Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study

Protocol No.:	CUMC
Study identifier CUMC:	AAAP4461
Test Product:	AFM13
Indication:	Relapsed or refractory CD30-Positive Lymphoma with Cutaneous Presentation
Sponsor:	Columbia University Medical Center (CUMC)
Development Phase:	Ib/IIa
Sponsor Signatory:	CUMC
Sponsor Medical Expert:	Ahmed Sawas, MD
Principal Investigator:	Ahmed Sawas, MD Assistant Professor of Medicine Columbia University Medical Center
Date of the Protocol:	February 1st , 2019
Version of the Protocol:	1.4
ClinicalTrials.gov Identifier:	NCT03192202

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study

CUMC PROTOCOL NUMBER: AAAP4461

IND #129679

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study

PROTOCOL NUMBER: AAAP4461 CUMC

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Ahmed Sawas, M.D.	Date (day/month/year)

3 GENERAL INFORMATION

PROTOCOL TITLE: Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study

Protocol No.:	AAAP4461 CUMC/AFM13
Protocol Version and Date:	v1.2, January 31, 2018
Sponsor:	Columbia University Medical Center
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4 STUDY SYNOPSIS

Sponsor:
Columbia University Medical Center
Center for Lymphoid Malignancies 51 West 51st Street, New York, NY 10019

Title of Study:
Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study

Phase: Ib/IIa

Principal Investigator:
Ahmed Sawas, MD

Name of Investigational Product:
AFM13, Recombinant antibody construct against human CD30 and CD16A (TandAb®)

Study Center:
Columbia University Medical Center, 51 West 51st St., Suite 200, New York, N.Y.

Publications:
None.

Planned Study Period:
Q3 2017 to Q4 2019 (first patient first visit to last patient last visit)

Objectives:
The primary objectives are to:

1. Determine the intratumoral NK-cell and T-cell infiltrate and density
2. Determine the immunophenotype of immune cells (NK cells, T cells and others) in tumor and peripheral blood
3. Quantitate the plasma cytokine production and release in tumor and peripheral blood as a function of treatment.

Secondary objectives are to:

1. Evaluate the safety and toxicity of AFM13
2. Determine the clinical efficacy, namely objective response rate (ORR), [including complete response (CR) and partial response (PR)], duration of response (DOR) and progression-free survival (PFS) as defined in the Revised Response Criteria for Malignant Lymphoma 2007 and modified Severity-Weighted Assessment Tool (mSWAT)
3. Evaluate the pharmacokinetic profile (PK) of AFM13.

Exploratory objectives are to:

1. Determine the immunogenicity of AFM13
2. Detect and quantify circulating tumor cells (CTC).

Methodology:
This is an open label, Phase Ib/IIa study designed to evaluate primarily the biological and immunological activity of AFM13 in tumor and blood when administered as monotherapy to patients with CD30-positive lymphomas with cutaneous presentation. Four cohorts of 3 patients will be treated with different doses of AFM13 and dose regimens.

Number of Patients:
It is planned that at least 15 eligible patients will be accrued.

Diagnosis and Main Eligibility Criteria:
This study will enroll patients with relapsed or refractory CD30-positive lymphoma with cutaneous presentation.

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Inclusion criteria:

1. Age ≥18 years
2. Histologically confirmed CD30-positive lymphoma with cutaneous involvement
3. Failure or intolerance to at least one prior therapy for the current disease
4. Presence of one or more cutaneous lesions (measuring at least 1 cm x 1 cm in size; if only one lesion is present it should be up to the investigator discretion to determine eligibility)
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤2
6. Adequate organ and marrow function
   a) Platelets ≥50,000/μL
   b) Absolute neutrophil count ≥ 1,000/μL
   c) Bilirubin < 1.5 x institutional upper limit of normal (ULN) or < 3 x ULN in patients with Gilbert's disease or liver involvement
   d) Serum albumin ≥ 2.0 g/dL
   e) Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤2.5 × institutional ULN or, in the case of liver involvement by the primary disease AST/ALT ≤ 5 x ULN
   f) Creatinine≤1.5 x institutional ULN or estimated creatinine clearance of ≥45 mL/min by the Cockcroft-Gault equation or measured creatinine clearance >45 mL/min
7. Females of child bearing potential must have a negative serum pregnancy test with 7 days prior to first dose of treatment. Female patients of childbearing potential and all male partners must agree to use double barrier methods of contraception throughout the study period and for at least 30 days following investigational product discontinuation.
8. Ability to understand and the willingness to sign a written informed consent document.

Exclusion criteria:

1. Any cancer-related therapy for the current disease within 2 weeks of screening (all supportive care measures are allowed)
2. Major surgery within 2 weeks prior to first dose of study drug
3. Evidence of active central nervous system (CNS) involvement
4. Requirement for systemic immunosuppressive therapy (e.g. Graft-versus-Host Disease [GVHD] therapy within 12 weeks before the first dose of study drug)
5. Uncontrolled concurrent serious illness.
6. Concurrent malignancy requiring cytotoxic or immunotherapy based treatment.
7. Active infections including hepatitis B carrier status, hepatitis C virus (HCV) infection (patients with positive serology must have a negative Hep B and Hep C viral load at screening)
8. Known HIV-positive status
9. Any significant medical conditions, laboratory abnormality, or psychiatric illness that would exclude the subject from participation or interfere with study treatment, monitoring and compliance such as:
   a) unstable angina pectoris, symptomatic congestive heart failure (NYHA III or IV), myocardial infarction ≤ 6 months prior to first study drug, clinically significant and uncontrolled cardiac arrhythmia (e.g. atrial fibrillation/flutter ventricular cardiovascular physiology is allowed), cerebrovascular accidents ≤ 6 months before study drug start
   b) severely impaired lung function
10. Serious, systemic infection requiring treatment ≤7 days before the first dose of study drug
11. Any severe, uncontrolled disease or condition which in the investigator's opinion, may put the subject at significant risk, may confound the study results, or impact the subject's participation in the study.

Test Product, Dose and Mode of Administration:

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All patients will receive AFM13, administered by intravenous infusion according the schema shown for cohorts below. Dose administered will be determined according to cohort and treatment day:

- Cohort 1: 1.5 mg/kg weekly for 8 weeks
- Cohort 2: 7.0 mg/kg weekly for 8 weeks
- Cohort 3: 7.0 mg/kg weekly for 8 weeks (1 mg/kg applied as loading dose and 6mg/kg as continuous infusion for 5 days per week)
- Cohort 4: 200 mg weekly for 8 weeks

Reference Therapy, Dose and Duration of Administration:
None

Intended Duration of Treatment:
All patients will receive at least 1 cycle of treatment (8 weeks). Patients with clinical benefit (CR, PR, or SD) are eligible to receive a 2nd cycle of treatment (lasting 8 weeks). Patients can receive a maximum of 2 cycles of treatment.

Assessments:
Biological and immunological effects (primary endpoint)

- Intratumoral natural killer (NK)-cell and T-cell infiltrate and density
- Phenotypic characterization of immune cells (NK cells, T cells and other) in tumor and peripheral blood
- Cytokine production and release in tumor and peripheral blood

Safety Assessments (secondary endpoint)

- Determine the safety profile as a function of dose and schedule.
- Establish vital signs for each treatment
- Intermittent ECG monitoring

Activity Assessments (secondary endpoint)

- ORR (CR, PR)
- DOR
- PFS

Pharmacokinetic Assessments (secondary endpoint)

- Maximum measured plasma concentration (Cmax)

Other descriptive variables may be applied accordingly such as:

- Area under the curve (AUC)
- Distribution volume (VD)
- Terminal half-life ($t^{1/2}$)
- Clearance

AFM13 immunogenicity (exploratory endpoint)

- Screen for presence of anti-drug antibodies (ADAs)
- Neutralizing potential of ADAs
- NK cell cytotoxicity against CD30-positive targets and cytotoxic T lymphocyte (CTLs) function

Statistical Methods:

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As this is an exploratory study, no hypothesis will be tested and thus no formal sample size calculation has been undertaken. The response rate will be estimated and their respective exact 95% confidence intervals will be constructed based on Binomial distribution. Based on the prior Phase 1 study of AFM13, it is expected that approximately 78% of the patients will show immunological and biological activity. Observing 12 patients out of 15 with immunological and biological response would lead to 95% exact binomial confidence interval of 52%-96% showing activity. The lower bound of 52% is assumed to be sufficient for evidence of activity in this exploratory study. No formal interim analysis is planned, however a safety committee (not a formal data safety monitoring board) will review the safety data from each cohort and advise on opening the next cohort.
Version and date of the Protocol: 1.4 February 1st, 2019

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADAs	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATL	Adult T-cell Leukemia/Lymphoma
AUC	area under the curve
B-ALL	B -Cell Acute Lymphoid Leukemia
BiKE	Bispecific Killer Engagers
BiTE	Bispecific T-cell engager
C-ALCL	Cutaneous Anaplastic Large Cell Lymphoma
CAR-T	Chimeric Antigen Receptor activated T cell
CFR	Code of Federal Regulations
CIVI	Continuous Intravenous Infusion
C_{max}	maximum plasma concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T cell lymphoma
CTL	Cytotoxic T Lymphocyte
CUMC	Columbia University Medical Center
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose Limiting Toxicity
DNAM1	DNAX accessory molecule 1
DOR	Duration of Response
DSMB	Data/Safety Monitoring Board
EBV	Epstein-Barr Virus
EC_{50}	Effective Concentration 50
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram

EoS	End of Study
EoT	End of treatment
FDA	Food and Drug Administration
^{18}FDG-PET	fluorodeoxyglucose-positron emission tomography
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GR	Global Response
GVHD	Graft-Versus-Host Disease
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IV	Intravenous
KIR	Killer cell Immunoglobulin-like Receptor
LILRB1	Leukocyte Immunoglobulin-Like Receptor subfamily B member 1
LPD	Lymphoproliferative Disorder
LyP	Lymphomatoid Papulosis
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis Fungoides
mSWAT	modified Severity-Weighted Assessment Tool
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCR	Natural Cytotoxicity Receptor

NF-κB	Nuclear Factor kappa-Beta
NGS	Next Generation Sequencing
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer
NKG2D	Natural Killer group 2, member D
NYHA	New York Heart Association
ORR	Overall Response Rate
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PMBL	Primary Mediastinal (thymic) large B-cell Lymphoma
pM	Picomolar
PR	Partial Response
PTCL	Peripheral T-cell Lymphoma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
scFv	Single chain fragment variable
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBSA	Total Body Surface area
TMF	Transformed Mycosis Fungoides
TNF	Tumor Necrosis Factor
TNFRSF	Tumor Necrosis Factor Receptor Super Family
TRAF	Tumor Necrosis Factor receptor-associated factor
Tregs	T cells (regulatory)
TriKE	Trispecific Killer Engagers
$t_{1/2}$	Half-life
ULN	Upper Limit of Normal
VD	Volume of Distribution
WHO	World Health Organization

7 INTRODUCTION

Natural killer (NK) cells represent approximately 15% of circulating lymphocytes and are considered one of the key innate effectors in host immune defense [1]. Although NK cells are primarily found in the blood, liver, spleen, bone marrow and, to a lesser extent, lymph nodes, inflammation and other factors can trigger NK cell migration into almost any tissue. NK cells were identified on the basis of their ability to lyse tumor cells without prior sensitization. In contrast to B- and T- lymphocytes, NK cells do not rearrange genes to acquire antigen-specific receptors. Instead, NK cells target tumor cells via an array of germ line-encoded cell surface receptors. Based on this characteristic, NK cells have traditionally been considered to be part of the innate immune response [1]. New observations that some NK cell subsets can be long-lived and show recall responses to certain stimuli has recently challenged this view, as these are properties characteristic of adaptive immunity [2-8].

NK cells can mediate cytotoxicity via several distinct mechanisms. The most studied pathway is degranulation, whereby NK cells inject perforin-1, and granzyme B into the cytoplasmic compartment of the target cell. This pathway is triggered by signals from activating cell surface receptors such as NK group 2 member D (NKG2D), DNAX accessory molecule-1 (DNAM1 or CD226), 2B4 (CD244), a member of the SLAM-related receptor family, and the natural cytotoxicity receptors (NCR), including NKp30, NKp44 and NKp46, counterbalanced by signals from inhibitory receptors, most of which bind to major histocompatibility complex (MHC) class I molecules [9]. Subsequent research has not only provided further insights into the intricate regulation of NK cell degranulation but also revealed that their functional capacity is tuned by interactions with self-MHC class I molecules [10-12]. In humans, killer cell immunoglobulin-like receptors (KIRs) and the CD94–NKG2A receptor are the only receptors known to mediate functional tuning (also referred to as NK cell education). However, the role for other receptors, such as leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1), in this process remains to be established. One receptor that can trigger potent degranulation without the need for simultaneous co-activation signals from other NK cell receptors is the Fc receptor CD16 which, upon interacting with antibody-coated cells, mediates antibody-dependent cellular cytotoxicity (ADCC).

Over the past few decades, drugs and cell-based therapies developed to bolster humoral and T-cell immunity represent an established and growing component of cancer therapeutics. Examples include: the engineering of T-cells with chimeric antigen receptors (CAR-T cells) in leukemia [13], and the recently approved bispecific T-cell engager (BiTE) molecule, blinatumomab for patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL) [14], which recruits cytotoxic T-cells to target tumor B-cells by linking the CD3 and CD19 antigens. Although NK cells have long been believed to have advantages over T lymphocytes in terms of their capacity to induce antigen-independent host immune responses against malignancies, their therapeutic potential in the clinic has been limited. A growing number of scientific discoveries into pathways that both activate and suppress NK cell function, as well as methods to sensitize malignancies to NK cell cytotoxicity,

have led to the development of numerous pharmacological and genetic methods to enhance NK cell antitumor immunity. These findings, as well as advances in the ability to expand NK cells *ex vivo* and manipulate their capacity to home to malignant tumors, have now provided investigators with a variety of new methods and strategies to harness the full potential of NK cell-based cancer immunotherapy in the clinic.

Bispecific antibodies and bispecific or trispecific killer engagers (BiKEs or TriKEs) are engineered molecules that exclusively act via ADCC by crosslinking epitopes on malignant cells with the CD16 receptor on NK cells. These molecules have advantages over monoclonal antibodies (mAbs) because they bind to a different epitope of the CD16 molecule, resulting in stronger NK cell ADCC [15]. *In vitro*, the CD16–CD33 BiKE seems to overcome inhibitory KIR signaling, leading to robust NK cytokine production and killing of myeloid malignancies. Several BiKEs and TriKEs are currently being developed and evaluated for targeting of various malignancies [16]. AFM13 is a bispecific mAb designed to bind to both CD16A on NK cells, and CD30 on malignant cells. A Phase I trial of AFM13 in relapsed and refractory Hodgkin Lymphoma (HL) patients has shown promising results [29, 34]

7.1 Background

7.1 Targeting Unique Cell-Surface Proteins in Lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with multiple histological subtypes. It is estimated that approximately 65,540 new cases of NHL were diagnosed in 2010 and 20,210 patients died of their disease [17]. Based on the World Health Organization (WHO) classification of hematological and lymphoid tumors, NHL can be broadly classified as B or T/NK cell neoplasms [18]. In the United States, about 85% of cases are categorized as B cell lymphomas and 15% are categorized as T/NK cell lymphomas [17].

