**Affimed GmbH**

# STATISTICAL ANALYSIS PLAN

## PROTOCOL AFM24-101

***A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AFM24 in Patients with Advanced Solid Cancers***

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| **Protocol code:** | AFM24-101 |
| **SAP Version:** | Final v 3.0 |
| **SAP Date:** | 27 January 2023 |
| **Author:** | [redacted] |

# DOCUMENT HISTORY

## VERSION HISTORY

| Version # | Version Date |
|---|---|
| Final 1.0 | 27 February 2020 |
| Final 2.0 | 08 October 2021 |
| Final 3.0 | 27 January 2023 |

## REVISION HISTORY

| Version # | Chapter | Revision Summary | Reason(s) for Revision |
|---|---|---|---|
| 2.0 | 2.1 | Endpoint list updated as per new protocol | Compliance with the new protocol |
| 2.0 | 7.7.1 | Confirmed response definition rules updated | Reviewers request |
| 2.0 | 7.7.2 | PK summaries have been removed. | PK will be summarized in a separate report. |
| 2.0 | 7.7.2 | Waterfall and swimmers plots for RECIST 1.1 assessments have been added. | Added to better visualize the data. |
| 2.0 | 7.7.3 | Clinical Benefit Rate analysis added. | Reviewers request |
| 2.0 | 7.7.3 | Kaplan-Meier plots added. | Added to better visualize the data. |
| 2.0 | 7.7.3 | Time to Response analysis added | To further explore the results |
| 2.0 | 7.8.1 | Treatment compliance analysis added | To further explore the results |
| 2.0 | 7.8.4 | EGC summaries for Phase 2 removed. | Too few data expected to be collected for a meaningful summary |
| 3.0 | 1 | The protocol version used has been changed | To refer to the latest available protocol |
| 3.0 | All | “KRAS” is replaced with “RAS” | Reflecting the same change made in the protocol |
| 3.0 | 2.2 | List of the exploratory objectives has been updated | Reflecting the same change made in the protocol |
| 3.0 | 7.2 | Protocol-defined windows for vital signs assessments have been updated | To reflect similar update in the new protocol |
| 3.0 | 7.7.1 | Reference to Technical Appendix has been removed | To reflect the change in the protocol |

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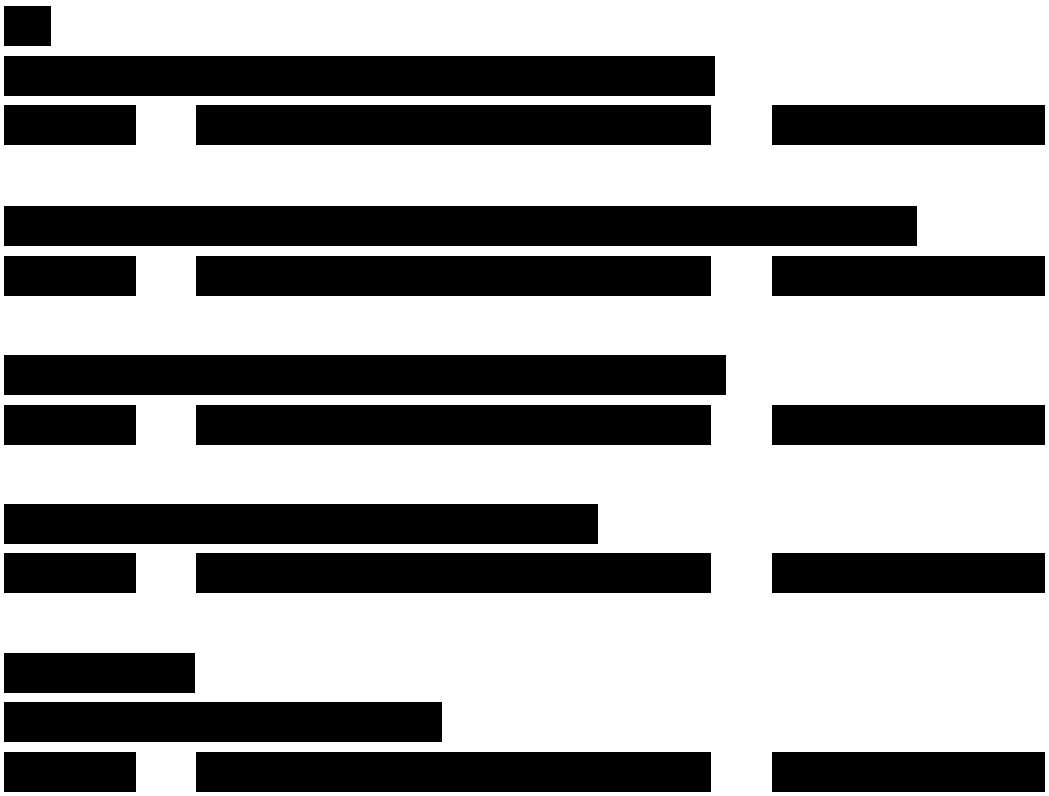
|---|---|---|---|
| 3.0 | 7.8.1 | Dose Intensity and Relative Dose Intensity definitions and description of associated analyses have been added. | To further explore the exposure data |

