up to 21 days prior to the safety lead-in phase (from Day -7 through Day -1). The screening period begins when the main ICF is signed and ends on the day before the first dose of AFM24 infusion on Day -7. Before entering the study, all study procedures and possible risks will be explained to each patient who is asked to participate in the study. After provision of main written informed consent for the study, screening assessments will include a careful review of the patient's medical history, assessment of Eastern Cooperative Oncology Group (ECOG) performance status (PS), physical examination, electrocardiogram (ECG), laboratory assessments, and tumor assessments by computed tomography (CT) or magnetic resonance imaging (MRI), and tumor histopathology. Screening assessments are to be performed within 21 days of the first dose of AFM24 infusion (i.e., on Day -7); however, radiographic tumor assessment is allowed up to 28 days prior to first dose of AFM24 infusion (i.e., on Day -7). Patients who do not meet 1 or more eligibility criteria may be re-screened. Patient's eligibility criteria must be re-confirmed on or within 7 days before Day -7, before administration of the first AFM24 infusion. The assessments for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) do not need to be repeated for re-screened patients if performed within 3 months before the first AFM24 infusion (i.e., on Day -7). Please review the inclusion (Section 5.1) and exclusion criteria (Section 5.2) to see allowed time periods of screening assessments.

4.2.2. Safety Lead-In Phase (for Both the Dose Escalation Phase [Phase 1] and the Expansion Phase [Phase 2a])

Seven days prior to Cycle 1 Day 1 (C1D1) (i.e., at Day -7), patients will receive a single dose of AFM24 (dose assigned to a given cohort) and will be observed for any AE for 1 week (from Day -7 through Day -1, the safety lead-in phase). Patients who have any Grade ≥3 cytokine release syndrome (CRS) or IRR symptoms lasting >6 hrs or any other possibly treatment-related Grade ≥3 non-hematological TEAEs or clinically significant hematological Grade ≥3 TEAEs during their

safety lead-in phase will be permanently discontinued from the study (please refer to Section 6.7 [redacted]. Patient's eligibility criteria must be re-confirmed on or within 7 days before Day -7, before the administration of the first AFM24 infusion; please refer to inclusion and exclusion criteria sections (Sections 5.1 and 5.2, respectively) to see allowed time periods of screening assessments.

Patients not proceeding to combination therapy (AFM24 + atezolizumab) will be replaced.

Note: Patients are required to receive premedication approximately 1 hour before each dose of AFM24; a list of premedications is provided in Section 6.3.

4.2.3. Dose Escalation Phase (Phase 1) Study Design

The aim of the dose escalation phase (Phase 1) is to determine the MTD/RP2D of AFM24 in combination with atezolizumab.

The 160 mg i.v. qw dose was selected as the starting dose for the AFM24-102 study, based on the data obtained from the FIH study (AFM24-101) ([redacted]). There are additional dose escalations planned for AFM24, where the dose increase will be based on data from AFM24-101 in conjunction with the safety and PK data emerging from this study ([redacted]). Dose increases will not exceed 200% of the current dose. All dose escalation (and de-escalation) decisions will be determined by the SRC.

It is estimated that approximately 18 patients will be treated in Phase 1 of the study. The number of patients is dependent on the tested dose cohorts and safety profile of AFM24 in combination with atezolizumab.

Dose cohorts

Patients will be enrolled sequentially in cohorts of 3 to 6 patients into dose escalation phase (Phase 1). The dose escalation will follow 3+3 dose escalation design. In each cohort there will be at least 3 patients enrolled. The first 2 patients of each dose cohort will begin treatment in a staggered approach with at least 7 days between first dosing of these 2 patients. Subsequent patients may be enrolled concurrently. All patients who start treatment need to complete the 28-day DLT observation period or experience a DLT within the first cycle of treatment to be DLT evaluable. A minimum of 3 patients needs to be DLT evaluable per dose cohort. If no DLT is observed, the dose is escalated for the next cohort of 3 patients. If 1 DLT is observed, 3 additional patients will be treated at this dose level with dose escalation only if no additional DLTs occur. If less than 3 patients are evaluable for DLT assessment, replacement patient(s) will be enrolled. DLTs will be assessed in the first treatment cycle (i.e., the first 4 weeks of treatment for each patient, starting C1D1), referred to as the DLT observation period (28-days). Dose limiting toxicity will be defined by the criteria listed in Section 4.2.3.1. The number of patients included in each dose cohort may be increased from 3 up to 6 patients based on SRC decision to allow for further collection of safety, pharmacodynamic and PK data.

A 3+3 design will be used to determine the RP2D, with the schematic escalation rules given below. The number of patients with DLT at a given dose level will be evaluated as:

1. If 0 out of 3
    - Escalate to next higher dose level

2. If 1 out of 3
    - Enter 3 more patients at this dose level:
        - If 0 of these additional patients experience a DLT, proceed to the next higher dose level
        - If 1 or more of these additional patients experience a DLT, the dose escalation will be stopped. Up to 3 additional patients will be entered at the lower dose level if only 3 patients were treated previously at that dose level. Alternatively, up to 6 additional patients could be entered to receive intermediate dose levels, based on the emerging safety, PK, and pharmacodynamic data observed in the FIH AFM24-101 study If this occurs in Cohort 1, there will be a de-escalation to Cohort -1.
3. ≥ 2 out of 3
    - Dose escalation will be stopped. Up to 3 additional patients will be entered at the lower dose level if only 3 patients were treated previously at that dose level. Alternatively, up to 6 additional patients could be entered to receive intermediate dose levels, based on the emerging safety, PK, and pharmacodynamic data observed in the FIH AFM24-101 study. If this occurs in Cohort 1, there will be a de-escalation to Cohort -1.

4.2.3.1. Definition of Dose-Limiting Toxicity (DLT)

DLT is defined as an AE or abnormal laboratory value assessed as unrelated to underlying disease, disease progression, inter-current illness, or concomitant medications, that occurs ≤28 days following the first dose of AFM24 in combination with atezolizumab (Cycle 1) and that meets any of the following criteria shown in Table 1. Clinically relevant toxicities will be evaluated according to the National Cancer Institute (NCI)/National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Patients who experience a DLT during Cycle 1 must permanently discontinue AFM24 and atezolizumab.

DLT observation period:

In order to be considered evaluable for DLT, patients must meet the following criteria:

- receive ≥ 75% of their assigned AFM24 dose in Cycle 1 ***and***
- receive ≥ 50% of their assigned atezolizumab dose in Cycle 1 ***and***
- either complete the 28-day DLT observation period ***or*** have had a DLT within the first cycle of treatment.

Patients discontinuing the study after the safety lead-in phase will not be included in the DLT evaluation.

Table 1: Definition of Dose-Limiting Toxicity

Toxicity	Any of the following criteria
Hematological[a]	≥CTCAE Grade 4 neutropenia (ANC<0.5×10^9/L) lasting for longer than 4 consecutive days
	Febrile neutropenia (ANC<1.0×10^9/L of any duration accompanied by fever ≥38.5°C or systemic infection) that does not resolve within 48 hours after start of antibiotics
	CTCAE Grade 3 thrombocytopenia (platelets 25 to <50×10^9/L) associated with bleeding
	CTCAE Grade 4 thrombocytopenia (platelets <25×10^9/L)
	≥CTCAE Grade 4 anemia that is considered to be treatment related
Non-hematological	Any ≥CTCAE Grade 3 AE including, but not limited to: • CTCAE Grade 3 infusion-related reaction/cytokine release syndrome not responsive to symptomatic treatment within 6 hours (i.e., no improvement to Grade 2 or better within 6 hours with optimal medical management) • CTCAE Grade 4 infusion-related reaction/cytokine release syndrome • QTcF prolongation (>500 msec) confirmed by 2 separate ECGs at least 6 hours apart or if associated with arrhythmias; • CTCAE Grade 3 hypertension for >14 consecutive days despite optimal anti-hypertension therapy; • CTCAE Grade 4 hypertension (any duration) • ≥CTCAE Grade 3 total bilirubin (>3×ULN); • ≥CTCAE Grade 3 ALT, AST, or alkaline phosphatase (>5×ULN) if not resolving to Grade 1 or baseline within 10 days; • ≥CTCAE Grade 3 diarrhea for ≥72 hours despite optimal anti-diarrhea treatment
	Any death at least possibly related to any study treatment
	Any other ≥CTCAE Grade 3 AE not listed above, except for the exceptions noted below
Exceptions to DLT criteria[b]	Isolated laboratory changes of any grade without clinical sequelae or clinical significance except for those laboratory changes outlined above
	CTCAE Grade 3 fever (in the absence of neutropenia) or fatigue that resolves to <Grade 3 within 72 hours
	CTCAE Grade 3 hypertension for ≤14 consecutive days
	CTCAE Grade 3 nausea, vomiting, diarrhea, or dehydration that resolves to <Grade 3 within 72 hours of initiating optimal supportive care treatment
	CTCAE Grade 3 infusion-related reaction/cytokine release syndrome responsive to symptomatic treatment within 6 hours (i.e., improvement to Grade 2 or better within 6 hours with optimal medical management)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; ECG = electrocardiogram; IRR = infusion-related reaction; NCI = National Cancer Institute; QTcF = corrected QT interval by Fridericia; SRC = Safety Review Committee; ULN = upper limit of normal

a. Patients may receive supportive care (e.g., use of granulocyte-colony stimulating factor, packed red blood cells, and platelets) as per local institutional guidelines. However, during the DLT observation period, it is not allowed to administer these supportive measures without clinical indication.
b. The SRC (in Phase 1) and IDMC (in Phase 2) will closely monitor and review all AEs including the incidences of the AEs listed under the "Exceptions to DLT criteria" during the scheduled and any ad-hoc SRC/IDMC meetings.

Note: NCI CTCAE v5.0 will be used for all grading.

4.2.3.2. Determination of Maximum Tolerated Dose

The MTD will be defined as the highest dose level below the maximum administered dose where the number of patients with DLT is <2 out of 6. At least 6 patients evaluable for the safety endpoint must be entered at this dose level and a toxicity rate of less than 0.33 must be observed to be confirmed as the MTD.

4.2.3.3. Recommended Phase 2 Dose (RP2D) Definition

An RP2D can be declared at any dose level or schedule where the MTD criteria were not met, yet clinical, PK, pharmacodynamics and/ or laboratory data indicate an optimal biologically active dose has been reached (with a toxicity rate of less than 0.33) and at least 6 patients have been treated at that given dose level.

4.2.4. Expansion Phase (Phase 2a) Study Design

Once all patients have completed Cycle 1 of the dose escalation phase (Phase 1), the SRC has reviewed all available safety, clinical, laboratory, and PK data and recommends continuing, and the MTD/RP2D of AFM24 in combination with atezolizumab has been determined, enrollment into the expansion cohorts for the selected cancer indications in the expansion phase (Phase 2a) will begin (Section 9.5.1).

A Simon two-stage optimal design will be utilized for EXP-1 and EXP-2. EXP-3 and EXP-4 are exploratory with no hypothesis testing. The expansion phase (Phase 2a) of the study is intended to collect preliminary evidence of efficacy and to further confirm the safety of AFM24 in combination with atezolizumab.

During the expansion phase (Phase 2a), up to 130 patients will receive weekly infusions of AFM24 at the RP2D in combination with every 2-weekly infusion of atezolizumab in 4-week cycles in the following 3 expansion phase cohorts based on tumor types:

- EXP-1 will enroll patients with advanced or metastatic *EGFR*-wild type (*EGFR*-WT) expressing NSCLC;
- EXP-2 will enroll patients with locally advanced, unresectable, or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma;
- EXP-3 will enroll patients with advanced or metastatic hepatocellular carcinoma (other than fibrolamellar and sarcomatoid subtype, Barcelona Clinic Liver Cancer Stage C disease or Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy), hepatobiliary-, or pancreatic adenocarcinoma;
- EXP-4 will enroll patients with advanced or metastatic EGFR-mutated NSCLC

Patients will receive the investigational treatment (AFM24 + atezolizumab) until disease progression, intolerable toxicity, Investigator discretion, or patient withdrawal of consent.

Additional treatment schedules of AFM24 administration (e.g., q2w) may be explored as part of the expansion phase (Phase 2a) within or across cohorts.

An Independent Data Monitoring Committee (IDMC), consisting of clinical experts who are not directly involved in this clinical study, will be established for Phase 2a of the study. The IDMC will review all safety data generated throughout the dose expansion phase (Phase 2a) of the study

on a regular basis. Based on the outcome of their review, the IDMC will provide recommendations to the Sponsor regarding study conduct or study procedures. The set-up and operational process for this IDMC will be described in a separate IDMC charter.

The following stopping rules for the expansion phase (Phase 2a) part of the study apply:

- ≥ 3 patients report the same AE occurring within 30 days of starting study treatment meeting the DLT criteria in the same expansion cohort or
- ≥ 3 patients reported the same SAE with at least possible relationship to the study treatment occurring within 30 days of starting study treatment within the same expansion cohort, or
- any death with at least possible relationship to the study treatment occurring within 30 days of starting study treatment, or
- ≥ 30% patients experiencing the same SAE with at least possible relationship to the study treatment occurring within 30 days of starting study treatment across expansion cohorts.

If at least 1 of the stopping rules is met, patient recruitment will be paused. Patients who are already receiving study treatment and are deriving clinical benefit may continue study treatment at the discretion of the Investigator. The ICF will be updated with the new safety information, and the patients will be reconsented once the ICF is approved and available. Following the stop of patient enrollment, a thorough investigation will be done jointly by the Sponsor and the IDMC. The study will continue only if the IDMC confirms a positive benefit/risk assessment of the study treatment. Following a positive assessment by the IDMC, a substantial amendment will be submitted to the regulatory authority, and enrolment can be restarted only after approval by the regulatory authority.

In addition, all study treatments must be paused in any patient who experiences a TEAE meeting the DLT criteria regardless of when it occurs pending further evaluation by the Investigator and/or IDMC.

4.2.5. Follow-Up

Patients who are permanently discontinued from the study during the safety lead-in phase should complete the EOT visit and the safety follow-up visit but will not require the long-term follow-up.

4.2.5.1. End of Treatment Visit

The EOT visit will be performed 14 days (± 2 days) from the last drug intake or before the start of any new anti-cancer treatment; whichever is sooner. For patients who discontinue prematurely, before disease progression, it must be performed as the last visit. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the electronic case report form (eCRF). The patient should be encouraged to return for the follow-up visit.

[redacted]

[redacted]

4.2.5.3. Long-Term Follow Up Period

Once a patient has confirmed disease progression the patient moves into the survival follow-up phase, the patient should be contacted by telephone, email or visit every 3-month intervals (±2 weeks) to assess for survival status until withdrawal of consent, death, or the end of the study, whichever occurs first.

4.3. Number of Patients

The total number of patients planned for this study is estimated to be up to 148*.

Each dose escalation cohort in Phase 1 will consist of 3 to 6 patients. Assuming 3 dose levels, there will be approximately 9 to 18 patients in the dose escalation part of the study (Phase 1). Following the determination of the RP2D, up to 130 additional patients will be treated in the dose-expansion part of the study (Phase 2a).

Note: *Additional patients may be entered to replace DLT non-evaluable patients in Phase 1 and to replace patients not evaluable according to the Full Analysis Set (FAS). Thus, the actual number of patients entered may exceed 148, but will not exceed 179 patients entered.

4.4. Study Duration

The total study duration will be approximately 12 months to complete the dose escalation phase (Phase 1) and from 24 to 48 months to enroll patients in and subsequently complete the expansion Phase (Phase 2a).

Patients may receive the investigational study treatment (AFM24 + atezolizumab) until disease progression, intolerable toxicity, Investigator discretion, or patient withdrawal of consent.

