# Safety and Preliminary Efficacy of ACTR707, Autologous T Lymphocytes Expressing an Antibody-Coupled T Cell Receptor, in Combination with Rituximab in Subjects with Relapsed or Refractory CD20-Positive B-cell Lymphoma

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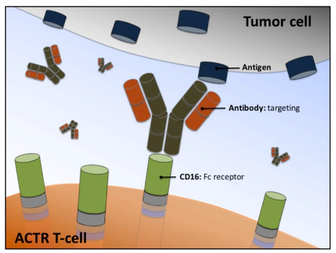
## Introduction

The Antibody-Coupled T cell Receptor (ACTR) platform is an autologous engineered T cell therapy developed to combine the tumor-targeting ability of antibodies with the cell-killing ability of T cells, in order to exert potent anti-tumor immune response and tumor cell killing. ACTR constructs are composed of the extracellular domain of CD16 linked to CD3ζ signaling and to a costimulatory domain. ACTR-expressing T cells are universal, and can be flexibly paired with desired therapeutic antibodies to target tumor antigens. The first ACTR in clinical development, ACTR087, is currently in clinical testing in combination with rituximab (NCT02776813). To expand on the ACTR platform ACTR707, the second ACTR in clinical development, was identified through preclinical screening of more than 100 different ACTR variants and evaluated through rigorous in vitro and in vivo testing in combination with a broad range of tumor targeting antibodies for use in hematologic and sold tumor indications. ACTR707 contains the extracellular domain of CD16, the cytoplasmic signaling domain of CD3ζ, and the costimulatory domain of CD28.

**Study ATTCK-20-03** (NCT03189836) is the first clinical trial of ACTR707. ACTR707 in combination with rituximab is being studied in subjects with relapsed or refractory CD20+ B-cell lymphoma previously treated with anti-CD20 monoclonal antibody (mAb) therapy. Here, we present data from the first dose level of ACTR707, where 6 subjects have been enrolled and treated with ACTR707 in combination with rituximab.

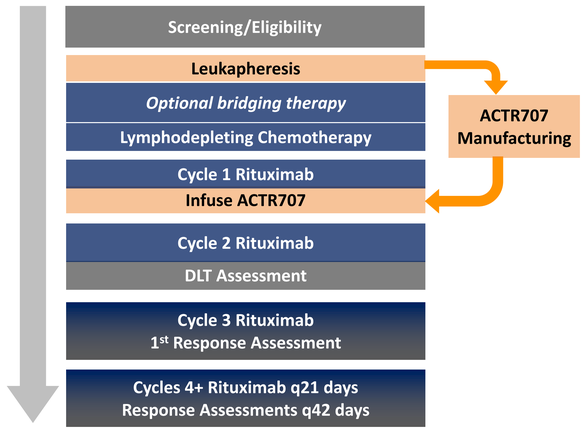
### *The Antibody-Coupled T Cell Receptor (ACTR) platform*




Schematic of the ACTR platform

The high affinity variant (V158) CD16 Fc receptor engages the Fc domain of tumor-targeting human IgG1 antibodies and triggers T cell activation and tumor cell cytotoxicity. The ACTR platform has demonstrated activity with multiple tumor-targeting antibodies, and the current work broadens our understanding of the applicability of the ACTR platform. ACTR T cell products are currently in clinical development in combination with rituximab (NCT02776813, NCT03189836), SEA-BCMA (NCT032666926), or trastuzumab (NCT03680560).

## ATTCK-20-03 Clinical Study Design and Subject Treatment




First-in-human, multicenter, Phase 1 dose escalation study of a single infusion of ACTR707, in combination with rituximab (375 mg/m$^2$ in 3-week cycles)

**Primary objective:** Evaluate the safety of ACTR707 in combination with rituximab (DLTs, AEs, and lab abnormalities)

**Secondary objectives:**

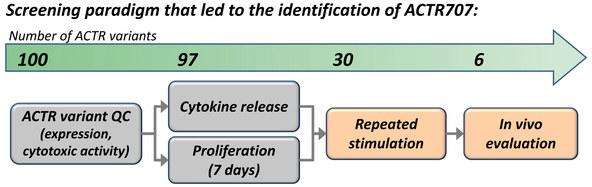
- Anti-tumor activity (ORR, DoR)
- ACTR707 T cell expansion and persistence
- Cytokine levels
- Rituximab PK

**Key subject eligibility criteria:**

- Histologically confirmed aggressive CD20+ B-cell lymphoma of DLBCL, MCL, PMBCL, Gr3b FL, or transformed FL subtypes
- Received prior anti-CD20 mAb therapy in combination with chemotherapy