# APPROVAL SIGNATURES

**STUDY TITLE**: A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AFM24 in Patients with Advanced Solid Cancers

**PROTOCOL NUMBER:** AFM24-101

**SAP** Final 3.0, 27 January 2023



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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-Drug Antibodies |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Aminotransferase |
| BLRM | Bayesian Logistic Regression Model |
| CR | Complete Response |
| CRC | Colorectal Cancer |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | Disease Control Rate |
| DDS | Dose-Determining Set |
| DLT | Dose Limiting Toxicity |
| DOR | Duration of Response |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal growth factor receptor |
| EGFRmut | Epidermal growth factor receptor mutation |
| EoI | End of Infusion |
| EWOC | Escalation with Overdose Control |
| FIH | First-in-Human |
| IDMC | Independent Data Monitoring Committee |
| iRECIST | Response Evaluation Criteria in Solid Tumors for Immunotherapy |
| KRAS-w | Kirsten Rat sarcoma genes-wild type |
| i.v. | Intravenously |
| mCRC | Metastatic Colorectal Cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTD | Maximum Tolerated Dose |
| NCA | Non-compartmental analysis |
| 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 | Pharmacodynamics, Progressive Disease |
| PE | Physical Examination |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetics |
| PR | Partial Response |
| QTcF | Corrected QT interval by Fridericia |
| R2PD | Recommended Phase 2 Dose |
| RAS | Rat sarcoma genes |
| RECIST | Response Evaluate Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Stable Disease |

| | |
|---|---|
| SOC | System Organ Class |
| SRC | Safety Review Committee |
| TEAE | Treatment Emergent Adverse Event |
| TFLs | Tables, Figures and Listings |
| WHO | World Health Organization |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis and reporting for the study protocol AFM24-101 (version 9.0) dated 03Nov2022.

# 2. STUDY OBJECTIVES

## 2.1 PHASE 1 (DOSE ESCALATION)

### 2.1.1 PRIMARY OBJECTIVE

Determine the maximum tolerated dose (MTD), select one or more recommended phase 2 doses (RP2D), and investigate the safety and tolerability of AFM24 in subjects with advanced or metastatic solid malignancies

### 2.1.2 SECONDARY OBJECTIVES

- Characterize the safety and tolerability of AFM24, including both acute and chronic toxicities
- Characterize the pharmacokinetics (PK) of AFM24 administered intravenously (i.v.)
- Characterize the immunogenicity of AFM24
- Assess the preliminary antitumor efficacy of AFM24

### 2.1.3 EXPLORATORY OBJECTIVES

- Assess the preliminary antitumor efficacy of AFM24, using Response Evaluation Criteria in Solid Tumors for immunotherapy (iRECIST) tumor response criteria
- Assess AFM24 pharmacodynamics

## 2.2 PHASE 2A (EXPANSION)

### 2.2.1 PRIMARY OBJECTIVE

Assess the preliminary antitumor efficacy of AFM24, by local Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

### 2.2.2 SECONDARY OBJECTIVES

- Characterize the safety and tolerability of AFM24, including both acute and chronic toxicities
- Characterize the PK of AFM24 administered i.v.
- Characterize the immunogenicity of AFM24
- Assess the preliminary antitumor efficacy of AFM24

### 2.2.3 EXPLORATORY OBJECTIVES

- Assess the preliminary antitumor efficacy of AFM24, using iRECIST tumor response criteria

- Assess AFM24 pharmacodynamics

- Explore the predictive potential of biomarkers measured in blood and/or tumor tissue in response to AFM24

# 3. STUDY DESCRIPTION

## 3.1 OVERALL STUDY DESIGN

AFM24-101 is a first-in-human (FIH) Phase 1/2a open-label, non-randomized, multicenter, multiple ascending dose escalation/expansion study evaluating AFM24 as monotherapy in subjects with advanced solid malignancies whose disease has progressed after treatment with previous anticancer therapies.