Patients may continue treatment after disease progression at their assigned dose if there is continuing clinical benefit per Investigator's judgment and in consultation with the Sponsor's Medical Monitor.

4.5. Study Initiation and Completion

The start of this clinical study is defined as the first act of screening (signing of the Main ICF) for a potential subject.

The end of the study is defined as when all patients have completed the first long-term follow-up interval, withdrawn, or died, whichever occurs first.

In the expansion phase (Phase 2a) of this study, patients will participate in recurring 4-week cycles until disease progression, intolerable toxicity, death, or discontinuation from study, whichever occurs first.

Patients who die or complete the study follow-up through study closure will be considered to have "completed" the study.

The study will be analyzed and reported once all patients of the study have experienced at least one of the following:

- Has been treated until at least 4 weeks after the 1st post-baseline tumor assessment
- Disease progression
- Withdrawal from treatment due to a drug related AE
- Fatal event
- Lost to long-term follow-up
- Withdrawal of consent
- Start of other anti-cancer treatment

In case patients are still being treated with study medication at the final data cut-off date for this study, such patients will be kept on treatment in the study and data collected will then be reported in an addendum to the final clinical study report (CSR). It will be noted in the final CSR that such a revised report may be provided.

4.6. Scientific Rationale for Study Design

Dose escalation phase (Phase 1) dose escalation consists of AFM24 administered qw at an escalating dose per each cohort with atezolizumab 840 mg q2w according to a 3+3 dose escalation design. The 3+3 design is a well-accepted design in oncology studies (Jaki, 2013), to expose the lowest possible number of patients to the investigational drug, while still being able to assess safety. Dose escalation will be performed until the MTD/R2PD is determined/confirmed with a 28-day DLT assessment period.

Once the MTD/R2PD is determined following completion of dose escalation phase (Phase 1), enrollment will initiate in Phase 2a with AFM24 given in combination with atezolizumab at the RP2D. Phase 2a is an open-label, multicenter basket study utilizing Simon's two-stage optimal design (Simon 1989). This design allows determination of AFM24 given in combination with atezolizumab anti-tumor activity while minimizing the expected sample size. The measurement of most toxicities using the CTCAE v5.0 and assessment of tumor size using the RECIST v1.1 criteria (Eisenhauer et al., 2009; Schwartz et al., 2016) represent objective endpoints.

5. SELECTION AND WITHDRAWAL OF PATIENTS

Patients will be considered eligible to be enrolled in the study if ALL of the inclusion and NONE of the exclusion criteria are met as defined below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Please note that based on various guidelines (e.g., *NCCN Guidelines: Cancer and COVID-19 Vaccination* [NCCN 2023] and *MHRA Guidance on Coronavirus [COVID-19])* [MHRA 2022], COVID-19 vaccination should be prioritized for patients with cancer with the understanding that there are limited safety and efficacy data in this patient group. These guidelines also state:

- "Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T cell and B cell immunity can be considered."
- "Systemic corticosteroids and targeted agents are expected to blunt immune responses to vaccination."

This study utilizes a mandatory premedication regimen that contains corticosteroids for at least the duration of the first cycle (i.e., Cycle 1). Therefore, every effort should be made to vaccinate patients prior to being considered for this study based on the Investigator's risk/benefit analysis for each patient. If a patient receives the COVID-19 vaccination prior to study participation, the vaccine should be administered at least 2 weeks prior to Day -7 or at least 4 weeks prior to Day -7 for live attenuated vaccines. For patients whose opportunity for COVID-19 vaccination arrives during the conduct of the study **(i.e., ongoing patients in the study)**, see instructions for COVID-19 vaccination provided in Section 6.8.1.1.

5.1. Inclusion Criteria

Patients will be considered eligible to be enrolled in the study if ALL the following inclusion criteria are satisfied unless otherwise specified:

1) Voluntary provision and understanding of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, or analysis.
2) Patients must be aged ≥18 years on the day of signing informed consent (or of an acceptable age according to local regulations, whichever is older).
3) Patients must have documented radiological progression during or after their latest therapy for all phases.
4) Patients have documented histologically or cytologically confirmed advanced or metastatic EGFR-positive (positive staining for EGFR in ≥1% of tumor cells determined by a locally validated immunohistochemistry assay) select cancer types, except for NSCLC patients (cohorts EXP-1 and EXP-4); and meet the following criteria:

   Dose Escalation Phase (Phase 1):

   Dose Escalation Cohorts: Patients who meet the criteria specified for the expansion cohorts.

Expansion phase (Phase 2a):

- **EXP-1**: patients with advanced or metastatic, *EGFR WT* expressing NSCLC whose disease has progressed after having received ≥1 prior lines of therapy for advanced disease. Patients must have received at least a platinum-based doublet in combination with an anti-PD-1/PD-L1 antibody or must have received an anti-PD1/PD-L1 antibody prior to or after a platinum-based doublet. Patients with a known actionable driver mutation (other than EGFR mutation) must have received an approved targeted treatment for the respective mutation. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate.
- **EXP-2**: patients with locally advanced, unresectable, or metastatic gastric or GEJ adenocarcinoma refractory to or, intolerant of, standard therapy. Patients must have received ≥1 prior chemotherapy regimen including a platinum and fluoropyrimidine doublet. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate.
- **EXP-3**: patients with advanced or metastatic hepatocellular carcinoma (other than fibrolamellar and sarcomatoid subtype; Barcelona Clinic Liver Cancer Stage C disease or Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy), hepatobiliary-, or pancreatic adenocarcinoma. Patients must have been treated with at least 1 previous line of an approved, SOC therapy for the respective disease type or, in the opinion of the Investigator, available SOC is not appropriate. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate.
- EXP-4: patients with advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation and whose disease has progressed on or after having received ≥1 prior lines of therapy for advanced disease including ≥1 prior TKI approved for EGFR mutated NSCLC, such as gefitinib, erlotinib, afatinib, dacomitinib or osimertinib. Subjects who were treated with a 1st or 2nd generation TKI in 1st line and developed a documented T790M mutation must have received a TKI targeting this mutation such as osimertinib or lazertinib to be eligible. Subjects must have documentation of EGFR mutated NSCLC as assessed by an approved test using genomic sequencing of tumor or circulating free tumor DNA. The patients should also have received a second line of treatment if approved and available, or they may be enrolled in the study if in the opinion of the Investigator it is in the patient's best interest, or the SOC is not appropriate.

[redacted]

5) Eastern Cooperative Oncology Group (ECOG) PS 0 or 1

9) Patients must have evaluable or measurable disease per RECIST v1.1 for the dose escalation phase (Phase 1). For the expansion phase (Phase 2a), patients must have

measurable disease by RECIST v1.1. Measurable disease per RECIST v1.1 is defined as at least 1 measurable lesion ≥10 mm by CT scan or MRI or ≥20 mm by chest X-ray; malignant lymph nodes are considered measurable if short axis is ≥15 mm as assessed by CT scan. The last imaging must have been performed within 28 days prior to the first dose of AFM24 (i.e., Day -7).

10) Female patients of childbearing potential must have a negative urine or serum pregnancy test at Screening and prior to first AFM24 infusion (i.e., Day -7) to be eligible in this study. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible. Non-childbearing potential is defined as:

    a. Postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

    b. Surgically sterile. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

11) Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of study drug through 5 months after the last dose of study drug. Acceptable highly effective birth control methods include:

    a. Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;

    b. Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;

    c. Intrauterine device;

    d. Intrauterine hormone-releasing system;

    e. Bilateral tubal occlusion;

    f. Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and

    g. Sexual abstinence. In the context of this study sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of study drug up to 5 months after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

12) Males who have female partners of childbearing potential must agree to use a highly effective method of contraception as described in Inclusion Criterion 11) starting with the first dose of study therapy through 5 months after the last dose of study drug.

5.2. Exclusion Criteria

Patients who fulfill ANY of the following criteria will not be enrolled into the study:

1) Currently receiving active treatment in any other clinical study, or administration of other investigational agent.

[redacted]

4) Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day -7 or anticipation of need for a major surgical procedure during the course of the study. Note: Procedures that are considered to be minimally invasive (e.g., peripherally inserted central catheters lines and/or port placements) will be exceptions.

[redacted]

6) Patients with toxicities (because of prior anticancer therapy) which have not recovered to baseline or CTCAE v5.0 ≤ Grade 1, except for AEs not considered a likely safety risk (e.g., alopecia, neuropathy, specific laboratory abnormalities).

[redacted]

8) History of any other invasive malignancy, unless previously treated with curative intent and the patient has been disease free for 3 years or longer. [redacted]

9) Untreated or symptomatic central nervous system metastases including leptomeningeal disease or spinal cord compression.

[redacted]

[redacted]

16) Patient's unwillingness to comply with the protocol [redacted] or inability to appreciate the nature, meaning, and consequences of the study and to formulate his/her own wishes correspondingly.

17) Known hypersensitivity to monoclonal antibodies or any components used [redacted]

18) Uncontrolled intercurrent illness including, [redacted]

19) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate.

5.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patients who do not meet the criteria for participation in this study for reversible reasons may be rescreened. A new patient number will be assigned upon screening.

5.4. Withdrawal of Patients in the Study and Replacement of Patients

5.4.1. Withdrawal of Consent

A patient may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the patient is otherwise entitled to. When a patient wishes to withdraw consent, it is important to distinguish between withdrawing his/her consent for a particular study procedure or visit versus withdrawing his/her consent from the study entirely (i.e., premature discontinuation).

When a patient withdraws consent from the study (or study procedure), the reason(s) for withdrawal will be recorded by the Investigator or designee on the relevant page of the eCRF.

5.4.2. Premature Discontinuation

Every reasonable effort should be made to encourage retention of patients in the study, maximize compliance with study drug, and facilitate attendance at all scheduled study visits/assessments.

All patients have the right to refuse further participation in the study at any time and for any reason. A patient's participation must, therefore, be terminated immediately upon his/her request.

The Investigator will make every attempt to ascertain the reason(s) for discontinuation and to document this in detail in the source documentation and the appropriate sections of the eCRF. A patient must be withdrawn from the study for any of the following reasons:

- Withdrawal by patient or the patient's legal representative.
- Protocol violation/noncompliance (defined as refusal or inability to adhere to the study procedures).

- Confirmed progressive disease (PD), as assessed by the treating Investigator in accordance with RECIST v1.1 (On a case-by case basis, patients may continue treatment after disease progression at their assigned dose if there is continuing clinical benefit per Investigator's judgment and in consultation with the Sponsor's Medical Monitor).
- Symptomatic deterioration (clinical deterioration suggesting that no further benefit from treatment is likely). This category is applicable to patients with a global deterioration of health status requiring discontinuation of treatment. However, per RECIST v1.1, symptomatic deterioration is not a descriptor of an objective response (OR); it is a reason for stopping study therapy. Thus, every effort should be made to continue disease assessments per protocol until documented objective progression or initiation of alternate therapy.
- The development of a DLT (as defined in Section 4.2.3.1) during the dose escalation part (Phase 1) of the study.
- Pregnancy while receiving study drug.
- At the request of the Sponsor, regulatory agency, or IRB/IEC.
- Physician decision.
- Loss to follow-up.
- Death, otherwise not explainable by the above options.
- Patient may be withdrawn from study treatment due to unacceptable or intolerable AEs.

Patients who discontinue study treatment should be seen for the EOT visit when feasible, at which time all the assessments listed for the EOT visit will be completed. Patients who discontinue study treatment, after having received at least one dose of both AFM24 and atezolizumab, without confirmed progression of disease as per RECIST v1.1 should continue tumor assessment scans until criteria for disease progression are met, or until initiation of alternate anticancer therapies.

5.5. Lost to Follow-up

Study patients will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. The following actions must be taken if a study patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study;
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a registered letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record; and
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Situations of non-compliance will be reviewed on a case-by-case basis with the Sponsor and the site will be provided guidance on patient withdrawal from treatment and/or the study, where appropriate.

5.6. Replacement of Patients

In Phase 1 (dose escalation), a patient who does not fulfill the DLT requirements (Section 4.2.3.1) and who discontinues study participation prior to completing the DLT observation period due to any reason other than a DLT, will be replaced for DLT evaluation but will remain in the "safety analysis set".

For the dose escalation (Phase 1) and expansion phase (Phase 2a), all patients who begin AFM24 treatment but discontinue prior to receiving any amount of atezolizumab will be replaced but will remain in the overall "safety analysis set". A replacement patient will be enrolled and assigned the same cohort or dose level.

6. STUDY TREATMENT

6.1. Assignment of a Patient Number and Dose Level

6.1.1. Assignment of a Patient Number

Either at the Pre-Screening visit or at the Screening Visit, each patient will have a unique patient ID number assigned for patient identification.

6.1.2. Assignment of Dose Level

Prior to the first AFM24 infusion (i.e., on Day -7), sites must submit a patient eligibility packet to the Medical Monitor for review and confirmation of eligibility. After Medical Monitor confirmation of eligibility, patients can be enrolled in the appropriate dose level of the applicable cohort.

6.2. Overview of Study Treatment and Administration

The investigational treatment (AFM24 and atezolizumab) will be administered according to the procedure defined in the pharmacy manual at the clinical study site by appropriately trained staff. The infusion should be given in a monitored setting that has ready access to an intensive care unit in case of a severe infusion reaction.

Patients are required to receive premedication approximately 1 hour before each dose of AFM24, a list of pre-medications is provided in Section 6.3.

AFM24 will be administered as an i.v. infusion, qw, in 4-week cycles. Atezolizumab will be administered as an i.v. infusion, q2w, in 4-week cycles. The order in which the study treatment should be administered is depicted in Figure 1.

On days when investigational treatment (AFM24 + atezolizumab) is to be administered, atezolizumab will be administered first over approximately 60 minutes, followed by an observation period of 1 hour. If the first infusion is well tolerated, the infusion time can be reduced to 30 minutes for all subsequent infusions. After the end of the atezolizumab infusion, the premedication regimen required prior to AFM24 infusion will be administered.

The first 2 subsequent AFM24 administrations (i.e., D-7 – Safety Lead-in – and C1D1 in qw dosing regimen and D-7 and C1D1 in q2w dosing regimen) should not take less than approximately 4 hours (-10 minutes) with the ability to pause in case of IRRs > Grade 1 CTCAE v5.0. In general, as the dose escalation continues into higher dosing cohorts, the baseline infusion time may increase to > 4 hours and may take as long as over 2 days (i.e., split day dosing) as detailed in the Pharmacy Manual for each cohort based on a given patient's tolerability. If the first 2 AFM24 infusions are well tolerated (defined as no IRR/CRS > Grade 2), then starting from the third infusion (C1D8 in qw and C1D15 q2w), the infusion time may be decreased to at least 1 hour at the discretion of the Investigator.

