INTERIM ANALYSIS OF A WT-1 AND PRAME "FAST-DC" VACCINE SHOWS SAFETY AS ACTIVE IMMUNOTHERAPY FOR THE PREVENTION OF AML RELAPSE

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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.

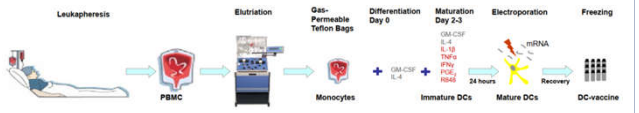
Dendritic cell (DC) vaccination to boost tumor antigen presentation is an attractive therapeutic strategy to prolong remission through immunosurveillance and immune system activation. Wilms tumor 1 (WT-1) and PReferentially expressed Antigen of MElanoma (PRAME) are tumor antigens presented on malignant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

A novel, fast and efficient method to generate autologous (patient-specific) mature DC loaded with WT1 and PRAME was developed (Medigene AG, Germany) to elicit strong T cell immune responses.

As a consequence, the use of this autologous DC vaccine against WT1 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.

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.



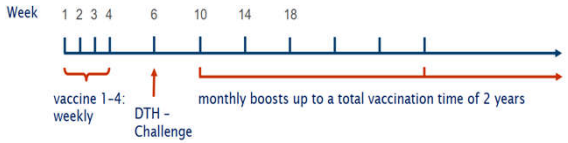
METHODOLOGY

A single-center, prospective, open-label phase I/II study is ongoing to assess the safety, feasibility and preliminary efficacy of the autologous WT1 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 WT1 with or without positivity for PRAME.

- The primary objective is to assess safety, and feasibility of the immunotherapy in this population. Safety is being monitored by a data safety monitoring committee (DSMB)
- 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 an interim analysis the first 12 months of treatment with MDG1011. Upon completion the phase I study (n=6), the DSMB recommended to conduct the phase II study (n=14).

DOSE & ADMINISTRATION OF DC VACCINE

- Every administration consists of 5-10x10^6 DCs, i.e. 2.5-5x10^6 DCs/antigen.
- Intradermal injections (each antigen in a separate injection)
- Once per week during the first 4 consecutive weeks and once per month from week 10 onwards for up to 2 years
- A delayed hypersensitivity (DTH) challenge was carried out in week 6



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%)
NMP1 positive (n= (%))	3 (15%)
FLT3-ITD positive (n= (%))	0 (0%)
CEBPA positive (n= (%))	0 (0%)
MLL (n= (%))	0 (0%)

*Measured before screening and start of induction chemotherapy (at diagnosis). Of note, at screening only 7/20 continued to be WT-1 positive, 4/20 patients were positive for WT1 and PRAME.
** During the study the ECOG remained 0 for the 3 NPM1 positive positive patients, 2 of these completed the 1-year treatment with MDG1011, whereas 1 patient relapsed after 3 iv infusions.
LCLR: last chemotherapy, last regimen.

SAFETY

A total of 66 adverse events (AEs) were reported in 17/20 patients (85%), of which 47 (71.2%) were grade 1, 13 grade 2 (19.7%) and 5 grade 3 (7.6%) in severity (and 1 grade 0).

Description	N° of patients with adverse event
≥ 1 AE	17 (85%)
≥ 1 AE possibly related to study treatment	12 (60%)
≥ 1 SAE	1 (5%)
≥ 1 SAE possibly related to study treatment	0
≥ 1 unexpected SAE possibly related to study treatment	0
Death due to progression of disease (one 217 and the other 337 days after first injection with study treatment)	2

As expected, the most common AE was injection site reactions, i.e. 35% of all AEs. Both injection site reactions and constitutional symptoms, all of mild severity and transient, occurred in 15/20 patients (75%) and that were considered at least possibly related to treatment for 84% of AEs.

For 25% of patients infections were reported considered not related to treatment.

Three severe (grade 3) AEs were reported, but considered not related to treatment, thrombocytopenia, observed in 3 patients immediate prior to relapse and without relationship to treatment, and two infections, one herpes zoster and one upper respiratory tract infection.

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PRELIMINARY EFFICACY

Eight patients (40%) relapsed within the time frame of first injection to the cut-off of 12 months treatment duration.

Two male patients died in the first 12 months of the study. Eighteen patients were still alive 12 months after first vaccination which results in a 1-year survival rate of 88.5% (95% CI: 61.4-97.0; see Figure 1 censored data for withdrawn or still alive at 12-months cut-off).

The probability of PFS, defined as not in complete remission (CR) and with a bone marrow aspirate blast number of at least 5% from the time from first vaccination to relapse of leukemia, was 60% (95% CI: 35.7-77.6; see Figure 2) censored for if no relapse occurred during the first 12 months after the first injection of study treatment).

Figure 1: Kaplan Meier estimates OS

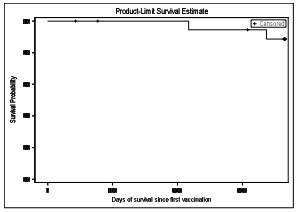
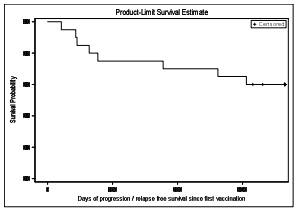


Figure 2: Kaplan Meier estimates PFS



RELAPSES

- Five out of 8 relapses occurred within the first 80 days after initiation of vaccination, suggesting a possible molecular relapse upon entering the study. In order to investigate the presence of mutations before the start of vaccination, genomic DNA was isolated from bone marrow samples and assessed for the presence of common mutations by next generation sequencing.
- The mutations analyzed included: ASXL1, BCOR, CALR, CBL, CEBPA, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF1.
- Two of the 5 early relapses, showed mutational load upon entering the study (IDH2 and DNMT3A mutation in one patient and multiple mutations in the second (RUNX1, KRAS, ETV6, BCOR, DNMT3A)).
- Two out of the 3 later relapses also showed mutational load before vaccination (one patient with a KRAS and TET2 mutation and one patient with RUNX1, IDH2, SRSF2 and DNMT3A mutations).

FEASIBILITY

- A DC vaccine could be produced for all 20 patients, despite the intense chemotherapeutic pretreatment
- Seventeen out of 24 DC vaccine productions yielded 20 or more vaccine doses, allowing vaccination for more than one year, underlining the robustness of the GMP production protocol
- After the culture time of 72 to 96 hours, all DC productions showed a mature phenotype with high expression of typical DC surface markers and downregulation of the monocyte marker CD14.
- All productions met the specification of <40% contaminating (non-DC) cells with a purity of >70% in general
- Viability after thawing of vaccines was >70% with one exception

CONCLUSIONS

Vaccination with 'fast DCs' against WT-1 and PRAME in AML for the prevention of relapse is safe and feasible with encouraging overall- and progression free survival results after one year of treatment.