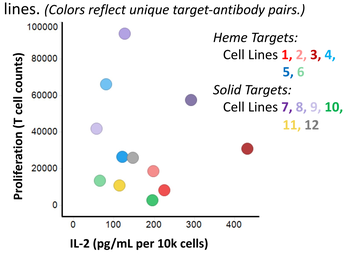
## ACTR707: Discovery and Pre-Clinical Evaluation

### *Screening paradigm that led to the identification of ACTR707:*

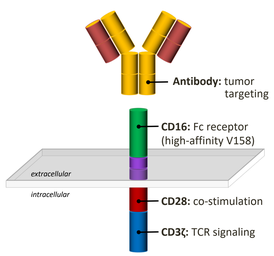



**ACTR T cell variants** were evaluated in short- and long-term activity assays. On the basis of their in vitro activity, the number of variants was reduced from 100 to 6, which were then evaluated in vivo.

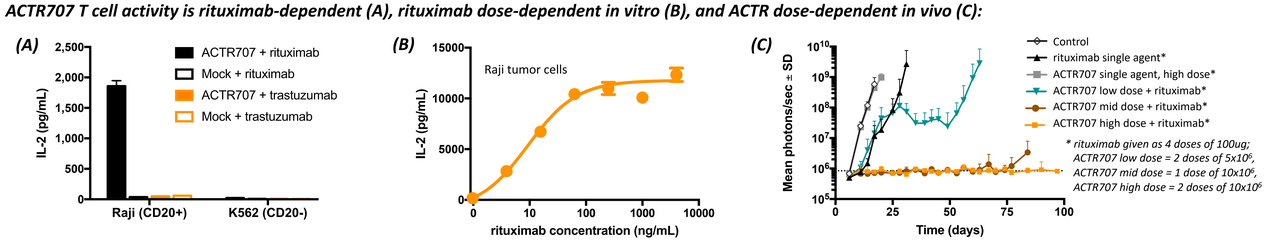
**ACTR707 T cells** in combination with tumor-targeting antibodies have potent activity across a diversity of both hematological and solid tumor cell lines. *(Colors reflect unique target-antibody pairs.)*




**ACTR707** contains CD16, CD3ζ signaling domain, and CD28 co-stimulation:




### *ACTR707 T cell activity is rituximab-dependent (A), rituximab dose-dependent in vitro (B), and ACTR dose-dependent in vivo (C):*




## ATTCK-20-03 Clinical Results: 6 subjects in Dose Level 1 (40 × 10$^6$ ACTR+ T cells)

### *Demographics and Baseline Disease Status*

| Characteristic | Dose Level 1 (n=6) |
|---|---|
| Diagnosis: DLBCL, n (%) | 5 (83) |
| Diagnosis: Gr3b FL, n (%) | 1 (17) |
| Median age, years (range) | 61 (57-76) |
| Age ≥ 65 years, n (%) | 2 (33) |
| Men, n (%) | 5 (83) |
| ≥ 3 prior therapies, n (%) | 3 (50) |
| Refractory to immediate prior therapy*, n (%) | 4 (67) |
| Received autologous stem cell transplant, n (%) | 2 (33) |
| Received optional bridging therapy, n (%) | 5 (83) |
| Mean baseline SPD of target lesion, cm$^2$ (range) | 42 (6-112) |

Database snapshot: 04Sept18

** Refractory = no response, or initiation of a new treatment, within 6 months after the last treatment regimen prior to study entry.*
*SPD = sum of product diameters*

### *Safety in Dose Level 1*

- No DLTs were reported in Dose Level 1 subjects

| Term | Subjects with TEAEs, regardless of causality, n (%) | | |
|---|---|---|---|
| | TEAEs (any grade) in >1 subject | TEAEs ≥Grade 3 in >1 subject | SAEs^ |
| Neutropenia | 2 (33) | 2 (33) | 0 |
| Thrombocytopenia | 2 (33) | 2 (33) | 0 |
| Febrile neutropenia | 2 (33) | 2 (33) | 2 (33) |
| Nausea | 2 (33) | 0 | 0 |
| Vomiting | 2 (33) | 0 | 0 |
| Arthralgia | 2 (33) | 0 | 0 |
| Decreased appetite | 2 (33) | 0 | 0 |
| Neurologic event* | 2 (33)* | 0 | 0 |

Database snapshot: 04Sept18

*^ There were no other SAEs.*
** Defined as standardized MedDRA query (SMQ) of "noninfectious encephalopathy delirium" or preferred term of "neurotoxicity"; reported events were Gr 1 disorientation and Gr 1 muscular weakness.*

| Adverse Events of Special Interest *(as defined in clinical study protocol)* | Subjects with AESI, n |
|---|---|
| New malignancy | 0 |
| Cytokine release syndrome | 0 |
| Use of therapeutic plasma exchange for any non-disease related AE | 0 |
| Clinically significant neurologic disorder | 0 |
| Clinically significant rheumatologic/ autoimmune disorder | 0 |
| Clinically significant hematologic disorder (excluding cytopenias related to LD chemo) | 0 |

