The ACTolog® Approach: Multi-target Adoptive Cell Therapy using Endogenous Antigen Specific T cells

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Background
Adoptive cellular therapy (ACT) has demonstrated substantial clinical progress in hematologic cancers; however, only a small proportion of solid tumor patients have benefited from these advances due to i) lack of suitable immunotherapy targets with high specificity in solid tumors, ii) frequent relapse following immunotherapy against single targets often associated with loss of target expression in the tumor. The ACTolog® concept, utilizing antigen specific T cells against targets identified by the Immatics’ proprietary XPRESSION® technology, is intended to overcome these limitations by addressing multiple novel relevant tumor antigens per patient. ACTolog® is a personalized, multi-targeted ACT approach in which autologous T-cell products are manufactured against the most relevant tumor target peptides for individual patients whose tumors are positive for at least one target from a predefined target warehouse. IMA101 (ACTolog®) targets up to four antigens per patient, selected from a predefined target warehouse and identified using Immatics’ proprietary XPRESSION® technology. One key defining feature of the approach 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 these products 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 compared to current therapies.

Target Identification with XPRESSION®
To identify antigens for ACTolog® drug products, the following steps are involved:

1. Quantification of HLA-bound tumor-associated peptides (TUMAPs) from primary human tumor samples using liquid chromatography tandem mass spectrometry (LC-MS/MS). Over-expression is confirmed by over-expression using RNAseq.
2. Peptide selection: TUMAPs are considered to be presented by the tumor if expression of corresponding mRNA is above the threshold.

Manufacturing of ACTolog® Drug Products
4. Two rounds of rapid expansion (REP) are performed to expand peptide-specific T cells.
5. Antigen-specific T-cell products are analyzed for lymphocytes content, CD3CD8, and CD3CD8 Tetramer content.

Biomarker Development: IMA_DETECT
Determination of the expression of IMA Detect biomarkers is performed.

References
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Figure 1. Process flow of patient’s drug product manufacturing. Leukapheresis is taken from the patient to isolate PBMCs if at least one target is expressed. COS7-depleted PBMCs and antigen-loaded autologous dendritic cells (DC) are used for in vitro priming (STIM) for up to four targets in parallel. Antigen-specific T cells are sorted on the MACSQuant Tyto under aseptic conditions using clinical grade pHLAtetramers. After two rounds of rapid expansion (REP) as vise the drug substance (DS) is filled in infusion bags and stored until patient infusion. In addition to numerous in-process controls, each drug product (DP) is subjected to a final release testing.

Figure 4. Analysis of final T-cell products by flow cytometry. After two rounds of rapid expansion (REP), antigen specific T-cell products are analyzed for lymphocytes content, CD3CD8, and CD3CD8 Tetramer content.