Phase I Adoptive Cellular Therapy Trial with *ex vivo* Stimulated Autologous CD8+ T cells Against Multiple Targets (ACTolog® IMA101) in Patients with Relapsed and/or Refractory Solid Cancers

Apostolia M. Tsimberidou, M.D., Ph.D.[1], Borje S. Andersson, M.D., Ph.D.[1], Chad Stewart, M.S.[2], Hong Ma, M.D. [2], Oliver Schoor, Ph.D.[2], Arun Satelli, Ph.D.[2], Jens Fritsche, Ph.D.[2], Yannick Bulliard, Ph.D.[2], Ali Mohamed, Ph.D.[2], Amir A. Jazaeri, M.D.[1], Patrick Hwu, M.D.[1], Cassian Yee, M.D.[1], Toni Weinschenk, Ph.D.[2], Carsten Reinhardt, M.D. & Ph.D.[2], Steffen Walter, Ph.D.[2], and Harpreet Singh, Ph.D.[2]

[1] The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030; [2] Immatics US, Inc., 2130 Holcombe Blvd., Suite 11.300, Houston, Texas 77030

Abstract ID # TPS77

Background

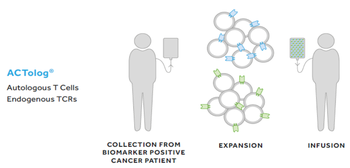


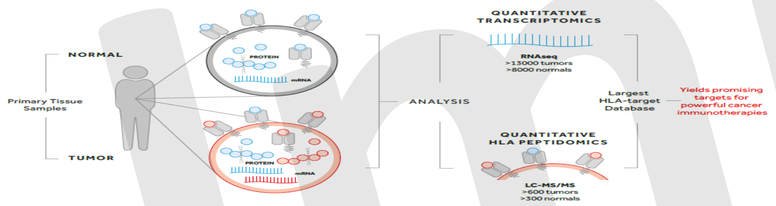
Figure 1. The ACTolog® concept.

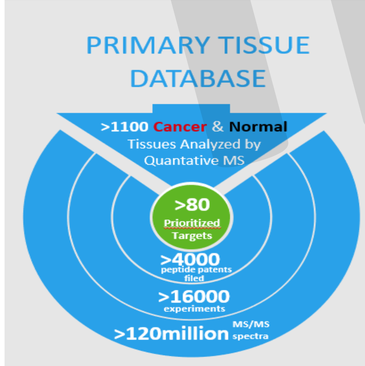
Immunotherapy has dramatically changed the landscape of therapeutic options in oncology. Adoptive cellular therapy (ACT), which includes the administration of autologous or allogenic anti-tumor T lymphocytes after *ex vivo* manipulation and expansion, is one of the major drivers of this success. To date, only a relatively small proportion of solid tumor patients has benefited from these advances due to i) lack of safe and relevant targets, ii) heterogeneity of tumor antigen expression associated with tumor escape (e.g. only one target was addressed).

The IMA101 (ACTolog®) targets up to four antigens per patient (from a predefined target warehouse) identified using Immatics' proprietary XPRESIDENT® technology. One key defining feature of the approach used in this trial is the generation of robust and clinically effective T cells following a proprietary process where autologous T cells are primed in the presence of IL-21 followed by HLA tetramer-guided cell sorting and rapid expansion. Immatics has an exclusive platform to create this product through its in-licensing of the IL-21 mediated approach, which results in higher frequencies of central memory T cells, extended *in vivo* persistence, and a more robust clinical response. [1,2]

Target identification with XPRESIDENT®

Figure 2a. Overview of the XPRESIDENT® platform. HLA-bound, tumor-associated peptides (TUMAPs) are identified and quantified directly from primary human tumor and normal tissue samples by liquid chromatography tandem mass spectrometry (LC-MS/MS). Over-presentation on peptide level is confirmed by over-expression using RNAseq. Furthermore, healthy tissue analyses help to predict potential on- and off-target toxicities.





Cancer Tissues from 20 Mayor Indications
AML
Bladder Cancer
Breast Cancer
CLL
Colorectal Cancer
Esophagus Cancer
Gallbladder
Gastric Cancer
Glioma
Liver Cancer
Melanoma
Multiple Myeloma
Non-Hodgkin lymphoma
NSCLC
Ovary
Pancreas Cancer
Prostate Cancer
Renal Cell Carcinoma
SCLC
Uterus

Control Tissues from 40 Normal Tissues	
Adipose tissue	Ovary
Adrenal Gland	Pancreas
Artery	Peripheral nerve
Bladder	Pituitary gland
Blood cells	Placenta
Bone Marrow	Pleura
Brain	Prostate
Breast	Rectum
Cartilage	Salivary gland
Cervix	Skin
Colon	Small intestine
Esophagus	Spleen
Eye	Stomach
Gall bladder	Testis
Heart	Thymus
Kidney	Thyroid
Liver	Trachea
Lung	Ureter
Lymph node	Uterus
Muscle	Vein

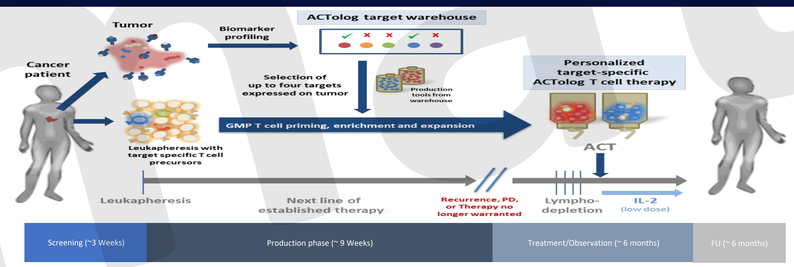
Figure 2b. Key figures of the XPRESIDENT® database. Largest database of peptide-HLA information worldwide.