For the first 2 AFM24 infusions (Safety Lead-in D-7 and C1D1), patients must be observed for at least 4 hours after the end of AFM24 infusion, with regular checks of vital signs. In case of a split day dosing (over 2 days) patients must be observed for at least 4 hours after the end of AFM24 infusion on each day. Starting from the third AFM24 infusion (i.e., at any time point in the study starting from C1D8 in qw schedule and C1D15 in q2w dosing schedule), the below listed changes

may also be made for those patients who do not experience IRR/CRS symptoms > Grade 2 during the previous infusion, keeping in mind that **only 1 modification** should be made at a time per infusion day:

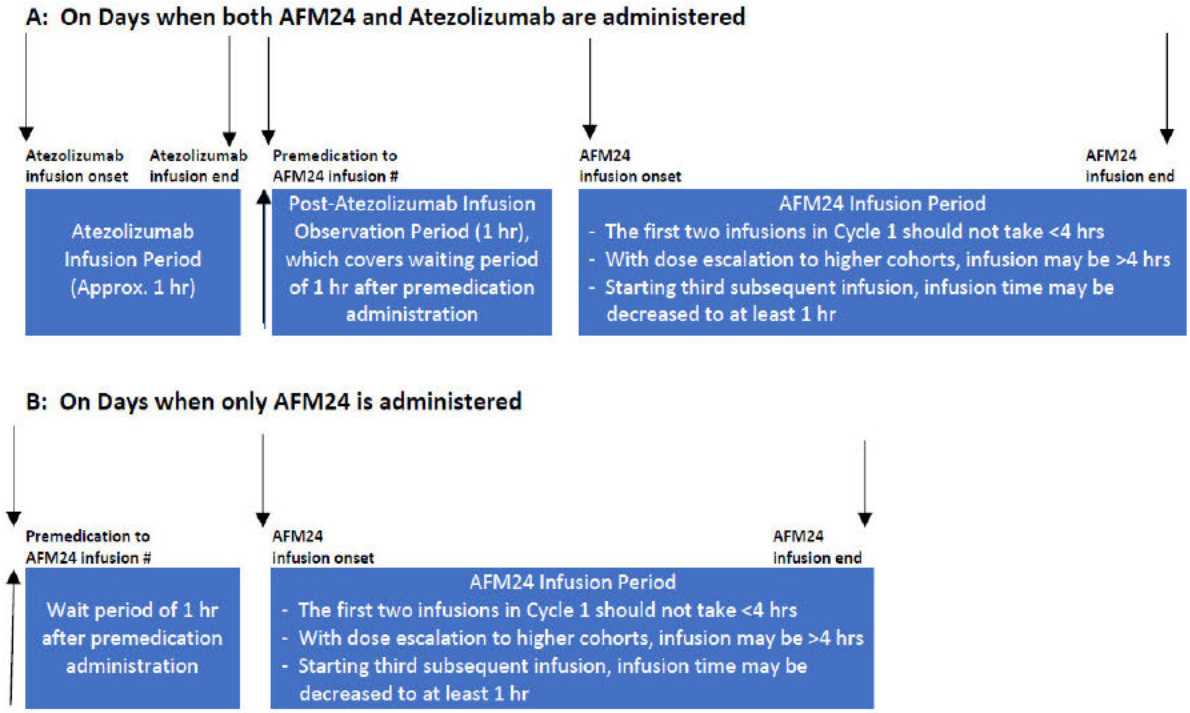
- Decrease the infusion time to at least 1 hour,
- Reduce observation period from 4 hours to ≥2 hours, or
- Taper the steroid or any other premedication.

Additionally, [redacted] provides guidance for the management of symptoms associated with IRR/CRS due to study treatment. For infusion times that span over 2 days (i.e., split day dosing), PK sampling times may be affected, and the Schedule of Assessment and the Pharmacokinetic Assessments should be referenced for details.

Patients may receive AFM24 and atezolizumab until disease progression, intolerable toxicity, Investigator discretion, or patient withdrawal of consent.

Please refer to the Pharmacy Manual for full details regarding study drug administration.

Figure 1: Order of Study Treatment Administration for Phase 1 and Phase 2a



Notes:

#**Premedication**: See Section 6.3 for mandatory pre-medications required to administered approximately 1 hour before each dose of AFM24 is mandatory:

***Infusion time**: Please see Section 6.1 for additional details regarding the infusion time and observation period post infusion. Please refer to the current pharmacy manual for full details regarding drug administration.

6.3. AFM24 Infusion Premedication

[redacted]

Patients may also be administered prophylactic antiemetic medications as indicated. Additional oral premedication will be allowed on the day before each dose of AFM24 at the discretion of the Investigator, in particular for those patients who may experience persistent IRRs.

If the infusions in Cycle 1 are well tolerated (defined as no > CTCAE v5.0 Grade 2 IRR), then the medication(s) within the premedication regimen can be tapered/decreased as described above in Section 6.3.

Clinicians should be prepared for an IRR or CRS to occur during or shortly after each AFM24 drug administration, with frequent monitoring of vital signs and medical equipment and supplies readily available and standing orders in place for immediate intervention in line with their institutional guidelines/clinical practice. [redacted]

6.4. Safety Lead-in Phase

Patients enrolling to the dose escalation phase (Phase 1) or the expansion phase (Phase 2a) will be evaluated for AFM24 hypersensitivity during safety lead-in phase as described in Section 4.2.2.

For the safety lead-in phase during the dose escalation phase (Phase 1), each patient will receive the AFM24 infusion on Day -7 at the dose according to the assigned cohort.

For the safety-lead in phase during the expansion phase (Phase 2a), each patient will receive the AFM24 infusion on Day -7 at the MTD/RP2D dose level, which is determined based on the dose escalation phase (Phase 1).

6.5. Dose Escalation Phase (Phase 1) Treatment Assignment and Schedule

For the dose escalation phase (Phase 1), patients will receive AFM24 and atezolizumab in an open-label fashion according to the treatment schedule below for their assigned cohort. The dose cohorts may be adjusted according to emerging data from the AFM24-101 study. Notably, the Sponsor may choose to explore alternate dose cohorts based on the observed safety data.

Cohort 1 (N = 3 to 6)

- 160 mg AFM24 i.v. qw + atezolizumab 840 mg i.v. q2w

Cohort 2 (N= 3 to 6)

- Cohort 2: AFM24 i.v. qw (at dose to be based on the data from AFM24-101 in conjunction with the safety and available PK data emerging from this study, as determined by the SRC) + atezolizumab 840 mg i.v. q2w

Cohort 3 (N= 3 to 6)

- AFM24 i.v. qw (at dose to be based on the data from AFM24-101 in conjunction with the safety and available PK data emerging from this study, as determined by the SRC) + atezolizumab 840 mg i.v. q2w

Depending on the emerging safety and PK data from the ongoing AFM24-101 study, and timing for initiation of this study, an alternate starting dose and additional dosing cohorts may be considered (see Section 2.4).

6.6. Expansion Phase (Phase 2a) Treatment Schedule

Patients who are determined eligible post evaluation for AFM24-hypersensitivity during the safety-lead in phase (Day -7 through Day -1) will receive the investigational treatment (AFM24 + atezolizumab) as per the following regimens, with the RP2D defined as 480 mg as described in Section 2.5:

- EXP-1 (*EGFR-WT* NSCLC): AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w
- EXP-2 (gastric or GEJ adenocarcinoma): AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w
- EXP-3 (Hepatocellular Carcinoma, Hepatobiliary-, or Pancreatic Adenocarcinoma): RP2D AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w
- EXP-4 (advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation): RP2D AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w

If AFM24 is given on a q2w schedule the daily dose of AFM24 will not be higher than the highest daily dose that was tested in the phase 1 part of the study and was considered safe.

Additional treatment schedules of AFM24 administration (e.g., q2w) may be explored as part of the Phase 2a within or across cohorts.

6.7. Dose Interruptions, Delays, Modifications and Discontinuations

AFM24

Treatment may be delayed for up to 3 weeks to allow sufficient time for recovery from treatment-related toxicities to baseline or Grade ≤1 (except for alopecia), except during the DLT observation period during the dose escalation phase (Phase 1). See Section 5.4.2 for criteria requiring permanent discontinuation of study treatment.

Dosing delays longer than > 3 weeks may be permitted in a case-by-case basis per the Investigator's judgement after consultation with the Medical Monitor. No dosing delays (including planned dosing delays such as elective surgery) will be allowed during the DLT observation period. Tumor assessments should continue as per protocol even if dosing is delayed.

If an AE occurs during the AFM24 infusion Safety Lead-in (D-7), and the dose is interrupted, the patient can restart upon recovery to baseline or Grade ≤1 within the same day. If the patient already received 80 mg of the prescribed dose of AFM24 on the day of dose interruption or cannot recover within the same day of the event, the rest of the dose should be omitted.

Weekly dosing schedule:

If the patient recovers from an AE and can continue study treatment within 72 hours of the planned dose, the patient should receive the delayed dose and continue treatment as per the original schedule, by not shifting any later doses. There should be at least 3 days between infusions before the patient receives the next dose. An example: if the patient has an AE on Cycle 1 Day 15 and recovers in time and can receive the missed dose by Cycle 1 Day 18, then the next dose for the patient would be on Cycle 1 Day 22.

If the patient does not recover from an AE within 72 hours the missed dose(s) should be skipped and the patient should receive the next dose as per original schedule. An example: a missed dose on Cycle 2 Day 1 and the patient recovered on Cycle 2 Day 9, the next dose for this patient is on Cycle 2 Day 15.

Every-2-weeks dosing schedule:

If the patient recovers from an AE and is able to continue study drug within 1 week from the original scheduled dosing day then the patient should receive the delayed dose and continue treatment as per the original schedule, by not shifting any later doses. There should be at least 7 days without treatment before the patient receives the next dose. An example: if the patient has an AE on C1D1 and recovers in time and can receive the missed dose latest on C1D8, then the next dose for the patient is on C1D15.

If an AE happens during the AFM24 infusion, and the dose is interrupted, the patient can restart upon recovery to baseline or Grade ≤1 within the same day. If the patient already received ≥75% of the prescribed dose of AFM24 and 50% of atezolizumab that day at the time of the interruption or cannot recover within the same day of the event, the rest of the dose could be omitted.

Patients who experience a DLT during the DLT observation period must permanently discontinue the study drugs.

In addition, AFM24 re-challenge following a CTCAE Grade ≥3 IRR or CRS should be handled as the following and the Investigator should refer [redacted] for details:

- Grade 3 IRR or CRS that are NOT responsive to symptomatic treatment (i.e., no improvement of IRR-related symptoms to Grade 2 or better within 6 hours with optimal medical management): AFM24 should be discontinued permanently.
- Grade 4 IRR or CRS in all phases: AFM24 should be discontinued permanently.

IRRs other than anaphylaxis responsive to symptomatic treatment (i.e., improvement to Grade 2 or better within 6 hours with optimal medical management):

- Restart if symptoms resolve to CTCAE Grade ≤1 or baseline only at the discretion of the investigator based on the clinical status of the patient.
- If re-challenge is considered, infuse the next AFM24 infusion with a >4-hour infusion time.

Dose Modification:

During the dose escalation phase (Phase 1), if a patient is tolerating AFM24 in combination with atezolizumab well (i.e., no drug-related Grade ≥2 toxicity) without evidence of disease progression following 2 cycles, the patient may, beginning with Cycle 3 or a subsequent cycle, have the dose increased to a dose that has already been established as tolerable by the SRC, and with the agreement of the SRC.

Atezolizumab

Atezolizumab dosage modifications in case of related adverse reactions should be managed according to the recommended dosage modifications provided in the label (TECENTRIQ PI, 2022) and as summarized in [redacted] For IRRs considered related to atezolizumab, interrupt, slow the rate of infusion, or permanently discontinue based on severity of the infusion reaction *(*[redacted]).

Continuation of therapy on-study in the setting of discontinuation of one component (AFM24 or Atezolizumab) of the study therapy

If one component of the study therapy is permanently discontinued secondary to toxicity, then therapy with the other component may continue at the discretion of the investigator and the patient should remain on-study with full adherence to all protocol-related requirements, provided the patient continues to meet entry criteria and does not have evidence of disease progression.

6.8. Permitted and Restricted Concomitant Medications

6.8.1. Acceptable Concomitant Medications

All treatments and supportive care that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the standards of medical care of the study site except for the prohibited concomitant medications listed in Section 6.8.2. All concomitant medication will be recorded in the patient's medical records and in the eCRF including all prescription, over-the-counter, herbal supplements, and i.v. medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date needs to also be included in the eCRF.

All concomitant medications received from Screening to the Safety Follow-up visit should be recorded (see Schedule of Assessments [redacted]). Concomitant medications administered after the Safety Follow-up visit should be recorded for SAEs which are considered related to study drug (Section 10).

6.8.1.1. COVID-19 Vaccination

Various guidelines (e.g., *NCCN Guidelines: Cancer and COVID-19 Vaccination* [NCCN 2023] and *MHRA Guidance on Coronavirus [COVID-19])* [MHRA 2022] have noted that COVID-19 vaccination should be prioritized for patients with cancer with the understanding that there are limited safety and efficacy data in this patient group. These guidelines also state:

- "Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T cell and B cell immunity can be considered."
- "Systemic corticosteroids and targeted agents are expected to blunt immune responses to vaccination."

This study utilizes a mandatory premedication regimen that contains corticosteroids (i.e., 20 mg of i.v. dexamethasone [or equivalent of long-lasting steroid dose]) for at least the duration of the first cycle (i.e., Cycle 1). Therefore, every effort should be made to vaccinate patients prior to being considered for this study based on the Investigator's risk/benefit analysis for each patient. If a patient receives the COVID-19 vaccination prior to study participation, the vaccine should be administered at least 2 weeks prior to Day -7 or at least 4 weeks prior to Day -7 for live attenuated vaccines.

For patients whose opportunity for COVID-19 vaccination arrives during the conduct of the study (i.e., ongoing patients in the study), the following should be noted:

- COVID-19 vaccination should be avoided during the DLT period or Cycle 1 of the study period.

- As stated in Section 6.2, Investigators may taper premedication with corticosteroids for those patients who do not experience IRR/CRS symptoms Grade >2 during the previous infusion starting with the third subsequent AFM24 infusion (C1D8 weekly schedule and C1D15 for q2w schedule).
- If the vaccination opportunity falls within the mandatory corticosteroid premedication period, there should be a consideration by the Investigator for holding or tapering the corticosteroid to prioritize vaccination on a case -by -case basis based on the risk/benefit analysis by the Investigator/treating MD.
- COVID-19 vaccination is not permitted on AFM24 dosing days. Vaccination should be administered at least 3 days before or 3 days after the AFM24 treatment administration day.
- It should be noted that no planned dose delays for study drugs are allowed during the DLT period (i.e., Cycle 1).

6.8.2. Prohibited Concomitant Medications

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study drug may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the Investigator and/or the patient's primary physician. However, in such cases, the decision to continue the patient on study regimen drug requires the mutual agreement of the Investigator, Sponsor, and patient.

Apart from the exceptions listed in the inclusion/exclusion criteria, patients are prohibited from receiving the following therapies during the Screening (see Section 5.2) and Treatment Period of this study, with exception of the treatment of AEs occurring during the study:

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Patients may receive other medications that the Investigator deems to be medically necessary.

6.9. Blinding and Procedures for Unblinding the Study

This is an open-label study, and there are no procedures for blinding and unblinding.

6.10. Management of AFM24-Related Toxicities

Any DLT during Cycle 1 in the Phase 1 part: Permanently discontinue AFM24.

Please see [redacted] for a summary of management of IRR/CRS, and other AFM24-related AEs.

IRRs: [redacted] for detailed grading criteria and detailed guidance on management.

CRS: [redacted] for detailed grading criteria and detailed guidance on management.

Dermatological toxicities: Investigators are asked to pay special attention to ALL dermatological toxicities and consult with a dermatologist if needed. In cases of Grade ≥3 skin toxicity, AFM24 treatment should be interrupted or postponed until the reaction resolves to Grade ≤1 or baseline. Patients should be asked to limit direct sunlight exposure and apply protective sun cream during treatment with AFM24. A rechallenge should be considered at the discretion of the Investigator but AFM24 should be permanently discontinued with a recurrence of Grade 3.

Electrolyte abnormalities: Consider withholding AFM24 for Grade ≥2 electrolyte abnormalities and resume when resolved. Replenish electrolytes as medically appropriate.

