Poster
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# A Phase 1 Study Investigating AFM11 in Patients with Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia: Preliminary Results

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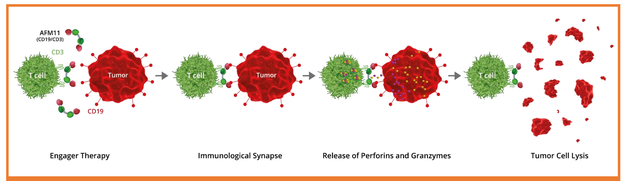
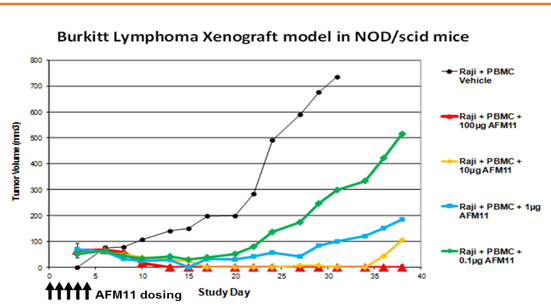
## Introduction

- AFM11 is a bispecific, tetravalent T cell-engaging antibody construct binding to CD19 on tumor cells and to CD3 on T cells
- AFM11 elicits T cell-mediated killing of CD19-positive (CD19+) leukemia and lymphoma cells




Mechanism of action of AFM11

- *In vivo* anti-tumor activity of AFM11 was investigated in a Raji tumor xenograft model in NOD/scid mice reconstituted with human PBMCs
- Tumor growth in all AFM11-treated groups was significantly reduced
- The lowest dose group showed delayed (~60%) tumor growth
- All animals in the highest dose group achieved complete tumor remission (Reusch et al., 2015[1)])




AFM11 completely suppresses tumor growth in Burkitt lymphoma xenograft model

## Methods

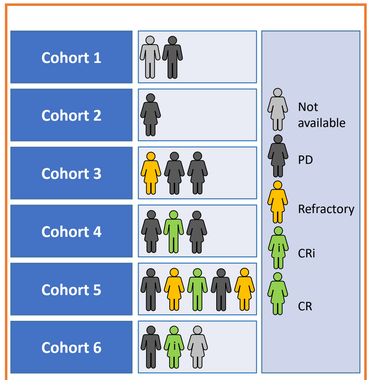
- **Study type/primary objective**: Dose escalation study to determine MTD of AFM11 in adult patients with R/R ALL
- **Eligibility**: ≥ 18 years, ineligible for SCT, CD19-targeting therapy naïve; If Ph+: need to have failed ≥2 prior TKIs
- **Study design**: Accelerated titration design with 1 patient per cohort until toxicity is observed, then switch to classical 3+3 design
- **AFM11 administration**: Continuous infusion over weeks 1 and 2 of each 4-week cycle for up to 3 cycles; initial lower dose in Week 1 of Cycle 1, then escalated to target dose starting day 8
- **Pre-treatment (for patients with rapidly progressing disease):** Cyclophosphamide + dexamethasone daily over 3-5 days before initiating AFM11
- **Tumor assessments:** Local bone marrow evaluation and peripheral blood laboratory results between days 15 and 18 of each cycle

| | Week 1 | | Week 2 and subsequent cycles | |
|---|---|---|---|---|
| | Per day ng/kg | Per week ng/kg | Per day ng/kg | Per week ng/kg |
| Cohort 1 | 0.1 | 0.7 | 0.3 | 2 |
| Cohort 2 | 0.3 | 2 | 0.9 | 6 |
| Cohort 3 | 1 | 7 | 2.9 | 20 |
| Cohort 4 | 2.9 | 20 | 8.6 | 60 |
| Cohort 5 | 8.6 | 60 | 26 | 180 |
| Cohort 6 | 19 | 130 | 57 | 400 |

Dosing algorithm

## Response

- 3 patients enrolled in Cohorts 4 through 6 achieved a complete response (2 CRs, 1 CRi)
- In all 3 patients, the responses were seen after cycle 1
- In 2 of 3 patients (1 in Cohort 4 and 1 in Cohort 6 whose doses were reduced to Cohort 5 dose level due to toxicity), the responses were transient and the patients relapsed after cycle 2
- In 1 patient (Cohort 5), the CR deepened to MRD negativity after cycle 3 and the investigator reported continued CR for several months post-study



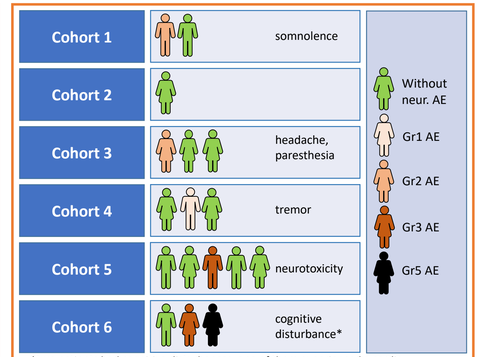

Response assessment

## Safety

- No DLTs were observed in Cohorts 1 through 5; 2 DLTs were observed in cohort 6
- Most common treatment related AEs were pyrexia (n=7) and neurotoxicity (n=5); Cytokine release syndrome was not observed
- Neurotoxicities included reversible tremor, somnolence and cognitive disorder, and were Grade 1 to 3 in severity
  - 1 patient in Cohort 5 experienced reversible Grade 3 neurotoxicity in Cycle 3 (outside of the DLT observation period)
  - 1 patient in Cohort 6 had reversible Grade 3 cognitive disturbance (with expressive dysphasia) after the first 3 days of AFM11. AFM11 dosing was interrupted, then re-started on Cohort 5 dose and the patient achieved a complete response
  - 1 patient in Cohort 6 had a fatal cardio-respiratory arrest, assessed as probably related to AFM11. The patient experienced cognitive disturbance and agitation after the first 6 days of treatment, then suffered a cardio-respiratory arrest several hours later and died two days thereafter. The patient was profoundly neutropenic throughout the study and also had sepsis as confirmed by blood culture on the day of the cardio-respiratory arrest