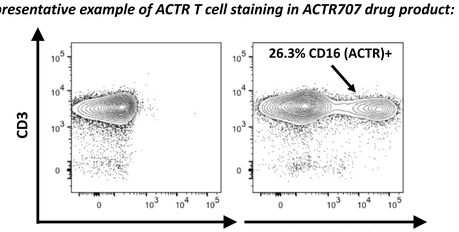
Database snapshot: 04Sept18

*Clinically significant = in the opinion of the Investigator, clinically meaningful, requires medical intervention, and medically important within the context of study treatment.*

### *Successful Manufacturing of ACTR707*

There were no manufacturing failures in Dose Level 1 (n = 6), with a mean of 26 days between leukapheresis and drug product release, inclusive of 12.5 days (mean, 50% of time period) for release testing.

***Representative example of ACTR T cell staining in ACTR707 drug product:***




### *Anti-Tumor Activity in Dose Level 1*

6 subjects were response evaluable *(defined as having both baseline and post-baseline radiographic disease response assessments)*

- **3 subjects had complete responses as assessed by the investigator:**

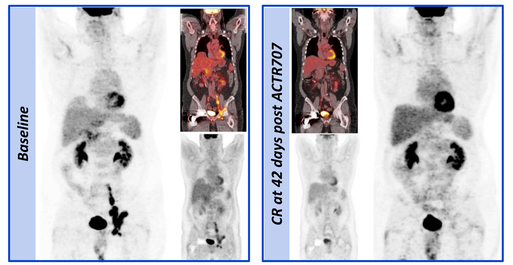
| Response (n=3) | Duration of Response (days) | Diagnosis | # prior therapies* | Refractory^ to immediate prior therapy |
|---|---|---|---|---|
| Complete | 148+ (ongoing) | Gr3b FL | 3 | No |
| Complete | 121+ (ongoing) | DLBCL | 5 *(includes ASCT)* | Yes |
| Complete | 85 | DLBCL | 3 | Yes |

Database snapshot: 04Sept18

** All subjects received rituximab as prior therapy*
*^ Defined as no response or relapse within 6 months of therapy*
*ASCT = autologous stem cell transplant, DLBCL = diffuse large B cell lymphoma, Gr3b FL = Grade 3b follicular lymphoma.*

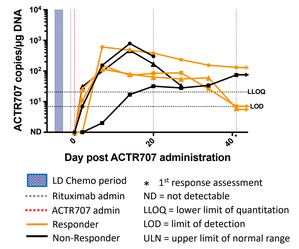
- **3 subjects had progressive disease:**
  - 2 progressed during 28-day DLT evaluation period
  - 1 progressed at Study Day 84 (indeterminate response at Study Day 42)

***PET image for subject with Gr3b FL:***

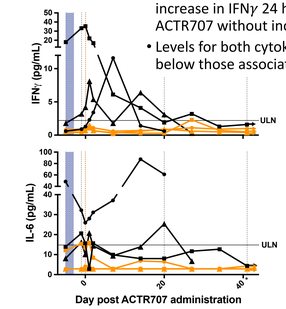



### *Biomarkers: ACTR707 Expansion and Persistence and Key Cytokines*

- All subjects demonstrated ACTR707 expansion in peripheral blood.
- ACTR707 is detectable 40 days post infusion or last day on study.




- Most subjects exhibited modest increase in IFNγ 24 hrs after ACTR707 without increase in IL-6.
- Levels for both cytokines were below those associated with CRS.

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## Conclusions

In the first dose level studied, in subjects with relapsed or refractory, aggressive CD20+ B cell lymphoma:

- Complete response in 3 of 6 subjects, with 2 ongoing
- ACTR707 has an encouraging safety profile, with no DLTs and no severe/serious events of CRS or neurotoxicity
- ACTR+ T cells demonstrate expansion and are detectable 40 days post infusion in subjects on study
- No evidence of elevation in CRS-related cytokines

Dose Level 2 has completed enrollment, and enrollment in Dose Level 3 is ongoing.

## Acknowledgements

We would like to thank the patients and their families for their participation in this trial.

We would also like to thank the study team members and staff at the following clinical centers for the successful conduct of this study:

- University of Minnesota
- Ohio State University Comprehensive Cancer Center
- Sarah Cannon Research Institute
- Winship Cancer Institute, Emory University
- Indiana Blood and Bone Marrow Transplantation at Franciscan Health