Pulmonary symptoms: In the event of acute onset or worsening of pulmonary symptoms, interrupt AFM24 therapy. Discontinue AFM24 therapy if interstitial lung disease is confirmed.

Hepatotoxicity: If severe (>CTCAE Grade 3) hepatic impairment develops for patient with / without liver metastasis, AFM24 should be discontinued permanently.

Gastrointestinal Perforation: Permanently discontinue AFM24 in patients who develop gastrointestinal perforation.

Other: For all CTCAE Grade 3 toxicities other than those that meet the definition of a DLT during Cycle 1 of the dose escalation (i.e., Phase 1) phase, and other than those described above, interrupt treatment with AFM24 until resolved to Grade ≤1 or baseline. If CTCAE Grade 3 toxicity recurs upon rechallenge or in case of CTCAE Grade 4 toxicity, permanently discontinue treatment.

6.11. Management of Atezolizumab-Related Toxicities

Atezolizumab-related toxicities should be managed according to recommendations provided in its label (TECENTRIQ PI, 2022) and IB v19. Recommended dose modifications for adverse reactions that are anticipated with the atezolizumab infusion are summarized in Table 2 and additional details are provided in [redacted]

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity [a]	Dosage Modification
Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1) Section of TECENTRIQ PI]		
Pneumonitis	Grade 1	Consider withholding
	Grade 2	Withhold [b]
	Grade 3 or 4	Permanently discontinue
Cardiac Events (Immune-mediated Myocarditis, Immune-mediated pericardial disorders)	Grade 2 to 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold
	Grade 4	Permanently discontinue
Dermatologic Events	Grade 3	Withhold
	Grade 4	Permanently discontinue
Endocrinopathies	Grade 2	Consider withholding
	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 5 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold [b]
	AST or ALT increases to more than 5 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and	Withhold[b]

Adverse Reaction	Severity [a]	Dosage Modification
	increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	
	If ALT/AST increases to >10x ULN or total bilirubin increases to >3x ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3	Withhold
	Grade 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or >1.5 to 3.0 x ULN)	Withhold[b]
	Grade 3 or 4: (creatinine level > 3.0 x baseline or >3.0 x ULN)	Permanently discontinue
Meningoencephalitis	All grades	Permanently discontinue
Myasthenic Syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue
Myositis	Grade 2	Withhold
	Grade 3	Withhold
	Grade 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Ocular events	Grade 2	Withhold
	Grade 3 or 4	Permanently discontinue
Pancreatitis	Grade 2 or 3	Withhold
	Grade 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions [see Warnings and Precautions (5.2)]	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue
Suspected HLH or MAS	Any grade	Permanently discontinue

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson syndrome, TEN = toxic epidermal necrolysis, HLH = Hemophagocytic lymphohistiocytosis, MAS = Macrophage activation syndrome

[a.] Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.

[b]. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

[c.] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TECENTRIQ based on recommendations for hepatitis with no liver involvement.

Source: (TECENTRIQ PI, 2022).

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug Materials AFM24 and Atezolizumab

7.1.1. Investigational Product

AFM24 is a tetravalent, bispecific, chimeric (anti-human EGFR × CD16A) recombinant antibody construct and is supplied for intravenous infusion. Please see the Pharmacy Manual for further details.

Atezolizumab will be commercially procured and supplied by the Sponsor. Atezolizumab injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion in 840 mg/14 mL single-dose vial. Further details for atezolizumab will be found in the package insert (TECENTRIQ PI, 2022).

7.1.2. Provision and Replacement of AFM24 and Atezolizumab

Sufficient doses of investigational treatment (AFM24 and atezolizumab) will be supplied. Where investigational drug supplies (or packaging) are apparently damaged on receipt or considered unfit for use by the study site, the Sponsor (or their delegate) must be notified immediately. Where required, clinical study supplies will be replaced. Further details on the handling of AFM24 and atezolizumab at site will be described in the Pharmacy Manual. Further details for atezolizumab will be found in the package insert (TECENTRIQ PI, 2022).

7.1.3. Labeling of AFM24 and Atezolizumab

AFM24 drug product is manufactured by [redacted] AFM24 and atezolizumab clinical study supplies will be labeled in compliance with Good Manufacturing Practice Annex 13 requirements, (US Food and Drug Administration (FDA) requirements, and any other applicable local regulatory guidelines.

7.1.4. Storage of AFM24 and Atezolizumab

AFM24 lyophilized powder and atezolizumab must be stored at 2°C to 8°C (36-46°F). The investigational treatment for this study (AFM24 and atezolizumab) will be shipped to the site and must be stored at the site in a secure location under controlled conditions and in the required temperature range. Please see the Pharmacy Manual for further details.

7.1.5. Handling and Disposal

The infusions for investigational treatment (AFM24 and atezolizumab) should be made on the day of dosing and used immediately after preparation. If not administered immediately, the infusion solutions should preferably be stored at 2°C -8°C (36-46°F). A warm-up time of at least 30 minutes should be allowed before the start of infusion. Please see the Pharmacy Manual for further details.

7.2. Accountability

The Investigator is obliged to keep sufficient documentation of the delivery, use, and destruction or return of unused, used, or partially used investigational treatment (AFM24 and atezolizumab study drug). The documentation must include dates, quantities, patient numbers, batch numbers,

or other identification number. The Investigator may assign some or all the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the Investigator Site File.

The Investigator should maintain records that document adequately that the patients were administered the doses specified in the protocol and reconcile all AFM24 and atezolizumab investigational treatment received for the study. The local clinical research associate (CRA) will be responsible for checking the drug accountability records maintained by the site during study monitoring visits.

The investigational treatment (AFM24 and atezolizumab) provided for this study is for use only as directed in the protocol. It is the Investigator and their institution's responsibility to establish a system for handling study drug to ensure that:

- Deliveries of investigational treatment (AFM24 and atezolizumab) are correctly received by a responsible person;
- Such deliveries are recorded;
- Investigational treatment (AFM24 and atezolizumab) is handled and stored safely and properly as stated on the label;
- Investigational treatment (AFM24 and atezolizumab) is only dispensed to study patients in accordance with the protocol; and
- Any unused investigational treatment (AFM24 and atezolizumab) is destroyed locally or returned for destruction in liaison with the CRA after written approval by the Sponsor.

Certificates of delivery and return must be signed by the responsible pharmacist and copies retained in the Pharmacy File. Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock of AFM24 and atezolizumab. To help with compliance checks, records of usage should include an appropriate form of identification of the patient to whom the study treatment was dispensed (using an indirect form to allow cross reference to the patients' identity), plus the quantity and date of dispensing.

The return or destruction of unused drug will be conducted after written approval by the Sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

7.3. Treatment Compliance

Administration of investigational treatment (AFM24 and atezolizumab) will be supervised by the Investigator or sub-Investigator. Any delegation of this responsibility must follow the standard procedures.

All patients will be dosed at the site; thus, they will receive study drug(s) directly from the Investigator or designee, under medical supervision. The date, time, and total amount delivered of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. Should the total amount of study drug not be delivered or there is an interruption to dosing, the reason(s) and any associated AEs will be recorded in the source documents and recorded in the eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

Please see [redacted] for a schematic study design ([redacted] and Schedule of Assessment Tables [redacted]) for dosing regimen with AFM24 administered qw and atezolizumab infusion administered q2w throughout the study (i.e., in dose escalation phase [Phase 1] and expansion phase [Phase 2a]),

Please see [redacted] for a schematic study design ([redacted]) for dosing regimen with AFM24 administered qw and atezolizumab infusion administered q2w in the dose escalation phase (Phase 1) and both AFM24 and atezolizumab administered q2w in expansion phase (Phase 2a) and Schedule of Assessment Tables ([redacted]) for dosing regimen of both AFM24 and atezolizumab administered q2w in expansion phase (Phase 2a).

Details of the procedures to be followed for specified study assessments are provided in [redacted]. During the study, additional assessments may be carried out as clinically indicated.

Safety will be assessed by periodic vital signs, physical examinations, ECOG PS, 12-lead ECGs, clinical laboratory assessments, and monitoring of AEs. AEs will be graded using the NCI CTCAE, v5.0 (NCI 2017).

The PK profile will be assessed by determining serum levels of AFM24 in combination with atezolizumab at the time points described in the Schedules of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments [redacted]

8.1. Informed Consent, Medical History, and Demographics

For the pre-screening of EGFR positivity, patients will have to sign a pre-screening informed consent form. Before starting the screening process, written informed consent will be obtained. Demographic information will be collected during the Screening visit. There will be a baseline assessment of relevant medical history and cancer history conducted at Screening to confirm eligibility and to record significant medical history and concurrent illnesses. Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation) that worsen in severity or frequency from this baseline assessment during the study should be reported as AEs.

8.2. Safety Assessments

All patients who receive at least one dose of AFM24 or atezolizumab will be considered evaluable for safety. Pre-existing conditions that are detected prior to administration of the first dose of study drug and are not related to study procedures will be recorded as part of the medical history. Refer to Section 10.3 for information on the timelines for reporting AEs/SAEs.

8.2.1. Adverse Events

Adverse events will be assessed and recorded as specified in the Schedule of Assessments [redacted]). Adverse events will be assessed by the Investigator according to NCI-CTCAE v5.0 and recorded in the eCRF (see Section 10).

Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation) that worsen in severity or frequency from this baseline assessment during the study should be reported as AEs (see Section 10).

8.2.2. DLT Analysis

The MTD and/or RP2D dose of AFM24 in combination with atezolizumab as determined during the DLT evaluation period in the dose escalation phase (Phase 1), will be used in the expansion phase (Phase 2a). DLT is defined as an AE or abnormal laboratory value assessed as unrelated to underlying disease, disease progression, inter-current illness, or concomitant medications, that occurs ≤28 days following the first dose of AFM24 in combination with atezolizumab (Cycle 1) and that meets any of the following criteria shown in Table 1. Please see Section 4.2.3.1 for details on DLT analysis.

8.2.3. Physical Examinations

Physical examinations and weight will be performed at timepoints depicted in [redacted]. A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the Screening assessment, the physical examination may be reduced to a symptom-directed assessment.

Height and weight will be measured at Screening. Weight will be measured within 24 hours of administration of AFM24 plus atezolizumab on Day 1 of each cycle. Height and body weight will be obtained while the patient is wearing light clothing (without shoes).

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

8.2.4. Vital Signs

Vital sign parameters will be taken at timepoints depicted in [redacted]. The date and time of collection will be recorded in the source data and in the eCRF.

On all days when AFM24 is administered, vital sign parameters to be measured include temperature, resting heart rate, seated blood pressure (systolic/diastolic) after 5 minutes resting, oxygen saturation and respiratory rate. On all days when AFM24 is administered, vital signs are to be recorded following the schedule of vital signs parameters described in Table 3. **Note**: For the first two administrations of AFM24, patients must be observed for at least 4 hours after the end of infusion, with regular checks of vital signs.

If the first two infusions of AFM24 are tolerated well (i.e., no IRR/CRS Grade >2), then starting from the third infusion (e.g., C1D8 in the escalation phase) the observation period after the end of infusion may be reduced from 4 hours to ≥ 2 hours (at least 2 hours), with vital signs recorded following the schedule of vital signs parameters described in Table 3 until the completion of infusion. **Note:** Please refer to Section 6.2 to note that **only 1 modification** should be made at a time per infusion day.

On all days when atezolizumab is administered, vital signs are to be measured following the schedule of vital sign parameters described in Table 3.

Table 3: Recording Schedule of Vital Sign Parameters for Atezolizumab and AFM24 Infusions

	Vital sign timepoints on dosing days (First 2 AFM24 infusions)	**Vital sign timepoints for subsequent dosing days if no CRS or IRR (no Grade >2) observed (Third consecutive AFM24 infusion) [a]**
Before atezolizumab infusion	Baseline (within 15 minutes before start of the infusion)	Baseline (within 15 minutes before start of the infusion)
During atezolizumab infusion	30 (±5) minutes after start of infusion 60 (±5) minutes after start of infusion At the end of infusion (EOI ±10 minutes) [b]	30 (±5) minutes after start of infusion 60 (±5) minutes after start of infusion At the end of infusion (EOI ±10 minutes) [b]
After atezolizumab infusion	+30 (±10) minutes post EOI	+30 (±10) minutes post EOI
Before AFM24 infusion[c]	Baseline (within 1 hour before start of the infusion)	Baseline (within 1 hour before start of the infusion)
During AFM24 infusion [c]	30 (±10) minutes after start of infusion Every 30 (±10) minutes thereafter until EOI At the EOI (±10 minutes)	30 (±10) minutes after start of infusion [d] As clinically indicated [d]
After AFM24 infusion [c]	+60 (±10) minutes post EOI Every 60 (±10) minutes thereafter until the end of the observation period	As clinically indicated, with a minimum observation period of two hours [d]

Note: In addition to the above listed time points, patients should be additionally monitored in accordance with the institutional guidelines/clinical practice and as clinically indicated.
[a] If no CRS or IRR (no Grade >2) events are observed during or after the first two consecutive AFM24 dosing days, then a reduced schedule of vital signs assessments may be followed as indicated for Cycle 1 Day 8 and beyond.
[b] Not required if timepoint aligns with a previous timepoint (e.g., infusion ends at 60 minutes after the start of infusion)
[c] The recording schedule should be followed on both dosing days if a subject is assigned to a dose cohort that requires split dosing (Section 6.2 and Section 6.3)
[d] In case of the occurrence of Grade >2 events of CRS or IRR at a later infusion (i.e., on Cycle 1 Day 8 or beyond), then the same schedule for increased vital signs assessments should be performed as done for Day -7 and Cycle 1 Day 1. If, after two consecutive infusions, the subject does not have an CRS or IRR event Grade > 2, then a reduced schedule of vital signs assessments may be followed.

8.2.5. Electrocardiogram

A resting 12-lead ECG will be performed at timepoints (with respect to AFM24 infusion) [redacted] **For Phase 1 only**, triplicate ECGs should be taken at least 5 minutes apart before infusion and within approximately 15-20 minutes after the end of infusion (note plus only). **For Phase 2a**, ECGs will be performed in triplicate approximately 5 minutes apart at the Screening visit only, all subsequent required ECGs will be performed as single ECGs and should be performed prior to treatment infusion.

For those occasions when both an ECG and peripheral blood sample (PK and pharmacodynamic [cytokines]) collection are required at the end of infusion (EOI) of AFM24, the blood draw must

be completed first, as close to the AFM24 EOI as possible, followed by the ECG. Both procedures should be completed approximately within 15-20 minutes after the AFM24 EOI (**note** plus only).

In case of split day dosing of AFM24, ECG assessments should be performed on the first day of the split day dosing before treatment start (Phase 1 and Phase 2a) and on the second day of the split day dosing after the end of infusion in Phase 1 only.

All 12-lead ECGs should be recorded while the patient is in supine position. ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual patients. The Investigator or designated physician will review the ECG results. If any clinically significant findings are identified during the study, the Investigator will record these as an AE where the finding represents a change from baseline.

An unscheduled ECG might be performed at any time if clinically indicated.

8.2.6. Clinical Chemistry, Hematology, Urinalysis, Coagulation

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken as described in Schedule of Assessments [redacted] Patients must demonstrate adequate organ function when assessed within 7 days before the first AFM24 infusion on Day -7 to remain eligible as outlined in Section 5.1 (Inclusion Criteria 6). Clinical Chemistry, hematology, urinalysis, and coagulation samples must be taken on or the day before infusion (i.e., up to one day prior to atezolizumab infusion on dosing days when both atezolizumab and AFM24 are administered, and up to one day prior to AFM24 infusion on days when only AFM24 is administered).

Hepatitis B, hepatitis C, and HIV serology testing will be performed at Screening.

