Vaccination using an Allogeneic Leukemia-derived Dendritic Cell Vaccine, maintains and improves frequencies of circulating antigen presenting dendritic cells correlating with relapse free and overall survival in AML patients

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INTRODUCTION

- Active immunotherapy relies on the patient's immune system for induction of an effective immune response. Not only the frequency, number and exhaustion or activation status of T-cells is important for an efficacious tumor cell lysis, but the quality, number and distribution of different antigen presenting cells is of equal importance, in particular DCs (Pittet et al, 2023[1]).
- Vididencel is an allogeneic leukemia-derived dendritic cell vaccine used in AML patients in first complete remission (CR1/ CRi), but with MRD positivity, to mount an immune response through intradermal injection (ADVANCE-II, Clintrials.gov: NCT03697707). Intradermal vaccination is known to induce a specific immune response, by recruitment of skin and blood derived dendritic cells, which process antigen and present them to the immune system.
- In this study circulating dendritic cells and monocytes have been investigated before and during treatment with vididencel to investigate the effect on the composition of circulating antigen presenting cells in relation to clinical responses.

MODE OF ACTION VIDIDENCEL

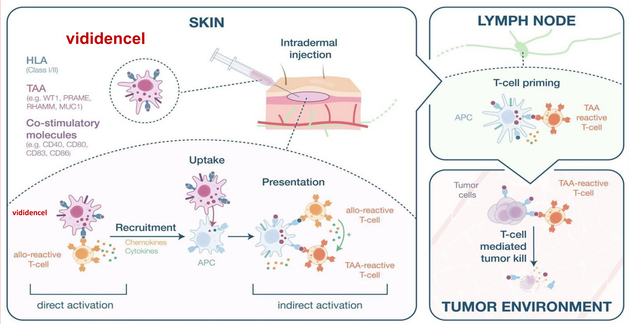

Figure 1. Graphical representation of the mode of action of vididencel. *Vididencel is administrated intradermally.*

DESIGN OF THE CLINICAL TRIAL

A total of 20 evaluable AML patients, in CR1/CRi, with measurable residual disease (MRD$^+$) and ineligible for HSCT at inclusion, received 4 biweekly doses of vididencel, followed by 2 booster doses at week 14 and 18.

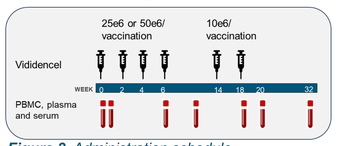

Figure 2. *Administration schedule.*

RESULTS

Previous analyses already indicated higher baseline levels and an increase in cDC1 in PBMC after vididencel injection, in patients who remain in CR in peripheral blood (Fig 3, 4 and 5). Current analysis further deepens the dynamics of dendritic cells during vididencel injection in AML patients.

Peripheral blood mononuclear cell analysis by 40-parameter flow cytometry indicated a difference in baseline levels of lineage negative (CD3, CD19, CD14, CD15, CD16) cell subsets. In patients who remained in CR the HLA-DR+ and CD45RA+ cells were present in high numbers, in contrast to patients who relapsed (Fig 3).

Changes and increases in several subsets were observed during treatment, most notably in subsets with cDC1, cDC2 and pDC characteristics, like expression of CD141, CLEC9A, CD1c and CD123. At week 32 the changes are shown for patients remaining in CR (Fig 4).

With the median follow-up of 24 months, the (relative) frequencies of dendritic cell subsets was correlated to longer overall and relapse free survival at baseline and after completion of treatment. In patients remaining in CR, vaccination further increased or maintained dendritic cell subset frequencies, of which classical cDC1 and cDC2 correlated with longer overall survival (Fig 6).

