# LONG-TERM FOLLOW-UP OF A "FAST-DC" IMMUNOTHERAPY AGAINST WT-1 AND PRAME AS A POST-REMISSION STRATEGY FOR ACUTE MYELOID LEUKEMIA

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## BACKGROUND & RATIONALE FOR THE STUDY

Limited solutions are available for a long-term disease control in patients with acute myeloid leukemia (AML) not amenable to hematopoietic stem cell transplantation (HSCT). These patients are usually treated with intensive chemotherapy to induce remission. Unfortunately, a significant proportion of these patients suffer a relapse of the original disease.

Dendritic cell (DC) vaccination to boost tumor antigen presentation is an attractive therapeutic strategy to prolong remission through immunosurveillance and immune system activation. Wilms tumor 1 (WT-1) and PReferentially expressed Antigen of MElanoma (PRAME) are antigens presented on malignant cells, which can elicit a specific T cell response.

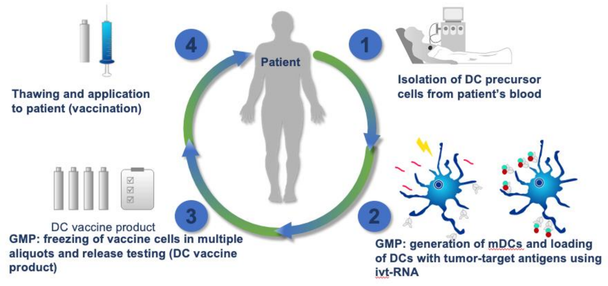
A novel, fast and efficient method to generate autologous (patient-specific) mature DCs loaded with WT-1 and PRAME was developed (Medigene AG, Germany) to elicit strong T cell immune responses to malignant cells.

As a consequence, the use of this autologous DC vaccine against WT-1 and PRAME was hypothesized to be of interest as a therapeutic solution to prevent or delay relapse of AML. This formed the rationale to design and conduct a phase I/II study. Upon completion of the 2-year study, patients were followed-up outside of the study protocol for survival outcomes.

## DC VACCINE

Autologous monocytes are isolated and the vaccine is generated according to GMP standards with a rapid production protocol of 3 to 4 days. The manufacture uses RNA electroporation encoding the full-length protein antigens PRAME and WT-1 as well as a cocktail containing a TLR-7/8 agonist for maturation.

**Figure 1: DC vaccine manufacturing process**




### Dose & administration

- Vaccination once per week during the 4 consecutive weeks and once per month from week 10 for the 2-year duration of the study. At week 6 a DTH test was performed.
- Every administration by intradermal injection consists of 5-10x10$^6$ DCs, i.e. 2.5-5x10$^6$ DCs/antigen.

## METHODOLOGY

A single-center, prospective, open-label phase I/II study to assess the safety, feasibility and preliminary efficacy of the autologous WT-1 and PRAME RNA-loaded dendritic cells in AML patients with a morphologic remission with or without hematological recovery after induction chemotherapy. Key eligibility criteria required the patient, aged 18 to 75 years, to be positive for WT-1 with or without positivity for PRAME.

### Objectives

- The primary objective is to assess safety, and feasibility of the immunotherapy in this population.
- Secondary objectives include overall survival, (OS) progression/elapse-free survival (PFS), time to progression (TTP), control of minimal residual disease (MRD) and induction of immune responses

The data presented here, reflect post-hoc long-term follow-up data after the completion of the 2-year study. Upon completion the phase I study (n=6), the DSMB recommended to conduct the phase II study (n=14), for a total of 20 eligible patients.

**www.clinicaltrials.gov: NCT02405338**

## BASELINE CHARACTERISTICS & DEMOGRAPHICS

| Parameter [unit] | Outcome |
|---|---|
| Number of subjects (n=) | 20 |
| Number of females & males n= (%) | 5 (25%) & 15 (75%) |
| Age (years) | |
| · Mean±SD | 54.4±14.8 |
| · Median (min-max) | 59 (24-73) |
| ECOG 0 (n= (%)) | 20 (100%) |
| AML Hovon/SAKK risk stratification (n=(%)) | |
| · Good | 13 (65%) |
| · Intermediate | 5 (25%) |
| · Poor | 2 (10%) |
| Time from start of LCLR to start of IMP treatment | |
| · Mean±SD month | 7.3±3.5 |
| · Median (min-max) | 6.9 (2.0-14.8) |
| Months from first diagnosis to start of IMP treatment | |
| · Mean±SD months | 10.1±3.7 |
| · Median (min-max) months | 9.8 (4.5-17.5) |
| WT-1 positive* (n= (%)) | 20 (100%) |
| PRAME positive* (n = (%)) | 15 (75%) |

**Measured before screening and start of induction chemotherapy (at diagnosis). Of note, at screening only 7/20 remained WT-1 positive, 4/20 patients were positive for WT1 and PRAME.*

### Follow-up time

- The mean and median follow-up time (cut off September 29th 2020) was 56 and 51 months (range 40-77) after diagnosis and 45 and 44 months (range 34-63) after the first vaccination.