There will be 2 parts to this study: a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2a). The aim of the dose escalation phase (Phase 1) is to determine the MTD and/or establish a RP2D. An adaptive 2 parameter BLRM guided by the EWOC principle will be used in the escalation phase to guide determination of the MTD and/or RP2D in subjects with advanced solid malignancies.

The dose escalation phase (Phase 1) will be followed by the dose expansion phase (Phase 2a) once the MTD and/or 1 or more RP2Ds of AFM24 monotherapy has been determined. The dose expansion phase (Phase 2a) of the study is intended to collect preliminary evidence of efficacy and to further confirm the safety of AFM24 as a monotherapy in distinct patient populations. The expansion phase will have 3 cohorts based on tumor type, as described in Figure 2 in the Protocol. The expansion cohorts may be opened in parallel or subsequently.

The full study scheme can be seen in the Protocol section 3.1.

## 3.2 PHASE 1

Phase 1 will employ an adaptive BLRM with 2 parameters guided by the EWOC principle to make dose recommendations and estimate the MTD (see Section 7.7.1 of the SAP). It is estimated that approximately 25 to 35 patients will be enrolled into Phase 1 of the study. The number of patients is dependent on the tested dose cohorts and safety profile of AFM24. As multiple centers will contribute to the enrollment a communication plan will be established to ensure distribution of safety data and study progress amongst the participating centers.

DLTs will be assessed in the first treatment cycle (i.e., the first 4 weeks of treatment for each patient), referred to as the DLT observation period.

## 3.3 PHASE 2A

Once at least 1 RP2D dose has been determined, then enrollment into 1 or more expansion cohorts for selected cancer indication in the dose expansion phase (Phase 2a) will begin. Other expansion cohorts may follow with the same or a different RP2D dose level. An optimum Simons two-stage design will be applied for the preliminary efficacy analyses for the following expansion cohorts:

• Expansion Cohort A will enroll up to a total of 39 subjects with microsatellite stable CRC with RAS wild type tumor, the interim analysis (IA) will be conducted after 11 subjects;

• Expansion Cohort B will enroll up to a total of 41 subjects with ccRCC, the IA will be conducted after 15 subjects;

• Expansion Cohort C will enroll up to a total of 41 subjects with advanced NSCLC with an EGFR mutation, the IA will be conducted after 15 subjects.

## 3.4 STUDY TREATMENT

All doses of AFM24 will be administered as an i.v. infusion. During the dose escalation phase (Phase 1), subjects will receive AFM24 as a weekly infusion. Additional dosing regimen (ie, every 2 weeks) may be explored in the dose expansion phase (Phase 2a) only. Patients may receive AFM24 as long as they continue to show clinical benefit, as judged by the Investigator, or until disease progression, other treatment discontinuation criteria are met, or withdrawal of consent. Refer to the Pharmacy Manual for full details regarding study drug administration.

## 3.5 SAFETY REVIEW COMMITTEE (SRC)

The SRC will convene to make a decision on the dose escalation.

All details regarding the SRC composition, meetings, reviewed data and the decision-making process will be documented in the study-specific SRC Charter.

## 3.6 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

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

# 4. SAMPLE SIZE AND POWER CALCULATION

Please refer to the protocol section 9.4 for sample size justifications.

# 5. ANALYSIS ENDPOINTS

Please refer to the protocol section 2.0 for Study Objectives and Endpoints.

# 6. ANALYSIS POPULATIONS

## 6.1 SAFETY SET

The safety set will consist of all patients who received at least one dose of AFM24. The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship, and for all efficacy related endpoints.

## 6.2 DOSE-DETERMINING SET

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.

Patients must receive ≥80% of their assigned AFM24 dose in Cycle 1, complete the 28-day DLT observation period and have at least one post-baseline assessment of the following safety parameters: Physical Examination, Vital Signs, Laboratory, and ECG, or have had a DLT within the first cycle of treatment to be considered evaluable for DLT.

## 6.3 PK SET

The PK set consists of all patients who have received at least 1 dose of study drug and have at least 1 post dose PK measurement.

