Results of the First-in-human Clinical Trial with Personalized Multi-target Adoptive Cell Therapy (ACTolog® IMA101)

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BACKGROUND

Background

- Adoptive cell therapy (ACT) in solid tumors is challenging due to lack of targets with high tumor specificity, tumor heterogeneity and tumor escape by loss of single antigen (Ag) expression.
- ACTolog® (IMA101) is a personalized multi-target adoptive cell therapy (ACT) approach in which autologous T cell products are directed against multiple novel defined peptide-HLA (pHLA) cancer targets identified by the target discovery platform XPRESIDENT®.
- ACTolog® target warehouse: COL6A3 exon 6, PRAME, MAGEA1, MAGEA4, MAGEA8, CTAG1A/NY-ESO-1, MXRA5, MMP1. Targeting the novel tumor stroma target COL6A3 exon 6 is intended to disrupt the tumor microenvironment.
- Tumors positive for ≥1 target from the ACTolog® target warehouse (HLA-A*02:01 restricted targets) are identified using the *in vitro* diagnostic device IMADetect™ (qPCR assay).
- Up to 4 tumor-specific T cell products are manufactured from leukapheresis product.
- Clinical proof of concept in melanoma established (Cassian Yee, MD Anderson) with a single-target T cell product demonstrating T cell persistence long-term at levels >1% and objective responses *Chapuis et al, Sci Transl Med (2013)* and *Chapuis et al, JCO (2016).*

Study Objectives

- **Primary:** To evaluate the safety and tolerability of ACTolog® alone (**Cohort 1**) or in combination with atezolizumab (**Cohort 2**)
- **Secondary:** To evaluate *in vivo* persistence of transferred T cells and tumor response
- **Exploratory:** *Ex vivo* functionality of transferred T cells, T cell infiltration in the tumor, progression-free survival (PFS) and overall survival (OS)

METHODS

Patients

HLA-A*02:01 positive patients with relapsed/refractory solid tumors whose tumor expressed ≥1 cancer target underwent leukapheresis, and endogenous T cells specific for up to 4 targets were primed and expanded *in vitro*.

Eligibility criteria are listed in www.clinicaltrials.gov NCT02876510.

Treatment (Cohort 1)

- Preconditioning regimen: fludarabine 40 mg/m² and cyclophosphamide 500 mg/m² on days -6 to -3
- ACTolog® up to 4x10^{10} total cells (day 0)
- IL-2 (1x10^{6} IU SC BID, 28 doses)

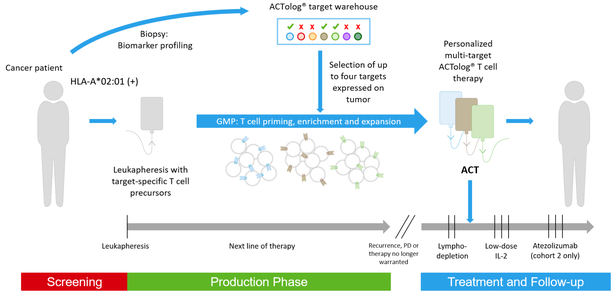
Patients in **Cohort 2** also received atezolizumab starting on day 21 or later upon hematologic recovery (1200 mg IV every 3 weeks up to 12 months).

Severity of **adverse events (AE)** was assessed according to CTCAE v5.0 and AE were coded according to MedDRA. Patients are counted only once per adverse event and severity classification.

Response was assessed by RECIST 1.1 and irRECIST. Progression-free-survival (PFS) was measured from date of entry on the treatment part of the study to date of disease progression or treatment discontinuation. Overall survival (OS) was measured from date of entry on the treatment part of the study until date of death or last follow-up.

All data are as of October 6th, 2020 (unclean data).

Figure 1. ACTolog® Treatment Schema



RESULTS

Table 1. Patients Screened and Treated

Screening/Treatment Status	No. of Patients (%)
Screened	214 (100)
HLA-A*02:01-positive	99 (46.3)
Screening tumor biopsy	61 (28.5)*
≥1 Target positive	54 (25.2)
Leukapheresis	43 (20.1)
Cohort 1 (intention-to-treat)	4 (1.9)
Cohort 2 (intention-to-treat)	10 (4.7)
Total treated with T cell product	14 (6.5)

* 60/61 tumor biopsies were evaluable for assessment of target expression.

