Combination of a TCR-engineered Autologous PRAME-targeting T Cell Therapy with a PRAME-encoding mRNA for the Treatment of Solid Tumors

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Fabian Brunk[1], Rafael Blasco Patino[2], Claudia Wagner[1], Filippos Porichis[2], Alper M. Kursunel[1], Jing Sun[2], Adi Diab[3], Dejka M. Araujo[3], Patrick A. Ott[4], James Smithy[5], Norbert Hilf[1], Delfi Krishna[6], Brendan Weiss[2], Andrea Mayer-Mokler[1], Christine Lukacs[2], Karine Pozo[6], Lin Guey[2], Simone Mori[2], Cedrik M. Britten[1]

[1] Immatics Biotechnologies GmbH, Tuebingen, Germany; [2] ModernaTX, Inc., Cambridge, MA, USA, [3] MD Anderson Cancer Center, Houston, TX, USA; [4] Dana Farber Cancer Institute, Boston, MA, USA; [5] Memorial Sloan Kettering Cancer Center, NYC, NY, USA; [6] Immatics US, Stafford, TX, USA

Introduction

ACTengine IMA203 is an adoptive T cell therapy for solid tumors in patients with advanced or recurrent cancers. It consists of genetically modified patient T cells expressing a recombinant T cell receptor targeting an HLA-A*02:01-restricted Preferentially Expressed Antigen in Melanoma (PRAME) epitope. In a Phase 1 trial, IMA203 showed a favorable tolerability profile with a confirmed overall response rate of 54% in melanoma patients. To further improve its anti-tumor activity, IMA203 will be combined with a lipid nanoparticle (LNP) encapsulated mRNA encoding the IMA203 PRAME-derived target peptide. A preclinical proof-of-concept supports this combination, and a First-In-Human Phase 1 study is planned.

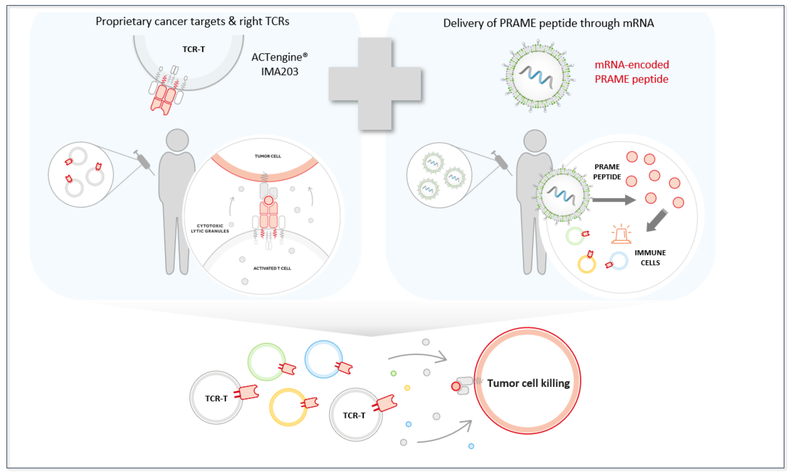

Figure 1: A diagram summarizing the mode of action of the ACTengine® IMA203 + PRAME mRNA combination therapy

Methods

Experiment set-up

- *In vitro* differentiated human CD14+ monocytes into monocyte-derived Dendritic Cells (moDC) were transfected with either increasing concentrations of mRNA - Lipid Nanoparticle (LNP) encoding PRAME, or non-coding mRNA "mock" negative control.
- Co-cultures with either IMA203 T cells or non-transduced "NTD" negative controls were established
- The following readouts were used:
  - IFNγ release (ELISA)
  - Flow cytometry: upregulation of T cell activation markers CD25, CD69, CD137
  - Flow cytometry: proliferation

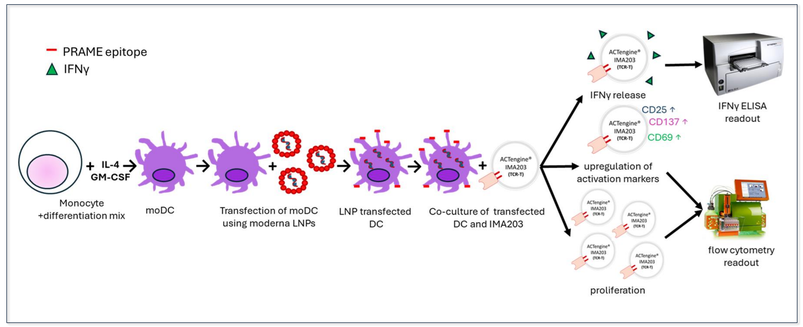

Figure 2: A diagram depicting the experimental workflow of monocyte derived dendritic cells (moDC), transfection of moDCs, co-culture set up and readouts of experiments