The expression of unique proteins on the cell surface allows for the identification and diagnosis of different malignancies. These cell markers have been exploited as targetable treatment by immunotherapeutics, such as Rituximab, a genetically-engineered chimeric IgG1 mAb that targets CD20. CD30 was identified in the early 1980s as a protein recognized by mAb Ki-1 [19] and abundantly and selectively expressed on the surface of Hodgkin and Reed-Sternberg cells. Later on, its expression in other neoplastic cells was demonstrated such as anaplastic large cell lymphomas (ALCLs), and other lymphoid malignancies as well as on several non-lymphoid malignancies including selected germ cell tumors. Expression of CD30 on normal cells is highly restricted, thereby allowing differential targeting of malignant cells. CD30, a member of the tumor necrosis factor (TNF)-receptor superfamily (TNFRSF) has pleiotropic biologic functions, and antibodies targeting CD30 and other TNF family receptors can exhibit both agonistic and antagonistic signaling functions. Recently, antibody-drug conjugates targeting CD30, such as brentuximab vedotin, have shown striking activity in phase I and II trials, with manageable toxicity. This has defined an important emerging role for targeting of CD30 in the setting of HL, ALCL, and possibly other CD30-positive malignancies.

Primary cutaneous T-cell lymphomas (CTCL) represent a heterogeneous group of neoplasms derived from skin-homing T cells. Apart from mycosis fungoides (MF), primary cutaneous CD30-positive lymphoproliferative disorders (LPDs) are the most common group, accounting for approximately 25% of all CTCL. This group includes primary cutaneous CD30-positive (anaplastic) large T-cell lymphomas (LTCL) and lymphomatoid papulosis (LyP), a chronic recurrent, self-healing papulonodular skin eruption with histologic features of a CD30-positive CTCL [20].

7.2 CD30-Positive Lymphoid Malignancies

In hematologic malignancies, CD30 expression is strongly increased in HL and ALCL, but has also been noted in other lymphoid malignancies, such as diffuse large B-cell lymphoma (DLBCL), including primary mediastinal (thymic) large B-cell lymphoma (PMBL), peripheral T-cell lymphoma (PTCL), Lyp, MF, and Epstein-Barr Virus (EBV)-driven clonal LPD enteropathy-associated T-cell lymphoma type I, human T-cell lymphotropic virus type 1

(HTLV-1)-associated adult T-cell leukemia/lymphoma (ATL), primary effusion lymphoma harboring human herpes virus-8 [21- 25]. Additionally, CD30 expression is regularly observed in primary CTCL.

7.3 AFM13

The target of AFM13 is CD30, which is a 120-kDa type I transmembrane protein that contains six cysteine-rich pseudo-repeat motifs in its extracellular domain and a cytoplasmic tail with several TNF receptor-associated factor (TRAF)-binding sequences that mediate activation of nuclear factor kappa-B (NF-κB) [26, 27]. CD30 has a broad spectrum of biologic effects depending on the cellular context, including induction and regulation of cytokine secretion and inflammation, induction of apoptosis, and promotion of cell survival and proliferation [28]

Please refer to the Investigator's Brochure (IB) for more details of non-clinical and clinical studies conducted with AFM13.

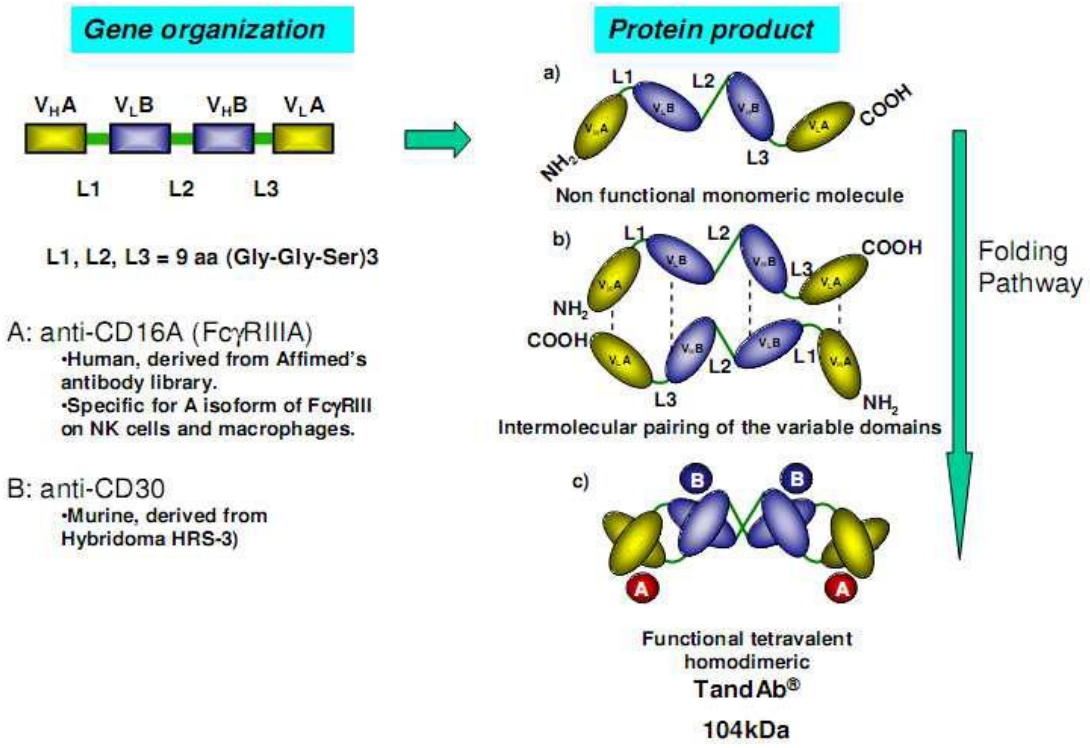
7.4 Pharmaceutical and Therapeutic Background

7.4.1 Antibody generation and folding pathway

The investigational medicinal product AFM13 is a tetravalent bispecific chimeric (anti-human CD30 x anti-human CD16A) recombinant antibody construct (TandAb®) for the treatment of HL.

AFM13 is constructed by means of recombinant technology as a homodimer of a polypeptide comprising four antibody variable domains, each one being separated from the neighboring domains by a glycine-serine linker of nine amino acids. The four-domain gene product is unable by itself to bind antigen, since the lengths of the linkers between the domains are too short for intramolecular pairing of the corresponding heavy and light chains. However, they are arranged in an order that permits formation of the corresponding antibody V_H/V_L domains after non-covalent dimerization. The result of this folding process is a homodimer molecule with a molecular weight of 104-kDa as outlined in Figure 1.

Figure 1: Folding pathway of AFM13



The tetravalent bispecific format, as represented by AFM13, is designed to recruit cytotoxic effector cells of the immune system effectively against pathogenic i.e. tumor target cells.

7.4.2 Mode of action

The tetravalent bispecific antibody AFM13 is designed to re-direct cytotoxic effector cells of the immune system against CD30-positive malignant cells.

Natural killer cells are cytotoxic effector cells and represent a potent subset of lymphocytes for targeting and killing tumor cells. In contrast to T-lymphocytes, they do not need to be pre-activated. Their inherent cytotoxic activity is stimulated by the FcγRIIIA (CD16A), which is expressed on the surface of NK cells as well as on macrophages, and activated monocytes. Interestingly, recent studies have provided evidence that NK cell can be pre-activated prior to cytolysis. More important observations have been made regarding the development of a memory NK cell that can be primed prior to cytotoxicity against stressed cells (i.e., infected or transformed cells) [2-8].

Regarding AFM13-mediated NK cell-directed cytotoxicity, *in vitro* studies have shown that AFM13 simultaneously binds to CD16A on NK cells and CD30 on Hodgkin- and Reed-

Sternberg cells and that this leads to the lysis of Hodgkin and Reed-Sternberg cells by the NK cells via cellular cytotoxicity.

7.5 Non-clinical studies

Of the CD30-positive lymphomas, HL has been targeted for the development of AFM13. Due to the lack of an appropriate animal model of HL, most primary and secondary pharmacodynamic data of AFM13 have been generated *in vitro*.

The pharmacokinetic behavior of AFM13 has been investigated in stand-alone studies in mice, and in cynomolgus monkeys as the only relevant species. Furthermore, toxicokinetic data were generated in cynomolgus monkeys in parallel with the toxicological assessment of AFM13.

Further details of all non-clinical studies are provided in the IB.

7.5.1 Characterization of affinity and specificity

The affinity and specificity of AFM13 to its nominal ligands CD30 and CD16A have been extensively characterized. The results demonstrate high affinity of AFM13 to both of its ligands. AFM13 binds to human CD16A with an affinity of ~ 1.6×10^{-9} M and to human CD30 with an affinity of ~ 1.3×10^{-9} M. The experiments using different isoforms of CD16 also confirmed the specificity of AFM13 for CD16A, and revealed comparable binding to both tested CD16A allelic variants. No binding of AFM13 to different variants of CD16B was detectable. Using flow cytometry, cell surface binding of AFM13 on CD30-positive and CD16-positive cells could be unequivocally demonstrated. The flow cytometry data using cell lines transfected with different CD16 isoforms also clearly confirmed specificity of AFM13 for the A isoform of CD16. CD30- and CD16-specific tissue binding of AFM13 could be well demonstrated. Staining patterns of AFM13 on selected frozen human tissue sections corresponded to those seen with control mAbs directed against either CD16 or CD30.

7.5.2 Primary pharmacodynamic activity

In vitro AFM13 induces specific and selective killing of CD30-positive target cells by NK cells with an EC_{50} typically seen in the order of ~ 5 – 250 pM (depending on the target cell line and effector cells used). AFM13-induced target cell lysis is specific since AFM13-activated killing of CD30-positive target cells by NK cells does not affect CD30-negative bystander cells. The onset of AFM13-mediated target cell lysis is immediate and does not require pre-activation of NK cells. AFM13 which is already bound to CD30-positive target cells or CD16A-positive effector cells is able to mediate target cell lysis even in the absence of free soluble AFM13. The data suggests a difference between PK and pharmacodynamic half-life *in vivo*. There is substantial inhibition of the AFM13-mediated cytolytic response by human IgG and soluble human CD30.

7.5.3 Secondary pharmacodynamic activity

Secondary pharmacodynamic properties of AFM13 were investigated in several *in vitro* systems. These *in vitro* studies encompassed the ability to induce cytokine release in human peripheral blood mononuclear cells (PBMCs) and the ability to induce proliferation in CD30-positive and CD16A-positive cells. The ability of free soluble AFM13 to induce cytokine release from human PBMC is minimal. Nevertheless, it is not possible to claim that AFM13 is free of cytokine releasing potential. Measurement of plasma concentrations of IL-2, IL-6, TNF-α, and IFN-γ, which are known to be most relevant for cytokine-related adverse reactions, did not indicate cytokine release in the pivotal 28-day repeated dose toxicity study in cynomolgus monkeys up to a dose level of 10 mg/kg.

Additional data do not indicate strong induction of cytokine release from human PBMC by immobilized AFM13 or AFM13 in the presence of physiological and non-physiological cross-linkers. The most effective cross-linker with regard to induction of cytokines (especially TNF-α and IFN-γ) by AFM13 seems to be CD30-positive target cells. This may be part of the mode of action since activation of NK cells is normally associated with release of IFN-γ. Binding of AFM13 to CD16A-positive cells in cultures of human PBMC or binding to CD30-positive on HL cells does not trigger or affect proliferation.

7.6 Safety pharmacology

A number of safety pharmacology end-points concerning the central nervous system (CNS), cardiovascular system, respiratory system, gastrointestinal system, renal/urinary system, and hematopoietic system, have been integrated into standard toxicity studies of AFM13 in cynomolgus monkeys. No alerts with regard to safety pharmacology arose from these studies that might call for additional in-depth investigations of AFM13.

7.6.1 Tissue cross-reactivity

In human non-epithelial tissues the staining pattern shown by AFM13 is consistent with its specificity, detecting only CD16- and CD30-positive cells. However, AFM13 shows strong immunostaining of a number of secretory-type human epithelia, including those of breast ducts, pancreatic ducts, acinar cells of the prostate, sweat glands of skin, and glandular epithelium of the uterine cervix. Furthermore, AFM13 shows staining of some non-secretory epithelia, including those of the urinary bladder, the fallopian tube, the ureter, and epididymal epithelial cells in the testis. The relevance of these findings is unclear. However, the same pattern of epithelial binding has been observed in cynomolgus monkeys without adverse toxicity.

Overall, AFM13 has a low toxic potential but potentially adverse hematological effects have to be taken into account.

7.7 Phase I clinical trial in relapsed or refractory Hodgkin lymphoma

A clinical phase I study, AFM13-101, was conducted in patients with heavily pre-treated relapsed/refractory HL [29]. The trial results are summarized in the sections below.

7.7.1 Results of the AFM-101 phase I trial

7.7.1.1 Patient population and treatment

Twenty-eight patients with HL including 16 males and 12 females were enrolled in the AFM13-101 trial. The median age was 38.5 years. The patients had a median of 6 (range 3-11) previous lines of therapy for HL including ASCT in 22/28 patients and previous radiotherapy in 24/28 patients. Fourteen of 28 patients were refractory to the most recent therapies, 9/28 patients had received brentuximab vedotin.

The included patients received treatment with AFM13 in the planned 8-dose cohorts. In the dose escalation part, 24 patients received increasing doses of AFM13 ranging from 0.01 mg/kg to 7.0 mg/kg on a weekly dose schedule for 4 weeks. In addition, 4 patients were treated with AFM13 at a dose of 4.5 mg twice weekly for 4 weeks. Nineteen of 28 patients completed the study; the remaining 9 patients discontinued the treatment due to disease progression (n=2), adverse events (AEs) (n=1), withdrawal of consent (n=3) and other reasons (n=3). Eight of the 9 patients who discontinued had received at least one complete treatment cycle and an imaging after the last dose before being withdrawn.

All 28 patients were included in the safety analysis. Two patients were excluded from the efficacy population: patient 001-03 in Cohort 1 (0.01 mg/kg) completed cycle1, but left the study to start another treatment before completing the final study visit. Patient 002-01 in Cohort 4 (0.5 mg/kg) discontinued due to AEs (hemolytic anemia followed by aspergillus pneumonia and multi-organ failure) before completing cycle 1.

7.7.1.2 Safety results of AFM13-101 trial

Twenty-three of 28 patients experienced at least AE which was evaluated as treatment-related by the investigator. Most AEs were mild or moderate; only 18 of 196 documented AEs were National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 3 AEs; in only 1 patient (patient 002-01) a dose-limiting toxicity (DLT), a hemolytic anemia CTCAE grade 4, possibly related to AFM13, was documented. The patient subsequently died due to aspergillus pneumonia and multi-organ failure which was assessed as not or unlikely related to the study drug.

The most frequent AEs were infusion-related reactions (IRR) including pyrexia, chills, headache, nausea and other IRRs. Treatment-associated infections were rare; nasopharyngitis was noted in 5 patients and pneumonia in 4.