Table 2. Patient Characteristics and Outcomes

Pt ID	Age/ Gender	Tumor Diagnosis	No. of prior Rx[1]	Yrs from Dx[2]	Targets Positive	Viable/ Specific Cells Infused per Product [x10^{10}]	Cohort[3]	Best Response (wk)[4]	PFS [mo]	OS [mo]
012	56/F	Breast adenocarcinoma	10	18	COL6A3, MXRA5	MXRA5: 0.42/ 0.10	1	SD [4]	2.4 (PD)	28.4 (D)
028	28/F	Synovial sarcoma	5	10	PRAME, COL6A3, MXRA5, NY-ESO-1	PRAME: 1.16/ 0.84 MXRA5: 1.02/ 0.42 NY-ESO-1: 1.37/ 0.59	1	SD [4]	3.3 (PD)	22.8 (D)
027	36/M	Myxoid liposarcoma	12	7	PRAME, COL6A3, NY-ESO-1	PRAME: 1.16/ 0.76 COL6A3: 1.16/ 1.09 NY-ESO-1: 1.16/ 1.07	1	SD [12]	4.7 (PD)	21.6 (D)
048	37/M	SCC of nasopharynx	5	13	COL6A3, MMP1	COL6A3: 1.69/ 1.47	1	SD [10][5,6]	12.9 (PD)	22.2 (D)
096	58/F	SCC of anus	8	5	PRAME, COL6A3	PRAME: 0.97/ 0.49 COL6A3: 0.76/ 0.26	2	SD [6]	3.4 (PD)	10.6 (D)
071	31/F	Infiltrating duct breast cancer	9	4	COL6A3, PRAME, MMP1	COL6A3: 1.61/ 1.27 PRAME: 0.33/ 0.03	2	SD [6]	3.2 (PD)	7.9 (D)
095	49/F	Synovial sarcoma	5	4	PRAME, COL6A3, MXRA5	PRAME: 1.74/ 1.58 COL6A3: 0.91/ 0.63 MXRA5: 1.32/ 0.82	2	SD [17]	5.8 (PD)	8.6 (D)
139	24/F	Ovarian cancer	4	2	COL6A3, MMP1, MXRA5	COL6A3: 1.16/ 0.97 MMP1: 1.41/ 0.85 MXRA5: 1.16/ 1.00	2	SD [24][5]	7.3 (PD)	18.6 (A)
145	56/F	Invasive duct breast cancer	3	4	COL6A3, NY-ESO-1	COL6A3: 1.04/ 0.89 NY-ESO-1: 1.74/ 1.61	2	PD [6]	1.8 (PD)	6.7 (D)
163	63/F	Mesothelioma of the peritoneum	8	6	PRAME	PRAME: 0.68/ 0.55	2	SD [52]	13.7 (PD)	13.9 (A)
173	32/F	Infiltrating duct breast cancer	8	4	COL6A3	COL6A3: 1.39/ 1.09	2	SD [6]	3.4 (PD)	4.7 (D)
164	57/F	Colon adenocarcinoma	5	2	COL6A3	COL6A3: 0.72/ 0.40	2	PD [6]	2.0 (PD)	4.0 (D)
172	44/F	SCC of anus	3	4	COL6A3	NA[7]	NA	NA	NA	NA
199	20/F	Small cell sarcoma of mandible	7	6	COL6A3	COL6A3: 0.58/ 0.44	2	SD [11][5]	3.7 (SD)	3.7 (A)
205	56/F	Colon adenocarcinoma	4	3	COL6A3, MMP1	COL6A3: 0.77/ 0.46	2	PD [6]	1.8 (PD)	2.9 (D)

[1] prior systemic treatments. [2] years from diagnosis. [3] intention-to-treat. [4] weeks from T cell infusion. [5] Patients did not progress per RECIST1.1 while on study. [6] Left study with SD (RECIST1.1) at week 10 and remained SD for 12.9 months during follow-up without further treatment. [7] The patient received lymphodepletion, but was not infused with T cell product. (D) Deceased; (A) Alive

Feasibility (Table 1, 2)

- 54 of 60 (90%) evaluable patients who underwent a tumor biopsy were positive for ≥1 target from the ACTolog® target warehouse.
- Very high ACTolog® cell doses (mostly >10^{10}) were administered.
- 50% of patients received multi-target ACTolog® products (up to 3).

Clinical Outcome (Table 2)

- The median PFS was 3.4 months (95% CI, 2.0-7.4 months).
- The median OS was 10.6 months (95% CI, 4.7-22.8 months).
- Six (42.9%) of 14 evaluable patients had disease stabilization at 12 weeks. Prolonged disease stabilization was noted in three patients for 12.9 months, 7.3 months, and 13.7 months.

