Targeting Solid Tumors with IMA402, a Next-generation Bispecific T Cell Engaging Receptor (TCER) against PRAME

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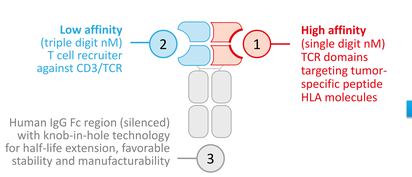
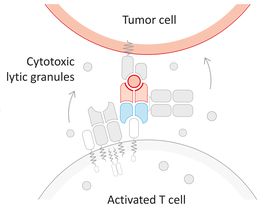
The Next-generation of TCR Bispecifics – TCER

The use of T cell engaging bispecifics redirecting T cells towards human leukocyte antigen (HLA)-presented peptides is emerging as a promising treatment modality for patients with solid tumors. Improving drug safety, efficacy and dosing schedule are key considerations for the generation of optimized bispecific molecules. Here, we show preclinical data for our next-generation T cell engaging receptor (TCER) candidate IMA402 targeting an HLA-A*02:01-presented peptide derived from PRAME, which is highly prevalent across multiple solid tumors.



Proprietary TCER format consisting of three distinct elements designed for optimal efficacy and minimal toxicity risk in patients



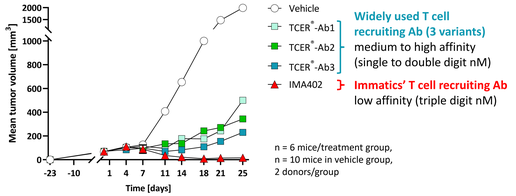
TCER binds to target, recruits and activates T cells and initiates tumor cell killing

TCER Format Is Designed for Optimized Efficacy and Safety

TCER molecules are designed with a high affinity TCR and a low affinity T cell recruiting Ab to optimize biodistribution*. The design intends a selective T cell activation at the tumor site but not in the periphery for reducing immune-related toxicities, like cytokine release syndrome, and reaching relevant doses in tumor tissue to achieve meaningful clinical responses.

* Refer to literature data for other low-affinity recruiters (e.g. Harber *et al.*, 2021, Nature; Trinklein *et al.*, 2019, mAbs)

Superior tumor control using a novel, low-affinity recruiter with high T cell activation capacity



n = 6 mice/treatment group,
n = 10 mice in vehicle group,
2 donors/group

Figure 1. *In vivo* efficacy assessment of TCER molecules incorporating the identical tumor-targeting TCR domains, but different T cell recruiting antibodies (Ab) in Hs695T (melanoma) tumor cell line xenograft model in NOG mice. Weekly intravenous injections of 0.025 mg/kg body weight of PRAME-specific TCER molecules for three weeks starting at study day 1 after intravenous transfusion of human PBMC. TCER IMA402 utilizes a novel, low affinity recruiter against both CD3/TCR (triple digit nM affinity). Analogous TCER molecules TCER-Ab1, Ab2 and Ab3 utilize medium to high affinity recruiter against CD3 (TCER-Ab1: 39 nM, TCER-Ab2: 9 nM, TCER-Ab3: 31 nM).

Reduced target-unrelated recruiter-mediated cytokine release in whole blood using a low-affinity recruiter

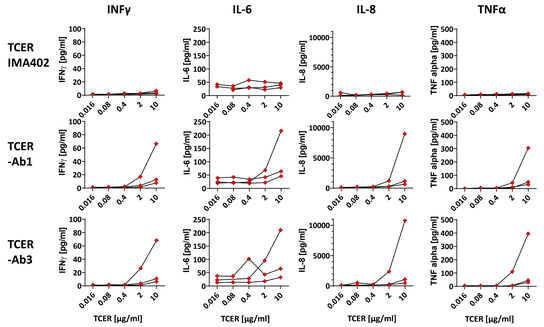


Figure 2. Whole blood cytokine release assay to assess the risk of different recruiters to induce cytokines in absence of target. Non-specific activation by T cell recruiter arm was assessed by measuring TCER-mediated cytokine release in whole blood of 3 HLA-A*02-positive donors 48 h after coculture of TCER IMA402, TCER-Ab1 or TCER-Ab3 and human endothelial cells (HUVEC). N = 16 cytokines tested, individual values for 4 exemplary cytokines shown. Higher background of IL-6 is due to the presence of HUVEC. TCER-Ab2 was not tested.

IMA402 Shows Tumor Cell Killing at Low PRAME Peptide Levels *in vitro*

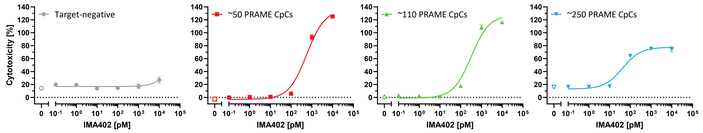


Figure 3. T cell-mediated cytotoxicity of IMA402 against tumor cells presenting PRAME target peptide at different copy numbers per cell (CpCs). Cytotoxicity was calculated based on LDH release from tumor cells after 48 hours of coculture with PBMCs. PRAME CpCs on cell lines and cancer tissue measured by AbsQuant.