| TRAEs, all CTCAE grades | Safety population (N=17) No. (%) | TRAEs ≥ CTCAE Gr3 | Safety population (N=17) No. (%) |
|---|---|---|---|
| Pyrexia | 7 (41%) | Febrile neutropenia | 2 (12%) both Gr3 |
| ALT increase | 3 (18%) | ALT increase | 1 (6%); Gr3 |
| AST increase | 3 (18%) | Cardio-respiratory arrest | 1 (6%); Gr5 |
| Bone pain | 2 (12%) | Neurotoxicity | 1 (6%); Gr3 |
| Febrile neutropenia | 2 (12%) | Cognitive disorder | 1 (6%); Gr3 |
| Myalgia | 2 (12%) | | |
| Neutropenia | 2 (12%) | | |
| Tremor | 2 (12%) | | |

Most common TRAEs in ≥ 2 patients: CTCAE all grades and ≥ Gr3




*two patients had cognitive disturbances, one of them experienced a cardio-respiratory arrest which followed several hours later (see text)

Patients with adverse events of the neurological system, listed by highest grade observed per patient per cohort

## Enrollment status

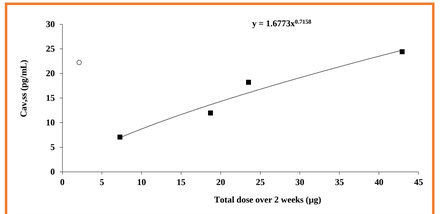
- 17 patients were enrolled in 6 dose cohorts
- 14 patients completed the DLT observation period, 3 discontinued early due to disease progression
- No DLTs were observed in Cohorts 1 through 5
- Two DLTs were observed in Cohort 6, including one fatal event
- Study was put on hold to investigate the fatal event

| Characteristic | Total patient population (N=17) No. (%) |
|---|---|
| Age, years, median (range) | 48 (19 to 70) |
| Gender | 10 female (59%); 7 male (41%) |
| Prior therapies, No. | |
| 1 | 8 (47%) |
| 2 | 7 (41%) |
| 3 | 2 (12%) |
| Prior stem cell transplant | 5 (29%) |

Baseline demographic characteristics (N=17)

## Pharmacokinetics

- Serial serum PK samples were measured in all patients. In 11 patients, samples were below LLOQ (4.5 pg/mL) and PK parameters could not be derived
- In 5 patients from cohorts 3 to 6, PK samples were measurable and a one-compartment PK model was fitted to the serum concentration profiles
- In 1 patient, the PK parameters (CL and Vss of 285 mL/h and 5.5 L, respectively) were appreciably different from the other 4 patients (empty circle in figure)
- In 4 patients, average serum concentrations at steady state ($C_{av,ss}$) increased with dose but the increase was less than dose proportional; i.e. exponent of the power model (0.72) was <1 (see figure)
- The estimated Vss (equivalent to total body water volume) is 6-7-fold greater than expected (with the exception of the apparent outlier). In cases where antibodies show high-affinity, high-capacity binding in tissue, the true Vss may be higher, which is typical for a monoclonal antibody




| PK | Patient | | | | Geometric | CV |
|---|---|---|---|---|---|---|
| Parameter | 1 | 2 | 3 | 4 | mean | (%) |
| CL (mL/h) | 5231 | 3060 | 3841 | 4655 | 4113 | 23.8 |
| Vss (L) | 54.9 | 46.6 | 39.6 | 46.9 | 46.7 | 13.5 |
| $t_{½}$ (h) | 7.28 | 10.6 | 7.14 | 6.99 | 7.87 | 19.9 |
| $C_{av,ss}$ (pg/mL) | 24.4 | 7.08 | 18.2 | 12.0 | 13.9 | 57.9 |

PK parameters

## Conclusions

- **AFM11 was well tolerated in the first 5 dose cohorts of the Phase 1 dose-escalation study, with the MTD not yet defined**
- **Neurological toxicities observed in the study appeared similar in frequency and severity compared to other CD19-targeting agents**
- **AFM11 treatment was able to elicit CRs in three patients treated at tolerable dose levels, with one CR reported as durable for several months post-study**
- **Additional clinical testing of AFM11 is needed to define the MTD and to establish the clinical benefit of AFM11 in a larger group of R/R ALL patients**

#Corresponding author; Presenting author; A.B.S., A.G., A.M., A.P., F.F., G.S., J.M., M.D. and S.G. receive research funding from Affimed; A.S., C.C-J., L.A., S.E.S., S.K.,S.S. are employees of Affimed. References: 1) Reusch U et al., *mAbs. 2015;7(3):584-604*

**ALL**, acute lymphoblastic leukemia; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; $C_{av,ss}$, average serum concentrations at steady state; **CL**, clearance; **CR**, complete remission; **CRi**, complete remission with incomplete hematological recovery; **CTCAE**, common terminology criteria of adverse events; **CV**, coefficient of variance; **DLT**, dose limiting toxicity; **LLOQ**, lower limit of quantification; **MRD**, minimal residual disease; **MTD**, maximal tolerated dose; **PBMC**, peripheral blood mononuclear cell; **Ph+, p**hiladelphia chromosome positive; **SCT**, stem cell transplantation; **Vss**: volume of distribution at steady state