# 7. ANALYTICAL PLAN AND STATISTICAL METHODS

## 7.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All analyses will be performed using SAS® statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.4 or higher of SAS for Windows [SAS Institute Inc.; Cary, NC, USA]).

Descriptive statistics for continuous variables will include the number of patients, mean and standard deviation, median, and minimum and maximum values. All raw data will be presented to the original number of decimal places. Means, medians, and confidence intervals will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data. Summary statistics for categorical variables will contain count and percentage. Percentages will be presented to one decimal, except for one hundred percent, which will be presented as 100%. Unless otherwise specified, percentages for baseline summaries will be based on the total number of patients in the treatment arm or overall for the indicated population (dependent on table column heading), percentages for post-baseline summaries will be based on the total number of patients with non-missing values in the treatment arm or overall.

Unless otherwise stated, all analyses will be descriptive in nature, no formal statistical comparisons of data from different arms or cancer type will be done.

Data will be listed individually by patient.

The summaries and the listings will be done separately for two phases. Phase 1 summaries will be presented by the dose level, and phase 2a summaries – by Expansion Arm.

## 7.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Baseline is defined as the last non-missing observation prior to the first dose of study drug (screening assessment for most of the parameters, or C1D1 pre-dose, where applicable).

Data will be analyzed in accordance with the visits recorded in the case report form (CRF), no visit reassignment will be done.

Timepoints for analysis of vital signs will be assigned using protocol-defined windows. The windows are shown below:

| | **Vital sign timepoints for first 2 consecutive AFM24 dosing days (ie, Cycle 1 Day 1 and Day 8)** | **Vital sign timepoints for subsequent AFM24 dosing if no Cytokine Release Syndrome or Infusion-related reaction (no Grade >1) observed during or after first 2 consecutive AFM24 dosing days (ie, Cycle 1 Day 15 and beyond)** |
|---|---|---|
| Before infusion | Baseline (within 1 hour before start of the infusion) | Baseline (within 1 hour before start of the infusion) |
| During infusion | 30 (±10) minutes after start of infusion<br>Every 30 (±10 minutes) thereafter until EOI<br>At the EOI ±10 minutes | 30 (±10) minutes after start of infusion<br>As clinically indicated |
| After infusion | +60 (±10) minutes post EOI<br>Every 60 (±10) minutes thereafter until the end of the observation period | As clinically indicated |

EOI = End of Infusion

## 7.3 HANDLING OF MISSING DATA

The following approach will be used to impute missing start date of Adverse Events and Concomitant Medications:

- If only day is missing and the month and the year match the date of the first study drug injection, then impute the first date of the study drug injection

- If only day is missing and the month and the year do not match the date of the first study drug injection, then impute the first day of the month

- If the day and the month are missing and the year matches the date of the first study drug injection, then impute the first date of the study drug injection

- If the day and the month are missing and the year does not match the date of the first study drug injection, then impute 01 January of the year

Details of imputation of missing severity and causality for Adverse Events are given in Section 7.8.2. No other imputation for the missing data will be done.

## 7.4 PATIENT DISPOSITION

Total number of patients screened, enrolled and failed screening will be summarized on all screened patients, together with reasons for the screen failure. All patients who have signed the informed consent form are considered screened; enrolled refers to the CRF field called “Was Subject enrolled in the study?” Number of patients included in each analysis set and reasons for study discontinuation will also be summarized. Summaries will be done for all enrolled patients,

Dose-Determining Set and Safety Set for Phase 1, and for all enrolled patients for Phase 2a.

Listings of all screened patients, reasons for screen failure, study populations, inclusion/exclusion criteria and not met will be created. Study discontinuation data will also be listed.

## 7.5 PROTOCOL DEVIATIONS

Protocol Deviations will be summarized by counts and percentages. Major and minor deviations will be summarized separately. Rules for identifying and treating protocol deviations are described in the Protocol Deviations Management Plan. Summaries will be done for all enrolled patients. A listing of all protocol deviations, along with their grade as major or minor, will be provided for all screened patients.

## 7.6 PATIENT CHARACTERISTICS

All summaries in this section will be done for Safety Set for Phase 1 and Phase 2a.

### 7.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Following characteristics at Baseline will be summarized:

- Age (years)
- Sex
- Female with childbearing potential (and a reason, if not)
- Race and Ethnicity
- Height
- Weight

Listings of the baseline demography data will be prepared for the Safety Set.

