Treatment with a leukemia-derived dendritic cell vaccine induces innate and adaptive immune response correlating with clinical response in AML patients in CR1 with measurable residual disease

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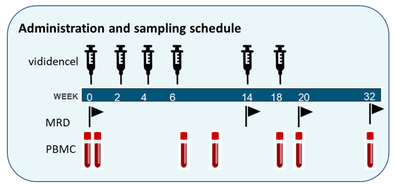
Introduction

- Persistence of measurable residual disease (MRD) is a poor prognostic factor and predicts relapse in patients with acute myeloid leukemia (AML). New treatment modalities to treat residual disease and deepen responses are urgently needed
- Vididencel is an allogenic, leukemic cell-based relapse vaccine and expresses co-stimulatory molecules, resembling activated dendritic cells, and tumor associated antigens (TAA) such as WT1, PRAME and RHAMM. It is injected intra-dermally and leads to an inflammatory response and indirect priming of the immune system
- A phase 1 study showed that vididencel is safe and can induce both humoral and cellular immune responses[1] leading to unexpectedly long survival times
- The current phase 2 study aims to investigate the ability of vididencel to generate an anti-leukemia response in patients with AML in complete remission (CR), but MRD positive (Clinicaltrials.gov: NCT03697707).

Clinical study design and outcome

STUDY DESIGN

- AML patients in Complete Remission (CR1), ineligible for HSCT and MRD positive by flow cytometry and/or RT-PCR or NGS
- Patients are given 4 bi-weekly vaccinations with vididencel intradermally followed by two booster vaccinations at week 14 and 18
- Primary endpoint: MRD responses & immune response assessment



CLINICAL OUTCOME (22NOV22)

- 20 evaluable patients for MRD response assessment
  - 14 patients remained in CR
    - 5 patients (25%) converted to MRD negative (MRD response)
    - 2 patients (10%) had at least a 10-fold decrease in MRD levels (MRD response)
    - 7 patients (35%) had stable MRD levels (MRD stable)
    - 6 patients (30%) relapsed in the first 32 weeks
- Median RFS is not yet reached; estimated 12 months RFS 64% (41-80%)
- Median OS = 30.9 months; estimated 12 months OS 85.3% (65-94%)

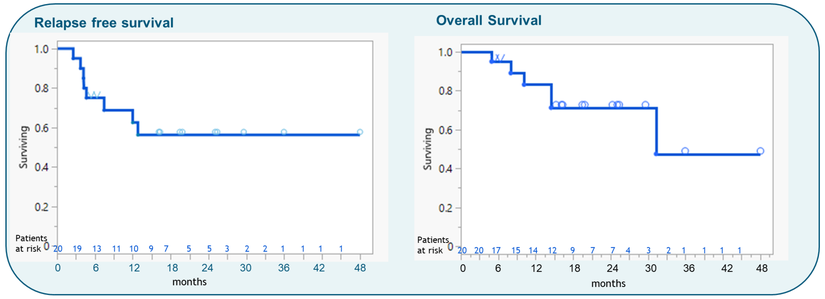


Figure 1. *Relapse free and overall survival. Median follow-up for the population is 19.4 months (22NOV22)*

Methods

Immunomonitoring of peripheral blood mononuclear cells was performed frozen PBMC, which were isolated using a standardized protocol by trained staff

IFNγ ELISPOT

Samples were analysed by restimulation with WT1, PRAME or RHAMM peptide pools. Vaccine Induced Response (VIR) was defined as at least a 2-fold increase of the specific, mock-corrected baseline response

Flow cytometry

Multiparameter flow cytometry was performed using a 40-marker panel using Cytek Aurora on frozen PBMC samples. Flowsom analysis on subsets was performed on concatenated files (using the plug-in as provided, based on the method described by Sophie van Gassen[2]) , with added metadata on visit number and clinical response (MRD responder, stable MRD and relapse at week 32). tSNE plots were generated for the full immune samples, and on separate immune subsets, CD4, CD8, monocytes. Overlays of tSNE plots, with 2% and 5% contour plots were used to identify the largest differences in populations. Confirmation of the identified subsets was performed on the original .fcs data files and statistical analysis was performed using JMP17

Results

Baseline immune cell composition shows differences related to clinical response

A higher relative level of B cells, and relative lower CD8 CM in patients who remain in CR is observed at baseline (Figure 2). Statistical analysis shows a significant difference on the level of $CD19^+$ B cells and $CD8^+$ $CD45RA^-$ $CCR7^+$ central memory T cells.