After review of the safety data, the independent data monitoring committee (IDMC) concluded that the maximum dose of 7 mg/kg in the weekly dose schedule was reached without any toxicity concerns and without reaching the maximum tolerated dose (MTD). Additionally, the 4 patients treated with 4.5 mg/kg twice weekly completed the treatment without toxicity concerns of the IDMC. Apart from the documented DLT in patient 002-01 the administration of AFM13 was not associated with clinically significant changes in any laboratory parameters, nor was it associated with clinically significant changes in any vital signs or electrocardiogram (ECG) parameters.

Thus, the AFM13-101 trial showed that AFM13 is safe and well tolerated at the examined doses and dose schedules.

7.7.1.3 Efficacy analyses of the AFM13-101 trial

All 28 patients had measurable levels of sCD30 at the start of cycle 1 and in 24 patients the sCD30 level was decreased at the end of the first cycle. All patients treated in the dose cohorts of 1.5 mg/kg AFM13 experienced a marked decrease of sCD30. Furthermore, immunophenotypic analyses showed that AFM13 resulted in an increase of activated NK cells in the peripheral blood as measured by CD69 expression on their surface.

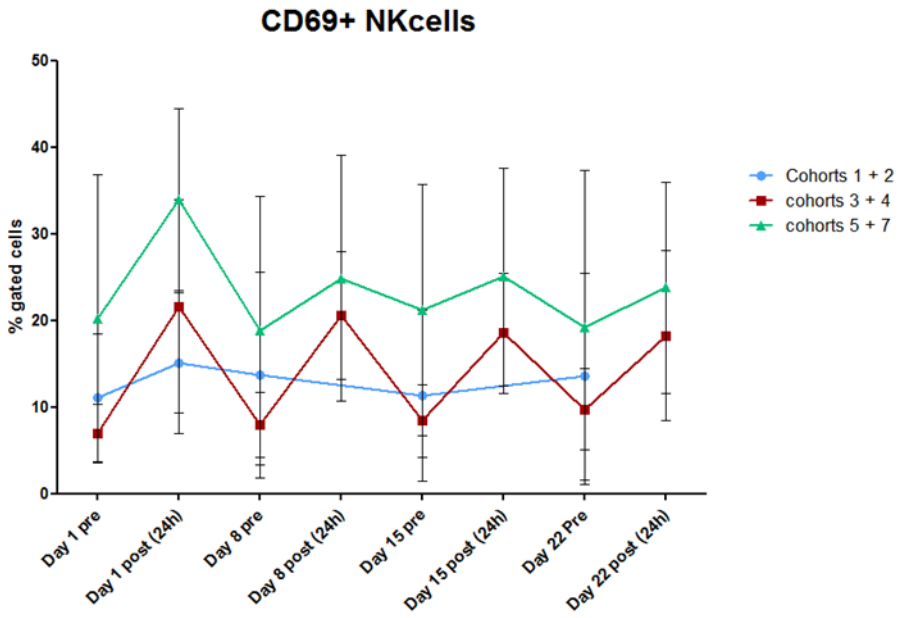
Of the 26 patients who were eligible for efficacy assessment, 3 patients achieved a partial response (PR), and 13 patients experienced a stable disease (SD) as documented at the final study visit. More detailed efficacy analyses indicate that the clinical activity is more pronounced at or above a dose of 1.5 mg/kg. Of the 13 patients treated at or above a dose level of 1.5 mg/kg, 7 patients experienced a SD and only 3 patients developed a progressive disease (PD) at the end of the trial. Two of the reported PRs were documented at a dose level of 1.5 mg/kg and one PR at the dose level of 4.5 mg/kg given twice a week. A waterfall plot analysis showed a reduction of the tumor volume in 8 patients treated at a dose level of 1.5 mg/kg or above [29, 34].

7.7.1.4 Pharmacokinetic analyses of the AFM13-101 trial

Pharmacokinetic analyses revealed that weekly dosing is suboptimal because the documented half-life of AFM13 was between 9 - 19 h in the dose cohorts ≥ 1.5 mg/kg and because the serum levels in the weekly dose schedule were mostly below the serum level of 400 ng/ml which was defined as trough blood level as a result of *in vitro* data. Also, the bi-weekly regimen did not result in adequate trough levels at the end of the infusion intervals.

Furthermore, the measurement of NK cell activation with immunophenotypic analysis of CD69+ cells in the peripheral blood showed a correlation between the biological activity of AFM13 and its PK (Figure 2).

Figure 2: Correlation between NK Cell Activation and PK of AFM13



Thus, these PK data indicate that the dosing has to be done more frequently than bi-weekly at least for some defined period of time.

7.8 Rationale

Natural killer cells play an important role in tumor immune-surveillance [8, 10, 30]. Their function is regulated by a repertoire of inhibitory and activating surface receptors. NK cell-mediated cytotoxicity can occur through distinct mechanisms: (1) by activating the receptor NKG2D and NCR, and (2) through the potent activating receptor CD16 (FcγRIII) which mediates ADCC [8]. Enhanced expression of NK cell antigens has been shown to correlate with systemic anti-tumor response in early primary CTCL [31]. Further, phase I clinical data with AFM13 indicate that engagement of NK cells results in pharmacodynamic and clinical activity in relapsed/refractory HL. However, NK cell migration into the tumor, cytokine release in the tumor, potential effects on the adaptive immune response and other biological processes triggered by NK cell activation have not been investigated and are not understood so far.

Thus, we hypothesize that if we are able to engage the innate immune system through a specific activation and recruitment of NK cells via CD16A to tumors expressing CD30, then we intend to demonstrate an immunological and/or tumor response that might be broadly described in relation to dosing/PK parameters and could serve as a good and useful parameter in predicting clinical response.

The therapeutic potential of manipulating NK cell function via CD16 for the treatment of cancer has been previously demonstrated through the use of mAbs [32]. Presently, novel single chain fragment variable (scFv) recombinant reagents (BiKE and TriKE), which specifically target CD16 expressed on effector NK cells and antigens-of-interest on tumor cells, are being developed and tested for clinical use [33]. Further, a novel tetravalent bispecific CD30/CD16A antibody, AFM13, was investigated in a phase I study in HL patients and was demonstrated to be safe and active [29, 34]. We plan to investigate AFM13 and evaluate its ability to facilitate and redirect the NK cells in eliminating CD30-positive lymphoma targets in the skin and, by inference, other organs involved by the lymphoma.

Primary cutaneous CD30-positive lymphoproliferative LPD represent a spectrum from LyP, to primary cutaneous anaplastic large cell lymphoma (C-ALCL), to transformed mycosis fungoides (TMF). The most indolent form of primary cutaneous CD30-positive LPD is LyP, which is usually well controlled with low dose oral methotrexate, but control of the disease frequently requires life-long therapy. In contrast, TMF is an aggressive disease which does not have a standard of care, as patients are treated with various modalities of care with variable outcomes [20]). The spectrum of other CD30-positive lymphomas with cutaneous presentation is very broad and involves systemic B and T cell lymphomas with various clinical behaviors. Again, redirecting NK cells towards these CD30-positive malignancies through direct engagement with AFM13 is expected to induce tumor cell killing through NK cell-mediated and T cell-mediated cytotoxicity (i.e., cytotoxic T lymphocytes [CTL]).

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of this study are to:

1. Determine the intratumoral NK-cell and T-cell infiltrate and density
2. Determine the immunophenotype of immune cells (NK cells, T cells and others) in tumor and peripheral blood
3. Quantitate the plasma cytokine production and release in tumor and peripheral blood as a function of treatment.

8.2 Secondary Objectives

Secondary objectives are to:

1. Evaluate the safety and toxicity of AFM13
2. Determine the clinical efficacy, namely objective response rate (ORR), [including complete response (CR) and partial response (PR)], duration of response (DOR) and progression-free survival (PFS) as defined in the Revised Response Criteria for Malignant Lymphoma 2007 and modified Severity-Weighted Assessment Tool (mSWAT)
3. Evaluate the pharmacokinetic profile (PK) of AFM13.

8.3 Exploratory Objectives

Exploratory objectives are to:

1. Determine the immunogenicity of AFM13
2. Detect and quantify circulating tumor cells (CTC).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1 Description

This is an open label, Phase Ib/IIa study designed to evaluate the biologic activity of AFM13 in patients with relapsed or refractory CD30-positive lymphomas with cutaneous involvement.

The primary objective of this trial is to study the biologic and immunologic effects induced by the administration of various doses of AFM13, when given as a single agent. The study will enroll at least 9 patients with CD30-positive cutaneous lymphoma. Patients will be assigned to 3 dose cohorts of 3 patients each. As this is not a dose-finding study, there are no stringent criteria for initiation of subsequent cohorts: subsequent cohorts will be progressively enrolled after all 3 patients from the previous dose cohort have received their first planned treatment dose(s) during the first week of the cycle, and the safety of the patients on Week 2 Day 1 of the first cycle is deemed acceptable by involved investigators (Table 1).

After preliminary analysis of Cohorts 1-3, input from a scientific advisory board and the companies own experience in the Hodgkin's Study of AFM-13, it was decided to investigate an intermediate dose of 4.5mg/kg. Studying the intermediate dose may optimize some of the efficacy seen in Cohort 1 while reducing steroid use seen in Cohort 2 to manage infusion related reactions. An additional 3 patients will be recruited into Cohort 4. Afterwards a three patient expansion will be planned to confirm efficacy and tolerability of the selected cohort for a phase 2 study.

Table 1: Treatment Cohorts and Dosing Schedule (one cycle of treatment)

Cohort	Dose regimen			Total exposure
	Dose	Timing	Period	
Cohort 1	1.5 mg/kg	weekly	weeks 1-8	12 mg/Kg
Cohort 2	7.0 mg/kg	weekly	weeks 1-8	56 mg/Kg
Cohort 3	7.0 mg/kg (1 mg/kg applied as loading dose and 6mg/kg as continuous infusion for 5 days per week)	weekly	weeks 1-8	56 mg/Kg
Cohort 4	200mg	weekly	weeks 1-8	1600mg

Prior to recruitment into this trial, all patients will be assessed individually to document eligibility into the trial according to the Inclusion and Exclusion Criteria. Additionally, documentation of patient briefing and signed informed consent form (ICF) are mandatory requirements for trial participation. The protocol mandates that the primary diagnosis of CD30-

positive lymphoma be confirmed by the Department of Pathology at Columbia University Medical Center (CUMC). Patients whose diagnosis was made at a different institution will consent to have their biopsy material forwarded to CUMC for confirmation. CD30 expression will be confirmed using the BerH2 antibody. To date, there is a suggestion that the level of CD30 may not be important in predicting response; it is unclear what the lower limit should be. The data from Kim et al. [37] suggest that patients with <5% positivity for CD30 respond less well than patient who have more than 5%. Although this is the first paper to suggest a relationship on a lower level of expression and response..

Each patient eligible for the study will be asked to give consent for the collection of fresh tumor material. The completion of all staging assessments is also mandatory before registration into this trial. The patient will receive one 8-week cycle of protocol treatment followed by 3 weeks off and will be assessed for treatment/tumor response thereafter at week 11. All patients who achieve at least SD will receive a second cycle of protocol treatment at the same dose administered during Cycle 1, starting in what would be considered Week 12. During treatment and follow-up, patients will be closely monitored for safety. The biological and immunological effects of the treatment will be assessed in Cycle 1 only. A schematic overview of treatment, interventions and assessments (safety, feasibility, and efficacy) is given in Table 2**.**

In cohort 1 and 2 AFM13 will be administered in all patients as a slow intravenous (IV) infusion over 4 hours. The duration of the infusions will be stepwise shortened by 30 minutes to a minimum infusion rate of 1 hour if well tolerated by the patient. In cohort 3 weekly treatment will consists of a loading AFM13 dose of 1 mg/kg to be applied on day1 as 1-hour infusion, followed by a 6 mg/kg AFM13 as continuous infusion over 5 days. For further specifications please refer to the pharmacy manual. Cohort 4 will use the same dosing schedule as cohorts 1 and 2.

The biological and immunological studies will investigate the NK cell phenotypic characteristics, proliferative response (Ki-67), activation status (CD69), and density in the peripheral blood. The same analyses will be conducted in the tumor tissue collected from all patients at different time points. In addition, tumor cell infiltrate by NK cell and their spatial distribution in the tumor and its microenvironment will be studied. NK effector function will be assessed in both compartments (peripheral blood and tumor) by assaying for ADCC, presence of cytolytic proteins (granzyme B, perforin-1), and the production and release of cytokines and chemokines. T cells phenotype and effector function (CTL) will also be studied. Additionally, tumors obtained from study participants will be analyzed for expression of CD30, major histocompatibility antigens (MHC Class-I), other immune cell infiltrates, and resident immune cells (myeloid-derived suppressor cells, regulatory T cells (Tregs).

The presence of anti-AFM13 antibody will be investigated, and their neutralizing ability assayed.

Continuous safety analyses (AEs, safety clinical laboratory assessments, vital signs, ECGs) will be regularly performed by a Principal Investigator-led safety team to ensure the safety of

the patients.in the case of a potential significant safety problem the Principal Investigator in consultation with groups such as the FDA, IRB, data monitoring committee and/or statisticians may decide on the termination or temporary cessation of the trial.

9.2 Dose Rationale

Different doses and dose regimens are investigated in this translational research study aiming to understand the impact of the dose regimen on the biological and immunological effects of AFM13 in the tumor. The selected dose regimens of the 3 cohorts are based on the target dose and dose regimen of AFM13 being investigated in a Phase II proof-of-concept study in relapsed/refractory HL. In the Phase II study, 2 dose regimens are investigated which are identical to dose Cohorts 1 and 2 of this study. A third cohort of continuous intravenous infusion was added which is identical to Cohort 3 of the HL study. A fourth cohort, of an intermediate dose between Cohort 1 and 2 was also added.

The rationale for the selection of dose and dose regimen in Phase II is based on data from the phase I trial including a PK modeling as well as pre-clinical cytotoxicity data.

In the phase I study, it was shown that pharmacodynamics and clinical effects are more pronounced at AFM13 doses ≥1.5 mg/kg without having a negative effect on the safety profile. It was therefore concluded that the dose in future studies should be at least 1.5 mg/kg (Cohort 1 of the current study).

Phase I PK data have been collected and analyzed after weekly doses of AFM13. Data revealed that a defined minimum trough plasma level of AFM13 could not be maintained with weekly infusions (Refer to Figure 1). This minimum plasma level of 400 ng/mL, indicated by the dotted line in Figure 2, was calculated based on the EC_{50} of *in vitro* cytotoxicity assays and considering physiological conditions like the presence of IgG in blood as well as the barrier from the vascular compartment to the HL lesion.

In parallel to the AFM13 plasma levels, the portion of activated NK cells (relative to the total number of NK cells) increased after AFM13 infusion but dropped during the weekly infusion period back to baseline prior to the next infusion. This finding supports that more frequent dosing is needed at least in the initial phase of treatment. PK modeling revealed that 1.5 mg/kg AFM13 administered 3x per week succeeds in maintaining AFM13 plasma levels above 400 ng/mL (Figure 2). Therefore, this dose regimen was defined for the initial 2-week treatment phase with AFM13.

Considering clinical feasibility aspects, it was decided for the Phase II study that, after the initial treatment phase, AFM13 will be dosed 7 mg/kg weekly (Cohort 2 of the current study). The dose regimen of 1.5 mg/kg 3x per week over 2 weeks followed by 7 mg/kg weekly over 6 weeks (Figure 3) is currently in Phase II clinical development. AFM13 is administered in 8-week cycles.

