LONG-TERM FOLLOW-UP OF A “FAST-DC” IMMUNOTHERAPY AGAINST WT-1 AND PRAF E 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). It is 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 immunoresponsiveness and immune system activation. Wilms tumor 1 (WT-1) and PRAF are antigens presented on the surface of 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 PRAF 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 PRAF 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 IIb study. Upon completion of the 2-year study, patients were followed-up outside of the study protocol for survival outcomes.

DC VACCINE
Not all monocytes are activated 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 PRAF and WT-1 as well as a cocktail containing a TLR ligand for maturation.

Figure 1: DC vaccine manufacturing process

Figure 2: Patient disposition

Figure 3: Kaplan Meier estimates of OS from first vaccination

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

METHODOLOGY
A single-center, prospective, open-label phase IIb study to assess the safety, feasibility and preliminary efficacy of the autologous WT-1 and PRAF vaccine-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 and/or positivity for PRAF.

Objectives
• The primary objective is to assess safety, feasibility and preliminary efficacy of the immunotherapy in this population.
• Secondary objectives include overall survival, OS progression/lapse-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 II study (n=6), the DSMB recommended to conduct a phase IIb study (n=14), for a total of 20 eligible patients.

BASELINE CHARACTERISTICS & DEMOGRAPHICS

Parameter [unit] | Outcome
--- | ---
Number of patients & males (%) | 20 (100%)
Age | Median (min-max) months 9.8 (4.5-17.5)
WT-1 positive* (n= (%)) | 20 (100%)
PRAME positive* (n = (%)) | 15 (75%)

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 34.43) after the first vaccination

SAFETY OF THE 2-YEAR STUDY
No vaccine-related serious adverse events were reported.
• Compliance was very high, and there were no patient withdrawals from the study due to toxicity or intolerability
• Grade 1 toxicity was experienced by 90% of patients
• Grade III toxicity was experienced by 25% of patients
  • 3 patients with thrombocytopenia due to an intravenous infusion
  • 1 upper respiratory tract and 1 herpes zoster infection
• Most common adverse event: transient grade I injection site reactions, accounting for 28% (23/82) adverse events

FEASIBILITY
• A DC vaccine could be produced for all 20 patients, despite the intense chemotherapeutic pretreatment
• For 86 DC vaccine productions yielded at least 20 vaccine doses, underlying 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
• 3 patients relapsed, whereas 11 patients were in remission after 2 years of vaccination
• A higher mutational load was observed for relapsed patients

CONCLUSIONS
Vaccination with autologous fast DCs against WT-1 and PRAF 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.

REFERENCES
A standard set of references is provided.