Abstract 1522

A Phase 1 Study Investigating the Combination of AFM13 and the Monoclonal Anti-PD-1 Antibody Pembrolizumab in Patients with Relapsed/Refractory Hodgkin Lymphoma after Brentuximab Vedotin Failure: Data from the Dose Escalation Part of the Study

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Abstract

Background: AFM13 is a tetravalent, bispecific NK cell-engaging antibody construct binding to CD30 on Hodgkin Lymphoma (HL) cells and CD16A on NK cells. By engaging CD16A-positive NK cells, AFM13 elicits NK-cell mediated killing of CD30-positive lymphoma cells[1]. Pembrolizumab is a PD-1 blocking antibody that prevents tumor immune evasion and has been shown to induce high single-agent response rates in patients (pts) with relapsed or refractory (R/R) HL[2]. AFM13 has shown first signs of clinical activity in R/R HL as single agent in a preceding Phase 1 study[3]. Preclinical in vivo data of the combination of AFM13 with PD-1 inhibition suggest potential synergistic activity and the potential for induction of cross-talk between innate and adaptive immunity[4]. Thus, the combination of the two agents might improve outcomes in pts with R/R HL.

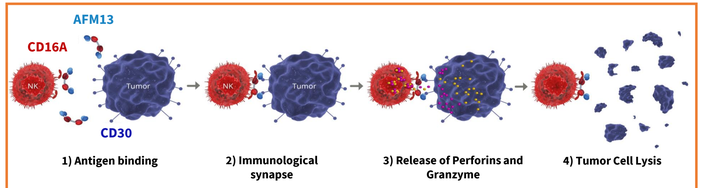
Methods: A Phase 1b study is ongoing to evaluate the safety and tolerability of the combination of AFM13 with pembrolizumab (Keytruda) as salvage therapy after failure of standard therapies including brentuximab vedotin in HL (NCT02665650). Pts receive escalating doses of AFM13 in combination with pembrolizumab at a flat dose of 200 mg administered every 3 weeks following the classical 3+3 design. Upon completion, recruitment continues into an extension cohort. Response assessment is performed every 12 weeks by PET/CT according to the Lugano Classification Revised Staging System for malignant lymphoma[5].

Results: As of November 1, 2017, 12 pts with R/R HL have been enrolled into the dose escalation part of the study. The median age of the pts is 35 years (range 25 to 73 years). All pts have failed standard treatments including brentuximab vedotin; 67 % (8/12) have failed prior autologous stem cell transplantation (ASCT). All pts were heavily pretreated with at least 4 prior lines of therapy (range 4 to 7). At the time of the data extract, all 12 pts had completed the 6-week dose-limiting toxicity (DLT) observation period. Three pts were enrolled into cohorts 1 and 2 each and 6 pts were enrolled into cohort 3. One DLT was observed in cohort 3, which was a repeated grade 2 infusion-related reaction (IRR), leading to discontinuation of AFM13 treatment. This event classified as a DLT according to the protocol definition. No additional DLTs occurred. The most frequently observed adverse events (AEs) were IRRs (10 pts), nausea (5 pts), diarrhea (4 pts), headache (4 pts), pyrexia (4 pts) and rash (4 pts). Most of these events were of grade 1 or 2 severity. There were a total of 4 grade 3 AEs observed in the study with three events being deemed at least possibly related to both AFM 13 and pembrolizumab: grade 3 IRR, grade 3 nausea and grade 3 vomiting. The remaining grade 3 AE of duodenal ulcer was assessed as not related to either study treatment. All 12 pts enrolled into the dose escalation phase were evaluable for efficacy at Week 13 (3 months). By the investigator assessment, in Cohort 1, there were 2 Partial Metabolic Responses (PmRs) and 1 Progressive Metabolic Disease (PmD). In Cohort 2, one Complete Metabolic Response (CmR), 1 PmR and 1 PmD were observed. In Cohort 3, five PmRs and 1 PmD were observed. The ORR for the dose selected for the extension cohort (dose used in Cohort 3) was 83% (5/6) by both local and independent assessments. Additionally, a deepening of response is reported where a single case of PmR is converted into CmR at the 6-month assessment (independent assessment).