### 7.6.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Prior Cancer History (Cancer Type, Cancer Stage, Histopathological Type, Extent at Screening, Location of Metastases, Mutation/Alteration status) together with the screening ECOG value will be summarized for Phase 1. Similar summaries for Phase 2a will also include Tumor Mutation Status.

Listings of Cancer History data will be created.

Prior and Concurrent medical conditions other than cancer will also be summarized. All conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.1 or higher. Summaries will be split by SOC and Preferred Term. A condition will be considered prior if its end date is prior to the first date of the study drug administration. A condition will be considered concurrent if its end date is equal to or greater than the first date of the study drug administration.

Separate listings for Prior and Concurrent conditions will be created.

### 7.6.3 PRIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

Prior Cancer Related Surgeries (number of surgeries and residual disease), Cancer Related

Radiotherapy (number of radiotherapies and total dose) and Prior Cancer Therapy (number of regiments, regiment type, number of cycles, best response, reason for treatment discontinuation and coded therapy term) for cancer will be summarized. Numbers of prior surgeries and prior lines of treatment are calculated as the number of unique lines recorded on the respective CRF page. Prior Cancer Therapies will be coded using WHO Drug Dictionary from March 2019.

Prior and Concomitant Medications will also be coded according to WHO Drug Dictionary from March 2019. They will be summarized by counts and percentages splitting by ATC2 and ATC4. Medications will be considered prior if the end date is prior to the first date of the study drug administration. A medication will be considered concomitant if its end date is equal to or greater than the first date of the study drug administration.

Separate listings will be created for Prior Cancer-Related Surgeries, Radiotherapies and Therapies, and also for prior and concomitant medications. In addition, listings of Surgeries and other Procedures and Post-Study Anti-Cancer Treatment will be created.

## 7.7 EFFICACY ENDPOINTS AND ANALYSIS

All the efficacy tables will be run for Safety Set for Phase 1 and for Phase 2a. Where specified additionally, sensitivity analyses on DDS will be run.

In addition, a sensitivity analysis on ORR (as defined by RECIST by investigator and the independent assessor) will be performed for all patients in the safety set for patients receiving at least one full planned dose.

### 7.7.1 ANALYSIS OF PRIMARY ENDPOINT

***Phase 1 (Dose Escalation)***

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 (Cycle 1) and that meets any of the following criteria shown in Table 1. The CRF record of DLT will be used to determine the DLT. 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.

Patients must receive ≥80% of their assigned AFM24 dose in Cycle 1 and complete the 28-day DLT observation period or have had a DLT within the first cycle of treatment to be considered evaluable for DLT. The exact definition of the DLT is given in Section 3.4.2 of the Protocol.

A 2-parameter BLRM (Neuenschwander et al., 2008) will be used for dose escalation of the monotherapy. The model will be run in house by Affimed. Detailed description of the process can be found in the Protocol.

The model is formulated as follows:

$\text{logit}(p(d)) = \log(\alpha) + \beta * \log(d/d^*)$,

where $\text{logit}(p) = \log(p/(1-p))$. $p(d)$ represents the probability of having a DLT in the first cycle at dose d, $d^* = 180$ mg is the reference dose, allowing for the interpretation of $\alpha$ as the odds of a

DLT at dose d*, and θ = (log(α), log(β)) with α, β >0 is the parameter vector of the model.

Non-clinical data have been used to determine an informative prior distribution for θ. The details for the calculation can be found in the Protocol section 9.3.4.2. The resulting distribution is as follows:

The analysis of the primary endpoint will be done on DDS. Number and percentage of the DLTs for every dose level will be summarized, together with the predicted DLT probability and predicted probability of overdosing. The analysis will be repeated on the updated data before each SRC. Final results obtained from complete data from Phase 1 will be reported in the CSR.

Listing of all the DLTs will be created as a part of AE listings and separately.

***Phase 2a (Dose Expansion)***

Primary endpoint for this phase will be Overall response rate (complete response [CR] + partial response [PR]) assessed by local RECIST v1.1. Best confirmed overall response will be used to define the ORR. The table below summarizes the confirmation rules:

| Response at first visit | Response at consecutive visit (at least 4 weeks after the initial assessment) | Confirmed Response at visit |
|---|---|---|
| CR | CR | CR |
| CR | PR | PD |
| CR | SD | SD* |
| CR | PD | PD |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD* |
| PR | PD | PD |
| SD | CR | SD* |

| | | |
|---|---|---|
| SD | PR | SD* |
| SD | SD | SD* |
| SD | PD | PD |

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

* - In order to assign Stable Disease as a confirmed response, there has to be another assessment of at least SD no less than 7 weeks after the initial visit. If this criterion is not satisfied, assign PD.