- TCER IMA402 induces killing of tumor cells with PRAME target copies as low as 50 CpCs
- Physiological PRAME levels detected in majority of cancer tissues from patients are 100 – 1000 CpCs

IMA402 Achieves Durable Tumor Control of Large Tumors *in vivo*

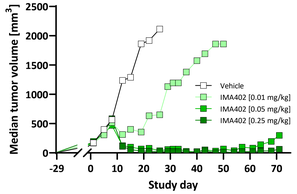


Figure 4. *In vivo* efficacy of IMA402 in large (average tumor volume of ≈ 195 mm³) melanoma cell line-derived tumors in MHC I/II knock-out NSG mice over a prolonged observation period of 71 days. Weekly intravenous injections of IMA402 starting at study day 1 after intravenous transfusion of human PBMC. Treatment was discontinued when complete response was noted. Median values for n = 6 mice/group, 2 donors/group.

- Dose-dependent efficacy of IMA402 in cell line-derived *in vivo* mouse model
- Durable shrinkage of large tumors including complete responses over prolonged period
- Sufficiently high drug doses are key to achieving desired anti-tumor effect

Half-life Extended Format of IMA402 Confers Terminal Half-life of >1 Week in Mice

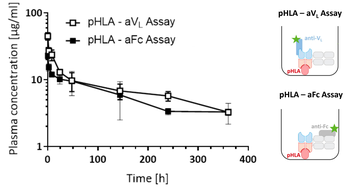


Figure 5. Pharmacokinetic analysis of IMA402 in mice. NOG mice received a single intravenous injection of IMA402 [2 mg/kg]. TCER plasma concentrations at different time points were determined by ELISA detecting binding of IMA402 to the PRAME target via pHLA. The integrity of the molecule was confirmed via aV$_L$ or aFc detection. Terminal half-life ($t_{1/2}$) was calculated via linear regression of time points between 24 h and 360 h (n=3 per timepoint, mean ± SD).

- IMA402 shows a terminal serum half-life of ≈ 8 days in mice
- IMA402 will be initially dosed weekly in the clinical trial
- Dosing frequency may be adapted based on clinical data

In vitro Safety Assessment Confirms Favorable Safety Profile

Favorable safety profile for all 20 tested normal tissue types

Organ	Cell type	
Brain	iHA	iPSC-derived astrocytes
	iHN	iPSC-derived GABAergic neurons
Kidney	HRCEpC	renal cortical epithelial cells
Liver	iHH	iPSC-derived hepatocytes
Heart	iHCM	iPSC-derived cardiomyocytes
	HCM	cardiomyocytes
	HCMEC	cardiac microvascular endothelial cells
	HCASMC	coronary artery smooth muscle cells
	HCAEC	coronary artery endothelial cells
Vessels	HAoEC	aortic endothelial cells
	HTSMC	tracheal smooth muscle cells
Respiratory tract	HPF	pulmonary fibroblasts
	HPMEC	pulmonary microvascular endothelial cells
	HBEpC	bronchial epithelial cells
Skin	HDMEC	dermal microvascular endothelial cells
	NHDF	dermal fibroblasts
	NHEK	epithelial keratinocytes
Muscle	SkMC	skeletal muscle cells
Bone	hMSC	mesenchymal stem cells
Blood	PBMC	

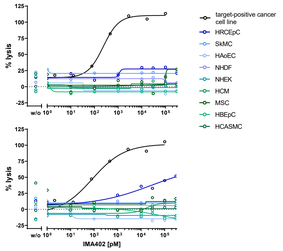


Figure 6. Toxicity screening. IMA402 was screened against 20 HLA-A*02:01+ iPSC-derived and primary normal human cell types isolated from different tissues. Percent IMA402 T cell-mediated target cell lysis was determined by LDH-release assay. No relevant reactivity was observed against any of the tested primary cell types. For one donor, weak signal in renal cells, expressing PRAME at very low levels, was detected at high TCER concentrations. Representative data for 9 normal cell types and positive tumor control shown.

