

Start 01/07/2019

yr 1

yr 2

yr 3

yr 4

yr 5

yr 6

yr 7

30/06/2026 End

**Pr. 1:** High resolution tumor and immune cell profiling

- WP0.** Sample collection from patients (LiMeT clinical study)
- WP1.** DNA, RNA analyses (bulk & sc RNA-, Whole Exome-, ATAC-seq) on tumor cells
- WP2.** Spatial transcriptomics
- WP3.** Protein analyses (high dimensional flow cytometry) on immune cells
- WP4.** Validation by multiplex IF and IHC
- WP5.** Study of antigenic repertoire in liver MTS (TCR-seq&hunting, CAR-design)

**Milestone 1 (yr 3):** Identification of immune suppressive/exhaustion pathways to be harnessed in program 2 & 3

**Milestone 2 (yr 4):** Development of a library of tumor-specific TCRs and identification of new CAR targets in CRC and PDAC MTS

**Pr. 2:** Adoptive cell therapy with genetically engineered T-cells

- WP1.** TCR gene editing
- WP2.** Genetic disruption of immunosuppressive genes in T cells
- WP3.** Generation & in vitro validation of tumor specific TCR-redirection T cells
- WP4.** Generation and in vitro validation of tumor specific CAR-redirection T cells
- WP5.** In vivo validation of CAR- and TCR T cells
- WP6.** Combinatorial adoptive T cell therapy and vascular/stroma targeting
- WP7.** IFNAR1 stabilization on tumor-specific T cells
- WP8.** In vivo imaging of CAR and TCR cell dynamics

**Milestone 3 (yr 4):** Generation and validation of innovative TCR and CAR redirect T cell products to be implemented in clinical trials

**Pr. 3:** In vivo gene-based targeted cytokine delivery

- WP1.** In vivo efficacy & safety validation of LV-based cytokine delivery to the liver
- WP2.** In-vivo study of LV-based cytokine delivery to tumor-specific T-cells
- WP3.** Development of leading candidate cytokine LVs
- WP4.** New nano-systems for targeted delivery of cytokines

**Milestone 4 (yr 4):** Identification of the leading candidate cytokine delivery system

**Pr. 4:** Toward clinical implementation

- WP1.** Identification of a leading ATMP candidate, safety and biodistribution studies
- WP2.** GLP safety/toxicity and biodistribution studies of elected ATMP(s) in small and large animal models
- WP3.** Scale-up of manufacturing of LV and cell products with GMP-ready protocols; set up of QC tests
- WP4.** Scientific advice and preparation of filing for ATMP application with AIFA/ISS