PK modelling based on the data gathered from the phase I study and as well from the currently ongoing phase II study revealed that a more stable serum levels of AFM13 can be achieved

with continuous infusion (CIVI) of 6mg/kg over 5 days after a loading dose of 1 mg/kg. Therefore, a new cohort is currently being investigated with the German Hodgkin Study Group to assess efficacy of a CIVI dosing scheme identical as planned in this study. (Cohort 3 of the current study)

Figure 1: PK profile for 1.5 mg/kg AFM13 administered weekly

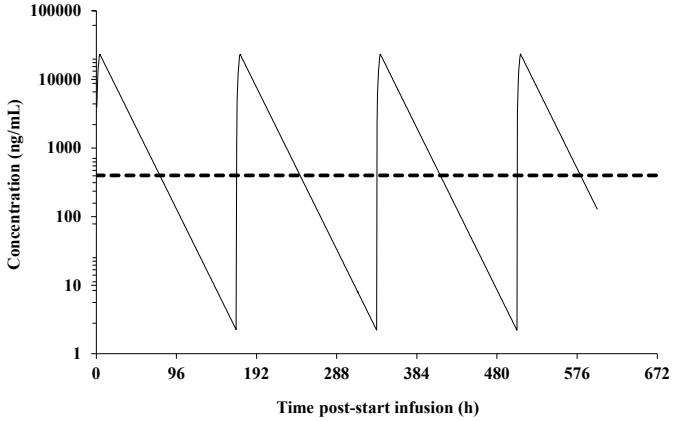


Figure 2: Simulated PK profile for 1.5 mg/kg AFM13 administered three times per week

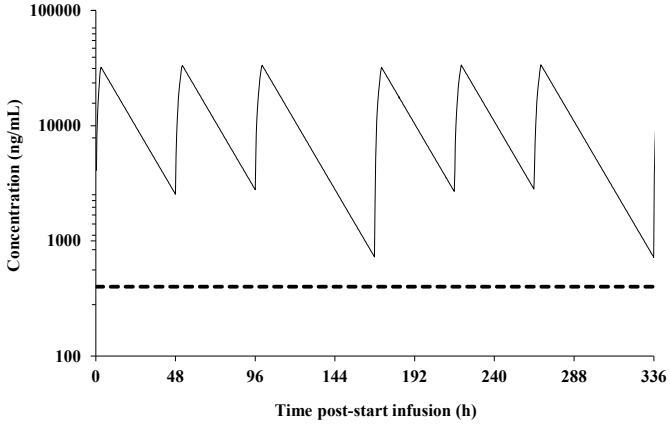


Figure 3: Simulated PK profile for 1.5 mg/kg AFM13 administered weekly over 2 weeks followed by 7 mg/kg weekly over 6 weeks

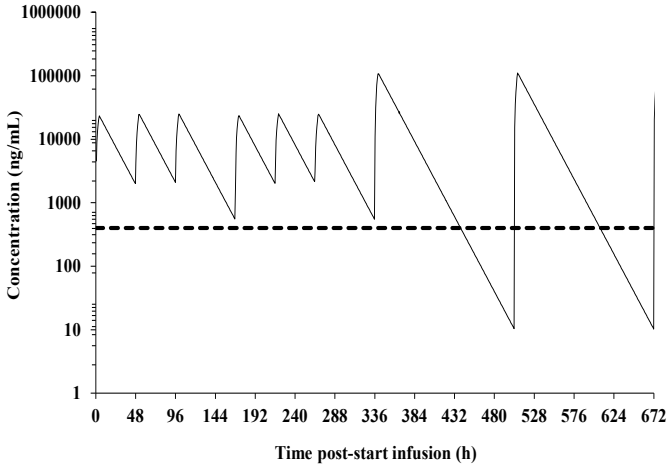
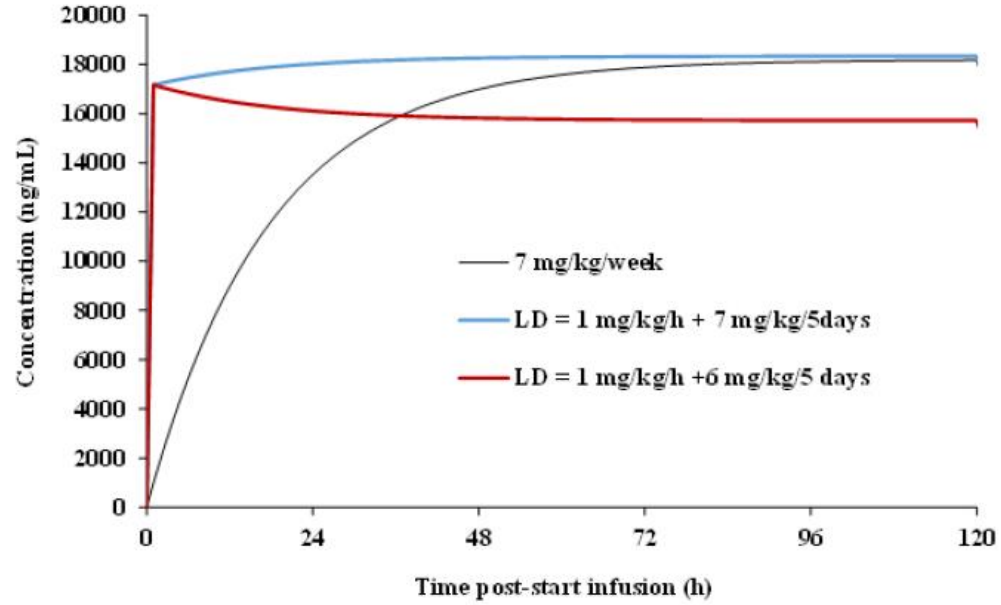
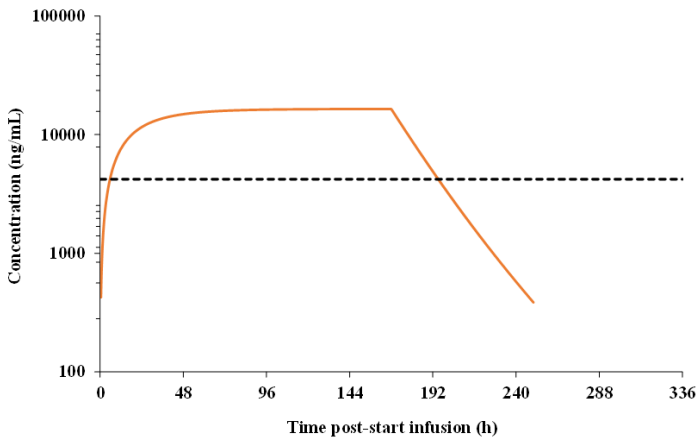


Figure 4: Simulated PK profile for 7.0 mg/kg AFM13 administered weekly by continuous infusion





For Cohort 4: The rationale for the selected dose and schedule of 200 mg is based on an updated analysis of the overall pre-clinical and clinical experience from the completed AFM13-101 Phase I study and the other ongoing AFM13 clinical studies (including present study). An exposure-response analysis was completed based on the data from the AFM13-101 Phase I study.

The PK data from the AFM13-101 showed that overall, the systemic exposure to AFM13 increased in a slightly greater than dose proportional fashion (an increase of 2.14 and 2.30-fold for C_{max} and $AUC_{0-\infty}$, respectively), the systemic exposure increase from the dose 1.5 mg/kg to 7 mg/kg (4.7-fold), geometric mean C_{max} and $AUC_{0-\infty}$ increased 9.6-fold and 13.2-fold, respectively i.e. approximately 2- to 3-fold greater than expected based on a proportional relationship.

Exposure-response analyses for the study showed that achieving an AUC0-∞ of at least 100,000 h*ng/mL appears to be important to increase the likelihood of achieving clinical benefit and the proposed stratified flat dose of 200 mg corresponded to a dose of

approximately 3 mg/kg; which is also significantly lower than the dose of 7 mg/kg, a dose level that was associated with increased incidence and severity of AFM13-associated IRRs.

Completed population PK analysis using data from AFM13-101 and the current study, there were three variables that had a statistically significant impact on PK parameters as listed below:

- Dose: higher doses had a greater effect on the central volume of distribution (i.e. with higher doses, more of the drug stays within the central compartment)
- Body surface area (BSA): higher BSA had proportionately lower C_{max}; however, BSA had no significant impact on the AUC
- Albumin: lower albumin led to faster clearance, thereby impacting the AUC.

While these results do not alter the proposed dose selection of 200 mg, an interim PK analysis using further PK data from patients treated in this study will be utilized to determine if the above described effect on albumin is confirmed and to determine if a higher dose of AFM13 is warranted for patients with very low albumin.

9.3 Number of Centers

This study will be conducted at CUMC in the United States of America (USA).

9.4 Number of Subjects

The study will enroll 15 evaluable subjects. Evaluable patients are defined as having 1 biopsy pre-treatment and at least 1 biopsy post treatment.

9.5 Schedule of Assessments

See Table 2 for Schedule of Assessments. The details for blood draw per assay are given in the Immunobiology Research Manual.

Table 2: Schedule of Assessments

Week		**Screening**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**EoS/PD[p]**
Day		**-28 to 0**	**1**	**5**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1§**	
AFM13 Administration[a]	Cohort 1		x		x	x	x	x	x	x	x		
	Cohort 2		x		x	x	x	x	x	x	x		
	Cohort 3		x		x	x	x	x	x	x	x		
	Cohort 4		x		x	x	x	x	x	x	x		
Informed consent		x											
Eligibility		x											
Demographics		x											
Medical/surgical history		x											
ECOG performance status		x											
Pregnancy test[b]		x											
Histology CD30+ lymphoma[c]		x											
Physical examination[d]		x	x		x	x	x	x	x	x	x	x	x
ECG (rest 12-lead) [e]		x			x		x		x		x		x
Vital signs[f]		x	x		x	x	x	x	x	x	x	x	x
Clinical chemistry		x	x		x	x	x	x	x	x	x	x	x
Hematology		x	x		x	x	x	x	x	x	x	x	x
Coagulation		x					x					x	x
Urinalysis		x					x					x	
Trough serum levels[g,j*]			x		x	x	x	x	x	x	x		
Full AFM13 PK sampling[h, j]			x[h]					x[h]					
Skin biopsy[i]			x	x			x				x		x[n]
Blood immunology			x	x			x				x		x
Blood cytokines[j,k]			x	x			x				x		x
sCD30[j]			x	x			x				x		x
ADAs[j]			x			x							x
Tumor assessment[o] :		x										x	
(m)SWAT[m]		x										x	
Flow Cytometry [18]FDG-PET and CT-Scans[l]		x										x	
Concomitant medication		x	x		x	x	x	x	x	x	x	x	x
Adverse event		x	x		x	x	x	x	x	x	x	x	x

Optional 8 Week Schedule

Week		1	2	3	4	5	6	7	8	11	EoS/PD[p]
Day		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1§**	
AFM13 Administration[a]	Cohort 1	x	x	x	x	x	x	x	x		
	Cohort 2	x	x	x	x	x	x	x	x		
	Cohort 3	x	x	x	x	x	x	x	x		
	Cohort 4	x	x	x	x	x	x	x	x		
Physical examination[c]		x	x	x	x	x	x	x	x	x	x
ECG (rest 12-lead) [d]		x	x		x		x		x		x
Vital signs[e]		x	x	x	x	x	x	x	x	x	x
Clinical chemistry		x	x	x	x	x	x	x	x	x	x
Hematology		x	x	x	x	x	x	x	x	x	x
Coagulation		x			x					x	x
Tumor assessment[o] : ^{18}FDG-PET and CT-Scans[l]										x	
(m)SWAT[m]										x	
Flow Cytometry										x	
Concomitant medication		x	x	x	x	x	x	x	x	x	x
Adverse event		x	x	x	x	x	x	x	x	x	x

ADA=anti-drug antibody; CT=computerized tomography; CTC=circulating tumor cells; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EoS=end of study; ^{18}FDG-PET=fluorodeoxyglucose-positron emission tomography; MRI=magnetic resonance imaging; m(SWAT)=modified Severity-Weighted Assessment Tool; PD= progression of disease. PK=pharmacokinetics; SD=stable disease;

Additional assessments may be conducted as clinically indicated

Assessments made on drug administration days are to be conducted prior to the start of study medication infusion, unless specified otherwise

Patients with clinical benefit (SD, PR, CR) will receive a second cycle starting after week 11.

All study procedures have a +/- 3 day window, unless otherwise specified.

§ Restaging is to be done at each Week 11 Visit +/- 2 weeks.

a. AFM13 is infused over 4 hours at the first infusion day. Infusion duration is to be stepwise reduced by 30 min to a minimum of 1 hour at the following infusion days. Cave: measures related to infusion duration in case of adverse events. In cohort 3 weekly treatment will consists of a loading AFM13 dose of 1 mg/kg to be applied on day1 as 1-hour infusion, followed by a 6 mg/kg AFM13 as continuous infusion over 5 days.
b. Pregnancy test done at screening must be within 7 days of treatment initiation.
c. A histological confirmation of CD30-positive lymphoma can be made using the previous tumor biopsy (paraffin-embedded tissue block and slides).
d. Physical examination will include recording the patient's weight and height at Screening and weight at the End of Study visit. Symptom-directed physical examinations at other time points are to be done as needed.
e. Additional ECGs will be obtained if clinically indicated. All ECGs will be done on local equipment.
f. Vital signs include temperature, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate.
g. Collected prior to all infusions, during Cycle 1 only
h. Blood samples for full PK to be taken for cohort 1, 2 and 4 prior to infusion and at the following times points after end of first infusion on Week 1 Day 1 and Week 5 Day 1 only: 0, 2, 4, and 24 +/- 4 hours, for cohort 3: prior to infusion and at the following time points after end of the loading dose on Week 1 Day 1 and Week 5 Day 1 only: 0,2,4, and 24 +/- 4 hours
i. Skin biopsies on Day 1, pre-treatment (can be taken -7 days from day 1) and 5 (can be taken -1 day from day 5 or up to +3 days) should be taken from different lesions, if possible. If this is not possible, the biopsy on Day 5 should be taken from as far away as possible from the first one (at least 3 cm).
j. Blood needs to be centrifuged and serum to be frozen.
k. Blood for cytokines has to be taken prior to infusion, at the end of infusion and 2 hours after end of infusion on Week 1 Day 1, Week 4 Day 1 and Week 8 Day 1. Optional sample will be collected upon PD or EoS.
l. ^{18}FDG-PET and CT-Scans carried out within 4 weeks prior to the first dose.
m. Skin examination with photo-documentation (part of SOC); evaluation using mSWAT Tool
n. Optional biopsy investigator discretion
o. All assessments will be performed at screening, only positive assessment needs to be followed for response
p. Follow up guidelines per section 10.11

9.6 Study Assessments

This study comprises a screening period of up to 28 days, an 8-week treatment period, during which patients attend at least 1 weekly visit depending on the dose cohort (see Table 1), and a 3-week treatment-free follow-up/rest period, with visits held at week 11. Patients achieving a CR, PR, or SD will be allowed to receive a second cycle of therapy at the same dose and schedule as their Cycle 1 treatment. Patients will then have an end-of-study (EoS) visit at week 11 or after their last treatment.

