Abstract
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A Phase II Open-label Multicenter Study to Assess the Efficacy and Safety of AFM13 in Patients With Relapsed or Refractory CD30-positive Peripheral T-cell Lymphoma or Transformed Mycosis Fungoides (REDIRECT)

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Introduction

Peripheral T-cell Lymphoma

- In hematologic malignancies, CD30 expression is strongly increased in Hodgkin lymphoma (HL) and anaplastic large-cell lymphoma (ALCL), but has also been noted in other lymphoid malignancies, such as peripheral T-cell lymphoma (PTCL)[1]
- While the identified subtype of the PTCL can lead to different survival rates, chemotherapy treatment results in a median time from original diagnosis to relapse or progression, and median overall survival of patients with PTCL, measured in months[2]
- In an international prospective cohort study, the majority of PTCL patients (several subtypes, the majority were PTCL, not otherwise specified [NOS]) received chemotherapy +/- radiotherapy as first-line treatment including consolidation with high-dose therapy and hematopoietic stem cell transplantation (HSCT)[3]
  - For refractory/relapsed (R/R) patients receiving HSCT or not receiving HSCT as salvage therapy, median survival after relapse (SAR) was 5.8 months, 3-year SAR rates were 21% and 28% for refractory and relapsed patients, respectively[3]
- There is no clear standard of care treatment for R/R PTCL with the exception of brentuximab vedotin (BV) for the ALCL subtype and there is a paucity of data regarding long-term outcomes for these patients[4]
- For those patients who are potential candidates for autologous or allogeneic HSCT, achieving an objective response as a bridge to transplant is vitally important[5]

Transformed Mycosis Fungoides

- Primary cutaneous T-cell lymphoma (CTCL) represents a heterogeneous group of neoplasms derived from skin-homing T-cells that also express CD30[6,7]
- Mycosis fungoides (MF) is the most common subtype of primary CTCL and is a mature T-cell lymphoma with cutaneous presentation but with potential systemic involvement[6]
- Large cell transformation (often associated with a poor prognosis), is the histopathological transformation of neoplastic lymphocytes to a clonally identical large cell phenotype, occurs in 20%-50% of patients with advanced MF[8]
  - Such transformation is often associated with poor prognosis and a mean 5-year OS of 33%[7]
- Currently, the only known potentially curative therapy for patients with transformed mycosis fungoides (TMF) is allogeneic HSCT and patients are in dire need for other therapeutic options[9]

AFM13 Structure and Function

- AFM13 is a bispecific, tetravalent, innate cell engager that binds and activates natural killer (NK) cells and macrophages via CD16A as well as to CD30+ on lymphoma cells[10] (**Figure 1**)
- AFM13 therefore acts as a bridge to innate immunity by recruiting and activating innate immune cells (NK cells and macrophages) in close proximity to tumor cells, enabling potential lysis of tumor cells (**Figure 2**)[10]

Figure 1. AFM13 Structure[10]

A) Anti-CD16A (FcγRIIIA)
- Human, derived from Affimed's antibody library
- Specific for A isoform of FCγRIII on NK cells and macrophages

B) Anti-CD30
- Murine, derived from Hybridoma HRS-3

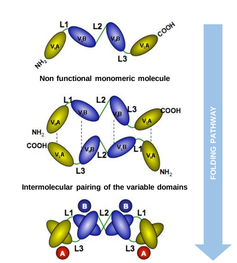
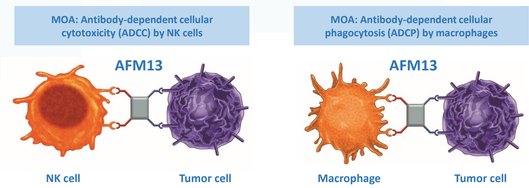


Figure 2. AFM13 Function



Objective:

The objective of the REDIRECT clinical trial is to investigate the efficacy and safety of AFM13 in patients with relapsed or refractory CD30-positive peripheral T-cell lymphoma or transformed mycosis fungoides

Targeting CD30-Positive Lymphoma with AFM13

Ongoing Clinical Development

- An open-label, phase 1b/2a, investigator-sponsored study is ongoing for AFM13 in patients with R/R (≥1 prior therapy) CD30-positive lymphomas with cutaneous involvement at Columbia University Medical Center
- Data presented from the Columbia University clinical study is summarized below (**Table 1**):[11-12]
  - AFM13 demonstrated a high overall response rate of 50% (1 CR and 4 PRs)
  - AFM13 is active post-brentuximab vedotin failure
  - Overall, this initial data supports the potential of AFM13 as a novel immunotherapeutic to treat CD30-expressing lymphomas[11-12]

Table 1: AFM13 Monotherapy Has Shown Efficacy in Patients With CD30-Positive Lymphoma[a]

Cohort	Disease	Toxicity	Response
1	S-ALCL, Alk (-)	No AE	PR
	TMF	No AE	POD
	C-ALCL	Rash (G4) Skin Infection (G3)	CR
2	MF	IRR (G1)	SD
	TMF	IRR (G1)	SD
	TMF	Skin Infection (G3) IRR (G1)	Not Assessed
3	TMF	No AE	PR
	S-ALCL, Alk (-)	No AE	PR
	MF	No AE	POD
4	TMF	No AE	PR

[a]Ten patients treated in 4 dose cohorts[11]

Abbreviations: AE, adverse event; Alk, anaplastic lymphoma kinase; CR, complete response; IRR, infusion related reactions; MF, mycosis fungoides; PR, partial response; POD, progression of disease; S-ALCL, systemic anaplastic large cell lymphoma; SD, stable disease; TMF, transformed mycosis fungoides.