If the closest consecutive visit is closer than 4 weeks, or is not evaluable, use the next available assessment for confirmation. The last visit has no confirmed response. For iRECIST data similar approach will be used to define the confirmed response at visit.

Simon's two-stage design will be used to determine the outcome of the study in each of the three cohorts. The table below shows the decision thresholds for the design for all three cohorts:

| **Indication** | **Interim Analysis** | | **Final Analysis** | |
|---|---|---|---|---|
| | **Number of subjects** | **OR, that may lead to stop** | **Number of subjects*** | **OR (rejection of the null hypothesis)** |
| RAS-wt, microsatellite stable CRC | 11 | ≤1 | 39 | ≥4 |
| ccRCC | 15 | ≤2 | 41 | ≥10 |
| NSCLC EGFRmut | 15 | ≤2 | 41 | ≥10 |

CRC = colorectal cancer; EGFRmut = epidermal growth factor receptor mutant; RAS-wt = rat sarcoma genes-wild type; NSCLC = non-small cell lung cancer; OR = objective response
*Up to a total of N~40 subjects per Cohort

The final analysis will take place after the last expansion arm was closed for futility or the last patient of the last expansion arm had the final end-of-study visit. Summaries will include the count and percentages of different best confirmed overall responses for each cancer type and observed ORR. In the final analysis, a p-value using the exact binomial test will be calculated comparing the response proportion to the probability stated under $H_0$ for each indication separately.

Listing of CT scan data, reporting both confirmed and unconfirmed responses at all visits will be created. Additionally, biopsy data will be listed.

### 7.7.2 ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

***Phase 1 (Dose Escalation)***

Non-compartmental analysis (NCA) will be conducted using concentration time data of AFM24. In addition, a population PK analysis may be conducted. Separate PK analysis plan(s) will be created as applicable and results will be presented in separate PK report(s). Plots for individual PK concentrations will be generated. PK concentrations will be listed.

ADA results (both screening and confirmatory results as well as titer) will be summarized by visit

and change from baseline to worst-post-baseline. Listing of ADA data will be created. The Immunogenicity data will be summarized both for the Safety Set in Phase 1.

Overall response rate (CR + PR) and disease control rate (CR + PR + stable disease [SD]), assessed by Local RECIST v1.1 will be summarized. Best confirmed overall response will be used to define the ORR. Best response is defined as the best observed response (CR>PR>SD>PD) throughout the study. See Table 1 for rules of response confirmation. Summaries will include the count and percentages of different best confirmed overall responses, ORR and DCR for each dose level. The percentages will be based on the total number of patients in the Safety population for a given dose level.

In addition, waterfall plots for percentage change from baseline for sum of longest diameter and swimmer plots showing timing and results of RECIST 1.1 response assessments (both from the central reader and the investigator).

***Phase 2 (Dose Extension)***

The secondary endpoints for Phase 2a match the ones for the Phase 1. Similar analyses will be performed, but the presentation will be done by Expansion Arm rather than by dose level. Analysis of Adverse Events is described in section 7.8.2.

Waterfall and swimmer plots will also be created, similar to what is described for Phase 1, but additionally color coding the Best confirmed Overall Response.

### 7.7.3 ANALYSIS OF EXPLORATORY EFFICACY ENDPOINTS

***Phase 1 (Dose Escalation)***

Overall response rate (CR + PR) and disease control rate (CR + PR + SD), assessed by: Local iRECIST; Central RECIST v1.1 and Central iRECIST will be summarized.

In addition, Clinical Benefit Rate will be calculated and summarized. It will be defined similarly to DCR, but additionally requiring for SD to last at least 24 weeks.

Duration of Response (DOR) will be defined as (date of first progression or death – date of first response (unconfirmed))/30.4375. Patients without response will be excluded from the analysis. Patients without progression or death will be censored at the date of the last tumor scan.

Progression-Free Survival (PFS) will be defined as (date of first progression – date of first study drug injection)/30.4375. Patients without progression or death will be censored at the date of the last tumor scan.