The assessments to be carried out at each visit are described below. Details of the procedures to be carried out are presented in Sections 0 through 10.7.

All study visits are allowed ±3 day window. All visits should occur as close as possible to the protocol specified time. All assessments pre- and post-treatment have a window of ±15 minutes.

9.6.1 Registration Procedures

Eligible patients will be enrolled by the study team.

To register a patient, the following documents should be completed by a member of the research staff and delivered to the study coordinator:

- Eligibility Screening Worksheet
- Copy of required laboratory results and imaging tests
- Signed patient ICFs
- Signed Health Insurance Portability and Accountability Act (HIPAA) form.

The Study Coordinator will verify eligibility. To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Confirm registration with the Principal Investigator and treating physician.

Following enrollment, patients will be screened and should begin protocol treatment within 28 days. If a patient does not receive the study drug within 28 days of enrollment, the patient will be replaced at the discretion of the Principal Investigator.

9.6.2 Screening Period (Day -28 to Day 0)

Subjects are to undergo a screening visit ≤28 days prior to the planned first day of study treatment. Prior to conducting any Screening activities that are not considered standard of care, the investigator or designee is responsible for obtaining signed and dated written ICF and HIPAA authorization from the patient (Sections 9.6.1& 10).

Screening assessments are as follows:

- Check eligibility against study Inclusion and Exclusion Criteria (Sections 10.11.1 and 0, respectively)
- Record demographic information (age, race, gender, ethnicity)
- Record medical and surgical history
- Assess ECOG performance status
- Perform a pregnancy test on women of childbearing potential; negative results must be confirmed within 7 days prior to administration of first treatment (pregnancy testing must use same test format for all patients)
- Histological confirmation of CD30-positive lymphoma
- Physical examination (including weight and height)
- 12-lead ECG
- Vital signs (temperature, systolic blood pressure, diastolic blood pressure, respiratory rate)
- Clinical laboratory tests (chemistry, hematology, coagulation and urinalysis)
- Tumor assessment (fluorodeoxyglucose-positron emission tomography [^{18}FDG-PET] and computerized tomography (CT) scans not older than 4 weeks prior to the first dose can be used as baseline).
- mSWAT skin examination with photo-documentation (part of SOC)
- Documentation of concomitant medications and AEs.

10 INFORMED CONSENT AND OTHER STUDY PROCEDURES

Study Informed Consent

Before beginning of trial-specific screening examinations described in Section 9.6.1 and 9.6.2, the patient will be informed about the trial, including the following main points: title and aim of the trial, procedures, nature of treatment, duration, side-effects, risks, discomforts, benefits, incentives, passing on of data and material samples, confidentiality, alternatives to participating, insurance, the ethics committee's approval, patient's freedom to decide, and who to contact. Independent of the consent to the treatment with AFM13 within the trial and to treatment-related diagnostics, the patient will be informed about the scientific research project. She/he will receive the respective patient information and will be asked for the informed consent to the laboratory research project (biological and immunological analyses).

Study personnel must obtain documented consent from each potential patient prior to entering in the clinical study. Consent must be documented on the Institutional Review Board (IRB) approved ICF by obtaining the dated signature both of the patient and of the investigator conducting the consent discussion. If the patient is unable to sign the ICF, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the ICF, if capable. The impartial witness should also sign and date the ICF along with the individual who read and discussed the informed consent (i.e., study staff personnel).

The information from the ICF should be translated and communicated to the subject in language understandable to the subject. ICFs will be available in English and Spanish. When the study participant is non-English and non-Spanish speaking the CUMC IRB short form will be utilized and the consent process followed and documented as per CUMC IRB policy. A copy of the signed and dated ICF should be given to the patient before participation in the study.

The initial informed ICF and any subsequent revised written informed ICF, and written information will receive the IRB approval. The patient or his/her legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be documented.

10.1 Consent and Use of Tissue Specimens for Research

The study ICF will be inclusive for the collection of tumor tissue biopsy and blood specimens for the correlative laboratory research (biological and immunological analyses) will be explained to each patient, and, if willing to participate in this sub-part of the study, must be signed by the patient. The investigator or designee is responsible for explaining and verifying the subject's consent before obtaining any biopsy.

An additional biopsy may be requested from the patient at the EoS visit (4 weeks following the last dose of treatment). This biopsy is optional. Patients are required to undergo skin biopsies of the cutaneous tumor at no more than 6 different time points during the course of the study.

Blood specimens will be obtained from patients for the study of the immunological and biological effects of AFM13. For each patient, the analyses of the peripheral blood will be paired with those of the tumor tissue obtained at the time of the cutaneous biopsies.

10.2 Treatment Period (8 weeks)

One treatment cycle is 8 weeks, though prolongation of this period may occur due to safety reasons or unforeseen circumstances. This treatment period will be followed by 3 weeks of rest during each cycle. Study visits will be done according to the schedule of assessments (Table 2). These visits will be referred to according to the treatment Week (W1-8) and day of the treatment week (D1, 3 or 5/6), e.g. the first visit during the treatment period will be W1D1.

10.3 Week 1

During Week 1, the following will be performed:

W1D1:

On Day 1, the following assessments will be performed prior to treatment infusion:

- physical examination
- vital signs
- skin biopsy can be up to a week prior to therapy
- blood sampling for the following:
    - clinical chemistry and hematology
    - PK assessment of AFM13 trough serum levels (Cycle 1 only)
    - full AFM13 PK sampling (Cycle 1 only)
    - blood for immunology
    - blood cytokines
    - sCD30
    - anti-drug antibodies (ADAs)
- Review of concomitant medications.

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

After the end of treatment infusion (after the loading dose in cohort 3), the following will be done:

- blood samples will be taken for:
    - full AFM13 PK sampling at the following time points: 0, 2, 4, and 24 hours.
    - blood cytokines at the following time points: at the end of infusion and 2 hours post-infusion.
- Review of AEs.

On W1D5 the following will be carried out:

- blood samples (cycle 1 only) will be taken to assess:
    - blood for immunology
    - blood cytokines
    - sCD30
- skin biopsy (from different lesions than those on Day 1 if possible, or at least 3 cm from the Day 1 biopsy for larger cutaneous lymphoma (at least 5 cm in the greatest diameter ; Section 13.4)

10.4 Week 2, 3, 4, 5, 6, 7 and 8, Day 1 Visits

On W2D1 the following assessments will be performed prior to treatment infusion:

- physical examination
- 12-lead ECG
- vital signs
- blood sampling for the following:
  - clinical chemistry and hematology
  - PK assessment of AFM13 trough serum levels (cycle 1 only)
- Review of concomitant medication.
- Review of AEs.

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug. Occurrence of any AEs will be actively sought after completion of treatment.

On W3D1, the following assessments will be performed on all patients, prior to treatment infusion:

- physical examination
- vital signs
- blood sampling for the following:
  - clinical chemistry and hematology
  - PK assessment of AFM13 trough serum levels (Cycle 1 only)
  - ADAs.

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

Concomitant medications and AEs will be documented after completion of treatment infusions.

On W4D1, the following assessments will be performed on all patients, prior to treatment infusion:

- physical examination
- 12-lead ECG
- vital signs
- skin biopsy
- blood sampling for the following:
  - clinical chemistry and hematology

  - PK assessment of AFM13 trough serum levels (cycle 1 only, not repeated if patients receive a second cycle of treatment)
  - coagulation
  - blood for immunology
  - blood cytokines
  - sCD30
- urinalysis.

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

After the end of treatment infusion (end of loading dose infusion in cohort 3), blood samples will be taken for assessment of blood cytokines at the end of infusion and 2 hours post-infusion.

Concomitant medications and AEs will be documented after completion of treatment infusions.

On W5D1, the following assessments will be performed on all patients, prior to treatment infusion:

- physical examination
- vital signs
- blood sampling for the following:
  - clinical chemistry and hematology
  - PK assessment of AFM13 trough serum levels (Cycle 1 only)
  - Full AFM13 PK sampling.

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

Concomitant medications and AEs will be documented after completion of treatment infusions.

After the end of treatment infusion (end of loading dose infusion in cohort 3), blood samples will be taken for full AFM13 PK sampling at the following time points: 0, 2, 4, 20 and 24 hours post-infusion, in Cycle 1 only.

On W6D1, the following assessments will be performed on all patients, prior to treatment infusion:

- physical examination
- 12-lead ECG
- vital signs
- skin biopsy

- blood sampling for the following:
    - clinical chemistry and hematology
    - immunology
    - PK assessment of AFM13 trough serum levels (Cycle 1 only).

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

Concomitant medications and AEs will be documented after completion of treatment infusions.

On W7D1, the following assessments will be performed on all patients, prior to treatment infusion:

- physical examination
- vital signs
- blood sampling for the following:
    - clinical chemistry and hematology
    - PK assessment of AFM13 trough serum levels (cycle 1 only, not repeated if patients receive a second cycle of treatment).

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

Concomitant medications and AEs will be documented after completion of treatment infusions.

On W8D1, the following assessments will be performed on all patients, prior to treatment infusion:

- physical examination
- vital signs
- 12-lead ECG
- skin biopsy
- blood sampling for the following:
    - clinical chemistry and hematology
    - PK assessment of AFM13 trough serum levels (cycle 1 only, not repeated if patients receive a second cycle of treatment)
    - blood for immunology
    - blood cytokines
    - sCD30

Once the above assessments have been carried out, patients from all 3 cohorts will receive an infusion of study drug.

Concomitant medications and AEs will be documented after completion of treatment infusions.

After the end of treatment infusion (end of loading dose infusion in cohort 3), blood samples will be taken for assessment of blood cytokines at the following time points: at the end of infusion and 2 hours post-infusion.

10.5 Week 11, Day 1- Follow-up Period

All patients are to return to the study site for a follow-up visit in Week 11. At this visit, the following will be performed:

- physical examination (including weight and height)
- vital signs
- clinical laboratory tests (chemistry, hematology, coagulation and urinalysis)
- concomitant medication
- tumor assessment CT/^{18}FDG-PET plus CT
- (m)SWAT skin examination with photo-documentation (part of SOC)
- restaging.

If a second treatment cycle is administered, tumor assessments will also be performed at Week 11 of the Cycle 2.

If a serious and persistent side-effects of CTCAE grade 3 or grade 4 occur and the patient could not continue study drug, the assessment of treatment response should be performed within 4 weeks of the last dose of study drug.

10.6 Restaging Visit

Restaging is done concurrently with the tumor assessment for response (Week 11 of each cycle).

Assessments will include:

- interim case history (symptoms)
- physical examination
- laboratory assessments (clinical chemistry and hematology)
- (m)SWAT skin examination with photo-documentation (part of SOC)
- CT/MRI monitoring (if applicable)
- ^{18}FDG-PET mandatory

10.7 End of Study Visit

Subjects will return to the study site for an EoS visit after the last treatment or during week 11. At this visit the following will be performed:

- physical examination
- vital signs
- 12-lead ECG
- Optional skin biopsy, if requested by the investigator and agreed upon by the patient
- concomitant medication
- blood sampling for the following:
  - clinical chemistry, hematology and coagulation
  - blood for immunology
  - sCD30
  - ADAs

Patients who discontinue the study for any reason should undergo EoS assessments, if at all possible.

10.8 Duration of Follow Up

Patients will have an end of study visit after their last dose of drug to evaluate safety. Patients will be further followed every three months by phone call after the 4-week safety evaluation for one year, or until they begin a new treatment for their disease, for evaluation of delayed toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

10.9 Discussion of Study Design

This is an open label, Phase Ib/IIa study designed to evaluate the biological and immunological activity of AFM13 in the tumors and peripheral blood of lymphoma patients treated with this drug.

This study is to be carried out in patients with histologically-confirmed CD30-positive lymphoma with cutaneous presentation who have failed or have been intolerant to at least one prior therapy for the current disease with no further standard therapy available. AFM13 has shown preliminary anti-tumor activity in a Phase I study in patients with relapsed or refractory HL; a Phase II proof-of-concept study is underway in relapsed/refractory HL.

In the current study, doses of AFM13 will be administered to patients (Table 1). These doses have been chosen based on the results of the Phase I trial of AFM13 in patients with relapsed or refractory HL (see 10.10). Results from the Phase I study showed that AFM13 was safe across the dose range tested, with the MTD not reached. The safety profile was acceptable for

AFM13 doses in the range from 0.05 mg/kg to 7 mg/kg (i.e., over a 140-fold dose increase), and a more dose-intense, twice-weekly regimen of 4.5 mg/kg did not result in increased risk. Based on the safety data of the Phase I trial, it can therefore be anticipated that the administration of AFM13 at the proposed dose levels and drug exposure should also be safe and feasible. Anti-tumor responses were observed in patients who had received at least 1.5 mg/kg. A range of different dose regimens are being tested in the present study to try to gather as much information as possible about the optimum dosing regimen for AFM13.

The use of a placebo control would neither be considered ethical nor scientifically necessary in this exploratory study.

Activity assessments (response rate, response duration and PFS) will be assessed according to global assessment consensus recommendations for standardization of definition of response in skin, nodes, blood and viscera, GR (global response) score, and other endpoints in MF and Sezary syndrome. These recommendations are outlined in the consensus statement of The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer in 2011[36], and the Revised Response Criteria for Malignant Lymphoma [35].

10.10 Risk/Benefit and Ethical Assessment

The field of immune-oncology has been fueled by recent approvals of biological agents (i.e., mAbs,) for therapy of malignant melanoma, lung cancer, ovarian cancer so far (ipilimumab, nivolumab, pembrolizumab) [38-40]. Because tumor development and growth is known to be associated with failure of the immune system in its surveillance capacity, it has become increasingly clear that immunological and biological factors must exist in the body that either promote tumor development, provide growth advantage and survival, and/or abrogate the ability of the nascent malignant cell or that of the established tumor to survive the immunological attack. Knowledge of these factors is crucial to our understanding of how to refine the dose and schedule of our current drugs and drug candidates in order to develop more efficacious therapies. The main aim of this study is to identify and characterize immunological and biological factors that may correlate with clinical activity or resistance to therapy. Again, this knowledge is vital to our future efforts to design rationally drugs that are likely to have a positive clinical outcome for patients with lymphoma.

This study is to be conducted in patients with histologically-confirmed CD30-positive lymphoma with cutaneous presentation that has relapsed or is refractory to at least 1 prior therapy for the current disease, and has no further standard therapy available (Brentuximab Vedotin is only FDA approved in HL and ALCL with no approval in other lymphomas). AFM13 is a bispecific tetravalent CD30/CD16A chimeric antibody (TandAb) developed for the treatment of CD30-positive malignancies, and has shown promising anti-tumor responses in HL patients with relapsed or refractory HL [29, 34]. AFM13 is a novel drug candidate for CD30-positive lymphoma, which restricts its use in the current study to patients who have no further standard therapy available.

In the Phase I study in relapsed or refractory HL, treatment with AFM13 was well tolerated; AEs were mainly mild to moderate, with fever and chills being the most frequently reported events [29, 34]. One patient in the 0.5-mg/kg dose cohort developed a possibly drug-related grade 4 hemolytic anemia. Preclinical data did not indicate increased risk of hemolytic anemia, but autoimmune hemolytic anemia has been described in HL, in particular in patients with stages III and IV disease [41]. There were no signs of hemolytic anemia noted in other patients treated with AFM13, even at doses that were up to 14 times higher. The MTD was not reached, and an IDMC did not have safety concerns regarding AFM13 clinical development.

