BACKGROUND & RATIONALE FOR THE STUDY

Dendritic cells (DC) 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 (WT1) and PRAME (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.

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 and PRAME, as well as 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/relapse-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 of the first 12 months of treatment with MDG1011. Upon completion of the phase I study (n=8), the DSMB recommended to conduct the phase II study (n=14).

DOSE & ADMINISTRATION OF DC VACCINE

- Every administration consists of 5.10^9 DCs, i.e. 2.5-5.10^9 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 2 years
- A delayed hypersensitivity (DTH) challenge was carried out in week 6

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** | **\# of patients with adverse event** | **%**
---|---|---
WT1 & PRAME & FLT3 IDH 2 | 16/17 (94.1) | 100%
I. AE related to study treatment | 12 (60) | 75%
II. AE related to study treatment in PRAME positive | 1 (50) | 25%
III. AE pre-existing before vaccination | 0 | 0%
IV. AE unrelated to study treatment | 0 | 0%
V. AE related to vaccination not related to treatment | 2 | 13.3%

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, e.g. pulmonary embolism, observed in 3 patients immediately prior to relapse and without relationship to treatment, and two infections, one herpes zoster and one upper respiratory tract infection.

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 WT1 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.