Methods

Study Design

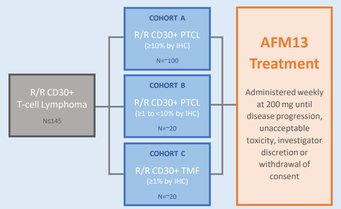
- AFM13-202 (REDIRECT) is a phase 2 open-label, multicenter, global study to investigate the efficacy and safety of AFM13 in patients with R/R CD30+ PTCL and TMF (**Figure 3**)
- REDIRECT is a registration-directed study and is currently recruiting

Figure 3. REDIRECT Phase 2 Study to Assess AFM13 in Patients With R/R CD30-positive T-cell Lymphoma or Transformed Mycosis Fungoides (NCT04101331)[13]

PRIMARY ENDPOINT:
- To assess the antitumor activity of AFM13 by Independent Review Committee-confirmed ORR

SECONDARY ENDPOINTS:
- To assess the antitumor activity of AFM13 by investigator-assessed objective response rate (defined as ORR-2)
- To assess the duration of response (DOR) to AFM13
- To assess the safety and tolerability of AFM13
- To assess the serum pharmacokinetics (PK) of AFM13
- To assess the immunogenicity of AFM13
- To assess quality of life (QoL) of patients while on treatment with AFM13

EXPLORATORY ENDPOINTS:
- Additional exploratory endpoints will be investigated



Study Parameters

INCLUSION CRITERIA OF NOTE:
- Eligible patients at least 18 years of age with CD30+ PTCL must have received at least 1 prior line of systemic therapy and, if diagnosed with systemic ALCL, must have failed or be intolerant to brentuximab vedotin (Cohorts A and B)
- Eligible patients at least 18 years of age with CD30+ TMF must have received at least 1 prior line of systemic therapy and have exhausted systemic therapies with regular approval for their disease (Cohort C)
- The PTCL subtypes allowed for cohorts A and B:
  - Enteropathy-associated T-cell lymphoma
  - Monomorphic epitheliotropic intestinal T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Peripheral T-cell lymphoma, not otherwise specified (NOS)
  - Angioimmunoblastic T-cell lymphoma
  - Follicular T-cell lymphoma
  - Nodal peripheral T-cell lymphoma with TFH phenotype
  - Anaplastic large-cell lymphoma, anaplastic lymphoma kinase (ALK)-positive
  - Anaplastic large-cell lymphoma, ALK-negative
  - Breast implant-associated anaplastic large-cell lymphoma
- The required cut-offs for the CD30-positivity are:
  - Cohort A (PTCL): ≥10% by IHC
  - Cohort B (PTCL): ≥1 to <10% by IHC
  - Cohort C (TMF): ≥1% by IHC
- Measurable disease by modified Lugano Classification for Cohorts A and B (PTCL)[14] and by Olsen Criteria for Cohort C (TMF)[15]
- Patients must have relapsed or refractory disease AND the following:
  - Completion of treatment with any radiotherapy, chemotherapy, antibody, immunoconjugates, and/or another investigational drug ≥4 weeks (or 5 half-lives of the drug, whichever is shorter) prior to first dose of study drug
  - Completion of an autologous HSCT at least 3 months prior to first dose of study drug (if applicable)
  - Resolution of any clinically significant therapy-related toxicity to ≤Grade 1 or to baseline if pre-existing condition (exception: patients with ≤Grade 2 peripheral neuropathy will be allowed)

EXCLUSION CRITERIA OF NOTE:
- Patients with the following subtypes of lymphoma:
  - T-cell prolymphocytic leukemia
  - T-cell large granular lymphocytic leukemia
  - Chronic lymphoproliferative disorder of NK cells
  - Aggressive NK-cell leukemia
  - Extranodal NK-/T-cell lymphoma
  - Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
- Current evidence of central nervous system involvement
- Has had an allogenic tissue hematopoietic stem cell/solid organ transplant within the past 3 years. *Note: Patients who have had a transplant >3 years ago are eligible as long as there are no signs/symptoms of graft versus host disease (GvHD)*
- Requirement for systemic immunosuppressive therapy (eg, GvHD therapy, <12 weeks prior to the first dose of study drug)
- Known history of human immunodeficiency virus (HIV), known active hepatitis B, or hepatitis C

ANTI-TUMOR ACTIVITY/DISEASE ASSESSMENT:

Assessments will be performed both locally and centrally. Treatment decisions should be based on local assessment.
- Cohorts A and B (PTCL): Modified Lugano criteria[14]
  - The modified Lugano Classification refers to the clinical protocol's use of CT-based response criteria from the Lugano Classification to guide clinical decisions and assessment of overall response
  - The PET–CT-based overall response will be one of the secondary endpoints
- Cohort C (TMF): Olsen criteria[15]
  - Global Response Score (mSWAT, lymph node, visceral disease, flow cytometry)

PHARMACOKINETICS:
- Serum trough levels of AFM13 in all patients, plus PK profiling in selected groups of 40 patients (Group 1 and Group 2)

Summary

- AFM13 is a first-in-class innate cell engager that induces specific and selective killing of CD30-positive tumor cells by engaging and activating NK cells and macrophages thereby leveraging the power of the innate immune system
- In an ongoing biomarker phase 1b/2a study in patients with R/R CD30-positive lymphomas with cutaneous involvement, AFM13 has shown clinical activity[11-12]
- Based on these findings, the REDIRECT trial is assessing AFM13 monotherapy for the treatment of patients with R/R PTCL and TMF in this phase 2 open-label trial
- The study is currently recruiting as of May 11th, 2020

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