**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. 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 HL (RR HL). AFM13 has shown first signs of clinical activity in RR HL as a single agent in a preceding Phase 1 study. Prophylaxis in cohort 2 of the combination of AFM13 with PD-1 inhibition suggest potential synergistic activity, the potential for induction of cross talk between innate and adaptive immunity. Thus, the combination of the two agents might improve outcomes in pts with RR HL.

**Methods:** A Phase 1b study is ongoing to evaluate the safety and tolerability of the combination of AFM13 with pembrolizumab (B.D., et al., J Oncol Pract 2017; 35:2125). This is a single arm, open label trial investigating cumulative dose escalation of AFM13 in combination with pembrolizumab at a flat dose of 230 mg administered every 2 weeks following the classical 3+3 design. Upon completion, recruitment continues into a 3+3 dose escalation every 12 weeks PET/CT imaging according to the Lucagine Classification Revised Staging System for malignant lymphoma.

**Results:** As of November 1, 2017, 12 pts with RR HL have been enrolled into the dose escalation part of the study. The median age of the pts is 39 years (range 20-73). All pts have failed standard treatments including brentuximab vedotin (1/2) who have failed prior autologous stem cell transplantation (ASCT). All pts were heavily pretreated with at least a prior of therapy (range 2 to 13). At the time of the data extract, 11/12 pts completed the dose escalation part into cohort 3. One DLT was observed in cohort 3, which was a 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 (AE) were: nausea (10/12 pts), rash (5/12 pts), diarrhea (3/12 pts), headache (2/12 pts), pyrexia (2/12 pts), and rash (3/12 pts). Most of these events were grade 1 or 2. There were a total of 4 grade 3 AEs observed in the study with the events being deemed at least possibly related to both AFM13 and pembrolizumab: grade 3 IRR, grade 3 nausea and grade 2 vomiting. The remaining 34/34 of all adverse events was assessed as not related to other study treatment. All 12 pts enrolled into the dose escalation phase were efficacious at doses 2 to 3 months. By the investigator assessment, in Cohort 1, there were Partial Metabolic Response (PRm) and Partial Progressive Disease (PPD). In Cohort 2, one Complete Metabolic Response (CRm), 1 PRm and 1 PPD were observed. In Cohort 3, four CRm and 2 PRm were observed. The ORR for the dose selected for the extension cohort (dose used in Cohort 2) was 45% (9/20) by both local and independent assessments. Additionally, a deepening of a response was reported where a single dose of Pembrolizumab is chosen Cut 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 HH with encouraging efficacy. Most AEs observed across all cohorts were mild to moderate in severity and manageable with standard therapy. While AEs were observed frequently, only one case was assessed as grade 3. The 3-month ORR of 45% (local and independent assessment) at the dose chosen for the extension cohort compares favorably to a 3-month ORR of pembrolizumab monotherapy in a similar patient population of post ASCT HL. At the time of data cut, 21 patients were enrolled and are currently accruing to two further cohorts.

**Methods:**

**Study design:** 3+3 dose escalation design with 3 dose escalation cohorts and a safety extension cohort in patients with Relapsed/Refractory HL patients.

**Primary objectives:**

- MTD determination
- Secondary objectives:
  - Safety evaluation
  - Anti-tumor activity
  - PK profile evaluation
- Study population:
  - Patients: All 12 patients from the dose escalation phase were evaluated for efficacy
  - Assessments: Both local and independent assessments should encourage 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 RR HL patients who are post or ill-suited for ASCT and have failed brentuximab vedotin.

**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 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 RR HL patients who are post-ASCT or have failed brentuximab vedotin.

**Population Characteristics**

**Efficacy**

- Patients: All 12 patients from the dose escalation phase were evaluated for efficacy
- Assessments: Both local and independent assessments should encourage 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 RR HL patients who are post or ill-suited for ASCT and have failed brentuximab vedotin.

**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 deepening of a response was 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 ≥20% of study treatment

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- Repeated CTCAE grade 2 IRR which led to missing ≥20% of study treatment

- An independent DRC has recommended continuation of recruitment to the extension cohort

**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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