Conclusions: Early data suggest that the combination of AFM13 and pembrolizumab is a well-tolerated salvage therapy in pts with R/R HL with encouraging efficacy. Most AEs observed across all cohorts were mild to moderate in severity and manageable with standard therapy. While IRRs were observed frequently, only one case was assessed as grade 3. The 3-month ORR of 83% (local and independent assessment) at the dose chosen for the extension cohort compares favorably to the 3-month ORR of pembrolizumab monotherapy in a similar patient population of post-ASCT or ineligible for ASCT and brentuximab vedotin (58-63%)[6] . Based on the risk/benefit analysis and recommendation by an independent data review committee (DRC) the extension cohort is currently accruing.

Introduction

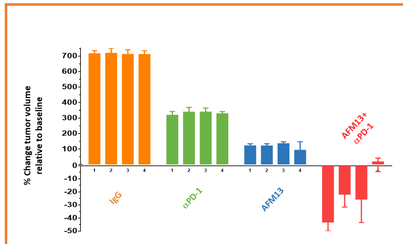
- **AFM13 is a first-in-class tetravalent, bispecific NK cell engager in clinical development**
- High-affinity binding to CD16A and CD30, independent of polymorphism, virtually no competition with IgG and potent cytotoxicity
- Synergy with checkpoint modulators in pre-clinical studies
- Established clinical activity with solid safety profile (Phase 1 study)



Mechanism of action of AFM13

Background

- **AFM13 shows synergy with anti-PD1 in a PDX model**



Tumor sections (8x8 mm) from newly diagnosed CD30+ HL were engrafted and grown over 28 days, autologous PBMCs infused at 2x106 PBMCs/mouse i.p. at baseline, CPIs and AFM13 given at 5mg/kg every week

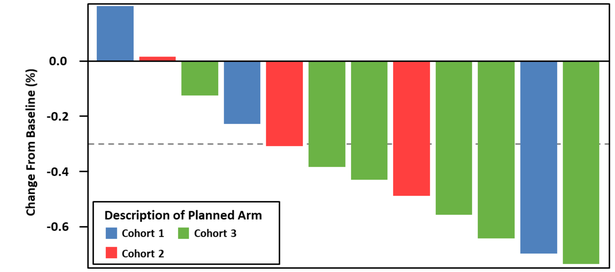
Synergy of AFM13 with anti-PD1

Population Characteristics

Characteristic	Total Patient Population (N=12) Number (%)
Age, years, median (range)	35 (25 to 73)
Gender	Female 3 (25%); Male 9 (75%)
Prior therapies, no.	
4	5 (42%)
5	3 (25%)
6	3 (25%)
7	1 (8%)
Prior autologous stem cell transplantation	8 (67%)
Prior brentuximab vedotin	12 (100%)
Brentuximab vedotin as last therapy	3 (25%)

Demographic and baseline characteristics, safety population

Best Response, Tumor Volume



Change in tumor volume measured by CT-scan, efficacy population

Methods

- **Study design:** 3+3 dose escalation design with 3 dose escalation cohorts and a safety extension cohort of up to 21 patients
- **Primary objectives:**
  - MTD determination
- **Secondary objectives:**
  - Safety/tolerability
  - Anti-tumor activity
  - PK profile evaluation
- **Study assessments:**
  - PET/CT imaging every 12 weeks (Lugano Classification Revised Staging System for malignant lymphoma)[5]

	Week 2 & 3	Weeks 4, 5, 6, 7, 8, 9	Weeks 10, 13, 16, 19, 22 & 25
Cohort 1	0.1 mg/kg x 3	0.5 mg/kg	0.5 mg/kg
Cohort 2	0.5 mg/kg x 3	1.5 mg/kg	1.5 mg/kg
Cohort 3	3 mg/kg x 3	7.0 mg/kg	7.0 mg/kg

Dose escalation of AFM13

Efficacy

- **Patients:** All 12 patients from the dose escalation phase were evaluable for efficacy.
- **Assessments:** Both local and independent assessments show encouraging overall response with one patient showing a deepening of a response at 6 months.
- **ORR:** The 3-month ORR compares favorably to that of pembrolizumab monotherapy for R/R HL patients who are post- or ineligible for ASCT and have failed brentuximab vedotin.

