# Specific NK cell activation to treat relapsed/refractory (r/r) Hodgkin Lymphoma (HL) patients – final, updated data on clinical outcome, pharmacokinetics and pharmacodynamics of a phase 1 study investigating AFM13, a bispecific anti-CD30/CD16A TandAb

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## Introduction

### TandAb – a tetravalent, bispecific antibody molecule

#### TandAb Features

- comprised solely of scFv domains
- expressed as a single gene product
- the linkers favor an intermolecular head-to-tail dimerization resulting in tetravalent bispecific TandAbs

#### TandAb Properties

- High affinity: bivalent binding of each target
- very potent cytotoxicity: recruitment of NK- or T-cells
- no renal filtration: not continuous infusion necessary
- high specificity: no off-target activity
- excellent drug-like properties (production and stability)
- off-the-shelf product

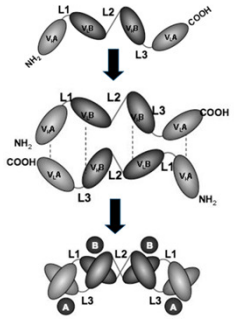



Fig. 1: Formation of TandAb

### AFM13 is a CD30/CD16A TandAb – Recruiting NK cells to kill tumors

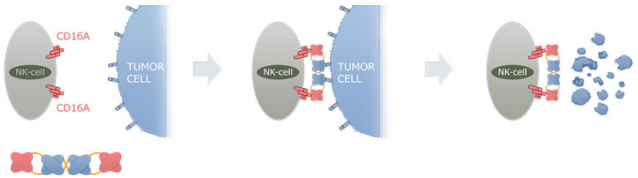



Fig. 2: Mode of action; AFM13 brings NK-cells in close proximity to tumor cell; NK-cells get activated and kill tumor cells

### Hodgkin Lymphoma with high medical need for efficacious and safe treatment

- Characterized by CD30+ malignant Reed-Sternberg cells
- Chemotherapy ± radiation therapy with a high cure rate but toxic; cardiac toxicity, organ failure, infertility, secondary malignancies
- 20-25% of HL patients relapse; 2nd line chemotherapy and autologous SCT induce durable remission in only 50% of the patients
- First targeted therapy for salvage treatment: brentuximab vedotin (BV), a CD30 – targeting antibody-drug-conjugate: high response rate but limited duration of response and progression free survival
- High medical need for effective and safe therapies → Immunotherapy may be an option

## Methods

### Phase 1 study: design

- Classical 3+3 dose escalation design: 0.01, 0.04, 0.15, 0.5, 1.5, 4.5, 7.0 mg/kg
- Infusion weekly for 4 weeks; 2nd cycle optional (5 pts.); 4 patients twice weekly regimen
- Inclusion criteria: progressive HL (CD30+); relapsed/refractory disease; > 2 prior treatments
- Objectives: Safety, tolerability, MTD, PK, PD, efficacy
- Twice weekly dosing could be initiated based on PK data

### Study assessments

- Safety by CTCAE version 4.02 (clinical examinations, AEs, DLTs, lab); ADAs
- Pharmacokinetics
- Tumor response ("Cheson criteria", 2007) 3 weeks after the last dose
- Pharmacodynamics (PD): sCD30, NK-cell populations, Cytokines (IFN-γ, TNF-α, IL-2, IL-6, IL-10, IL-12)

## Results

Tab. 1: Patients

| Patient characteristics | |
|---|---|
| Median age – years (range) | 38.5 (19-72) |
| Male – no. (%) | 16 (57.1) |
| Diagnosis CD30+ classical HL – no. (%) | 28 (100) |
| **Previous treatments** | |
| Stages III/IV at 1st diagnosis – no. (%) | 9 (32.1) |
| Months between 1st diagnosis and AFM13 initiation – median (range) | 52 (8-468) |
| Previous treatment lines – median (range) | 6 (3-11) |
| Previous radiotherapy – no. (%) | 24 (85.7) |
| Previous ASCT – no. (%) | 22 (78.6) |
| Previous brentuximab vedotin | |
| Total – no. (%) | 9 (28.6) |
| As most recent therapy – no. (%) | 7 (25.0) |

### Safety

- Most AEs were mild or moderate with only 18 (9.2%) of CTCAE grade ≥ 3
- MTD was not reached
- 8 patients (28.6%) experienced at least one SAE
- Only one DLT observed at dose level 0.5 mg/kg
  - Hemolytic anemia (CTCAE Grade 4), 3 doses of AFM13 received, assessed as possibly related by investigator; (patient subsequently died due to aspergillus pneumonia and multi-organ failure which was assessed not/unlikely related to study drug).
- An independent DMC considered each of the doses up to 7 mg/kg safe and well tolerated