In conclusion, AFM13 has a well acceptable safety profile and demonstrated preliminary activity in CD30-positive HL. Patients in this translational study will also have a CD30-positive lymphoma. Again no further standard treatment options are available to them. Hence, there is a huge medical need for safe and effective therapies in this patient population. Therefore, it is not unreasonable to conclude that the benefits may outweigh the risks, especially given the clinical experience with AFM13 in the previous Phase I trial in patients with heavily pre-treated relapsed or refractory HL [29, 34].

10.11 Selection of Study Population

10.11.1 Inclusion Criteria

Both men and women of all races and ethnic groups are eligible for this trial.

Patients eligible for enrolment in the study must meet all of the following criteria:

1. Age ≥18 years
2. Histologically confirmed CD30-positive lymphoma with cutaneous presentation
3. Failure or intolerance to at least one prior therapy for the current disease
4. Presence of one or more cutaneous lesions (measuring at least 1 cm x 1 cm in size; if only one lesion is present it should be up to the investigator discretion to determine eligibility)
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤2
6. Adequate organ and marrow function
    a. Platelets ≥50,000/μL
    b. Absolute neutrophil count ≥ 1,000/μL
    c. Bilirubin < 1.5 x institutional upper limit of normal (ULN) or < 3 x ULN in patients with Gilbert's disease or liver involvement
    d. Serum albumin ≥ 2.0 g/dL
    e. Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤2.5 × institutional ULN or, in the case of liver involvement by the primary disease AST/ALT ≤ 5 x ULN
    f. Creatinine≤1.5 x institutional ULN or estimated creatinine clearance of ≥45 mL/min by the Cockcroft-Gault equation or measured creatinine clearance >45 mL/min
7. Females of child bearing potential must have a negative serum pregnancy test with 7 days prior to first dose of treatment. Female patients of childbearing potential and all male partners must agree to use double barrier methods of contraception throughout the study period and for at least 30 days following investigational product discontinuation.

8. Ability to understand and the willingness to sign a written informed consent document.

10.11.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible the study:

1. Any cancer-related therapy for the current disease within 2 weeks of screening (all supportive care measures are allowed)
2. Major surgery within 2 weeks prior to first dose of study drug
3. Evidence of active central nervous system (CNS) involvement
4. Requirement for systemic immunosuppressive therapy (e.g. Graft-versus-Host Disease [GVHD] therapy within 12 weeks before the first dose of study drug)
5. Uncontrolled concurrent serious illness.
6. Concurrent malignancy requiring cytotoxic or immunotherapy based treatment.
7. Active infection including hepatitis B-carrier status, hepatitis C virus (HCV) infection (patients with positive serology must have a negative Hep B and Hep C viral load at screening)
8. Known HIV-positive status
9. Any significant diseases medical condition, laboratory abnormality, or psychiatric illness that would exclude the subject from participate or interfere with study treatment, monitoring and compliance such as:
    a. unstable angina pectoris, symptomatic congestive heart failure (NYHA III or IV), myocardial infarction ≤ 6 months prior to first study drug, clinically significant and uncontrolled cardiac arrhythmia (e.g. atrial fibrillation/flutter ventricular cardiovascular physiology is allowed), cerebrovascular accidents ≤ 6 months before study drug start
    b. severely impaired lung function
10. Serious, systemic infection requiring treatment ≤7 days before the first dose of study drug
11. Any severe, uncontrolled disease or condition, which in the investigator's opinion, may put the subject at significant risk, may confound the study results, or impact the subject's participation in the study.

10.12 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

10.13 Withdrawal of Patients

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or at the institution.

Any subject who withdraws consent to participate in the study will be removed from treatment and/or study observation immediately upon the date of request. All subjects who withdraw from treatment prematurely before completion of the protocol-specified tests and procedures are strongly encouraged to complete the safety follow-up visit.

If a patient's participation is terminated prematurely, the cause for the early termination and the date and time of the termination will be documented in the patient's case report form (CRF) and in the final Clinical Study Report (CSR).

Patients will be withdrawn from treatment for the following reasons:

1. Disease progression
2. Unacceptable toxicity, as defined by the CTCAE Version 4 and in the determination of the Principal Investigator
3. Withdrawal of consent
4. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator

Female patients of childbearing potential will be asked to adhere to the requirements of not becoming pregnant and using an acceptable method of contraception as specified in Section 0.

If a patient withdraws or is dismissed from the study, all procedures planned for the EoS visit (Section 10.7) will be completed, where possible. If a patient is withdrawn or dismissed from the study, all ongoing AEs should be followed up for 30 days after the last administration of study drug, with the exception of any ongoing study drug-related AEs, which should be followed until resolution or stabilization (if in the investigator's opinion, the AE is unlikely to resolve due to the patient's underlying disease).

10.14 Replacement of Subjects

Patients whose mandatory biopsies are not obtained during cycle 1, will be replaced, though the individual patient may continue their therapy if it is deemed that they are deriving benefit from it.

11 INVESTIGATIONAL PRODUCT

11.1 Identity of Study Treatment

AFM13 is a bispecific tetravalent CD30/CD16A chimeric antibody (TandAb) developed for the treatment of CD30-positive malignancies. It was developed to promote the recruitment of NK cells through the binding to CD16A, and through this engagement, the killing of CD30-expressing tumors. AFM13 is being manufactured in compliance with Current Good Manufacturing Practice (CGMP) regulations enforced by the United States (US) Food and Drug Administration (FDA). AFM13 was studied in a pilot Phase I trial in patients with relapsed or refractory HL, using a dose-escalation (3+3) design to evaluate the safety, tolerability, and determine the MTD [34].

Affimed will supply AFM13 for IV infusion to the investigator as a sterile lyophilized solid powder for reconstitution for infusion. Each 20 mL clear glass type I vial contains 10 mg AFM13. Excipients contained in AFM13 are listed in Table 3.

IL-CSM (Lörrach, Germany), Affimed's clinical supplies logistics partner, will send the study drug to the responsible pharmacist at the trial center through a third party drug warehouse and distribution contractor approved by the US government and/or the State of New York for drug storage and distribution.

One vial of study treatment contains 10 mg AFM13.

Table 3: Composition of AFM13 for Injection

Component	
Excipients	Polysorbate 20 0.01% (w/v) Trehalose dihydrate 8.0% (w/v) Sodium dihydrogen phosphate dihydrate 13.5 mM Di-Sodium hydrogen phosphate dihydrate 1.5 mM
Solvent	Water for Injection: 7.5 mL/vial
Stability	Stability testing of AFM13 revealed a shelf-life of 48 months
Storage and handling:	The investigational medicinal product AFM13 is stored at 2-8°C: After preparation, the solution may be stored at 2-8°C for a maximum of 24 hours before start of infusion. No special storage or handling instructions are required.

The Quality Control Standards and requirements for the study medication are described in separate release protocols/Certificate of Analysis.

11.2 Treatment Storage

As described in Table 3, AFM13 is to be kept at 2-8°C. After preparation, the solution may be stored at 2-8°C for a maximum of 24 hours before start of infusion.

All medications must be stored in a safe and locked place with no access for unauthorized personnel.

11.3 Treatment Packaging and Labeling

Clinical trial supplies will be provided in cartons containing single-use glass vials (20 mL vials) of lyophylized AFM13 for infusion (10 mg).

All vials and secondary packaging will be labeled for the purpose of the clinical trial in accordance with applicable regulatory requirements.

11.4 Preparation of Study Treatment

The solid is to be reconstituted with 7.5 mL of sterile water for injection to give a total volume of 8 mL at a concentration of 1.25 mg/mL AFM13, with a pH specification of 6.0 ±0.5 and isoosmolarity (300 ±50 mOsmol/kg). Details on the further dilution in sterile 0.9% saline to produce the final volume for infusion and the drug shipment and re-supply process are described in a separate Pharmacy Manual.

For a dose of 1.5 mg/kg, a patient with a body weight of 70 kg receives an absolute dose of 105 mg AFM13 which is equivalent to 10.5 vials. The solution of these vials will be further diluted in sterile 0.9% saline to a final volume of 500 ml.

11.5 Administration of Study Treatments

AFM13 is administered by IV infusion. For cohort 1 and 2 the first dose will be given over 4 hours; if the first dose is well tolerated, the subsequent infusion periods may be reduced by 30 minutes per infusion to minimum infusion duration of 1 hour. In cohort 3 weekly treatment will consists of a loading AFM13 dose of 1 mg/kg to be applied on day1 as 1-hour infusion, followed by a 6 mg/kg AFM13 as continuous infusion over 5 days. Cohort 4 will use the same dosing schedule as cohorts 1 and 2.

On Day 1 each treatment week, patients should receive premedication with antihistamines (e.g. 4 mg dimetindene) before AFM13 infusion start.

Treatment should begin immediately after the patient has been enrolled and in- and exclusion criteria are checked.

All patients should receive at least one 8-week cycle of AFM13. For those patients with a documented response or SD in Cycle 1 Week 11, a second cycle of AFM13 will be administered.

Before the administration of AFM13, rescue medication should be prepared for the case of AFM13 IRRs.

In order to assess protocol adherence during treatment and to evaluate dose reductions, treatment delays, early treatment terminations and reasons, the following measures have to be documented in the patient's CRF on each treatment day:

- date of treatment
- AFM13 dose
- reason for treatment delay or dose deviation (if applicable)
- date and reason for early treatment termination (if applicable).

11.6 Study Treatment Accountability

Records shall be maintained of the delivery of study treatments to the study center, the inventory at the study center, the use of each subject and the return of unused to the study center pharmacy.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study medication and to the study subjects.

The investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study medication received from the Sponsor is reconciled.

12 STUDY ASSESSMENTS

12.1 Informed Consent

Details for obtaining informed consent are provided in Section 10

12.2 Medical History and Physical Examinations

Vital signs including temperature, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate are to be taken as per institutional standard of care prior to, during, and after each dosing.

Physical examinations are to be performed as clinically indicated

12.3 Documentation of Side-effects

Exact documentation of side-effects by the treating physician is necessary. The evaluation should be based on the NCI-CTCAE version 4.0. The treating physician evaluates the side-effects during each cycle according to these criteria. Side-effects of grade 3 and grade 4 are documented. The documentation of SAEs is described in Section 0.

12.4 Reported Undesirable Effects

Adverse events most frequently observed with AFM13 in the Phase I trial included IRRs of mild or moderate severity. Infectious complications such as nasopharyngitis or pneumonia were significantly less frequent and were probably related to prior heavy chemotherapies. Only one DLT, a hemolytic anemia CTCAE grade 4, was reported; the patient subsequently died due to aspergillus pneumonia and multi-organ failure which was not assessed as drug-related. No further cases of anemia were documented; neither were other relevant laboratory findings reported.

12.5 Management of Infusion-related Reactions

AFM13 should be administered with antihistamine (H1/H2 antagonists) premedication as described in Section 11.5

The management of IRRs is described in detail in Table 4 In the case of the manifestation of an IRR, the AFM13 infusion should be stopped and, dependent on the severity of the reaction, the treating physician should decide about the application of an H1/H2 antagonist and corticosteroids. If fever or chills occur, the administration of acetaminophen is recommended. Dyspnea or hypertensive/hypotensive blood pressure dysregulation might require an intensive care treatment. The AFM13 infusion can be continued as described in Section 11.5 when the IRRs have resolved. Subjects in Cohort 4 may be dose reduced to 1.5 mg/kg if they encounter persistent IRRs at 4.5 mg/kg.

Table 4: Management of AFM13-associated Infusion-related Reactions

CTCAE Grade	Management of reaction	Current AFM13 dose	Any subsequent AFM13 doses
0	-	Premedication with H1 and H2 antagonist e.g. 4 mg dimetindene	
1	Additional medication not indicated	No change Consider reducing the infusion rate by ≥25%*	Premedication with H1 and H2 antagonists Consider reducing the infusion rate by ≥25% especially when Grade 1 IRR re-occurs*
2	Additional therapy with corticosteroids e.g. 150-200 mg iv prednisolone or equivalent Consider further antihistamines, NSAIDS, iv fluids, and narcotics	Stop infusion until symptoms resolved Continue infusion on same day. Reduce infusion rate by ≥25%* If patient does not tolerate AFM13 with reduced infusion rate omit dose	First occurrence: Premedication with H1 and H2 antagonist Re-occurrence: Premedication with H1 and H2 antagonist and corticosteroid Consider reduction of infusion rate by ≥25%* If Grade 2 events re-occur despite premedication (and reduced infusion rates), consider dose reduction to 1.5mg/kg or discontinue AFM13 treatment
3	Additional therapy with corticosteroids e.g. 150-200 mg iv prednisolone or equivalent Consider further antihistamines, NSAIDS, iv fluids, and narcotics	Cohort 1 and 2: stop and omit the rest of infusion Cohort 3 loading dose: stop and omit the rest of infusion, continue with CIVI at the next day If patient received CIVI, suspend CIVI for min. 24 hours.	Premedication with H1 and H2 antagonist and corticosteroid Reduce infusion rate by ≥25%* If Grade 3 events re-occur despite premedication and reduced infusion rates consider dose reduction to 1.5 mg/kg or permanently discontinue AFM13 treatment
4	Consider intensive care Additional therapy may include (but not limited to) corticosteroids, antihistamines, NSAIDs, iv fluids, narcotics, pressors, ventilation, epinephrine	Permanently stop AFM13 treatment	

*not applicable for the CIVI

12.6 Management of Other AFM13-related Side Effects

The management of other AFM13-related AEs is described in Table 5. . If a patient presents with symptoms indicative for nasopharyngitis or pneumonia, samples for microbiological diagnostics should be obtained. The patient should be admitted to hospital and an empirical antibiotic treatment should be immediately started in the case of pneumonia or if the infection is associated with a significant impairment of the general condition.

Continuous safety analyses (AEs, safety clinical laboratory assessments, vital signs, ECGs) will be regularly performed by a Principal Investigator-led safety team to ensure the safety of the patients. In the case of a potential significant safety problem the Principal Investigator in consultation with groups such as the FDA, IRB, data monitoring committee and/or statisticians may decide on the termination or temporary cessation of the trial.

Table 5: Management of Other AFM13-associated Adverse Events

CTCAE grade	Management of other AFM13-associated AEs
Grade 1	Symptomatic treatment as applicable
Grade 2 or 3	Interruption of AFM13 infusion if event develops during infusion; symptomatic treatment as applicable Delay next AFM13 dose until the AE has recovered to CTCAE Grade 0 or 1; if delay was more than 21 days, permanently discontinue AFM13 treatment Exception: in the case of documentation of a CTCAE Grade 2 or 3, non-clinically significant, laboratory value or non-clinically significant AE e.g. Grade 2 fatigue, the treatment can be continued under close monitoring of the laboratory changes (suggest two-day intervals)
Grade 4	Permanent discontinuation of AFM13, symptomatic treatment as applicable

AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events

12.7 Study drug adjustments

No study drug adjustment is permitted in the trial, except for the management of IRR as explained in Table 4. Adjustment in this case involves infusion rate.