Overall Survival (OS) will be defined as (date of death – date of first dose)/30.4375. Patients alive at the end of study will be censored on the last date of observation. Separate analyses for DOR and PFS will be created for local and central assessments. Censoring rules for all time-to-event endpoints can be seen in the table below.

| Endpoint | Situation | Date | Censored/Event |
|---|---|---|---|
| Overall Survival | A death is recorded | Date of death | Event |
| Overall Survival | No death is recorded | Latest available observed date | Censored |
| Duration of Response | A PD is observed | First date of PD | Event |
| Duration of Response | No PD is observed, but there is a death recorded | Date of death | Event |
| Duration of Response | Neither PD nor Death are observed | Date of the last Tumor scan | Censored |
| Duration of Response | New anti-cancer therapy is started before any event is recorded | Date of the new anti-cancer therapy | Censored |
| Time to Response | A Response is observed | Date of the earliest (unconfirmed) response | Event |
| Time to Response | No Response is observed | Date of latest tumor assessment | Censored |
| Progression-Free Survival | A PD is observed | First date of PD | Event |
| Progression-Free Survival | No PD is observed, but there is a death recorded | Date of death | Event |
| Progression-Free Survival | Neither PD nor Death are observed | Date of the last Tumor scan | Censored |
| Progression-Free Survival | New anti-cancer therapy is started before any event is recorded | Date of the new anti-cancer therapy | Censored |

PD = progressive disease

DOR, Time to Response (TTR), PFS and OS will be analyzed using Kaplan-Meier model. Summaries will include numbers and percentages of events and censored and product limit estimates of Median and the first and third Quartiles. Kaplan-Meier plots will also be created to support the summaries.

Listings of Tumor assessment data and of DOR, TTR, PFS and OS data will be created.

Lymphocyte subset counts, including number of total and activated NK cells and macrophages, will be summarized by descriptive statistics at each visit for each dose level. Listing of Lymphocyte subset counts and NK cells will be created as a part of the laboratory listings.

Summaries of the Cytokine values by visit will be created. Cytokine values will be listed.

Post-hoc subgroup analyses may be performed, where deemed necessary.

***Phase 2 (Dose Extension)***

The exploratory endpoints and assessments for Phase 2a match the ones for the Phase 1. Similar analyses will be performed, but the presentation will be done by Expansion Arm rather than by dose level. PFS analyses for iRECIST-based outcomes will only be performed if deemed necessary based on the interim results.

In addition, TTR will be summarized similarly to the other survival endpoints. TTR will be defined as (date of first (unconfirmed) CR or PR – data of first study drug injection)/30.4375. Patients without response of CR or PR will be censored at the last tumor assessment date. Patients with no post-baseline tumor assessments will be excluded from the analysis. TTR analyses for iRECIST-based outcomes will only be performed if deemed necessary based on the interim results.

## 7.8 SAFETY ENDPOINTS AND ANALYSIS

Summaries for safety parameters will be done for the Safety Set for Phase 1 and Phase 2a. Tables will be presented by dose level for Phase 1 and by Expansion Arm for Phase 2a.

### 7.8.1 EXPOSURE TO STUDY TREATMENT

Total exposure (planned and actual) to the AFM24 in mg will be summarized by visit and overall. Delays, Interruptions, Dose Adjustments and Deviations and reasons for those will be summarized as well. Listings of AFM24 exposure data (doses and all dose adjustments/deviations) will be created.

For Phase 2, the overall number of cycles, Duration of Exposure, Dose Intensity and Relative Dose Intensity will be summarized. Duration of Exposure in weeks will be defined as (date of the last AFM24 injection – date of the first AFM24 injection +7)/7. The above rule applies for weekly doses of AFM24, for the biweekly schedule the rule will be (date of the last AFM24 injection – date of the first AFM24 injection +14)/7. Dose Intensity will be defined as the total amount of AFM24 received by the subject in mg divided by the Duration of exposure. Relative Dose

Intensity will be calculated as the total dose of AFM24 received divided by the planned dose per cycle times the number of initiated cycles.

The Exposure data will be summarized both for DDS and the Safety Set in Phase 1.

### 7.8.2 ADVERSE EVENTS

AEs will be summarized with patient counts, percentages and event counts by MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs). Following categories of AEs will be summarized: AEs, related AEs, SAEs and related SAEs, AEs with NCI CTCAE Grades ≥3, AEs leading to premature discontinuation and interruptions or discontinuation of study drug and TEAEs on day of dosing (up to 24h after the dose) and on the first day after the dose. An event will be considered study drug related if it has 'possible', 'probable' or 'definitely' in relationship to study drug CRF field. TEAEs presented by SOC and PT will also be summarized by severity grades. For all TEAEs' summaries a number of patients with the event will be presented together with the total number of TEAEs.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, severity grade "4" will be imputed. If causality data is missing, 'Related to study medication' will be imputed.