No alloreactivity against a panel of 57 cell lines covering all frequent HLA class I alleles

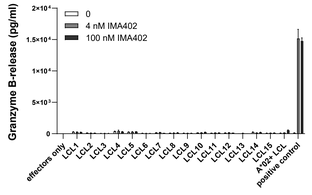


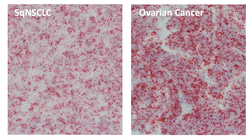
Figure 7. Alloreactivity assessment. IMA402 cocultured with T cells was screened against 57 different B-lymphoblastic cell lines (LCL) displaying all frequent HLA class I alleles (f ≥0.5%) with an overall coverage of 97.29% for all occurring HLA-A alleles, 93.93% for HLA-B alleles and 98.45% for HLA-C alleles. Two representative IMA402 doses of 6 doses (ranging from 0 to 100 nM) tested shown. Positive control: HLA-A*02:01+ B-LCL loaded with 10 µM target peptide. Representative data for 15 LCL shown.

PRAME Is Broadly Expressed Across Solid Tumors

A

Indication	% Positive Patients
Uterine Carcinoma	100%
Uterine Carcinosarcoma	100%
Sarcoma Subtypes	up to 100%
Melanoma	95%
Uveal Melanoma	90%
Ovarian Carcinoma	80%
Squamous NSCLC	65%
TNBC	60%
Small Cell Lung Cancer	55%
Kidney Carcinoma	up to 45%
Cholangiocarcinoma	35%
Adeno NSCLC	25%
Breast Carcinoma	25%
HNSCC	25%
Esophageal Carcinoma	20%
HCC	20%
Bladder Carcinoma	20%

B



PRAME peptide clinically validated

ACTengine IMA203 TCR-T targeting the same PRAME peptide as TCER IMA402 showed objective responses and so far, no signs for off-tumor toxicity in a clinical phase 1 trial.**

Figure 8. **A)** PRAME target prevalence in selected cancer indications as examples. Prevalence is based on TCGA (for SCLC: in-house) RNAseq data combined with a mass spec-guided expression threshold. Uveal melanoma target prevalence is based on IMADetect qPCR testing of screening biopsies from clinical trial patients (n=21). TNBC: Triple-negative breast cancer, NSCLC: Non-small cell lung cancer, HNSCC: Head and neck squamous cell carcinoma, HCC: hepatocellular carcinoma **B)** Homogenous detection of PRAME mRNA expression in tumor tissues by *in situ* hybridisation (ISH). ** ACTengine IMA203 phase 1a interim read-out at SITC 2021 by Wermke, *et al.*

IMA402 Phase 1/2 Clinical Trial to Start in 2023

CMC and supply activities on track for clinical trial

- Manufacturing process development completed
- High titer (>3.5 g/L) and good stability allowing liquid formulation

Trial Overview

Phase 1/2 clinical trial to evaluate safety, tolerability and anti-tumor activity of IMA402

HLA-A*02:01-positive patients with PRAME-expressing recurrent and/or refractory solid tumors

Phase 1: Dose Escalation

Adaptive design aimed at accelerating dose escalation → MTD/ RP2D

- Basket trial in focus indications for accelerated signal finding
- Initially weekly i.v. infusions#
- MABEL-based starting dose
- Dose escalation decisions based on cohorts of 1-6 patients in adaptive design (BLRM model)

Phase 2a: Dose Expansion

- Expansion cohort
- Expansion cohort
- Expansion cohort

- Specific indications plus ongoing basket
- Combination therapies
- Optional dose/application optimization

MABEL: minimum anticipated biological effect level; BLRM: Bayesian logistic regression model; MTD: maximum tolerated dose, RP2D: recommended phase 2 dose; #Pharmacokinetics data assessed throughout the trial might provide an opportunity to optimize scheduling.

TCER IMA402 – Next-generation TCR Bispecific Targeting PRAME

IMA402 is a next-generation, half-life extended TCR Bispecific directed against PRAME demonstrating enhanced anti-tumor activity, reduced T cell engager-associated toxicities and favorable pharmacodynamic characteristics in preclinical studies.

TCER format is optimized for efficacy and safety

- IMA402 using a low-affinity T cell recruiting antibody shows superior tumor control compared to analogous TCER molecules designed with higher-affinity variants of a widely used antibody recruiter
- IMA402 is optimized for reducing T cell engager-associated toxicities in patients, which is demonstrated by a reduced recruiting antibody-mediated cytokine release *in vitro*

Compelling preclinical data

- IMA402 shows potent and selective activity against PRAME-positive tumor cell lines *in vitro*
- *In vivo* studies in mice demonstrate dose-dependent anti-tumor activity of IMA402 and that sufficiently high drug doses are key to achieving desired anti-tumor effect over prolonged period
- *In vitro* safety assessment confirms favorable safety profile for IMA402
- IMA402 demonstrates a serum half-life of ≈ 8 days in mice suggesting a favorable dosing regimen and prolonged drug exposure at therapeutic levels when compared to TCR bispecifics lacking half-life extension strategies

Clinical trial evaluating IMA402 in patients with solid tumors to start in 2023

- IMA402 is designed to allow high dosing not limited by toxicities with the goal to reach relevant therapeutic doses in tumor tissue and achieve a meaningful clinical benefit in patients

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