ACTolog®: Target Presentation on Tumors

Target tumor association data		Ag08-01	Ag012-01	Ag001-02	Ag003-02	Ag007-01	Ag013-01	Ag016-02	Ag018-01
Target presentation on tumor samples									
Natural presentation directly shown in samples of	ovarian cancer	+	+	+	+	+	n.d.	n.d.	n.d.
	NSCLC	+	+	+	+	+	+	+	n.d.
	esophageal cancer	+	+	+	+	n.d.	+	n.d.	n.d.
	gastric cancer	n.d.	+	+	+	n.d.	+	n.d.	n.d.
	HNSCC	+	+	+	+	+	+	n.d.	n.d.
Exclusively identified on tumor samples (X) or over-presented (↑)		X	↑	X	X	X	↑	X	NA
Absolute quantification (median copy number per cell)		160	270	1100	810	3300	160	210	NA
Target prevalence (based on mRNA over-expression of ACTolog target source protein)									
Target prevalence	ovarian cancer	85	50	5	30	20	10	15	15
	NSCLC - adenocarcinoma	25	60	10	10	5	60	0	15
	NSCLC - squamous cell carcinoma	70	60	30	55	50	80	5	30
	esophageal cancer	30	75	20	30	25	85	15	20
	gastric cancer	15	70	10	15	10	75	35	15
	HNSCC	25	55	10	40	30	90	10	15

Table 1. Prevalence of ACTolog® Targets Expressed on Tumors: Abbreviations: HNSCC head and neck squamous cell carcinoma; NA not available; n.d. not detectable; NSCLC non-small cell lung cancer; RPKM reads per kilobase of transcript per million reads.

ACTolog®: Study Design



ACTolog® is a first-in-human clinical trial in patients with relapsed or refractory solid cancers. Patients will be included depending on their HLA type and the expression of warehouse target(s). Patients will undergo leukapheresis to collect mononuclear cells for manufacturing of IMA101 cells. IMA101 will be infused after pre-conditioning regimen (lymphodepletion) followed by low-dose IL-2. The study plans to treat 20 patients with ACTolog® IMA101 products.

Biomarker Development: IMA_DETECT

Personalization workflow based on mass spectrometry guided qPCR thresholds. Biopsies from cancer patients are used to measure mRNA expression of warehouse targets using qPCR. Target peptides are considered to be presented by the tumor if expression of corresponding mRNA is above the threshold. The screened cancer patient receives a personalized target-specific product.

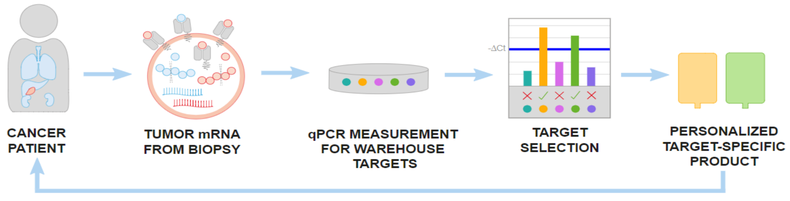


Figure 3. Application of a qPCR based biomarker panel (IMA_DETECT) for target and patient selection.

Study Objectives

Primary Objectives:
Safety and tolerability of the ACTolog® approach in target-positive solid cancer patients using T-cell products specific for targets identified by XPRESIDENT® platform.

Secondary Objectives:
- Evaluate feasibility of the ACTolog® manufacturing process
- Evaluate the *in vivo* persistence and *ex vivo* functionality of transferred T cells
- Assess anti-cancer activity and time-dependent clinical outcomes (PFS, OS)
- Assess feasibility of the *in vitro* diagnostic device IMA_DETECT
- Biobank tumor and RNA samples for future validation studies of the *in vitro* diagnostics device IMA_DETECT
- Assess tumor and blood biomarkers (e.g. target expression analysis, T-cell infiltration in the tumor, T-cell precursor analysis)

Key Eligibility Criteria

Inclusion criteria:
- Pathologically confirmed advanced/metastatic cancer prior to enrollment
- HLA phenotype HLA-A*02:01 prior to enrollment
- At least one lesion (metastasis or primary tumor) being considered accessible by tumor biopsy
- At least one target positive against ACTolog® warehouse
- Adequate bone marrow, pulmonary, cardiac, coagulation, renal and liver function
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1

Exclusion criteria:
- Patients with prior stem cell transplantation or solid organ transplantation
- Known history of HIV infection, active or uncontrolled Hepatitis B or C infection
- Known clinically significant cardiac, cardiovascular, and renal history
- History of hypersensitivity to cyclophosphamide, fludarabine or IL-2
- Serious autoimmune disease including history of active serious inflammatory bowel disease or autoimmune disorders, systemic Lupus Erythematosus or autoimmune vasculitis

Acknowledgement & Future Development

- This work was supported by a Product Development Research Grant from the Cancer Prevention Research Institute of Texas (DP150029).
- The enrollment is ongoing. A cohort of combination of IMA101 T cell with PD-L1 inhibitor is considered for future amendment.

References

1. Chapuis, AG, Desmarais, C, Emerson R, Schmit TM, Shibuya K, Lai, I, Wagener F, Chou J, Roberts IM, Coffey DG, Warren E, Robbins H, Greenberg PD, Yee C (2017). "Tracking the fate and origin of clinically relevant adoptively transferred CD8+ T cells in vivo." *Science Immunology* 2(9)
2. Yee C. "The use of endogenous T cells for adoptive transfer." *Immunol Rev*. Jan;257(1):250-63. 2014

Contact Information

Corresponding Author: atsimber@mdanderson.org
Sponsor Contact: stewart@immatics.com
Clinicaltrials.gov Identifier: NCT02876510