Tab. 2: Most common side effects occurring in more than 4 patients

| Preferred term | Safety population (n=28) | CTCA grade 1/2 | CTCA grade ≥ 3 |
|---|---|---|---|
| Pyrexia | 15 (53.6%) | 14 (50.0%) | 1 (3.6%) |
| Chills | 11 (39.3%) | 11 (39.3%) | 0 (0.0%) |
| Headache | 8 (28.6%) | 8 (28.6%) | 0 (0.0%) |
| Nausea | 5 (17.9%) | 5 (17.9%) | 0 (0.0%) |
| Nasopharyngitis | 5 (17.9%) | 5 (17.9%) | 0 (0.0%) |
| Vomiting | 4 (14.3%) | 4 (14.3%) | 0 (0.0%) |
| Pneumonia | 4 (14.3%) | 0 (0.0%) | 4 (14.3%) |
| Infusion reaction | 4 (14.3%) | 4 (14.3%) | 0 (0.0%) |
| Rash | 4 (14.3%) | 4 (14.3%) | 0 (0.0%) |

### Pharmacokinetics

- Dose proportional increase of systemic exposure to AFM13
- Between-subject variability in systemic exposure to AFM13 was generally low
- AFM13 was detectable in peripheral blood up to 168 h post infusion.
- t½: about 13-19 hours
- Weekly regimen likely to be not sufficient, in particular at lower doses

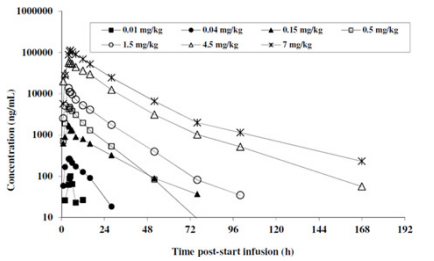
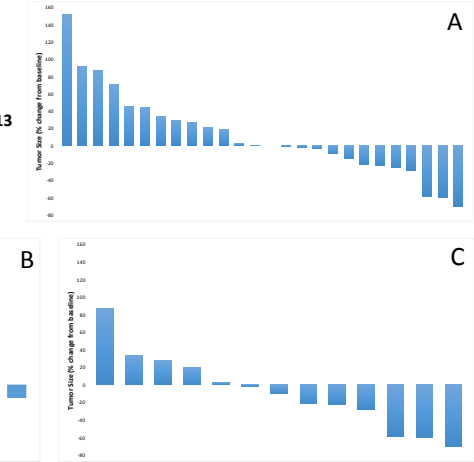



Fig. 2: Mean serum concentrations of AFM13 after single infusion

### Efficacy

Fig 3: Change in tumor volume measured by CT-scan;
A: Efficacy population (n=26);
B: Patients refractory to brentuximab vedotin as most recent) treatment prior to AFM13 (n=7);
C: Patients treated with AFM doses ≥1.5 mg/kg body weight (n=13)




### Pharmacodynamics

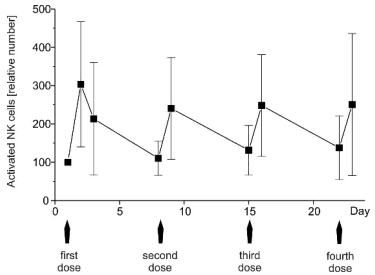



Fig. 4: CD69+ NK-cells relative to total number of NK-cells; dose cohorts ≥0.15 mg/kg

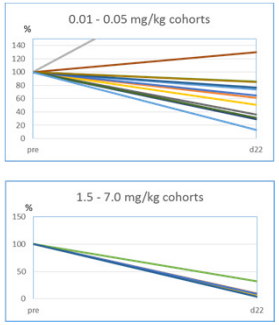



Fig. 5: sCD30 levels in serum; relative change from baseline

### Other PD parameters

- Quantifiable serum cytokine levels could only be measured for IL-6 (n=8), IL-8 (n=4), IL-10 (n=3) and TNF-α (n=7). No cytokines detected in patients receiving doses <0.5 mg/kg
- ADCC activity through quantification of granzyme B and serum outcome markers TARC, BAT3 and sMICA did not provide conclusive information

## Conclusions

- AFM13 is well tolerated
- AFM 13 showed activity in terms of pharmacodynamics and efficacy, incl. BV refractory patients
- Treatment duration and dose regimen need to be optimized
- A phase 2 study in r/r HL is in preparation

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