Listings of AE data (separate for each AE category listed above) will be created.

Summaries of all deaths reported and deaths within 28 days after the last dose of study drug along with causes of death will be created. Listing of the death data will be created.

### 7.8.3 LABORATORY DATA

Safety laboratory results (Serum Chemistry, Hematology, and Coagulation) will be graded by NCI CTCAE v5.0 if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. As only the local laboratory data are collected, no quantitative summaries of the laboratory data will be created. Urinalysis results will be summarized categorically.

For laboratory results reported with a "<" sign, half of the value that follows will be used for the analysis. Results reported after ">" sign will be analyzed as is.

Shift tables classified by reference range indicator (Low, Normal, and High) and also by CTCAE toxicity grades (worst toxicity grade in a period from the first dose until final visit, not including Follow-Up period) from baseline will be presented separately by laboratory test, where applicable.

All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

### 7.8.4 VITAL SIGNS AND OTHER SAFETY PARAMETERS

Vital signs will be summarized by descriptive statistics at each visit including change from baseline will be presented and a listing will be provided.

Local-read ECG data will be listed overall and a separate listing for any clinically significant finding in ECG values will be provided. The frequency and percentage of patients with clinically

significant ECGs and newly occurring qualitative ECG abnormalities will be tabulated as well. The summaries will only be done for Phase 1, Phase 2 ECG data will only be listed.

Physical Examination data will be summarized by visit. Listing of the PE data will be created.

## 7.9 EXPLORATORY ANALYSIS

### 7.9.1 BIOMARKER AND GENOMIC DATA ANALYSIS

Summary statistics of biomarkers and genomic markers (including ctDNA, Cytokines, CyTOF and RO) will be reported by dose group or pooled and examined for possible associations with Investigator assessed RECIST efficacy endpoints (this will be done by running analyses of the efficacy assessment, grouped by biomarker categories, if deemed relevant and enough data per subgroup) and listed.

A separate plan for Biomarker statistical analysis, containing all the details of the planned analyses will be created.

# 8. INTERIM ANALYSES

***Phase 1 (Dose Escalation)***

Each dose escalation step is considered to be an interim analysis, but without a formal interim analyses report. The BLRM will be updated with the respective number of patients treated and the number of DLTs observed in the last cohort. The updated model will then give a statistical recommendation for the next escalation step. In addition, a risk-benefit assessment that includes a comprehensive analysis of safety and available clinical information will be done to decide on the next escalation steps. SRC will review the data at this stage and make the final decision regarding the dose escalation. A separate SRC charter will be composed to describe the SRC activities.

In case of a CTCAE Grade 5 adverse event or a second CTCAE Grade 4 adverse event at least possibly related to AFM24 at any time during Phase 1, the Sponsor will suspend further enrollment and an interim safety analysis will be done. The interim safety analysis will be submitted to the applicable competent authorities for review prior to resuming the study.

***Phase 2a (Dose Expansion)***

An interim analysis will be performed for each cohort independently, once the defined number of subjects (11, 15, and 15 subjects for Cohorts A, B, and C, respectively) in the respective cohort have completed their first post-baseline assessment and its confirmation (2nd post baseline assessment, ie, ≥12 weeks post-baseline) to be categorized under the primary response endpoint or have withdrawn from the study. Each cohort will be then assessed for futility and recruitment will not be stopped until the IA is completed. The results from this IA will be non-binding, unless no signs of efficacy are observed. Safety criteria will also be evaluated to decide on the continuation of the cohorts. Since this is a non-comparative multiple arm study no adjustment for multiple testing is made.

# 9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

[redacted]

Apart from the above mentioned change, the planned analyses as described in this SAP do not deviate from the description in the protocol of the analyses to be performed.

# 10. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the *protocol number* will be presented. On the next line a *table/listing number* followed by the *title* of the table/listing and p*opulation* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under to the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9 format; for example, 07MAY2002.

The list of tables, figures, and listings (TFLs) is given in section below. Shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

For details regarding the BLRM (Bayesian logistic regression model) for dose escalations in the phase I part as part of the SRC, updated standard deviation prior parameter and updated scenarios, please refer to the Protocol.