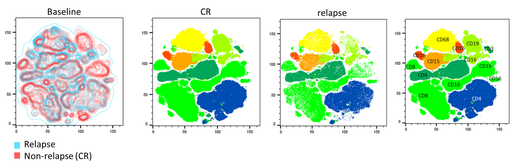


Figure 2. *tSNE plots at baseline comparing all immune cells in PMBC of patients whom remain in CR or relapse.*

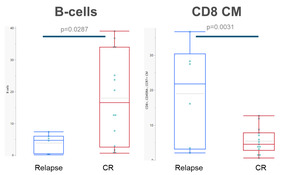


Figure 3. *Boxplots of baseline levels of B cells and CD8 CD45RA– CCR7+ cells of patients who remain in CR or relapse.*

At baseline, T cell subset differences were observed across the response groups (Figure 4). More tumor-reactive subsets were identified in patients remaining in CR, whereas more suppressive subsets were identified in relapsed patients, like $CD4^+$ $LAG3^+$ and $CD8^+$ $LAG3^+$ T cells (Figure 5).

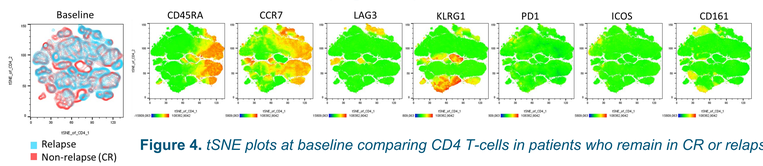


Figure 4. *tSNE plots at baseline comparing CD4 T-cells in patients who remain in CR or relapse.*

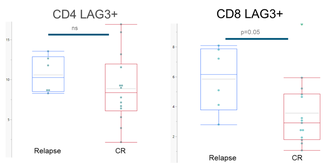


Figure 5. *Boxplots of baseline levels of $CD4^+LAG3^+$ and $CD8^+$ $LAG3^+$ T cells of patients who re-main in CR or relapse.*

Higher number and durable functional T-cell responses in patients with MRD response

Vididencel expresses WT1, PRAME and RHAMM and IFNγ ELISPOT towards these antigens shows responses in 17/20 patients (85%) in this study. The highest number of vaccine induced responses are observed in patients who had a MRD response. At several timepoints vaccine Induced responses to the same antigen were observed, indicative for a durable T cell response.

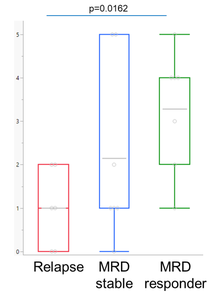


Figure 6. *Vaccine induced responses (Y-axis) as measured by IFNγ ELISPOT to WT1, PRAME and RHAMM are represented for the patients who relapsed, remained stable on MRD, or showed a MRD response.*

Improvement in immune cell subsets across all patient categories

After vaccination, levels of B-cells increased in the majority of patients, cDC1 levels increased, especially in those low at baseline, whereas inhibitory $CD8^+$ $LAG3^+$ T cells decreased, most notably in patients who relapsed.

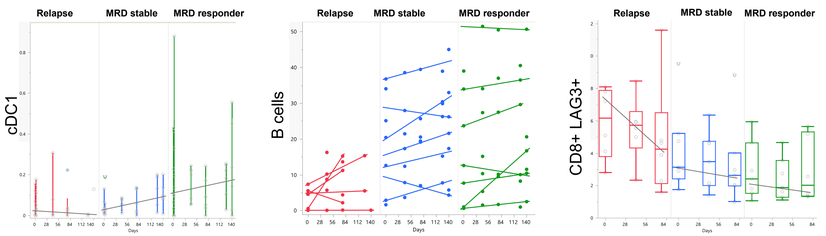


Figure 7. Vaccination induced changes in patients who did relapse in the first 32 weeks (red) or remained stable (blue) or had MRD response (green). **A** cDC1 frequency (CD45+, HLA-DR+, CD11b-, CD14-, CD11c+, CD141+, CLEC9A) in PBMC during vaccination, boxplots per timepoint and line of fit are shown. **B.** B cell frequency, indicated are the individual patient profiles and the change in B cells during vaccination. **C.** $CD8^+$ $LAG3^+$ T cells and the change after primary vaccination. Indicated are the boxplots per timepoint and line of fit.

Conclusion

- Innate and adaptive immune responses are observed after vididencel to allow for a beneficial environment for tumor control or eradication
  - Increasing levels of cDC1 and B-cells
  - Reduced or decreasing levels of inhibitory CD8+ LAG3+ T cells
- Functional T cell responses towards frequently expressed antigens in AML, i.e. WT1, PRAME and RHAMM, were observed in the majority of patients
- Vaccine induced responses are higher in patients with clinical response, especially in those with a MRD response
- RFS and OS indicate a durable disease control in this patient population which is at high risk for relapse

References 1 van de Loosdrecht AA et al., A novel allogeneic off-the-shelf dendritic cell vaccine for post-remission treatment of elderly patients with acute myeloid leukemia *Cancer Immunol. Immunother. 2018; 67;1508-18. 2* Sofie Van Gassen *et al.* FlowSOM: Using self-oraganising maps for visualization and interpretation of cytometry data. Cytomertry A *doi 10.1002/cyto.a.22625*