The laboratory variables to be measured are described in [redacted]

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to analysis of their first patient sample and maintained over the course of the study.

If a clinically significant clinical chemistry, hematology, urinalysis, or coagulation finding is identified during the study, the Investigator will assess whether this finding is also considered an AE.

8.2.7. ECOG Performance Status

ECOG PS will be assessed at Screening and at time points specified in [redacted] Details of the ECOG PS categories are presented in [redacted] Patients must be confirmed as ECOG PS 0 or 1 to be eligible for study participation.

8.2.8. Pregnancy and FSH tests

Female patients of reproductive potential will have a pregnancy test carried out at Screening and at timepoints specified in [redacted]. A urine test is acceptable; however, where a urine test is equivocal, a blood test must be performed to confirm the result. Patients confirmed as pregnant will be excluded from participation in the clinical study.

Female patients who require documented confirmation of post-menopausal status will have their FSH levels assessed at Screening. Where post-menopausal status is not confirmed, patients will be required to undergo pregnancy testing per protocol to confirm suitability to proceed.

[redacted]

8.3.1. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Objective response to study treatment will be evaluated using RECIST v1.1 (Eisenhauer, 2009; Schwartz et al., 2016). Radiographic imaging will be assessed locally by the Investigator.

8.3.2. Efficacy Parameters

8.3.2.1. Objective Response Rate

The ORR is estimated by the proportion (percentage) of participants with the best response of CR, or partial response (PR) by RECIST v1.1 criteria, with corresponding exact 95% confidence limits being reported. RECIST v1.1 for target lesions and assessed by CT or MRI: Complete Response, Disappearance of all target lesions; PR, ≥30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

8.3.2.2. Overall Survival

Overall survival (median) is determined by looking at the time from initial date of treatment to the date of death due to any cause. Survival data will be collected throughout the active treatment phase and during the long-term follow-up phase. Survival follow-up after patient discontinuation of investigational product will be conducted approximately every 12 weeks to assess for survival until patient death or withdrawal of consent.

8.3.2.3. Progression Free Survival (PFS)

Progression-free survival (median) is determined using the time measured from the initial date of treatment to the date of documented progression, or the date of death (in the absence of progression) of participants. Progression is defined using RECIST v1.1, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable unequivocal increase in a non-target lesion, or the appearance of new lesion.

8.3.2.4. Duration of Response (DOR)

Duration of response will be measured from the date at which response criteria (per RECIST v1.1 criteria) are met for CR or PR (whichever status is recorded first) until the first date of recurrence or PD or death.

8.3.2.5. Clinical Benefit Rate

Clinical benefit rate is measured per RECIST v1.1 criteria as the proportion of patients who achieve overall tumor response (CR or PR) or SD for at least 24 weeks.

8.3.2.6. Disease Control Rate

Disease control rate (DCR) at months 3, 6, 9, 12 and 15, as defined by achieving CR and/or PR and/or SD assessed by RECIST v1.1 will be presented by percentage rates and where appropriate the 95% CIs.

8.4.1. Volume of Blood Sampling

Total blood volumes required during study participation will be provided in the ICF provided to each patient. Efforts will be made to limit blood sampling to avoid any redundancy. The requirements for blood sampling will be described and maintained in the Lab Manual.

8.6. Disease Response Assessment

Disease response will be assessed by the Investigator, using RECIST v1.1. For both the dose escalation phase (Phase 1) and expansion phase (Phase 2a), imaging results will be collected and preserved for future independent central review, if needed. Tumor assessment with CT and/or MRI will occur at Screening as well as during the last week of Cycles 2, 4, 6, 8, 10, 12 and every 3 cycles thereafter. Partial or CR needs to be confirmed with repeated assessment at least 4 weeks after the initial assessment.

If initial radiological PD is observed, while the clinical condition of the patient is stable, treatment continuation is allowed at the discretion of the Investigator and in consultation with the Sponsor's Medical Monitor. If treatment is continued after initial PD, a confirmatory scan should be acquired

within 4-6 weeks. However, the first successive scheduled timepoint after the confirmatory scan may be skipped if the window is considered not clinically relevant (up to the discretion of the Investigator). The next subsequent timepoint following the skipped timepoint must adhere to the original schedule.

8.7. Tumor Genomics

Blood samples for the assessment of tumor genomics from circulating tumor DNA (ctDNA) and mRNA profiling will be taken as described in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments [redacted] Full details of sample collection and handling of the sample will be described in the Lab Manual for the study.

For diagnostic purposes, a tumor biopsy at Pre-Screening is needed for EGFR assessment if there is no archived tumor tissue available. Samples could also be used for additional research such as (but not limited to) phenotypic assessments.

Optional biopsies may be taken at the discretion of the Investigator, following the patient's consent, for additional research at baseline (if sufficient archival tissue is not available) and during treatment. The biopsies may be used to confirm a radiological response/disease progression to inform treatment decisions and may also be utilized for analysis of immunological and other effects of the drugs on the tumor microenvironment.

[redacted]

8.9. Immunogenicity (Anti-Drug Antibodies)

All patients will have blood samples drawn to assess for ADA as described in Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments [redacted]

Full details of sample collection and handling of ADA samples will be described in the Lab Manual.

9. STATISTICAL CONSIDERATIONS

In general, summaries will be presented by cohort for both the dose escalation phase (Phase 1) and the expansion phase (Phase 2a) and will include the mean, standard deviation, standard error (where appropriate), median, minimum, and maximum values for continuous data; the median, 25th and 75th percentiles, minimum and maximum values (if estimable) for time-to-event endpoints; and the number and percentage of patients in each category for categorical data. Confidence intervals (CIs) may also be estimated for the mean (continuous data), median (time-to-event endpoints), or percentage of patients (categorical data). Baseline values will be defined as the last non-missing value before receipt of the first dose of study drug.

Listings of all individual patient data will be produced. A stand-alone Statistical Analysis Plan with mock Tables, Listings and Figures will be prepared.

9.1. Population for Analyses

For the purposes of analysis, the following populations are defined:

The **safety analysis set (SAS)** will consist of all patients who received at least any amount of AFM24 or atezolizumab. The SAS set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

The **full analysis set (FAS)** will consist of all patients who received at least any amount of both, AFM24 and atezolizumab. The FAS will be the primary population for all efficacy related endpoints.

The **dose-determining set (DDS)** will consist of all patients in the safety set, who have either (a) experienced DLT at any time during Cycle 1, or (b) met the minimum safety evaluation requirements without experiencing DLT within Cycle 1.

Additional details of DLT observation period and criteria to determine patients available for DLT are described in Section 4.2.3.1.

The DDS will be used in the escalation phase (3+3 design) to estimate the dose-DLT relationship.

The **PK set** consists of all patients who have received at least one adequately documented dose of AFM24 and have at least one adequately documented post dose PK measurement.

Patients who are screened and sign the informed consent but do not receive any treatment will be listed including reason for screening failure and any SAE that is related to study procedure. These patients will not be part of any summary table except for summarizing disposition.

9.1. Sample Size Determination

[redacted]

[redacted]

9.1.1. Dose escalation phase (Phase 1)

A 3+3 dose finding design will be implemented. The number of patients dosed within each cohort is based on safety. The objective is to expose the lowest possible number of patients to the investigational drugs, while still being able to assess safety where the estimated MTD is the highest dose level with the observed toxicity rate less than 0.33.

Three to 6 patients will be enrolled in each cohort. If a DLT is observed in 1 of 3 patients, an additional 3 patients will be enrolled in that same dose cohort.

At least 6 patients must be treated at the MTD/RP2D (and a toxicity rate of less than 0.33 must be observed to be confirmed as the MTD).

Estimated number of patients: **18 patients** (3 cohorts × 6 patients)

The sample size is based on the **DDS**, i.e., patients who are not evaluable for a DLT might be replaced. Thus, the actual number of patients may exceed 18, but will not exceed 28.

9.1.2. Expansion phase (Phase 2a)

An optimum Simon's two-stage design will be used (Simon 1989) for EXP-1 and EXP-2. EXP-3 and EXP-4 is exploratory with no hypothesis testing. The assumptions and sample size calculations for different cohorts are summarized in [redacted] and the interim analyses are described in Section 9.4. Sample size estimation for EXP-3 and EXP-4 is provided in [redacted]

[redacted]

[redacted]

[redacted]

9.2. Statistical Hypotheses

For phase 1, there will not be any hypotheses testing.

[redacted]

9.3. Statistical Analyses

The statistical analysis plan will be developed and finalized before database closes. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Safety Analyses

All safety analyses will be performed on the SAS, unless specified.

For primary endpoint of the escalation phase:

Occurrence of DLTs (see Section 4.2.3.1 for the definition). Patients in the DDS who experience a DLT will be presented in a summary table and listing by dose.

Other safety analyses (all phases):

Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term and system organ class categories. Safety assessments will be summarized using descriptive statistics along with supportive listings. The number and percentage of TEAEs will be summarized by treatment group and overall, by system organ class, and preferred terms within each system organ class. Serious adverse events and AEs resulting in treatment discontinuation will also be summarized. Observed values and change from baseline in laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit. Prior and concomitant medication use will be summarized by World Health Organization Drug Dictionary Anatomical Therapeutic Class code and treatment group.

All AEs meeting the DLT criteria will be summarized and listed for all patients throughout the study (in addition to the separate analysis of dose-determination using the DDS).

COVID-19 impacts:

Patients may be diagnosed with COVID-19 and experience SAEs associated with the disease that are not causally related to the investigational drug. However, it also is possible that an investigational drug might be causally related to a SAE associated with COVID-19 by making study patients more susceptible to complications from COVID-19. However, it is not possible to establish this potential causal relationship with a small number of SAEs reported in a clinical study. Descriptive statistics will be conducted to present SAEs by known and suspected COVID-19 infection and no infection. If possible, with the existing literature, the rates in the clinical study will be compared to reports in patients with similar comorbidities and levels of care. If the difference in SAEs compared to an external population suggests a causal relationship between the investigational product and the SAEs in study patients diagnosed with COVID-19, this finding will be submitted to FDA as an Investigational New Drug (IND) safety report in accordance with United States Title 21 Code of Federal Regulations (CFR) Part 312.32.

9.3.2. Efficacy Analyses

Objective Response: The number and percentage of patients achieving each category of response for OR (including CR and PR) will be provided. Results will be presented by percentages and 95% CI.

Clinical benefit rate (defined as CR or PR [any duration] OR SD ≥24 weeks): Results will be presented by percentages and 95% CI.

Disease control rate (DCR) at months 3, 6, 9, 12 and 15, as defined by achieving CR and/or PR and/or SD assessed by RECIST v1.1 will be presented by percentage rates and where appropriate the 95% CIs.

Progression-free survival will be measured from the date of the first dose of AFM24 and atezolizumab study drug to the date of disease progression or death from any cause, whichever occurs first.

Overall survival will be measured from the date of the first dose of AFM24 study drug to the date of death for any cause.

Duration of response will be measured from the date at which response criteria are met for CR or PR until the date of recurrence, PD, or death. Progression-free survival, overall survival, and DOR will be summarized using the Kaplan-Meier method. Censoring rules will be provided in the statistical analysis plan.

9.3.3. Pharmacokinetic Analyses

The PK analysis plan for the assessment of AFM24 will be described in a separate Data Analysis Plan. Where feasible, non-compartmental analysis will be conducted using concentration time data of AFM24. Summary statistics of PK parameters such as C_{max}, time to C_{max} (T_{max}), C_{min}, and area under the concentration-time curve over the dose interval (AUC_{tau}) will be reported by dose group. Additional parameters or model-based analysis may be calculated depending on the available data.

In the expansion cohorts, owing to sparse data sampling population exploratory PK analysis may be conducted to provide more comprehensive PK parameters for these patients. If a population PK analysis is conducted, all available clinical PK data from AFM24 will be used.

9.3.4. Other Analyses

9.3.4.1. Demographics, Medical History, Prior Medication and Other Baseline Characteristics

Demographic characteristics, prior anti-cancer therapies and surgeries, medical history, prior medication, and other baseline data will be listed and summarized using descriptive statistics for numerical data and contingency tables for categorical data. Medical history and prior medication will be listed. Prior anti-cancer therapies will be coded by World Health Organization (WHO) Anatomical, Therapeutic and Chemical (ATC) terms and summarized. Prior cancer surgeries will be summarized.

9.3.4.2. Study Treatment

Exposure to AFM24 will be summarized with descriptive statistics for the total number of infusions received. The total amount of time on AFM24 (duration of dosing in weeks) and atezolizumab will also be derived and summarized. The number of infusions with interruptions (regardless of reason) will be summarized by dose cohorts and total.

9.3.4.3. Concomitant Medication

Concomitant medication, especially mandatory pre-medication, and significant non-drug therapies after the start of study treatment will be listed and summarized by WHO ATC term in contingency tables.

9.3.4.4. Immunogenicity

Immunogenicity parameters will be summarized by descriptive statistics and listed.

[redacted]

[redacted]

10. SAFETY MANAGEMENT

Timely and complete reporting of safety information is very important to assist in the identification of any untoward medical occurrence, thereby ensuring:

- The safety of study patients;
- A greater understanding of the overall safety profile of the investigational drug;
- Recognition of any dose-related investigational drug toxicity;
- Appropriate modification of study protocols;
- Improvements in study design or procedures as required; and
- Adherence to required ethical and regulatory requirements for clinical study conduct.

10.1. Safety Definitions

10.1.1. Adverse Events

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product or study procedures, whether assessed as related or unrelated to AFM24.

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. To prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs. Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the start of the study;
- Intercurrent illness;
- Drug interactions;
- Experiences related or possibly related to concomitant medications;
- Clinically significant abnormal laboratory values or shifts from baseline;
- Clinically significant abnormalities in physical examination, vital signs, weight, or ECG; and
- An accident or injury;
- Adverse events which are related to study procedures (for example: a biopsy).

Special Considerations related to AE Reporting

The term “disease progression” alone should not be used when reporting AEs or SAEs, due to its lack of specificity. Rather, symptoms of disease progression should be reported. If death occurs as consequence of disease progression, this would be considered an outcome, and NOT an AE.

Example, a patient died due to a pulmonary hemorrhage secondary to tumor progression; an SAE report should be submitted with the event pulmonary hemorrhage notified as a Grade 5 (fatal).

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly. Planned surgical measures and the condition(s) leading to these measures are not AEs if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case, the condition should be reported as medical history.

Pregnancy is not an AE, although a patient will be withdrawn from the study if a pregnancy occurs. Refer to Section 10.3.4.1 for more information on reporting pregnancy events.

10.1.2. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose or due to study procedure causes or qualifies as the following:

- Results in death;
- Is life-threatening;
  - "Life-threatening" means that the patient was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization;
  - This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event.
  - Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the serious criteria.
- Results in persistent or significant disability or incapacity;
  - "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect; and/or
- Is an important medical event.
  - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or repeated IRRs.

- A diagnosis of new cancer/ malignant tumor during a treatment should always be considered as medically important.
- For this study, any DLTs (as per Section 4.2.3.1) are considered as important medical events and should be reported as SAE.

All SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the event is otherwise explained, or the patient is lost to follow-up or withdraws consent.

10.2. Evaluation and Classification

10.2.1. Evaluation of Severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the patient's eCRF. Each event will be graded for severity using the classifications of NCI CTCAE v5.0 (NCI 2017).

For events not addressed in the NCI CTCAE v5.0 classifications, the following grading will apply:

- **Mild (Grade 1)** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)** - Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- **Severe (Grade 3)** - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
- **Life-threatening (Grade 4)** - Life-threatening consequences; urgent intervention indicated.
- **Fatal (Grade 5)** - Related to AE.