12.8 Treatment Schedule Interruptions (Delayed or Skipped Doses)

The treatment with AFM13 should be interrupted, if an AE occurs according to Table 4 and 5. Any skipped dose will not be made up. If there is a delayed of more than 3 weeks, the patient will be removed from study.

12.9 Study Drug Discontinuation

The study drug must be discontinued if a drug-related CTCAE Grade 4 AE occurs at any time.

Patients who discontinue study drug should be scheduled for an end-of-treatment (EoT) visit one week after the last dose of study drug, at which time all of the assessments listed for the EoS visit (Section 10.7) will be performed. A form should be completed, giving the date and reason for stopping the study drug. It is recommended to have these patients return for the Restaging Visit on what would have been their Week 11 of that cycle after the last AFM13 dose for post-treatment safety evaluations, for tumor assessments and restaging (Section 10.6). If a new therapy is planned to be started before Week 11, the final restaging visit should be performed before administration of this therapy.

12.10 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication specifically prohibited during the trial, discontinuation from trial therapy may be required. The final decision on any supportive therapy rests with the Principal Investigator in consultation with the patient and/or the patient's primary physician.

All treatments considered necessary for a patient's welfare may be administered at the discretion of the Principal Investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the CRF including all prescriptions, over-the-counter (OTC) medications, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial with exception of the treatment of AEs occurring during the study:

- antineoplastic systemic chemotherapy or biological therapy, including immunotherapy not specified in this protocol;
- investigational agents other than AFM13;
- radiation therapy;
- systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved at the Principal Investigator's discretion. However, chronic use of systemic steroids is not allowed. Note: Inhaled steroids are allowed for management of asthma.

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 trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited on entry to this trial.

There are no prohibited therapies following withdrawal of study treatment.

Treatment for IRRs is provided in Table 4. Dependent on the symptoms and the severity of the infusion-related reaction the additional application of acetaminophen, and 100 mg prednisone as well as epinephrine and/or bronchodilators might be indicated.

No drug interactions of AFM13 have been observed so far or are likely due of the biological nature of AFM13. The treating physician should carefully conduct a risk assessment based on the severity of clinical symptoms, and prepare a high-risk patient for intensive care management in an intensive care unit (ICU).

13 ASSESSMENT OF EFFICACY

13.1 Measurement of Biological Effects in Tumor and Blood

The primary objective of this study is to evaluate the immunological and biological effects of the study drug. Key analyses will be conducted by CUMC and contract clinical laboratory services providers. Details of the assays will be provided in the study Laboratory Manual Manual.

13.2 Measurement of Clinical Efficacy

Although clinical response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. Patients will be re-evaluated at the end of each cycle. Response will be evaluated with physical examination, Revised Response Criteria for Malignant Lymphoma, 2007, mSWAT, CT as defined by the guidelines of the global assessment consensus recommendations for standardization of definition of response in skin, nodes, blood and viscera, GR score, and endpoints in MF and Sezary syndrome as outlined by the consensus statement of The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer in 2011 [36]. PET/CT will be utilized as recommended by the Revised Response Criteria for Malignant Lymphoma, 2007 [35].

All assessments over all the treatment cycles will use the same definition for measurable disease. The measurable disease recorded in screening of the trial prior to treatment administration will be utilized as the reference for response.

13.3 Definitions

Evaluable for objective response. Patients who complete 1 cycle of therapy according to the study protocol, and have had their disease re-evaluated will be considered evaluable for response. When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. Similarly, patients whose tumour assessments are not repeated/incomplete will also be considered non evaluable for response. Patients evaluable for response will have their response classified according to the definitions stated below. Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered.

Table 6: Global Response Score

Global Score*	Definition	Skin	Nodes/Blood/Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any
		SD	CR/NI, PR, SD in any category and no category has a PD
PD	Progressive disease	PD	PD in any category
Relapse	Recurrence disease in prior CR		Relapse in any category

CR=complete response; NI=noninvolved; PD=progressive disease; PR=partial response; SD=stable disease
*It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation also be generated.

13.4 Skin Biopsy

Skin biopsies should be taken from different lesions if possible. Examples where lesions may be excluded from biopsy might include those lesions where the patient does not consent due to cosmesis or pain, where palliative radiotherapy has been administered, skin infection or trauma has arisen. If this is not possible, the second biopsy should be taken as far as possible away from the first one, preferably at least 3 cm away. Handling of tumor samples is described in a separate Immunobiology Research Manual. Patient inclusion criteria describe eligibility based on the number of cutaneous neoplastic lesions (see section 10.11.1: Inclusion Criteria).

13.5 Objective Response Rate

Objective Response Rate (ORR) = CR + PR based on evaluation of best response in each patient.

13.6 Modified Severity-Weighted Assessment Tool

The SWAT is an objective, quantitative, severity-weighted method to assess the extent of skin lesions. A SWAT score is derived by measuring each lesion as a percentage of total body surface area (%TBSA) and multiplying it by a severity-weighting factor (1=patch, 2=plaque, 4=tumor). All individual numbers are then added to produce a total score.

The body is divided into 12 regions with percentage of total body surface area (%TBSA) based on methodology used to assess burns. The extent of skin disease is assessed for each region and quantified by using the subject's palm as a "ruler" to measure the %TBSA involvement within each region.

Subject's palm with 4 fingers, excluding the thumb and measured from wrist to fingertips, is 1% of TBSA. Subject's palm without fingers is 0.5% of TBSA.

Table 7: Modified Severity-Weighted Assessment Tool

Skin Lesion Definitions		
Lesion Type	Abnormal Skin	Erythema
Patch	not elevated from normal skin	flat or with mild infiltration
Plaque	elevated from normal skin by < 5 mm	elevated or with moderate infiltration
Tumor	elevated from normal skin by ≥ 5 mm	with fissuring, ulceration, or tumor

SWAT Score Calculation

Total mSWAT (maximum score = 400) = sum of %TBSA from all body regions affected by patches x severity-weighting factor of 1 + sum of %TBSA from all body regions affected by plaques x severity-weighting factor of 2 + Sum of %TBSA from all body regions affected by tumors x severity-weighting factor of 4

Objective response rates will be evaluated using the global assessment consensus recommendations for standardization of definition of response in skin, nodes, blood and viscera, GR score, and endpoints in MF and Sezary syndrome as outlined by the consensus statement of The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer in 2011 [36] and the Revised Criteria for Malignant Lymphoma [35].

13.7 Computerized Tomography/Magnetic Resonance Imaging

If CT with contrast medium was used for disease measurement for initial staging, then the same modality must be used for restaging. The imaging modality used to assess the stage of disease and the target lesions used at baseline must be used again for response assessment, and for restaging. Additional imaging technique may be used to diagnose a new lesion (i.e. CNS involvement) when deemed appropriate.

The CT/MRI will be done per the facility's standard procedures.

13.8 Whole body ^{18}FDG-PET Scan

Tumor assessments will be done via whole body ^{18}FDG-PET scan.

The investigator will check the patient's fasting blood glucose prior to the ^{18}FDG-PET scan and ensure that the fasting blood glucose is below 200 mg/dL. The investigator should also ensure that the patient is able to lie down for 60 minutes.

13.9 Exploratory Studies

Exploratory analyses will be conducted on stored tissues and blood at a later time to investigate molecular profiling of the tumors using cytogenetics (using fluorescence in situ hybridization or FISH), gene profiling by New Genome Sequence (NGS) or other molecular techniques. Finally, CTCs will be analyzed at the same time points as those for the analysis of the biological effects, and will be determined during Cycle 1 only.

A comprehensive analysis of NK cell function may require as little as 3.5 ml of heparinized whole blood. We will conduct similar analysis in tissue samples. This will help in the characterization of NK cell subsets and assessment of NK cell activation in the peripheral blood. In addition, phenotypic and functional characterization of other immune cells, including T cells, MDSCs, Tregs and tumor cell surface and internal proteins identification and their role in specific pathways may be explored to gain potential insights into the key biochemical and molecular drivers of response or resistance to AFM13 therapy.

Anti-drug antibodies will be analyzed at an Affimed-contracted laboratory facility in UK.

These assessments and the assessment schedule are described in detail in the Immunobiology Research Manual.

14 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 9.5.

All patients will be evaluated for safety if they have received any study drug. The start and stop time of each AFM13 infusion must be documented. Toxicity assessments will be continuously performed during the treatment phase. Some of the assessments listed below may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically indicated.

14.1 Adverse Events

Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for enduring this.

Evaluable for toxicity.

All patients who have received at least one dose of study drug will be evaluable for toxicity starting from Day 1 of Cycle 1.

Adverse Event
An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse Reaction
An adverse reaction is any detrimental and unintentional reaction to an investigational drug, independent of the administered dose.

Serious Adverse Event
An SAE is defined as, but is not limited to, one that:

- Results in death
- Is life-threatening (Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.)
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A hospital stay is any stay in a hospital as an in-patient for at least one night. A hospitalization that has already been planned before the first administration of the investigational drug is not considered as an SAE.

14.2 Unexpected Adverse Reaction

An unexpected adverse reaction is an adverse reaction that does not correspond to the existing investigator brochure detailed information on the investigational drug in terms of the nature and severity of this reaction.

The existing information on the investigational product is stated in the current version of the AFM13 IB, which is to be used as a reference.

14.3 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a case in which the occurrence of a serious adverse reaction that could not be expected is suspected (there is a certain or possible relation to the administered protocol medication), and the nature and severity of this reaction do not correspond to the existing information on the respective investigational drug. The reaction is rated as serious and a relation between the investigational drug and the reaction is considered to be possible. If the relation between adverse reaction and protocol medication is not evaluable or not evaluated, the relation is regarded as possible in context of the SUSAR. The existing information on the respective investigational drug can be found in the IB.

14.4 Causality/Relationship

For each event that occurs, an assessment of causality has to be performed.

- Not Evaluable
  It is not possible to assess whether there is a relation with the administered investigational drug(s) or not.
- Not Evaluated
  An event that was reported as AE, but for which a relation with the administered investigational drug(s) was not established at the time of reporting because further data were necessary or is currently being compiled.
- No Relation
  An event on which there is sufficient information available to assume that there is no relation with the investigational drug.
- Possible Relation

An event that follows a matching chronological course after administration of the investigational drug, or that follows a known or expected scheme of response to the suspect investigational drug, but which could also have been caused by a number of other factors.

- Probable Relation
  An event that follows a matching chronological course after administration of the investigational drug, or that follows a known or expected scheme of response to the suspect investigational drug, and that disappears after the administration is discontinued or reduced to a lower dose, and that cannot be explained by the known clinical condition of the patient.
- Certain Relation
  An event that follows a matching chronological course after administration of the investigational drug, or an event due to which the concentration of the investigational drug in the body tissues or fluids is measured, that follows a known or expected scheme of response to the suspect investigational drug, and that disappears after the administration is discontinued or reduced to a lower dose and reappears after repeated exposure.

14.5 Recording of Adverse Events

For the purposes of this study, any detrimental change in the patient's condition, after signing the informed ICF and up to completion of the EOS assessments should be considered an AE.

Adverse events will be recorded the signing of informed consent until the EOS visit.

Every grade 3/4 AE must be documented, independent of the investigator's opinion whether there is a causative relation with therapy or not.

Unexpected AEs are to be documented on the respective CRF form (AE form). Documentation includes the nature of the event, beginning, duration, intensity/stage and causality.

All AEs have to be tracked until they have subsided or stabilized.

All AEs that are not rated as unexpected have to be documented.

All ongoing AEs should be followed up for 30 days after the last administration of study drug, with the exception of any ongoing study drug-related AEs, which should be followed until resolution, unless in the investigator's opinion, the AE is unlikely to resolve due to the patient's underlying disease. Any new SAEs occurring up to 60 days after the last administration of study drug should be reported to *spm^2 – safety projects & more GmbH*, the Affimed 's safety Clinical Research Organization (CRO) according to Section 14.3

At any time after the follow-up visit, if an investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the IRB/EC and FDA according to institutional and federal guidance, respectively. Affimed's safety *CRO spm^2* shall also be notified. The reports will be sent to

spm^2 – safety projects & more GmbH
Aurum 05
Goldbeckstr. 5
69493 Hirschberg a. d. Bergstraße, Germany
Safety Fax: +49 621 - 5 70 59 71
Email: Affimed-PHV@spm2-safety.com

The investigator will assess the degree of severity as follows:

- mild
- moderate
- severe
- immediately life-threatening

The evaluation is to be based on the official CTCAE version 4.0.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 14.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

14.6 Expedited Adverse Event Reporting

The Principal Investigator agrees to provide appropriate parties with copies of all serious adverse events within two working days. Reportable information should always be reported by the Principal Investigator directly to the IRB within 5 working days from when the Principal Investigator learns of the event or new information. Additionally, the Principal Investigator agrees to report any pregnancy occurring in association with use of study drug to the appropriate parties.

Serious adverse events (SAE) are defined above. The investigator must inform spm^2 in writing using a spm^2 SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to spm^2 by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including as assessment of the casual relationship between the event and the investigation product, if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The institutional protocol number should be included on the SAE reports (or on the fax cover letter) sent to

spm^2. A copy of the fax transmission confirmation of the SAE report to spm^2 should be attached to the SAE and retained with the patient records

NAME OF SAE REPORTING ADDRESS (as appropriate)
spm^2 – safety projects & more GmbH Aurum 05 Goldbeckstr. 5 69493 Hirschberg a. d. Bergstraße, Germany Safety Fax: +49 621 - 5 70 59 71 Email: Affimed-PHV@spm2-safety.com

The investigator is responsible for reporting any SAEs to the FDA. **Serious** AEs that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the IB, or reference safety information document should be reported promptly to the FDA by telephone (1-800-332-1088), fax (1-800-FDA-0178), or via MedWatch Online. Fatal or life-threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Note: All deaths on study require expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

Expedited AE Reporting Timelines

One business day; 5 calendar days – The investigator must initially report the AE within 1 business day of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.

10 calendar days - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited AE reporting exclusions.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported if the event occurs following treatment.

14.7 Adverse Event Updates/IND Safety Reports

The Principal Investigator shall notify FDA via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Affimed and/or spm^2 – safety projects & more GmbH and the IRB.

14.8 IND Reporting

During the course of the study, the Sponsor may determine that certain safety reports are required to comply with regulations. The Sponsor is responsible for submission of such reports to their IND. The Investigator may receive a letter called an "IND Safety Report" from this study and/or other Affimed sponsored studies (cross reports). These reports must be submitted to the IRB/EC as required.

Annual IND Report as well as any IND amendments will be to the reported to the CUMC IRB as well as the FDA.

14.9 Pregnancy

AFM13 might cause harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women.

Women of childbearing potential will be advised to avoid becoming pregnant while receiving treatment. Women enrolled in this study should either be post-menopausal, free from menses for >2 years, surgically sterilized, or willing to use 2 adequate barrier methods of contraception to prevent pregnancy or agree to abstain from heterosexual activity throughout the study, starting with Visit 1. Women of childbearing potential must have a negative serum pregnancy test (β-hCG) within 7 days prior to receiving the first dose of study drug. Men enrolled in the study must also agree to an adequate method of contraception for the duration of the study.

