First-in-Human Study of MDG1011, a TCR-T Cell Therapy directed against HLA-A*02:01-Restricted PRAME, for High-Risk Myeloid and Lymphoid Neoplasms (CD-TCR-001)

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Introduction

Background
- High-Risk Myeloid and Lymphoid Neoplasms, are malignant diseases of the hematopoietic system; they can be fatal within weeks, with an average age of onset of 65yrs, with significant numbers of patients eventually not responding or eligible for treatments.
- MDG1011 is a T cell receptor (TCR)-T cell therapy directed against HLA-A*02:01-restricted PRAME.
- PRAME is a cancer-testis antigen present in several solid and hematological malignancies.
- CD-TCR-001, a multicenter, open-label, non-randomized, dose-escalation clinical phase I/II study to evaluate the safety, feasibility and preliminary efficacy of PRAME/CD19 TCR transduced CD19+ T cells, MDG1011, in subjects with high-risk myeloid and lymphoid neoplasms (AML, MDS and MM).

Methods

Study objectives
- Primary: Assessment of safety and tolerability of MDG1011, the establishment of a maximum tolerated dose and (MTD)/or recommended Phase II dose (RP2D), and for manufacturing feasibility.
- Secondary: The secondary objectives are to evaluate overall response rate, evaluate the duration of response, time to progression, evaluate progression-free survival, assess overall survival, evaluate the correlation of PRAME expression with the antitumor response.
- Exploratory: Evaluation of biologic and immunologic parameters

Treatment
- Treatment was conducted with MDG1011 (i.v. administration) after lymphodepletion with fludarabine (25 mg/m² x 3) and cyclophosphamide (100 mg/m² x 3) in patients with HLA-
A*02:01- and PRAME-positive r/r disease. Dose escalation included 3 dose levels (DL): 1x1010 (DL1), 1x1012 (DL2) and 5x1010 (DL3) TCR+ cells/kg body weight (BW), respectively. The trial was run as a 3+3 design and a minimum of 3 dose cohorts. The optimal 4th dose level of MDG1011 (up to 1x1011 TCR- transduced T cells/kg + 20%) was not investigated (Fig 1).
- Data collection from all patients in a given cohort had to be complete for the 4-week dose limiting toxicity (DLT) period (up to visit 5) to proceed to the next cohort.

GMP Production (by CMO) of MDG1011 TCR-T cells
- Patient T cells were isolated via leukapheresis and enriched for CD8+ cytotoxic T cells via positive enrichment using magnetic CD8 beads. CD8-enriched cells were frozen and served as intermediate product. After activation of T cells in bags using anti-CD3 and anti-CD28 antibodies, T cells were retrovirally transduced using Retronectin as transduction enhancer. Transduced T cells were expanded in G-Res/5/7 (gas-permeable rapid expansion) flasks and frozen in cryo-bags. Cells were thawed at the bedside and re-infused into the patient.

Baseline demographics
- 13 heavily pretreated elderly patients with relapsed/refractory, myeloid and lymphoid neoplasms and a median age of 65 years were enrolled and underwent leukapheresis (n=10) with 31A/LM, n=1 with MDS/MPN and n=2 with MM.
- All patients were heavily pretreated with chemotherapy, whereas 6/13 patients underwent aHSCT of whom 5 were treated with MDG1011.

Primary Objective Results

Safety
- All 13 patients experienced adverse events (AEs), of which 54/124 AEs were grade 3 toxicities (NGI CTCAE v4.01, 31/124 AEs related to lymphodepletion and 21/124 AEs related to MDG1011. 12 SAFs were reported in 7/8 treated patients. Grade 1 cytokine release syndrome (CRS) occurred in 1 patient at DL2, grade 2 CRS in 1 patient at DL3 that was manageable with tocilizumab. Neurotoxicity (ICANS) or DLT were not reported (Table 3).
- Twelve Serious TEAEs in 8 patients (77.8%), of which 4 were considered related to MDG1011 (1 transduction reaction (DL2): 1 grade IV leukopenia, 1 grade III female neutropenia and 1 grade II CRS (all in DL3).

Table 3. TEAEs by SOC for patients treated with MDG1011

Dose Recommendation
- MTD and RP2D objectives were not met, as data was confounded by low dose response, however, a trend towards higher dose response was observed.
- No apparent dose-related pattern of toxicities

Manufacturing Feasibility
- MDG1011 manufacturing feasibility was excellent, with release criteria met for 12/13 patients (92.3%).
- No Detectable AML blast contamination in drug products (Fig 2).

Efficacy
- In patients receiving MDG1011, 1 patient with AML with extramedullary disease (DL1) experienced complete remission at week 4 but had progressed by month 3.
- 4 patients died from their disease (none in DL3, none considered related to MDG1011) and 4 patients experienced disease progression.
- 1 patient with multilineage MDS and MPM remained without progression to secondary AML after > 19 months; detection of TCR-T cells at EoT visit at 12 months; reduction of PRAME mRNA in blood and bone marrow.
- TCR-T cells were present in 6 of 8 patients within 4 weeks. PRAME (BM) decreased in 4 patients (3 AML, 1 MM) while a slight increase occurred in 1 patient (MM). PRAME (PB) decreased at week 4 for 2 patients treated at the highest dose but increased thereafter (Fig 3).

Conclusion
- 92% successful manufacturing of MDG1011 from heavily pretreated, elderly patients
- MDG1011 was well tolerated with no DLT or neurotoxicity
- MTD and RP2D objectives was not met
- Signs of biological and/or clinical activity (1x CR, 2x CRS, 1 AML patient without progression to AML after > 16 months still under observation; detection of TCR-T cells at EoT visit at 12 months; reduction of PRAME mRNA in blood and bone marrow)

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