	Complete Metabolic Response No. (%)	Partial Metabolic Response No. (%)	No Metabolic Response No. (%)	Progressive Disease No. (%)	Overall Response Rate No. (%)
Cohort 1 (N=3)	0 (0%)	2 (67%)	0 (0%)	1 (33%)	67%
Cohort 2 (N=3)	1 (33%)	1 (33%)	0 (0%)	1 (33%)	67%
Cohort 3 (N=6)*	0 (0%)	5 (83%)	0 (0%)	1 (17%)	83%

*Dose for Cohort 3 chosen as the dose for the extension cohort and currently accruing to a total of 21 patients

Metabolic response at 3-month by local assessment, safety population

	Complete Metabolic Response No. (%)	Partial Metabolic Response No. (%)	No Metabolic Response No. (%)	Progressive Disease No. (%)	Overall Response Rate No. (%)
Cohort 1 (N=3)	0 (0%)	2 (67%)	1 (33%)	0 (0%)	67%
Cohort 2 (N=3)	1 (33%)	1 (33%)	0 (0%)	1 (33%)	67%
Cohort 3 (N=6)	0 (0%)*	5(83%)*	1 (17%)	0 (0%)	83%

*A patient with a PmR at 3-month was assessed as a CmR at 6-month assessment.

Metabolic response at 3-month by independent, central assessment, safety population

Safety

- **Most AEs were CTCAE grade 1 or 2 (67%)**
- **Four CTCAE grade 3 AEs were observed, with 3 AEs assessed as at least possibly related to both AFM13 and pembrolizumab: nausea, vomiting and IRR**
  - The remaining AE of duodenal ulcer assessed as not related to either study treatment
- **MTD not yet reached**
- **1 DLT observed in Cohort 3**
  - Repeated CTCAE grade 2 IRR which led to missing >25% of study treatment(s)
- **An independent DRC has recommended continuation of recruitment to the extension cohort**

Preferred Term	Safety population (N=12)	CTCAE Grade ≥ 3
IRR	10 (83%)	1 (8%)
Nausea	5 (42%)	1 (8%)
Cough	4 (33%)	0 (0%)
Diarrhea	4 (33%)	0 (0%)
Headache	4 (33%)	0 (0%)
Pyrexia	4 (33%)	0 (0%)
Rash	4 (33%)	0 (0%)

Most common AEs observed in at least 3 patients

Key Conclusions

- **The combination of AFM13 and pembrolizumab is well tolerated.**
- **Most of the AEs observed are mild to moderate in nature and are manageable with standard of care.**
- **Based on local and independent assessments, the 3-month ORR for the combination at the dose selected for the extension cohort to date compares favorably to the historical ORR of pembrolizumab for R/R HL patients who are post-ASCT or ineligible for ASCT and have failed brentuximab vedotin.**

#corresponding author, Disclosures: S.A., P.A., R.C., N.B., A.F.T., I.L., and C.R. receive research funding from Affimed; A.S. C.C.J. and A.K. are employees of Affimed; References: 1) Reusch U., et al., mAbs 2014; 6(3): 728-39. 2) Armand P., et al., J Clin Oncol. 2016; 34 3) Rothe A., et al., Blood 2015; 125(26): 4024-31 4) Zhao X., et al., J Clin Oncol. 2015; 33 (suppl; abstr 3050). 5) Cheson B.D., et al., J Clin Oncol 2014; 32(27): 3059-3067. 6) Chen et al., J Clin Oncol 2017; 35:2125-2132.