Abstract
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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: Updated Safety and Efficacy Data

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Summary

Background: AFM13 is a bispecific, tetravalent 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 leads to NK-cell mediated killing of CD30-positive lymphoma cells.[1] Pembrolizumab is a PD-1 blocking antibody that prevents tumor immune evasion and induces high single-agent response rates in patients (pts) with relapsed or refractory HL (RRHL)[2]. AFM13 has shown single-agent clinical activity in pts with RRHL in a preceding Phase 1 study.[3] Preclinical *in vivo* data of the combination of AFM13 with PD-1 inhibition suggest synergistic activity and the potential for induction of cross-talk between innate and adaptive immunity.[4]

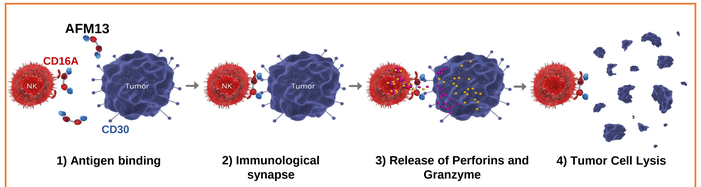
Methods: A Phase 1b dose escalation/extension study is ongoing to evaluate the safety and tolerability and preliminary efficacy of the combination of AFM13 with pembrolizumab (Keytruda®) as salvage therapy after failure of standard therapies including brentuximab vedotin in pts with HL (NCT02665650). Pts receive escalating doses of AFM13 (Table 1) in combination with pembrolizumab at the approved dose of 200 mg following the classical 3+3 design. Upon completion of dose escalation, 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] All available safety/efficacy data as of April 16, 2018 are presented.

Results: Thirty pts have been enrolled into the study. The median age is 34 years (range, 18-73), with a median of 4 (range 3-7) prior lines of therapy. All pts have relapsed or refractory disease and have failed standard treatments including brentuximab vedotin (BV) and 43% of pts (13/30) had BV as their latest therapy. Thirty seven percent (11/30) have undergone prior autologous stem cell transplantation. Twelve pts were enrolled into the dose escalation cohorts (Cohorts 1, 2, and 3) and 18 into the Extension Cohort. All 30 pts completed the 6 week dose limiting toxicity (DLT) observation period. No DLTs occurred in Cohorts 1 and 2, one DLT occurred in Cohort 3 (missed ≥25% of AFM13 during the DLT period due to persistent Grade (G)1/G2 infusion-related reactions (IRRs)) and one DLT occurred in the Extension Cohort (G4 IRR). Treatment-related Adverse Events (TRAEs) were mainly G1/G2 and included IRRs (80%), nausea (23%), pyrexia (23%), and rash (23%). Treatment-related G3/4 AEs included IRRs (13%), elevated aspartate aminotransferase (3%), gastritis (3%), hypotension (3%), nausea (3%), neutropenia (3%), and vomiting (3%). An interim efficacy analysis was performed for all pts who had a baseline and at least one post-baseline disease assessment as of April 16, 2018 (n=24). The best overall response rate (ORR) and complete response (CR) rate for pts treated at the dose and schedule chosen for expansion (n=18; Cohort 3 and Extension Cohort) were 89% and 28%, respectively, by both investigator assessment and independent central review.

Conclusions: Preliminary data suggest that the combination of AFM13 and pembrolizumab is a well-tolerated therapy in pts with RRHL with most AEs mild to moderate in nature. The ORR of 89% and CR rate of 28% seen to date at the dose and schedule chosen for the Extension Cohort compare favorably to monotherapy pembrolizumab in a similar RRHL population.[6]

Introduction

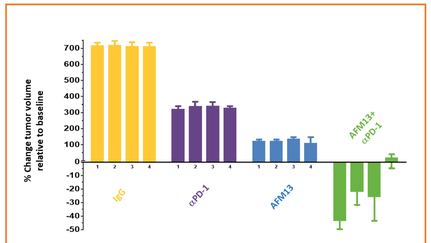
- **AFM13 is a first-in-class tetravalent, bispecific NK cell engager in clinical development**
- High-affinity binding to CD16A and CD30, independent of polymorphism, virtually no competition with IgG and potent cytotoxicity[1]
- Synergy with checkpoint modulators in pre-clinical studies[4]
- Established clinical activity with solid safety profile (Phase 1 study)[3]



Mechanism of action of AFM13

Background

- **AFM13 shows synergy with anti-PD-1 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