## SAFETY OF THE 2 –YEAR STUDY

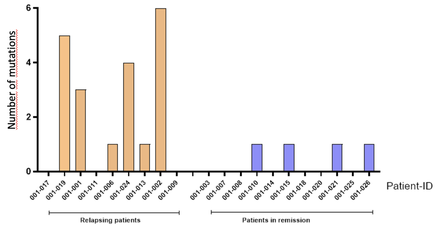
- No vaccine related serious and/or unexpected events reported
- Compliance was very high, and there were no patient withdrawals from the study due to toxicity or intolerability
- Grade I/II toxicity was experienced by 90% of patients
- Grade III toxicity was experienced by 25% of patients
  - 3 patients with thrombocytopenia due to an imminent relapse
  - 1 upper respiratory tract and 1 herpes zoster infection
- Most common adverse event: transient grade I injection site reactions, accounting for 28% (22/80) adverse events

## FEASIBILITY

- A DC vaccine could be produced for all 20 patients, despite the intense chemotherapeutic pretreatment
- For 85% DC vaccine productions yielded at least 20 vaccine doses, underlining the robustness of the GMP production protocol
- For 15 patients 1 apheresis was sufficient for the vaccine production, whereas for 5 a 2nd apheresis was required.
- Viability after thawing of vaccines was >70% with one exception

## RELAPSES & MUTATIONAL LOAD

- 9 patients relapsed, whereas 11 patients were in remission after 2 years of vaccination
- A higher mutational load was observed for relapsed patients

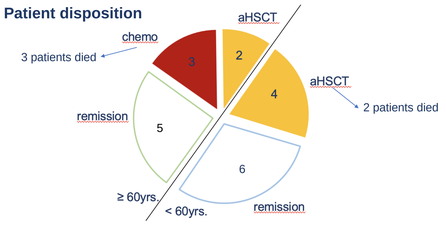



- 23 common mutations for AML were analyzed: ASXL1, BCOR, CALR, CBL, CEBPA, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF1.

## EFFICACY

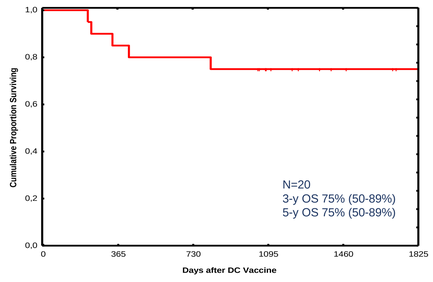
- 9 patients relapsed
  - 6 patients underwent HSCT
  - 5 patients died, 4 due to underlying disease and 1 due to GvHD following HSCT

**Figure 2: Patient disposition**



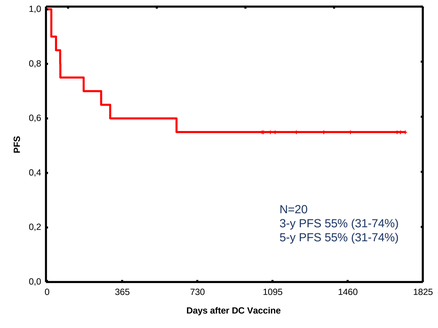

- The 5-year probability of survival (OS) from first vaccination was 75% (95% CI: 50-89%)
  - Patients < 60 years (n=10): 5-year OS 80% (95% CI: 41-95%)
  - Patients ≥ 60 years (n=10): 5-year OS 70% (95% CI: 33-89%)

**Figure 3: Kaplan Meier estimates of OS from first vaccination**




- The 5-year probability of progression survival (PFS) from first vaccination or first diagnosis was 55% (95% CI: 31-74%)
  - Patients < 60 years (n=10): 5-year PFS 60% (95% CI: 25-83%)
  - Patients ≥ 60 years (n=10): 5-year PFS 50% (95% CI: 18-75%)

**Figure 4: Kaplan Meier estimates of PFS from first DC vaccination**




## CONCLUSIONS

Vaccination with autologous 'fast DCs' against WT-1 and PRAME in AML for the prevention of relapse is safe, well-tolerated and feasible with encouraging long-term progression free and overall survival.

In particular, the 70% long term survival in the elderly patients warrants further studies to assess the efficacy of this vaccine approach in improving outcomes in patients with AML.

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