Table 3. Treatment-Emergent Adverse Events

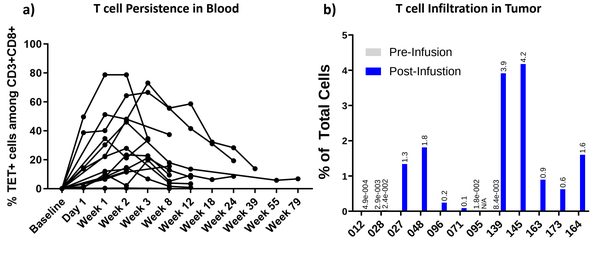
	All Grades		≥Grade 3	
Adverse event [by MedDRA term]	No.	%	No.	%
Anemia	14	93.3	12	80.0
Neutrophil count decreased	14	93.3	14	93.3
Platelet count decreased	12	80.0	7	46.7
White blood cell count decreased	12	80.0	10	66.7
Nausea	11	73.3	0	
Cytokine release syndrome	10	66.7	0	
Vomiting	9	60.0	0	
Lymphocyte count decreased	8	53.3	8	53.3
Constipation	7	46.7	0	
Hyponatremia	6	40.0	0	
Fatigue	6	40.0	0	
Hypokalemia	5	33.3	1	6.7
Febrile neutropenia	5	33.3	1	6.7
Hypotension	4	26.7	1	6.7
Abdominal pain	3	20.0	1	6.7
Device related infection	2	13.3	2	13.3
Electrocardiogram QT prolonged	1	6.7	1	6.7
Cellulitis	1	6.7	1	6.7
Dysphagia	1	6.7	1	6.7
Mucosal inflammation	1	6.7	1	6.7
Sinus bradycardia	1	6.7	1	6.7
Bacteremia	1	6.7	1	6.7
Staphylococcal bacteremia	1	6.7	1	6.7
Orthostatic hypotension	1	6.7	1	6.7

N=15. All treatment-emergent adverse events (TEAE) with grade 1-2 occurring in ≥6/15 patients and all events with ≥Grade 3 regardless of relatedness to study treatment and irrespectively of severity are presented.

Safety profile (Table 3)

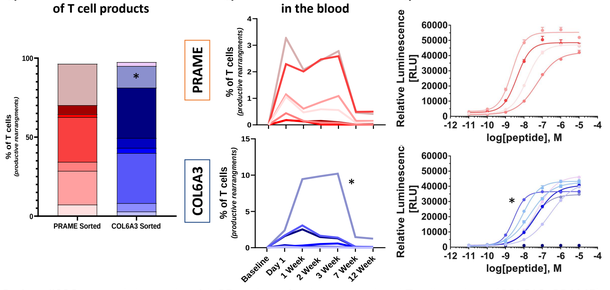
- The most common TEAEs were expected cytopenias, mostly associated with the lymphodepleting regimen.
- Grade 1-2 cytokine release syndrome was noted in 10 (71.4%) of 14 treated patients.

Figure 2. T cell Persistence and Tumor Infiltration



Infused T cells were tracked in patients' blood via flow-cytometry-based immunomonitoring (a) and in tumor biopsy via TCRβ sequencing (b). Target-specific T cells were in most cases not detectable in pre-infusion biopsies.

Figure 3. Characterization of TCRs in ACTolog®



Patient #096 entered the study with PD and received two polyclonal T cell products (COL6A3, PRAME). TCRs were identified from the T cell products and functional avidity was determined after TCR re-expression in Jurkat cells. Both products contained clones with high functional avidity (c). The clone with highest avidity gained dominance in the blood post-infusion (*) (a, b). Patient showed 26% tumor shrinkage at 6 weeks, associated with high T cell frequencies at 2 weeks (b). T cell frequencies dropped at 8 weeks (b) and phenotype shifted towards terminal differentiation (data not shown) associated with progression of the patient at 12 weeks.

CONCLUSIONS

- **ACTolog® demonstrates feasibility of a multi-target multi-T cell product approach**
  - To our knowledge, this is the first demonstration of feasibility of "actively personalized" (Britten *et al.*, Nat Biotech, 2013) ACT directed to multiple defined pHLA targets, where each product combination is guided by confirmed target expression in patient-derived biopsies.
  - **The target positivity rate of 90%** demonstrated that such a warehouse approach leads to minimal patient attrition due to lack of target expression which is common in other ACT trials.
- **ACTolog® was generally well-tolerated in heavily pretreated patients**
- **ACTolog® shows remarkable T cell persistence and tumor infiltration**
  - ACTolog® treatment resulted in high target-specific T cell levels and persistence with total frequencies up to ~80% of all peripheral CD8+ T cells in the blood (**Figure 2a**).
  - Target-specific T cells were detectable in post-treatment tumor biopsies (**Figure 2b**).
  - Individual TCRs in the endogenous T cell products showed a broad range of avidities, however the majority being of low avidity (EC50>10^{-8} M, data not shown), reflecting the range to be expected in the natural immune repertoire.
- **ACTolog® revealed long-term disease stabilization in some patients**
  - All three patients with prolonged disease stabilization showed high frequency of target-specific T cells (>40% of CD8+ T cells) in the blood post-infusion.
  - Two of these three patients received a COL6A3 exon 6-specific T cell product suggesting that targeting the tumor stroma may be a promising approach.
- **ACTolog® results warrant further evaluation of a multi-target ACT approach using potent high-avidity TCRs (i.e. autologous TCR-engineered T cells)**

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