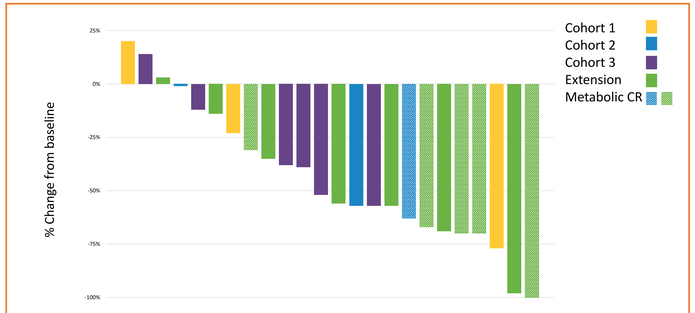
Synergy of AFM13 with anti-PD-1

Population Characteristics

Characteristic	Total Patient Population (N=30) N Number (%)
Age, years, median (range)	34 (18 to 73)
Gender	Female 10 (33%); Male 20 (67%)
Prior therapies, no.	
Unknown	1 (3%)
3	14 (47%)
4	6 (20%)
5	3 (10%)
6	4 (13%)
7	2 (7%)
Prior auto. stem cell transplant.	11 (37%)
Prior brentuximab vedotin (BV)	30 (100%)
BV as last therapy	13 (43%)
Refractory vs. relapsed	57% vs. 43%

Demographic and baseline characteristics, safety population

Best Response, Tumor Volume



Change in tumor volume measured by CT-scan, efficacy population (N=24)

Methods

- **Study design:** 3+3 dose escalation design with 3 dose escalation cohorts and an extension cohort of up to 24 patients (pts)
- **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 30 pts have completed DLT period. Efficacy analysis included best response amongst the 24 pts who had a baseline and at least one post-baseline disease assessment
- **Response:** 89% ORR and 28% CR rate by investigator and independent assessments at the dose chosen for expansion (3 mg/kg followed by 7 mg/kg)
- **Responders:** Three pts who had relapsed and/or were primary refractory to all prior therapies achieved an objective response (2 PmR, 1 CmR) on AFM13 + pembrolizumab

	Complete Metabolic Response No. (%)	Partial Metabolic Response No. (%)	No Metabolic Response No. (%)	Progressive Disease No. (%)	Overall Response Rate No. (%)
Cohorts 1&2 (N=6)	1 (17%)	3 (50%)	0 (0%)	2 (33%)	4 (67%)
Cohort 3 (N=6)	0 (0%)	5 (83%)	0 (0%)	1 (17%)	5 (83%)
Ext. Cohort (N=12)	5 (42%)	6 (50%)	0 (0%)	1 (8%)	11 (92%)
Coh3 + ExtC (N=18)	5 (28%)	11 (61%)	0 (0%)	2 (11%)	16 (89%)

Best metabolic response by investigator assessment, safety population

	Complete Metabolic Response No. (%)	Partial Metabolic Response No. (%)	No Metabolic Response No. (%)	Progressive Disease No. (%)	Overall Response Rate No. (%)
Cohorts 1&2 (N=6)	1 (17%)	3 (50%)	2 (33%)	0 (0%)	4 (67%)
Cohort 3 (N=6)	1 (17%)	4 (67%)	1 (17%)	0 (0%)	5 (83%)
Ext. Cohort (N=12)	4 (33%)	7 (58%)	0 (0%)	1 (8%)	11 (92%)
Coh3 + ExtC (N=18)	5 (28%)	11 (61%)	1 (5%)	1 (5%)	16 (89%)

Best metabolic response by independent assessment, safety population

Safety

- **All 30 pts have completed DLT period**
  - 2 DLTs observed
    - Missed ≥25% of AFM13 during DLT period (Cohort 3)
    - G4 IRR (Extension Cohort)
- **MTD not reached**
  - Extended dose/schedule of Cohort 3 (3 mg/kg followed by 7 mg/kg)
- **Treatment-related Adverse Events (TRAE)**
  - Most were Common Terminology Criteria for Adverse Events (CTCAE) G1 or G2 and manageable with standard of care measures

TRAEs, All Grades	Safety population (N=30)	TRAEs ≥ CTCAE G3	Safety population (N=30)
IRR	24 (80%)	IRR	4 (13%)
Nausea	7 (23%)	Elevated AST	1 (3%)
Pyrexia	7 (23%)	Gastritis	1 (3%)
Rash	7 (23%)	Hypotension	1 (3%)
Diarrhea	6 (20%)	Nausea	1 (3%)
Fatigue	5 (17%)	Neutropenia	1 (3%)
Headache	5 (17%)	Vomiting	1 (3%)

Most common TRAEs in at least 5 patients: All Grades and ≥ CTCAE G3

Key Conclusions

- **The combination of AFM13 and pembrolizumab is well tolerated with most AEs mild to moderate in nature and manageable with standard of care measures.**
- **Based on local and independent assessments, the ORR and CR rate for the combination at the dose selected for the extension cohort to date compare favorably to the historical data of pembrolizumab in a similar patient population.**
- **Based on these preliminary data, the combination of AFM13 and pembrolizumab might also be an attractive therapeutic option to be evaluated in patients who are relapsed/refractory to anti-PD-1 therapy.**

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