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ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Innate Cell Engager (ICE®) AFM13 Combined with Preactivated and Expanded (P+E) Cord Blood (CB)-Derived Natural Killer (NK) Cells for Patients with Refractory CD30-Positive Lymphomas: Final Results

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Pts with refractory Hodgkin (HL) and other CD30+ lymphomas have few effective therapies available and targeted NK cell immunotherapy is an active area of research. Transfer of non-targeted NK cells has shown limited clinical benefit as target recognition of cancer cells by NK cells constitutes a barrier. The innate cell engager AFM13 is a first-in-class CD30/CD16A bispecific antibody construct that induces selective killing of CD30+ tumor cells by engaging and activating NK cells. As a single agent, AFM13 has limited clinical activity against HL, likely due to the reduced effector function of autologous NK cells in these pts, which provides the rationale for combining AFM13 with allogeneic NK cells. Our prior preclinical work identified a promising combination of CB-derived NK cells that were first IL-12/IL-15/IL-18-preactivated followed by *ex vivo* expansion (P+E) with engineered K562 feeder cells expressing membrane-bound IL-21, 4-1BBL and CD48 and exogenous IL-2, and subsequently complexed with AFM13 just before infusion; these cytokine-induced memory-like NK cells presented chimeric antigen receptor (CAR)-NK-like features and increased *in vitro* and *in vivo* antitumor activity compared to either non-AFM13-precomplexed P+E NK cells or to AFM13 alone (Kerbauy et al, Clin Cancer Res 2021). Building on this work we wished to study this CB NK-cell therapy in pts with refractory CD30+ lymphomas.

METHODS This investigator-initiated single-center phase I-II trial (NCT04074746) evaluated the safety and activity of P+E AFM13-precomplexed CB NK cells followed by systemic AFM13. Pts ages 15-75 with CD30+ lymphomas refractory to brentuximab vedotin were enrolled. The goals were to identify the recommended phase 2 dose (RP2D) of NK cells, estimate the overall (ORR) and complete response (CR), event-free (EFS) and overall survival (OS) rates, and study NK cell activation and persistence. Each treatment cycle consisted of fludarabine/cyclophosphamide (days −5 to −3) followed by infusion (day 0) of the AFM13-precomplexed CB NK cells, cultured for 14 days as described above, and three weekly IV infusions of AFM13 (200 mg, days 7, 14 and 21). Two cycles were planned for pts 1-19 and up to 4 cycles from patient 20 on. Response was evaluated on day 28 of each cycle. Enrollment proceeded at 3 dose levels (DL) of 10^6, 10^7 and 10^8 NK/Kg, respectively. Each patient received the same NK dose in all cycles.

RESULTS Between 09/20-12/22 we enrolled 42 pts (37 HL, 5 NHL), pretreated with a median 7 lines, at DL1 (N=3), DL2 (N=3) and DL3 (N=36), with 1 (N=2), 2 (N=21), 3 (N=3) or 4 cycles (N=16). All had active progressive disease at enrollment and no bridging therapy was given. The cords used for each of the 117 cycles were selected without consideration for HLA match, which was 0/6 (N=53), 1/6 (N=46), 2/6 (N=14), 3/6 (N=3) and 4/6 (N=1). The product infused consisted of >94% NK cells

(expanded >2,700 fold), with only 0.02% T cells. The NK cells were 96% viable, 91% bound to AFM13, and 97.6% CD16+. The products were infused fresh.
There was 1 grade 2 infusion-related reaction (IRR) in 115 infusions of AFM13-NK (0.8%) and 27 IRR infusion related reactions in 350 infusions of AFM13 (7.7%) (1 G3, 26 G2). We saw no cases of CRS, ICANS or GVHD of any grade. DL3 (10^8 NK/Kg) was established as the RP2D. The ORR and CR were 92.8% and 66.7%, respectively (94.4% and 72.2%, respectively, in 36 pts treated at the RP2D). Nine pts had a response consolidated with SCT (5 allo, 4 auto).
At median follow-up of 14 (6-34) months, the EFS/OS rates are 31%/76%; median EFS/OS are 8 months/not reached. No relapses were associated with antigen loss. In the subset of pts planned for 4 cycles at RP2D, 15 of 23 pts remained event free at 6 mo (4 pts with and 11 without SCT consolidation), for 6-month EFS/OS rates of 65%/83%. Overall, 8 of the 9 pts (89%) receiving a consolidation SCT are event free at 10 to 34 months.
AFM-bound CB NK cells were detected in blood from day 1 post infusion for up to 3 weeks. Donor NK levels followed similar patterns after each cycle, which argues against a sensitization after the first NK infusion. CyTOF studies showed increased expression of AFM13 and activation markers in donor NK cells. We confirmed trafficking of AFM13-bound donor NK cells to tumor sites shortly after infusion.

CONCLUSIONS CB-derived cytokine-induced memory-like NK cells precomplexed with AFM13 have excellent tolerability and activity for pts with heavily pretreated and refractory CD30+ lymphoma.

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Baseline patient characteristics	N=42
Age, median (range)	43 (20–75)
Gender (male/female)	27 / 15
Diagnosis (HL / NHL)	37 / 5
No. prior lines therapy, median(range)	7 (1–14)
Prior brentuximab vedotin	42
Prior anti-PD-1	39
Prior SCT (autologous / allogeneic)	32 (22 / 10)
Prior CD30.CAR-T	4

Figure 1

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