During initial dosing and its respective post-observation period, any clinical finding despite its severity that represents a change from baseline (e.g., mild skin reaction, fatigue, myalgia, etc.) shall be recorded and followed until resolution.

Likewise, any clinically significant finding identified during the remaining course of the study, which represents a change from baseline would be required to be recorded by the Investigator.

10.2.2. Expectedness Assessment

The Sponsor will assess all SAEs whether they are expected or unexpected. An unexpected AE is any adverse drug event, the outcome, specificity, or severity of which is not consistent with those noted in the Reference Safety Information section of the current Investigator's Brochure (IB).

10.2.3. Causality Assessments

All AEs (including SAEs) will be assessed by the Investigator and Sponsor for the causal relationship of the AE to the study drug (AFM24, atezolizumab, or the combination of AFM24 and atezolizumab) using the following definitions described in Table 6.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably", and "Possibly" are to be considered as "having a reasonable causal relationship" to

study drug. In case of disagreement between the Investigator and the Sponsor, the more conservative assessment will determine the reportability of the case.

Table 6: Relationship to Study Drug

	Relationship	Description
1	Not related	This category applies to those AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
2	Unlikely (must have 2)	In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time when they are evaluated, are judged to be unrelated to the study drug. An AE may be considered unlikely if or when: 1. It does not follow a reasonable temporal sequence from administration of the test drug. 2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It does not follow a known pattern of response to the test drug. 4. It does not reappear or worsen when the drug is re-administered.
3	Possibly (must have 2)	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It follows a known pattern of response to the test drug.
4	Probably (must have 3)	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An AE may be considered probably related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia). 4. It follows a known pattern of response to the test drug.
5	Definitely (must have all)	This category applies to those AEs which the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the patient, however, a category of definitely related can only be used when a recurrence is observed.)

	Relationship	Description
		4. It follows a known pattern of response to the test drug.

AE = adverse event

10.3. Safety Reporting

10.3.1. Reporting Timelines for Adverse Events (Including Adverse Events of Special Interest)

For all patients, the AE reporting period will start with signing the pre-screening informed consent form (ICF) for AEs considered related to trial-specific procedures (for example, a biopsy). [redacted] Es occurring prior to the first study treatment are non-treatment-emergent AEs (non-TEAEs). The TEAEs are those events with onset at/or after the first study treatment. Extensive safety analysis will be mainly based on TEAEs.

10.3.2. Reporting timelines for Serious Adverse events

[redacted]

Please refer to the Table 7 below which describes AE/SAE reporting and documentation timelines:

Table 7: Documentation and Reporting Adverse Events and Serious Adverse Events

AE/SAE	Event occurred between Pre-Screening ICF and Main ICF	Event occurred between Main ICF and 1st Infusion	Event occurred at/after 1st Infusion
AE/SAE unrelated to Study Procedure (including Pre-screening period) happens…	Should not be documented	Should be documented as AE/SAE	Should be documented as AE/SAE
AE/SAE related to Study Procedure (including Pre-Screening period) happens…	Should be documented as AE/SAE	Should be documented as AE/SAE	Should be documented as AE/SAE

The following information shall be captured for all AEs/SAEs: date of onset and resolution, seriousness and seriousness criteria, severity of the event, causality assessment, treatment required for the AE, action taken with study drug, and information regarding resolution/outcome.

Where known, the diagnosis of the underlying illness or disorder should be recorded, rather than listing individual symptoms.

10.3.3. Reporting Serious Adverse Events and Adverse Events of Special Interest

Investigators shall report SAEs and AESIs within 24 hours of becoming aware of the event by entering all required information into the Electronic Data Capture (EDC) system by completing an electronic Case Report Form (eCRF) in accordance with the eCRF completion guidelines. Upon completion of the eCRF and submission of the eCRF, an automated notification will be triggered and will be received by the safety service provider and Sponsor.

[redacted]

10.3.3.1. Serious Adverse Events

[redacted]

Other supporting documentation of the event may be requested by the Sponsor or delegate and shall be provided by the investigational site as soon as possible, personal details of the patient or site staff on those records must be fully redacted. All SAEs/AESIs will be followed up until resolution or stabilization at a level acceptable to the Investigator and/or the Sponsor.

The Investigator is not responsible for actively seeking new SAEs after the follow up period; However, if the Investigator becomes aware of an SAE that is reasonably associated with study treatment after the study period including follow up, this must be reported to the Sponsor.

10.3.3.1.1. Follow-Up Information on a Serious Adverse Event

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently if not available at the time of the initial report and immediately sent using the same procedure as the initial SAE report. The Sponsor (or their delegate) will also review SAE reports for missing information and send queries to the site for resolution as appropriate. The information reported to the sponsor or delegate through a paper-based query form must be entered as well into the eCRF

to ensure consistency between the clinical and the safety database. The original signed paper-based query forms must be kept on file at the study site.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Investigator (or designee). An SAE is followed until it is considered resolved, returns to baseline, is chronically ongoing, stabilized or is otherwise explained by the Investigator.

10.3.3.1.2. Reporting of Serious Adverse Events to Regulatory Authorities

In accordance with the 21 CFR 312.32, the EU Clinical Trial Regulation 536/2014 (EU-CTR), and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor must submit written documentation in the form of an Investigational New Drug Application (IND) safety report or suspected unexpected serious adverse reaction (SUSAR) reports, respectively. The Sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirements. IND safety reports/SUSARs are required to be reported within 7 calendar days for life-threatening events and those resulting in death or 15 calendar days for all others. These timeframes begin with the first notification of the IND safety reports/SUSARs to the Sponsor or their delegate from the Investigator.

The Sponsor (or their delegate) will determine whether expedited reporting is necessary for SAEs depending on the assessment of seriousness, expectedness, and causal relationship. In case of disagreement between the Investigator and the Sponsor regarding causal relationship, the more conservative assessment will determine the reportability of the case.

The Investigator must ensure they are aware and comply with any additional local reporting requirements. For all SAEs regardless of expectedness and relationship, the Sponsor (or their delegate) will assign a case number to be used in all future correspondence regarding the event and can provide a MedWatch or Council for International Organizations of Medical Sciences form describing the event, for the Investigators to report to their IRB/IEC, or other committee. Other SAEs (e.g., expected or unrelated SAEs) should be reported per the relevant institution's procedures.

Where required, submission of safety updates by the Investigator to Competent Authorities must be handled according to local regulations. Otherwise, periodic safety reports to the regulatory agencies will be handled by the Sponsor (or their delegate). These safety updates will also include SAEs that do not require expedited reporting to the authorities.

Periodically (at least annually), the IB will be updated to include new and relevant safety information. Until such time that an AE becomes identified in the IB (see Summary of Data and Guidance for the Investigator), it should be considered unexpected.

10.3.3.2. Adverse Events of Special Interest

Infusion Related Reaction

Occurrence of IRRs is within the anticipated safety profile of AFM24, considering experiences with other EGFR and CD16 targeting agents. Thus IRRs are realized by the sponsor as AESIs, for which ongoing monitoring and rapid communication is appropriate.

Infusion related- reactions can manifest with allergic or anaphylactic symptoms, including but not limited to chills, flushing, hypotension, fever, hypoxia, loss of consciousness, bronchospasm, and even cardiac arrest. Although the majority of such IRRs are mild to moderate, in some rare cases these can be life-threatening or even fatal. Most of the IRRs are associated with the first infusion (during or shortly after the infusion); however, IRRs can happen during or after any infusion, despite the lack of previous signs or symptoms. In the nonclinical studies of AFM24, there were no signs of IRRs or anaphylactic symptoms. For more information, refer to the latest IB edition.

IRR events require further investigation in order to characterize and understand them. Of particular interest, is information related to the timely development of symptoms relative to dose per time, actions taken as well as outcome of events. IRR events must be reported within 24 hours of awareness as per Section 10.3.3. All symptoms suggesting an IRR should be mentioned in the report.

The data will not be subject to reporting to Independent Ethics Committee (IEC)/Independent Review Board (IRB)/Regulatory Authorities unless such an event qualifies as an SAE.

10.3.4. Other Reporting Obligations:

Study drug misuse, medication error, or overdose, although not categorized as “serious”, shall be reported in the eCRF, even if they may not result in an adverse outcome.

- **Overdose** is defined as: >10% above the intended AFM24 planned dose is given or a dose interval <4 days between two consecutive doses. If the pharmacy discovers that an overdose has or may have been administered, they should contact the Investigator and Sponsor (or their delegate) immediately. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

  In clinical trials with atezolizumab, doses of up to 20 mg/kg have been administered. The standard fixed dose of 1200 mg is equivalent to 15 mg/kg in a typical patient. No DLTs were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. An MTD has not been established. For this study, atezolizumab is supplied in vials containing the fixed 840 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal. The data available to date suggest that the potential for harm from overdose is very low.
- **Medication error** is defined as: An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.
- **Misuse** is defined: Situations where an investigational medicinal product is intentionally and inappropriately used not in accordance with the terms of the current protocol.

If any of the above events is associated with an SAE, it must be reported within 24 hours as per Section 10.3.3.

10.3.4.1. Exposure During Pregnancy or Lactation

Pregnancy and breastfeeding are considered exclusion criteria for this study (Section 5.2). Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) or pregnancy in a patient's partner that occurs during the study. Immediately discontinue AFM24 treatment permanently in case of pregnancy.

Pregnancies and lactations that occur in patients after the ICF is signed but before starting study drug must be reported by the Investigator if they cause the patient to be excluded from the study.

Pregnancies and lactations that occur in a study patient or a pregnancy in a patient's partner from the time of first study treatment through up to 60 days following cessation of AFM24 study treatment, must be reported by the Investigator.

All reported pregnancies must be followed to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome, i.e., the health of the infant, will be requested by the Sponsor. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Offspring should be followed up for at least 8 weeks after delivery. Longer observation periods may be determined by the Sponsor if an adverse outcome of the pregnancy was observed.

Such events must be reported within 24 hours to the Sponsor or delegate as per Section 10.3.4.1. The reporting procedures can be found in the SAE completion guidelines located in the Study Operations Manual (or equivalent).

10.3.4.2. Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the Sponsor immediately, following the guidance specified in the Pharmacy Manual. The same reporting timelines as for SAEs will apply.

11. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness and compliance, the study center should have processes in place for data review and quality control. Sponsor (or delegate) may also conduct a quality assurance audit.

11.1. Data Recording, Monitoring of the Study, and Regulatory Compliance

The project manager, or their designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit, the eCRF and other pertinent study materials will be reviewed with the Investigator's research staff. During the study, the CRA will make regular site visits to review protocol compliance, examine CRFs and individual patient's medical records, and assure that the study is being conducted according to pertinent regulatory requirements including ICH-GCP. Sites should ensure that source documentation is available to enable verification of all eCRF data entries. The review of medical records will be done in a manner to ensure that patient confidentiality is maintained.

All eCRF data will be collected using an eCRF within a fully validated and CFR 21 Part 11-compliant electronic data capture system. All data will be entered into the eCRF by the site staff. These data will then be source-data verified and reviewed by the CRAs before data cleaning by Data Management is performed. All queries will be raised and resolved within the electronic data capture system. During entry, programmatic checking of the data will be performed and once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the Statistical Analysis Plan approved and signed, and any summary/analysis populations approved, the database will be locked, and the data released for summary and analysis. All summary and analysis of the data will be performed using appropriate versions of SAS® and WinNonLin Pro, or equivalent.

11.2. Study Monitoring

Clinical research associates will be responsible for the monitoring of the study. The CRA will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review the eCRF, patient case notes, administrative documentation including the Investigator Site File, and frequent telephone/e-mail communications with site will be performed throughout the study.

At each study monitoring visit, the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the CRA, monitoring visits will be confirmed in advance of planned visits.

The process for study monitoring and source data verification requirements for the study will be specified in the Monitoring Plan (or equivalent).

11.3. Clinical Study Audit

The Sponsor, Sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Prior notice will be given to each site selected for audit in advance of a planned audit.

11.4. Clinical Study Report

The results of the study will be presented in an integrated CSR according to ICH guidelines. The CSR will be written once all expansion cohorts reached the primary endpoint assessment.

In case patients are still being treated with study medication at the final data cut-off date for this study, such patients will be kept on treatment in the study and data collected will then be reported in an addendum to the final CSR. It will be noted in the final CSR that such a revised report may be provided.

11.5. Data Availability

The Investigator is required to maintain copies of all essential study documentation, including the Site Study File, all eCRF data (including the full audit trail and all data queries), signed ICFs, and records for the receipt and disposition of study drug.

During the study, the Investigator must make study data accessible to the CRA, the Sponsor (or a third-party auditor assigned by the Sponsor), and relevant IRB/EC and regulatory agencies. A file (or appropriate records) for each patient must be maintained that includes the signed ICF and all source documentation related to that patient. The Investigator must ensure the availability of source documents from which the information in the eCRF was derived.

Please refer to Section 13.2 for details of required record retention for the study.

11.6. Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (or accepted equivalent) and a financial disclosure statement. All Sub-Investigators will be required to provide a current curriculum vitae and a financial disclosure statement.

11.7. Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor. Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/EC. The exception to this is where modifications are necessary to eliminate an immediate hazard to study patients, or when the change involves only logistical or administrative aspects of the study (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/EC by the Principal Investigator.

11.8. Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug;
- Failure of an Investigator(s) to comply with pertinent clinical study regulations;
- Submission of knowingly false information from the study site to the Sponsor, CRA, or Competent Authority; and
- Insufficient adherence to protocol requirements.

Study termination and/or site close out will be performed in accordance with applicable local regulations.

12. ETHICAL CONSIDERATIONS

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed, and dated. The ICF will contain all the Essential Elements of Informed Consent set forth in 21 CFR 50, the ICH Guideline for GCP, and the terms of the Declaration of Helsinki. Copies of the signed document should be given to the patient and filed in the Investigator's Study File, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

The final study protocol and patient ICF will be approved by the appropriate IRB/EC for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the study will be documented as amendments. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval to the relevant IRB/EC and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect patient safety, which will be implemented immediately.

If an amendment substantially alters the study design, increases the potential risk to the patients, affects the treatment of the patient, or might otherwise influence the willingness of the patient to participate in the study, then the ICF must be revised and submitted to the relevant IRB/EC and, where necessary, to the relevant competent authorities, for review and approval. When a patient is currently undergoing study procedures and is affected by the amendment, then the patient must be asked to consent again using the new ICF.

12.1. Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki, the European Union (EU) Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local IRB/EC, and the US Code of Federal Regulations, Title 21 CFR 50.

12.2. Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All patients will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

With the help of the ICF, the patient will be informed about the AFM24 and atezolizumab study drug and anticipated effects and the reason, design, and implication of the study. The patient must give consent to participate prior to enrollment in the study. This consent must be given in writing and sufficient time must be given between the explanation of the study and obtaining consent. The Investigator who conducts the informed consent discussion must also sign. The Investigator may delegate this responsibility to a suitably qualified member of the study team (e.g., Sub Investigator) if permitted by local regulations. This delegation of responsibility must be recorded in the Study File. By giving signed consent, the patient will confirm that his or her participation is voluntary and that he or she will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form will be kept by the Investigator. Prior to participation in the study, the patient should receive a copy of the signed and dated written ICF.

The ICF must include all elements required by law, local regulations, GCP guidelines, and ICH guidelines, including consent to allow the Sponsor, Sponsor representative, or external regulatory auditor to review the patient's medical records. This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study.

Any party with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the patients' identities and Sponsor's proprietary information. It is the CRA's responsibility to verify that each patient has consented, in writing, to direct access.