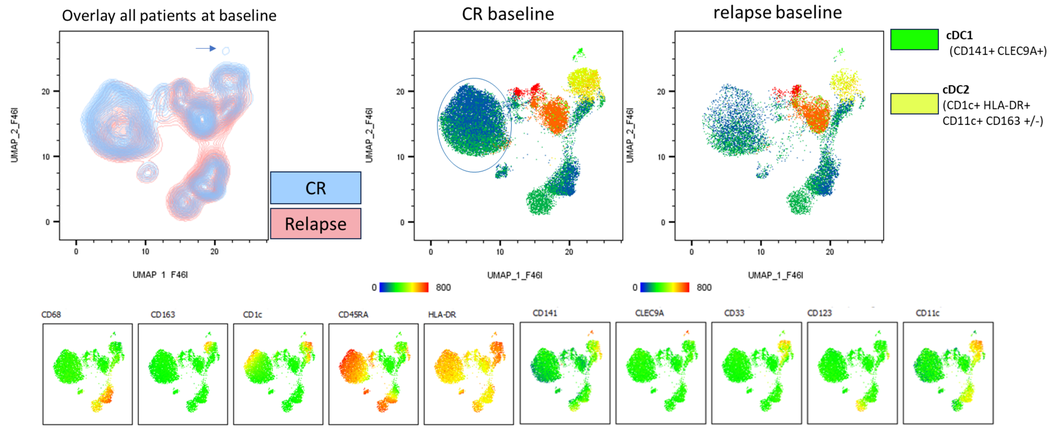

Figure 3. ***Analysis of Lin- (CD3, CD19, CD56, CD15, CD16 negative), CD11b– cells at baseline.*** *Patients remaining in CR had higher relative levels of CD45RA and HLA-DR cells (indicated by the circle), overlay indicates the cDC1 cells (arrow) higher in patients remaining in CR, as well in the UMAP plots with Flowsom derived cell clusters. Higher number of cDC1 and cDC2 dendritic cells can be observed. Expression levels of dendritic and myeloid cell markers are shown for the different cell clusters.*

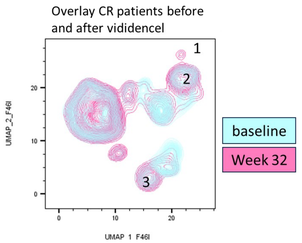

Figure 4. Vaccine induced responses at week 32. *Overlay indicates the changes in cell clusters for patients remaining in CR at baseline versus week 32. Indicated is the new cluster of cDC1 after vaccination (1). The cluster with cDC2 (2), CD123 (3) expression remains or improves in density.*

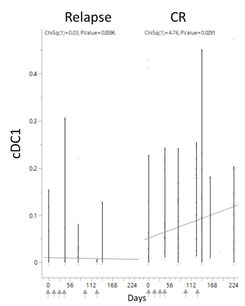

Figure 5. ***Frequency of cDC1 cells.***
Baseline levels of cDC1 (CD45+, CD14-, HLA-DR+, CD11b-, CD141+, CLEC9A+) are higher in patients remaining in CR and increase during vaccination.

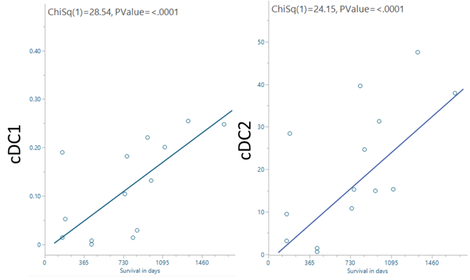

Figure 6. Correlation OS with cDC1 and cDC2 levels. *Frequencies of cDC1 (CD45+, CD14-, HLA-DR+, CD11b-, CD141+, CLEC9A+) and cDC2 (CD45+, CD14-, HLA-DR+, CD11b-, CD11c+, CD1c+) after vaccination, correlating with OS. Survival at data cut (03jul23) with censor for patients who went into HSCT.*

METHODS

Peripheral blood mononuclear cells were taken at baseline, week 6, 11, 14, 18, 20 and 32, ficoll isolated and stored in LN_2 until use. Analysis of immune cell composition was performed by spectral flow cytometry, using a single 40-marker panel. Immune subset analysis of dendritic (live, single cells, CD45+, Lin-(CD3, 56, 19), CD16-, CD15-) cells was performed and correlated to clinical response, relapse free and overall survival (data cut 3Jul23), by high dimensional analysis using FlowSOM[2].

References 1 Pittet et al., Dendritic cells as shepherds of T cell immunity in cancer. Immunity, *doi: 10.1016/j.immuni.2023.08.014.* 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*

CONCLUSIONS

- Baseline levels of cDC1 correlate with clinical response
- Patients who remain in CR have higher baseline levels of lineage negative CD45RA+ HLA-DR+ cells; possibly representing myeloid cells able to differentiate into dendritic cells
- Vaccination with vididencel increases dendritic cell frequencies in circulation
- Level of cDC1 and cDC2 at end of treatment with vididencel correlate with longer survival

UPDATED survival data of the ADVANCE-II study will be presented on Monday 11 December 10.30 AM, room 6CF by A. van de Loosdrecht (Abstract 769)

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