If a patient or their partner inadvertently becomes pregnant while on study, the patient will immediately be removed from the study and the drugs will be discontinued. Investigators will follow the patient monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to appropriate parties

within 24 hours if the outcome is an SAE (i.e. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study, the pregnancy will be reported to appropriate parties. Reporting of pregnancy will follow the guidelines outlined in Section 14.3.

14.10 Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Signs and symptoms as well as changes in the laboratory values should be documented in summary as one AE. Unusual laboratory values have to be assessed by the investigator regarding their clinical relevance and – only if they are assessed to be relevant – they have to be documented as an AE. Changes in the peripheral blood count are within the scope of this trial. Therefore, every grade 3/4 anemia, neutropenia, lymphopenia or thrombocytopenia has to be documented as AE.

14.11 Deaths

Should a death occur within the study period or within 60 days after the last administration of study drug an AE form and an SAE form should be completed, detailing the AE that resulted in the death (NB, death is an outcome, not an event). The SAE must be reported to the IRB according to institutional guidelines and FDA within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

14.12 Overdose

Drug overdose should be reported in the same format and within the same timelines as an SAE, even if they may not result in an adverse outcome. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

AFM13 overdose is defined as any dose administration where > 10% over 7 mg/kg is administered whether or not associated with an AE.

If the pharmacy discovers that an overdose has or may have been administered, they should contact the Study Investigator and Study Coordinator

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14.13 Laboratory Assessments

Blood and urine samples will be collected for the following analyses:

- Complete Blood Count
- Serum Chemistry
- Urinalysis

A serum pregnancy test will be done on all women of childbearing potential; a negative test result must be obtained prior to the first administration of study treatment.

Samples will be collected per institutional procedures and analyzed in the local laboratory.

14.14 Biological Parameters/Markers

Specifications for collection and handling of samples for the assessment of biological parameters/markers, are included in the Immunobiology Research Manual.

Biological parameters/markers will be analyzed according to the scope of work and laboratory capabilities at Principal Investigator's study center. Additional analyses will be performed at contract service laboratory facilities as detailed in the Immunobiology Research Manual.

14.15 Electrocardiogram Assessments

A resting 12-lead ECG will be done to assess the patient's general suitability for therapy as well as to record her/his initial status to enable assessing treatment-related toxicities that may occur later on.

ECGs will be performed after 5 minutes rest, in the supine position.

In case of pathological findings a printout of ECG is required.

Additional cardiac function tests may be required in case of suspected cardiac malfunction that warrants further investigation.

14.16 Physical Examination

Physical examinations shall include those areas of general physician assessment including but not limited to the skin, lymph nodes, spleen, and liver. Performance status and body weight should be assessed once weekly.

Further examinations may be necessary based on the patient's condition and are in the responsibility of the investigator.

Any new or worsening clinically significant changes have to be reported on the appropriate AE or SAE form.

14.17 Vital Signs

Assessment of vital signs will include temperature, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate per institutional standard of care prior to, during, and after each dosing.

Vital signs will be measured after 5 minutes rest, in the supine position

14.18 Assessment of Pharmacokinetics

Specifications for collection and handling of samples for PK assessments are included in the Immunobiology Research Manual. For adequate analysis of PK at one time point a blood sample of approx. 3 ml is required for analyses at CUMC. Additionally, PK assessments will be performed at Affimed's contract laboratory services in Germany.

PK analyses will be done in the center laboratory at CUMC, for analyses done locally.

Full PK assessments will include but may not be limited to estimates/calculations of:

- maximum measured plasma concentration (C_{max})
- area under the curve (AUC)
- distribution volume V_D
- terminal half-life
- clearance

15 STATISTICAL EVALUATION

15.1 Statistical Methods

The data will be analyzed by the Columbia University Medical Center. This is a single center study. The data will be summarized with respect to demographic and baseline characteristics, biological activity measurements, safety observations, efficacy observations, PK and potential biomarker observations. The data will be presented by dose cohorts and overall. The clinical database lock will occur after all data are reconciled (i.e. "cleaned") for all patients. A single clinical study report will be generated for this study. The Statistical Analysis Plan (SAP) will be finalized and signed before the database lock.

The data analysis will take place after the time of database lock when all patients have completed 2 cycles or discontinued the study prior and all data is cleaned. Further data for patients that are followed up past the two cycles will be summarized in an extension report once all patients have discontinued the study. All analyses are of exploratory nature.

15.2 Sample Size and Power

The planned total target accrual for this study is 15 subjects.

As this study is of exploratory nature no formal sample size calculation is done. However based on the prior phase I study of AFM13, it is expected that approximately 78% of the patients will show biological activity. Observing 12 patients out of 15 with biological response would lead to 95% exact binomial confidence interval of (52%, 96%). The lower bound of 52% is assumed to be sufficient for evidence of biological activity in this exploratory study.

15.3 Study Populations

Since this study is of exploratory nature only one data set is defined for all analysis.

The **safety set** consists of all patients that have received at least one dose of AFM13.

Patients will be analyzed in the cohort of the treatment they have actually received. Cohorts will be disjoint sets; each Patient will belong only to one cohort. For the primary outcome the analysis population will be a subgroup of the safety set, only patients with baseline measurements and have completed cycle 1 will be considered.

15.4 Demographics, Baseline Characteristics and Medical History

Demographics, baseline characteristics and medical history will be analyzed for the safety set by cohort and overall. For continuous variables, descriptive statistics will be presented including: mean, standard deviation, median and range. For categorical variables frequency and percentages will be presented. All data will be listed.

15.5 Treatment, Compliance, Disposition, Concomitant Therapies, Protocol Deviations

As a compliance measure the actual number of doses of AFM13 received will be summarized by dose cohort. The reason for discontinuation of study treatment and study including study completed as per protocol will be presented. Concomitant medication will be coded by ATC terminology and summarized by frequencies. Patients with major protocol deviations as defined by the study team prior to database lock will be summarized. The safety set will be used. All data will be listed.

15.6 Primary Objective

The primary objective of the study is to evaluate the biological effects of AFM13 in tumor and peripheral blood. For this, NK immunophenotypic characterization, proliferation, density, activation and effector function (cytokine production and release, ADCC) will be measured in peripheral blood. More importantly, intratumoral NK-cell infiltrate and density, phenotypic characterization, cytokine production and release will also be analyzed in the tumor. Similarly, T cells will be assessed for the same phenotype, activation and effector function (including CTL) both in the peripheral blood and the tumor tissue. Finally, cancer cells will be studied for CD30 expression, immunological receptors and other tumor markers. Other tumor resident immune cells will also be characterized (myeloid-derived suppressor cells, Tregs). Details of immunological and biological studies to be conducted in this protocol appear in the Immunobiology Research Manual.

These endpoints will be assessed by visit and presented by change from baseline. Mean, standard deviation, median and range will be calculated for continues measurements, frequency and percentages for categorical data. Correlation of biological and clinical outcome will be assed graphically. Non-parametric tests for change over time such as the Friedman-test and the signed rank test might be facilitated, however no adjustment for multiplicity is planned. All data will be listed. Only patients in the safety set that have also completed cycle 1 and have biopsies obtained at 2 scheduled time points for biopsy collection will be assessed and presented. No imputation of missing values is planned.

15.7 Secondary Objectives

15.7.1 Efficacy

Clinical efficacy will be estimated by ORR defined by achieving CR and/or PR, as defined in Section 13.3. For the overall cohort 95% exact binomial confidence intervals will be presented. The safety set will be used. All data will be listed.

15.7.2 Duration of response

The DOR defined as time from improved baseline tumor assessment achieved on study drug (CR and/or PR) to worsening will be estimated and summarized by descriptive statistics and listed.

15.7.3 Progression-Free Survival

Progression-free survival will be estimated only for the overall cohort. Patients with no event will be censored at their study discontinuation visit, including study completion. Kaplan-Meier estimates for the 25%, median and 75% quartiles with respective 95% confidence intervals will be presented and graphically displayed. The safety set will be used. All data will be listed.

15.7.4 Pharmacokinetics

A descriptive PK analysis will be conducted, Mean, standard deviation, median and range will be calculated for continues measurements, frequency and percentages for categorical data. Only patients in the safety set that have a respective baseline and at least one post-baseline measurement will be used

15.8 Safety Objectives

15.8.1 Adverse Events

All AEs recorded during the study will be coded by MedDRA (Medical Dictionary for Regulatory Activities). The incidence of AEs will be summarized by cohort, overall, primary system organ class, preferred terms and severity based on CTCAE version 4.0. Relationship to study drug, AEs leading to discontinuation of study drug, death and SAEs, will be summarized.

Infusion-related AEs will be summarized by preferred term and severity. A list of AEs related to skin disease using pre-defined MedDRA preferred terms will be used to identify any AEs of special interest. All AEs will be listed. The safety set will be used.

15.8.2 Laboratory Abnormalities

Laboratory values and severity grades will be calculated using CTCAE version 4.0. For those parameters where there is no CTCAE grading defined a classification into lower limit, normal and higher limit will be used. Shift tables for change from baseline will be presented as well as descriptive statistics mean, standard deviation, median, and range for absolute values by visit and change from baseline will be summarized. All lab values, abnormalities will be listed. The safety set will be used.

15.8.3 Vital Signs

Vital signs will be summarized by mean, standard deviation, median and range for absolute values by visit and change from baseline. The number of abnormal vital signs will be summarized by visit. All values will be listed. The safety set will be used.

15.8.4 Other Safety Parameters

All other safety parameters such as ECG will be listed for the safety set.

15.9 Exploratory Objectives

15.9.1 Presence of Anti-AFM13 Antibody

The presence of anti-AFM13 antibodies and their neutralizing function will be assessed by descriptive statistics (mean, standard deviation, median and range). The safety set will be used. All data will be listed.

15.9.2 Interim Analysis

No formal interim analysis is planned, however, an internal review by the PI and study team will be conducted 8 days after last patient of the cohort has received their first dose, and decide on enrolling the next cohort.

16 SOURCE DOCUMENTATION

Source data is all information contained in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the evaluation of the trial. Source data are contained in source documents, which may include hospital records, clinical and office charts, laboratory reports, memoranda, subjects' diaries, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, radiology and other ancillary service reports, subject files, patient visit notes, encounter forms, operative notes, patient medication diaries and electronic medical records.

For FDA-regulated trials, adequate and accurate source documentation is required. According to 21 CFR 312.62(b), an investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the CRFs and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s) and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

CRCs must provide direct access to source data and documents for trial-related monitoring, audits, IRB reviews and regulatory inspection.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Conduct of the Study

Columbia University Medical Center (Sponsor) shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with FDA regulations [US Code of Federal Regulations (CFR), Sections 312.50 and 312.56] and with ICH GCP (CPMP 135/95).

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change involves only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

17.2 Study Monitoring

The IRB at CUMC will monitor this study. Monitoring will be conducted in accordance with the Center for Lymphoid Malignancies

Data Safety Monitoring Plan.

17.3 Study Auditing

Investigator responsibilities are set out in the ICH guideline for GCP and in the US CFR.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by the CUMC IRB and CUMC regulatory representatives, IRB review, and regulatory inspections, providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

17.4 Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Affimed. Written verification of IRB approval will be obtained before any amendment is implemented.

17.5 Protocol Deviations/Violations

All deviations from and violations of Columbia policies or IRB determinations, including departures from the requirement for adherence to the approved protocol, must be reported to the IRB.

A protocol deviation is defined as a variation from the approved protocol for one subject or to address a temporary situation that is identified by the research team and approved by the IRB before implementation.

A protocol violation is defined as a variation from the approved protocol that was implemented without prospective approval by the IRB and was not implemented to avoid or minimize imminent harm. Protocol violations may be considered noncompliance with the federal regulations and institutional policies for the protection of the IRB Noncompliance Policy apply.

Requests for Protocol Deviations should be submitted to the IRB via the Modification module in Rascal as soon as the study team becomes aware of the need for the deviation. When applicable, the sponsor's concurrence (e.g., that an individual who does not meet eligibility criteria may be enrolled) should be provided with the submission. The IRB recognizes that some deviations regarding inclusion/exclusion criteria are identified shortly before the subject is scheduled for randomization or entry into the study and that a quick review by the IRB is important for the study. In time-sensitive situations, the PI should follow his/her submission to the IRB with an e-mail outside of Rascal to the Manager of the IRB that the approved the study. Please note that repeated Protocol Deviation requests related to eligibility suggest that the PI should revised the protocol to reflect more appropriate eligibility criteria for the study consistent with research participant safety and preservation of the scientific integrity of the data.

If a Protocol Violation is unanticipated, at least possibly related to the research, and involves risks to subjects or others, it should be reported to the IRB within one week (5 business days) via an Unanticipated Problem (UP) report in Rascal. Protocol violations related to medication dose errors should also be submitted as a UP whether the error involves an over- or under-administration of medication. If the error occurred within NYP, the situation should be discussed with the subject, in accordance with the underlying philosophy of NYPs Disclosure Policy (Policy #E145); discussion with the subject may also be appropriate for medication dose errors that occur outside of NYP in clinical studies under the purview of the IRB.

Violations other than UPs of the rights or welfare of subjects, negatively affect the integrity of the study, or require a change to the protocol or consent document(s) are considered to be major violations and require prompt reporting to the IRB as a Modification.

Minor violations are violations that are not UPs and do not meet the criteria to be considered major violations. These should be reported to the IRB at the time of continuing review, in a list or log that includes all UPs, deviation or major violation were made.

The description of the circumstances surrounding the deviation or violation should be clearly stated in the UP, in the summary section of the Modification Information Form or in the Renewal Form, as applicable.
The following information should be included:

- a complete description of the deviation or violation;
- an explanation of why the deviation is necessary, or why the violation occurred;
- whether the deviation affects, or the violation affected, the risk/benefit ratio for subjects, integrity of the research data and subjects willingness to continue study participation;
- for protocol violations, a description of the corrective measures that will be taken to prevent a recurrence of the same or similar violations; and
- for protocol deviations, a plan to inform the subject if the deviation may change the subject's willingness to participate in the research study.

17.6 Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and ICF have been reviewed and approved by the CUMC IRB. The IRB shall be appropriately constituted and perform its functions in accordance with FDA ICH GCP and local requirements as applicable.

The IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, Investigator's Brochure, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IRB and Regulatory Authority as applicable.

17.7 Written Informed Consent

The nature and purpose of the study shall be fully explained to each subject.

Written informed consent must be obtained from each subject prior to any study procedures being performed.

The consent documents to be used for the study shall include all the elements of informed consent shall be reviewed and approved by the appropriate IRB prior to use.

18 DATA HANDLING AND RECORD KEEPING

18.1 Responsibility for Data Submission

The Study Coordinator is responsible for compiling data for all participants and for providing the data to the Principal Investigator for review.

18.2 Data Safety Monitoring Board

The Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center's Data Safety Monitoring Board (DSMB) will oversee conduct of the study, patient safety and all interim analyses as specified in the data analysis plan. Detailed guidelines regarding the structure, function and decision-making mechanisms for the Data Safety Monitoring Board are provided in the DSMB charter.

18.3 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. During the course of the study, the Sponsor may determine that certain safety reports are required to comply with regulations. Columbia University Medical Center will cross-reference Affimed's AFM13 Investigational New Drug (IND) Application, and will hold the IND for this trial). These reports are required to be submitted to the IRB/EC.

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20 APPENDICES

There are no Appendices planned to be added to this study protocol.