12.3. Patient Participation Card

A study participation card will be provided to patients where required by local regulations or IRB/EC. The card will indicate that he or she is participating in a clinical study and give the name and contact details of the Sponsor and the Investigator/study site. The patient will be asked to retain this card while participating in the study and show it to any other medical practitioners consulted during this time. Patients will be advised to contact the Investigator/study site if there are any questions.

12.4. Insurance

Appropriate insurance for this study will be arranged by the Sponsor (or their delegate), as Sponsor of the clinical study, in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificate will be held in the Trial Master File and in the Investigator Site File.

12.5. Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the IRB/EC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/EC in compliance with current regulations of the FDA and the EU as applicable and in accordance with ICH GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/EC will be kept informed by the Investigator, contract research organization (CRO), or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected AEs.

12.6. Patient Privacy

The Investigator must ensure that patient privacy is maintained. On the eCRF or other documents submitted to the Sponsor, patients will be identified by a patient number only. Clinical study documents that are not submitted to the Sponsor (e.g., signed ICF) should be kept in a confidential file by the Principal Investigator.

In accordance with local, national, or federal regulations, the Investigator will allow the Sponsor or their designee personnel access to all pertinent medical records to verify the data gathered on the CRFs and to audit the data collection process. Regulatory agencies such as the FDA may also

request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

13. DATA HANDLING AND RECORDKEEPING

13.1. Recording of Data

The Investigator will be responsible for the recording of all data on the CRFs provided, as certified by the Investigator's signature and date. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRFs.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data.

13.2. Study Record Retention

All clinical study documents must be retained by the Investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator must retain all clinical study documents until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, or by local regulations.

Patients' medical files should be retained in accordance with applicable legislation and with the maximum period permitted by the hospital, institution, or private practice.

13.3. Data Confidentiality and Publication Policy

The original CRFs and all data generated during the clinical study are the property of the Sponsor. In addition, all information regarding AFM24 and the Sponsor's operations (e.g., patent applications, formulas, manufacturing processes, basic scientific data, or formulation information) supplied by the Sponsor to the Investigator and not previously published is considered confidential. This confidential information remains the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes, including publications and presentations, without the Sponsor's written consent.

The first publication of the study results shall be made by the Sponsor. Any proposed publication or presentation (including a manuscript, abstract, or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review prior to submission. Publication of the results will not include confidential information, including inventions, non-public intellectual property rights, and know how, without the permission of the Sponsor. The full terms of confidentiality, intellectual property, and publication policy are described in the current Clinical Trial Agreement between the Sponsor and the site.

The Sponsor may announce quality assured summary data to comply with Financial Regulatory Authorities, while ensuring, so far as possible, that such announcements will not compromise the Investigators ability to publish the data in appropriate scientific forums.

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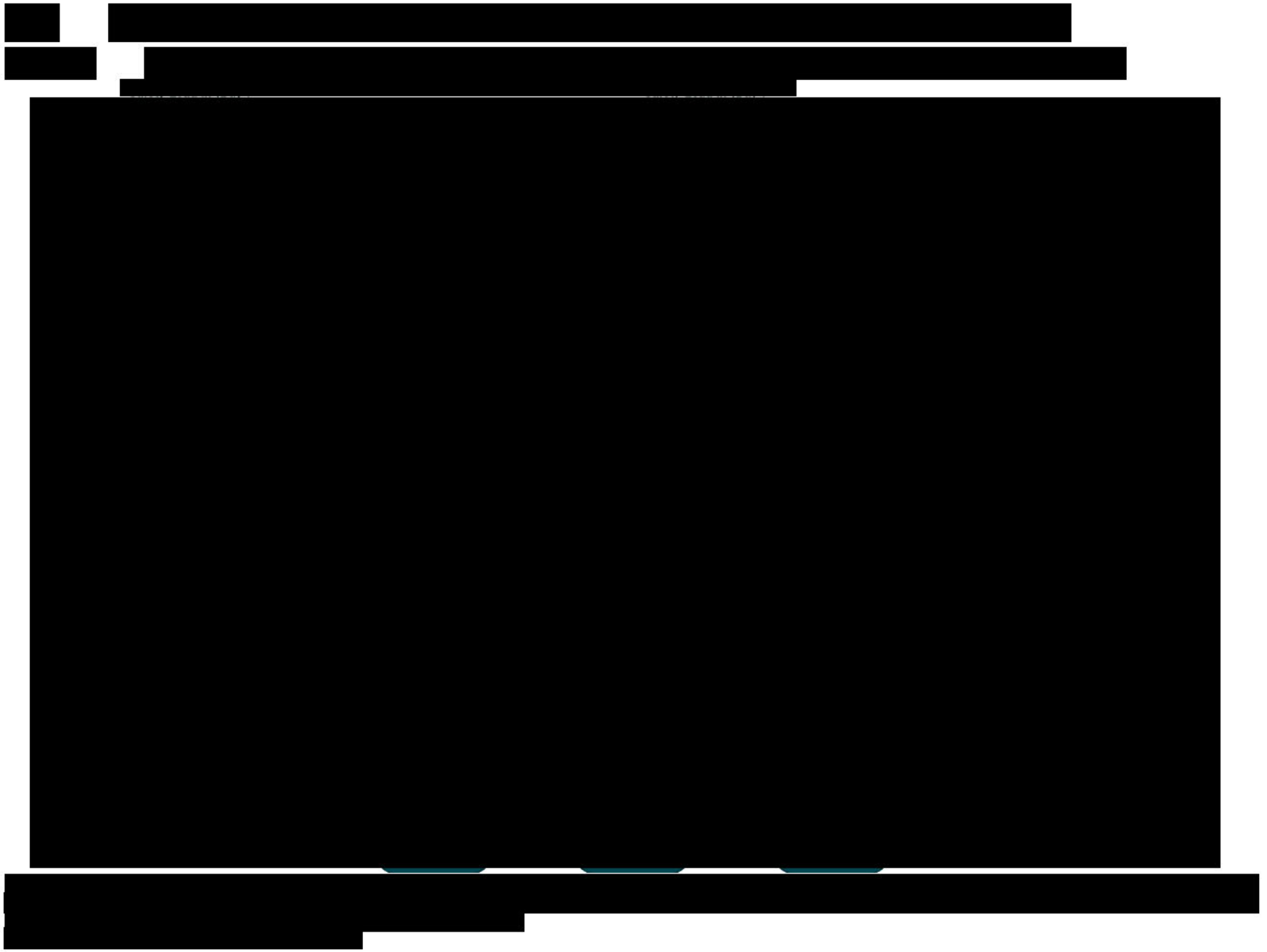

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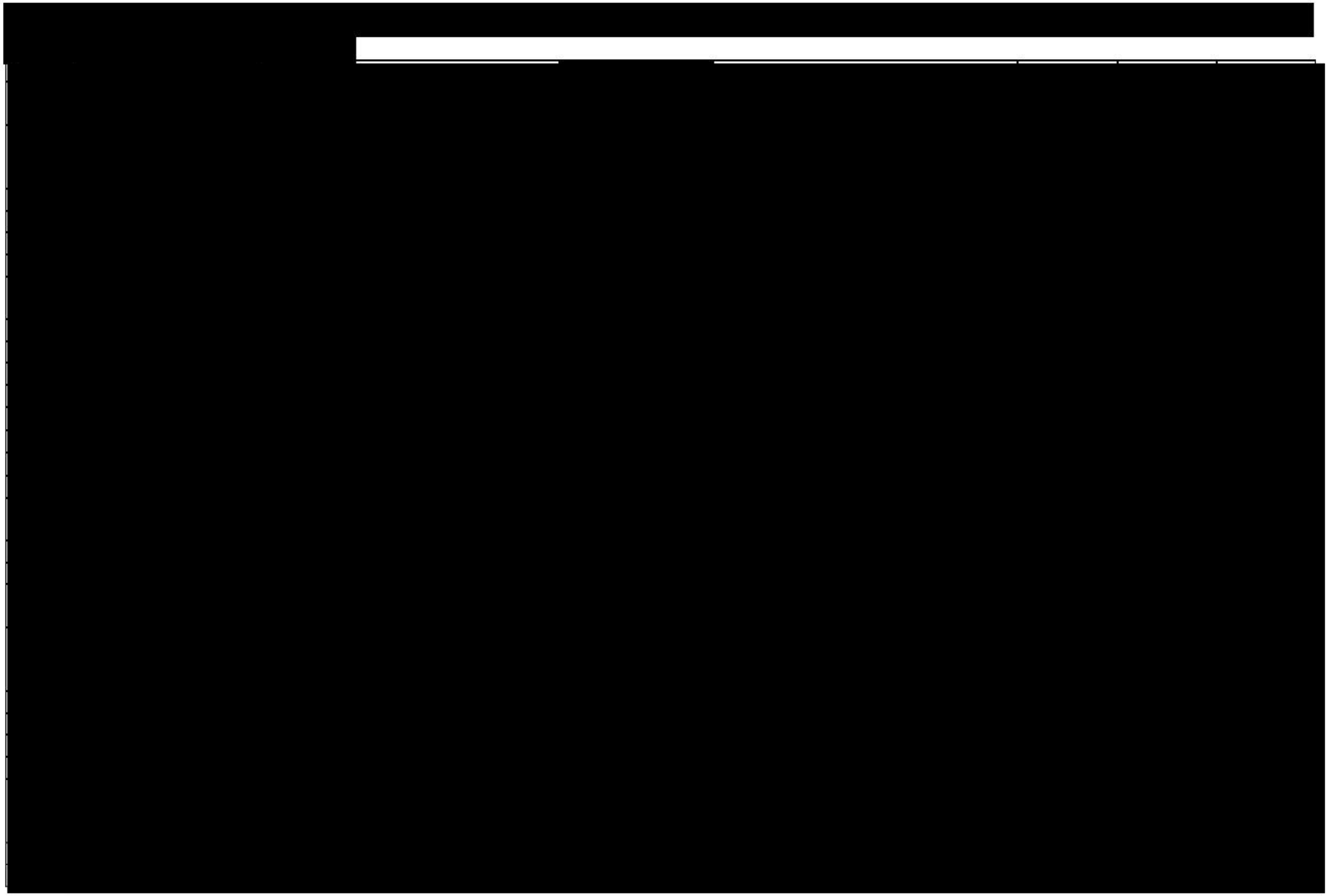