Results

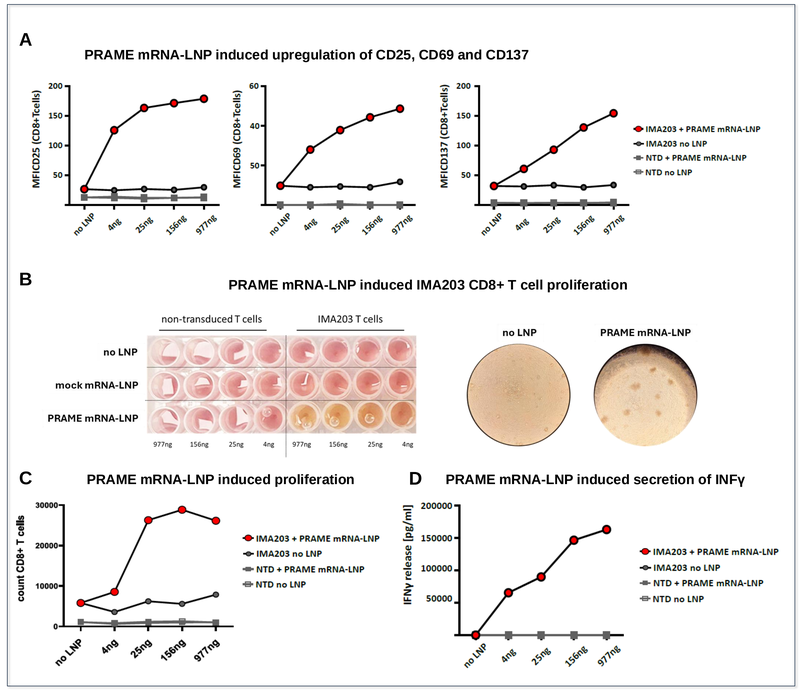

Figure 3: PRAME mRNA-LNP transfected moDCs were co-cultured with IMA203 T cells for 24h-72h at a T cell: DC ratio of 3:1-4:1. **A** Mean Fluorescent Intensity (MFI) of CD25, CD69 and CD137, respectively. Gated on CD8+ T cells, measured by flow cytometry (24h); **B left panel**, picture of a (section of) 96-well plate showing medium exhaustion as a results of T cell proliferation upon co-culture with mRNA-LNP transfected DCs; **B right panel**, microscope images, showing T cell clustering in PRAME mRNA-LNP transfected co-cultures; **C** absolute counts of CD8+ T cells after 72h co-culture; **D** Interferon-γ (IFNγ) secretion, measured by ELISA (24h)

Key Results

- **PRAME mRNA LNPs induced IMA203 T cell activation** as shown by the upregulation of all activation markers tested, including CD25, CD69 and CD137.
- **PRAME mRNA LNPs induced IMA203 T cell effector cytokine secretion** and in particular IFNγ production.
- **PRAME mRNA LNPs induced IMA203 T cell proliferation** as demonstrated by an increase in CD8+ IMA203 T cell counts upon prolonged co-culture conditions.
- **The effects were antigen-, TCR- and dose dependent** as demonstrated by the absence of response with the negative controls and the changes in responses to mRNA-LNP dilution series.

Clinical Trial Design

- This First-in-Human, phase 1a/1b trial is a multicenter, open-label, dose escalation/de-escalation (adaptive design) trial enrolling patients with recurrent and/or refractory melanoma and synovial sarcoma (including prior checkpoint inhibitors for skin melanoma).
- ***Primary objectives***: Maximum tolerated dose (**MTD**) and/or recommended dose for extension (**RDE**); **safety and tolerability**
- ***Primary endpoints***: Incidence of dose-limiting toxicities (DLTs); incidence and severity of AEs and SAEs after the administration of IMA203 alone and in combination with mRNA.
- ***Secondary objectives***: Describe **pharmacokinetics and anti-tumor activity** of IMA203 T cell therapy in combination with PRAME mRNA
- ***Secondary endpoints***: **IMA203 cellular kinetics (expansion, persistence)**; Overall response rate **(ORR)** based on best overall response (BOR) of complete response (CR) and partial response (PR) locally assessed using RECIST v1.1; Disease control rate of **CR, PR or stable disease (SD)** lasting 6 or more weeks following the infusion of IMA203 based on RECIST v1.1; Duration of response (DOR) of CR or PR based on RECIST v1.1; PFS based on RECIST v1.1

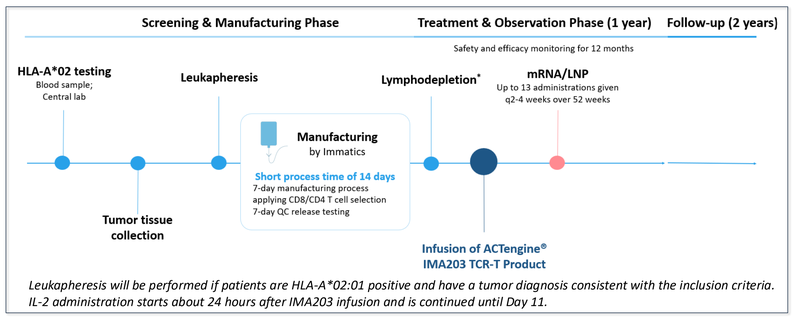

Figure 4: Clinical trial overview

Conclusions and outlook

- We have established preclinical proof-of-concept and showed that LNPs containing PRAME-encoding mRNA can strongly activate IMA203 T cells and induce their proliferation in a co-culture system.
- We have planned a First-In-Human clinical combination study of IMA203 with the selected PRAME mRNA-LNP construct to evaluate the safety, tolerability and efficacy of the combination therapy in up to 15 patients with advanced or recurrent cutaneous melanoma and synovial sarcoma.

Disclosure statement: RBP, FP, JS, BW, CL, LG and SM are employees of Moderna, Inc. and may own stock/stock options in the company.