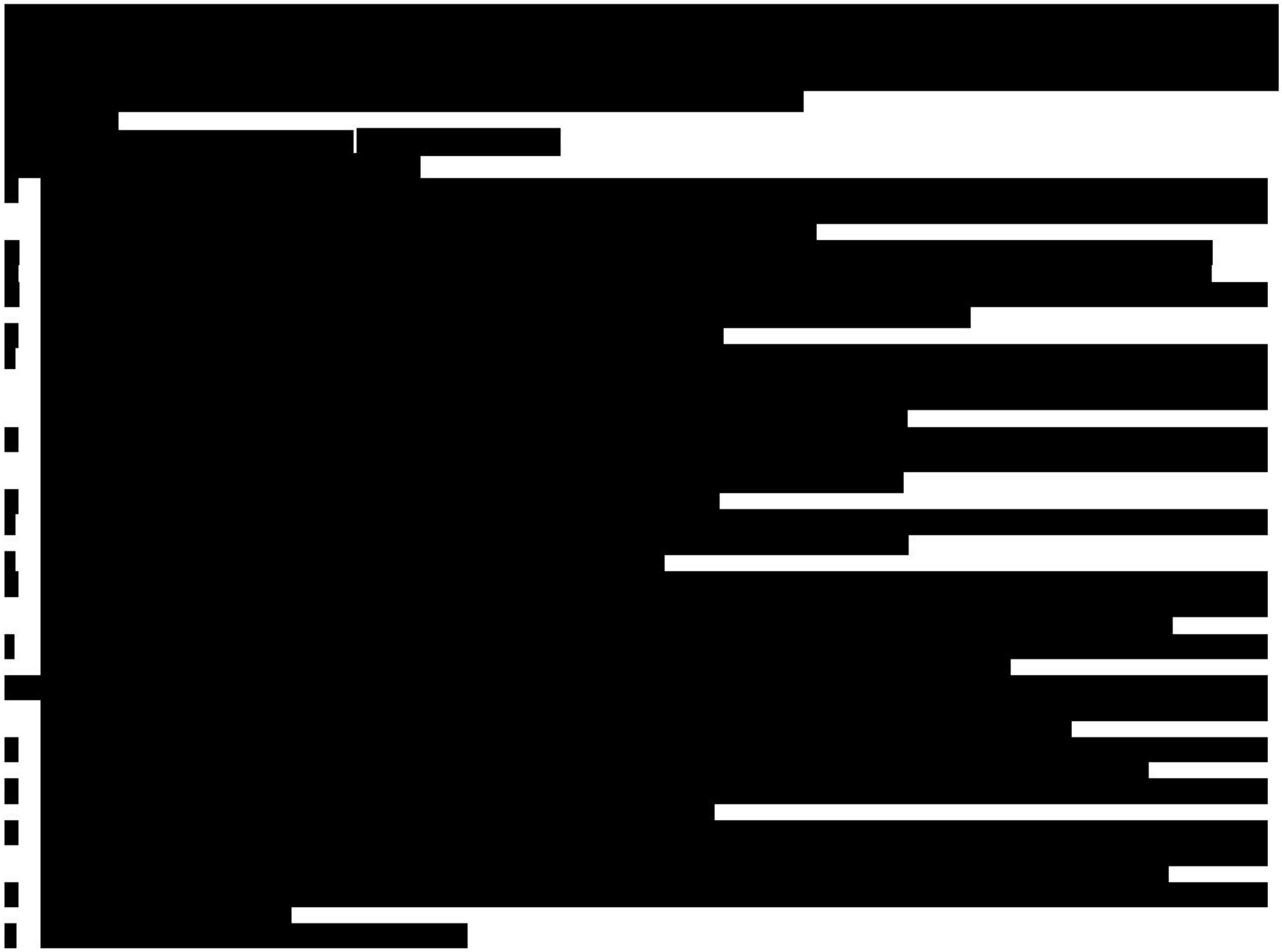

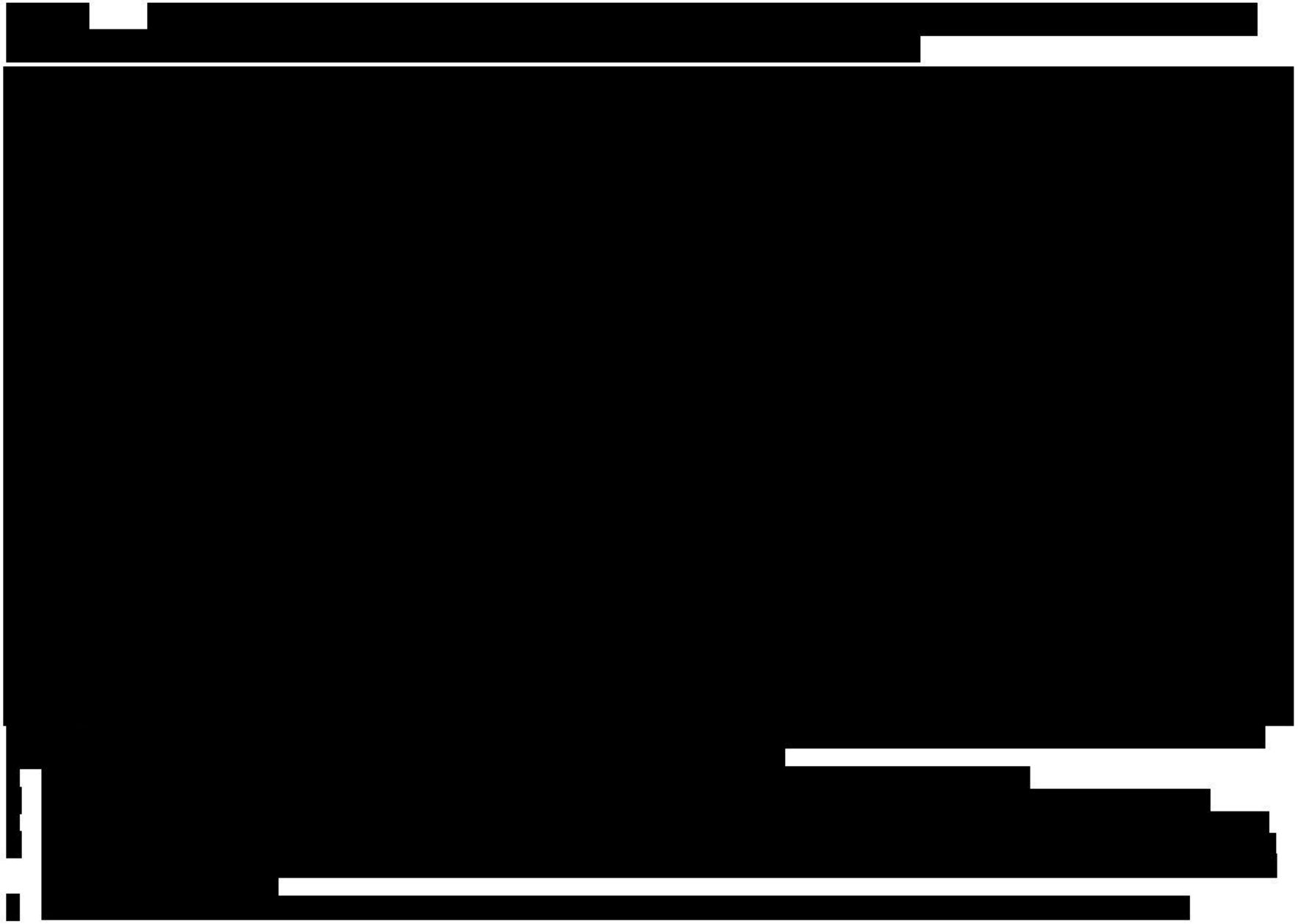

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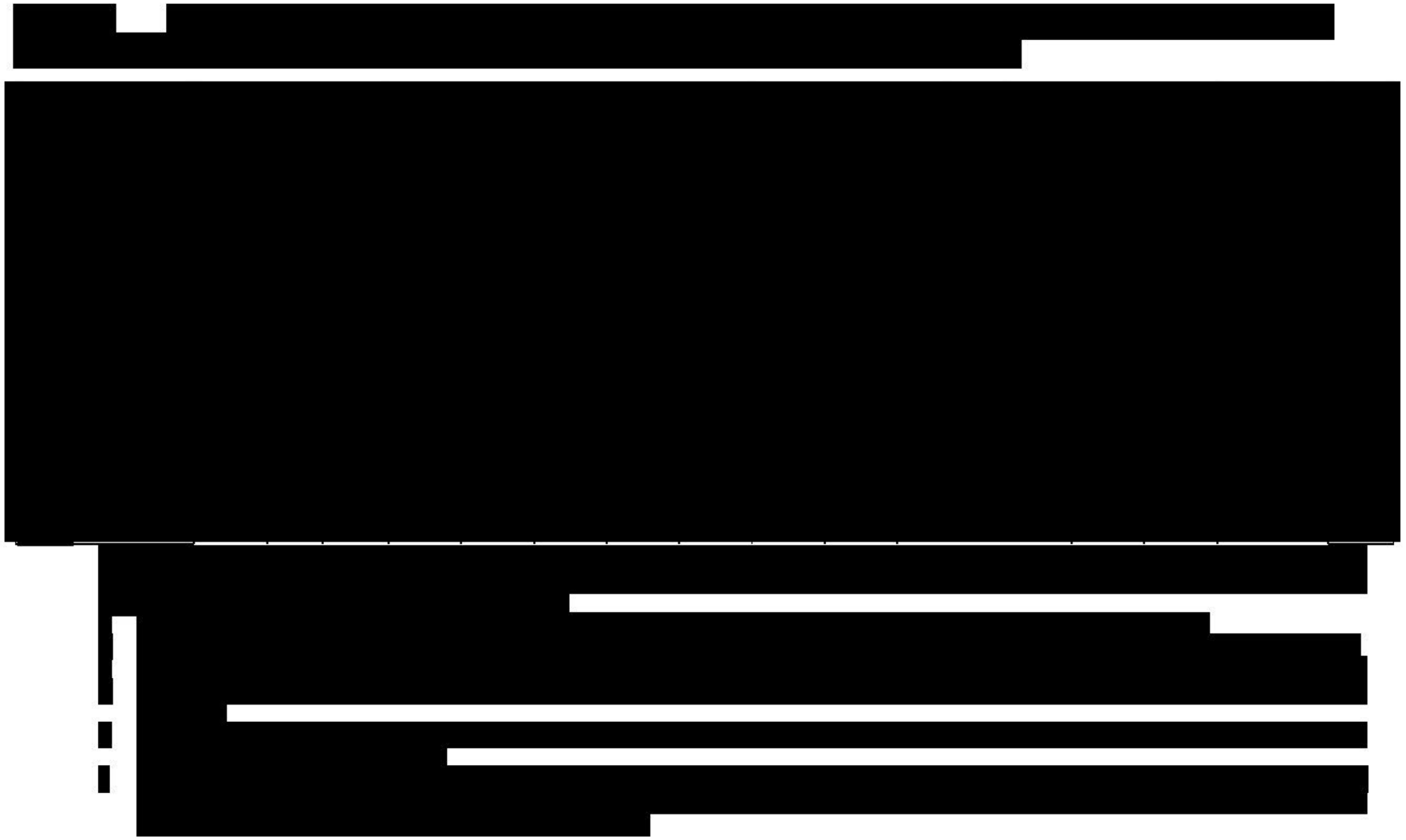

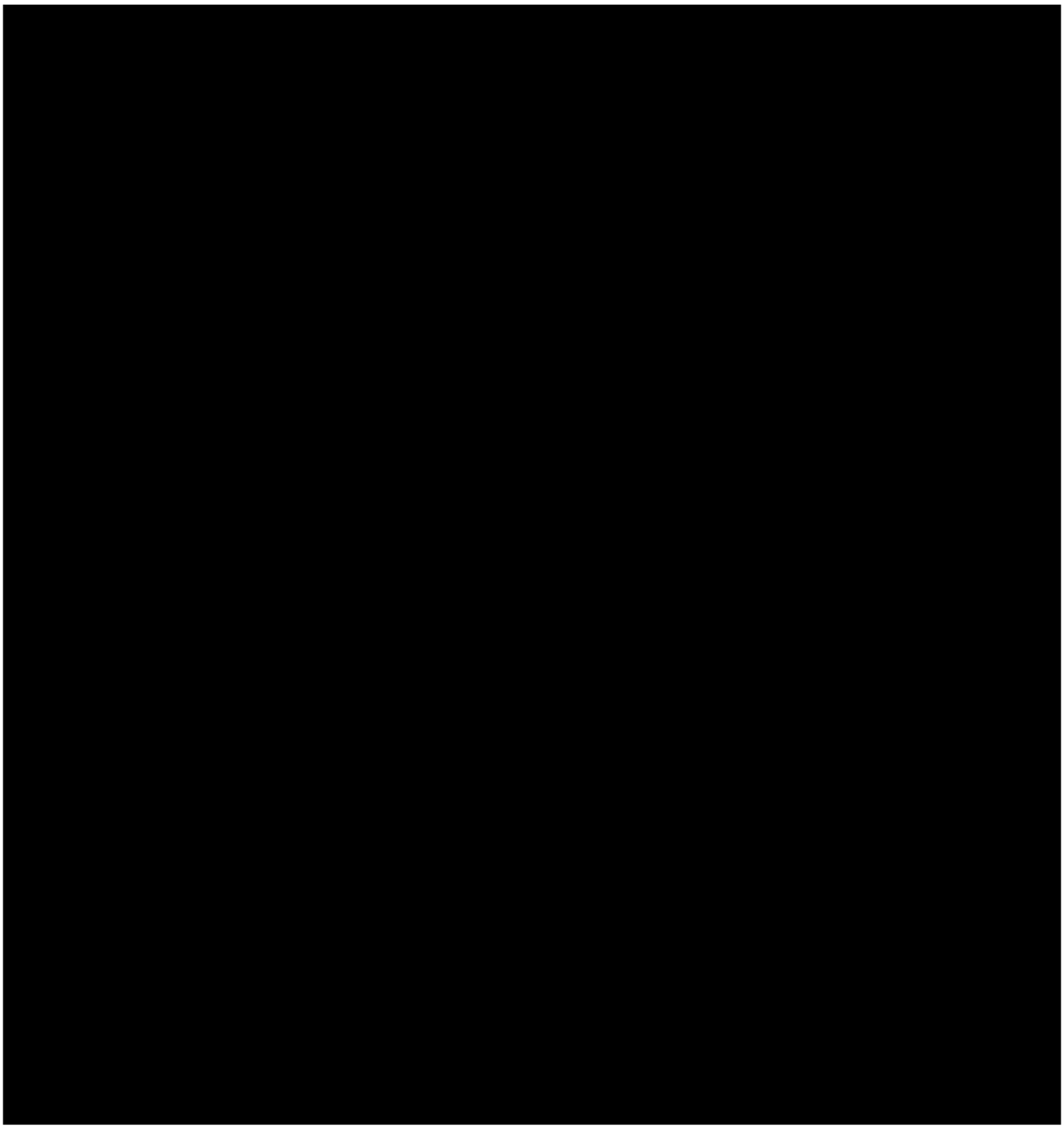

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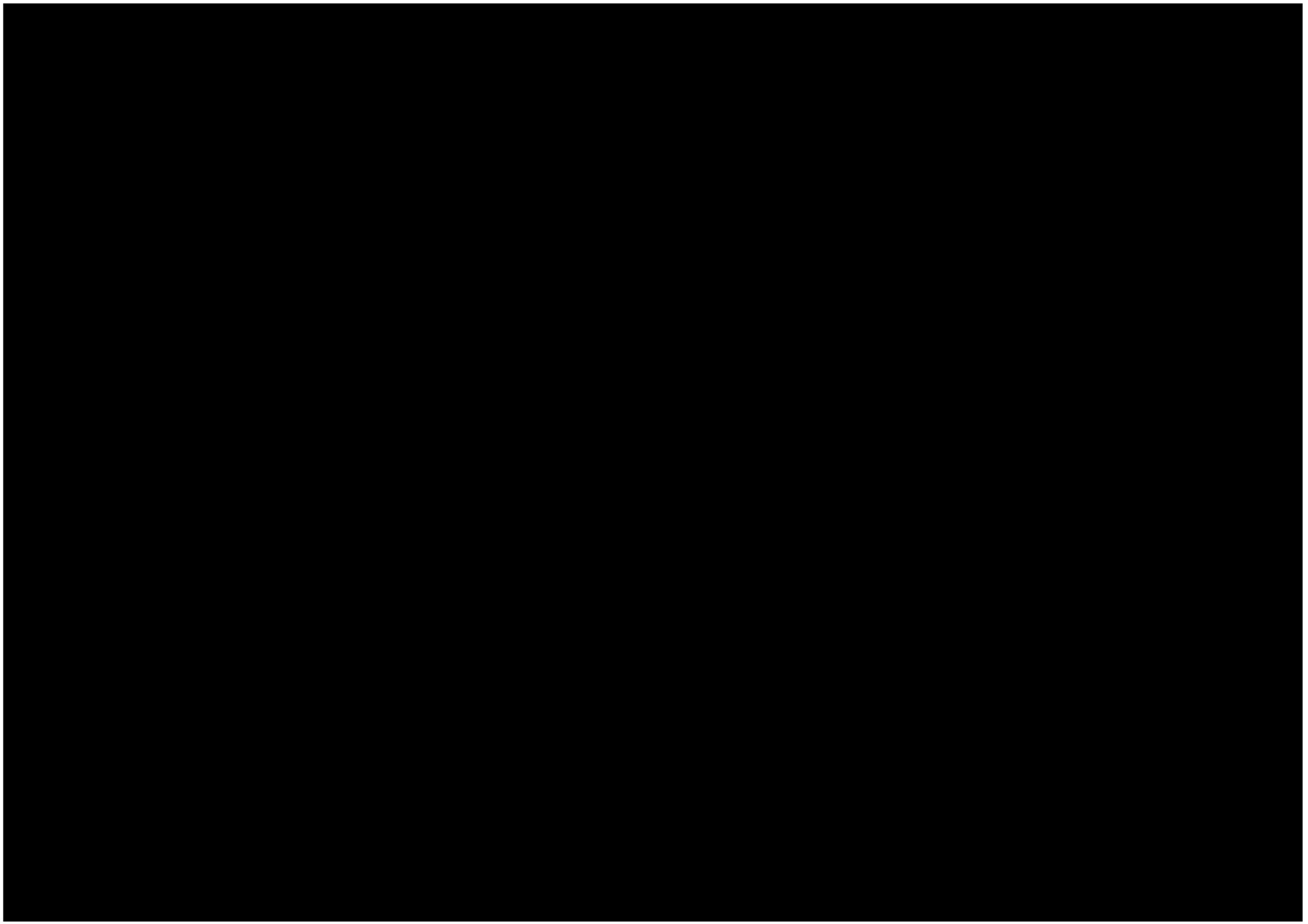

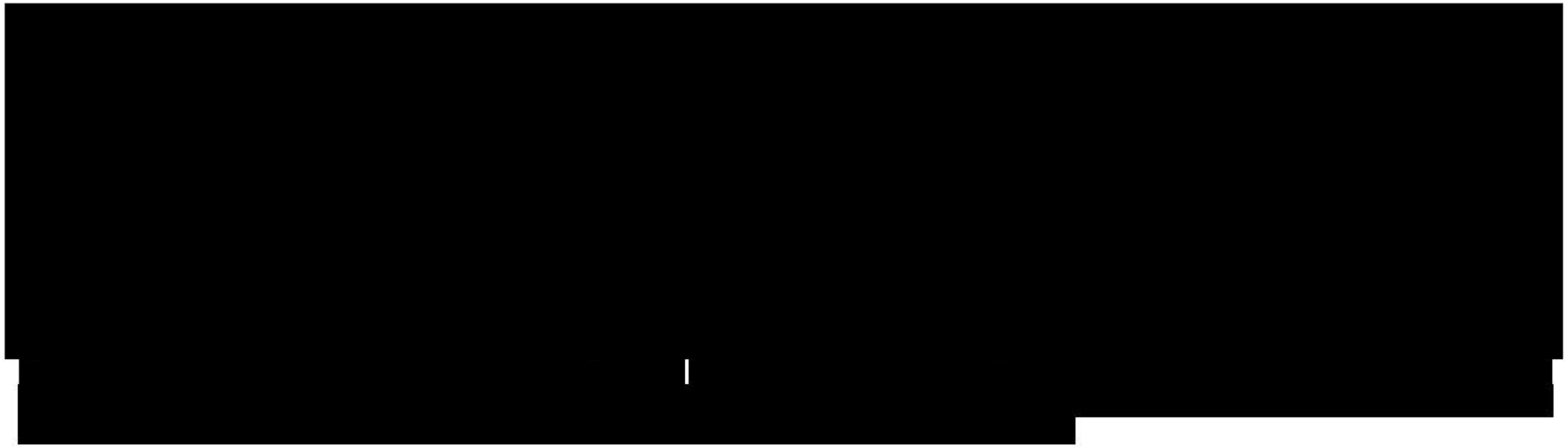

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