Preliminary Clinical Results of a Phase 1 Study Evaluating the Safety and Anti-tumor Activity of ACTR707 in Combination with Rituximab in Subjects with Relapsed or Refractory CD20+ B-cell Lymphoma

Ian Flinn[1], Jonathon Cohen[2], Luke Akard[3], Samantha Jaglowski[4], Michael Vasconcelles[5], Patricia Harris[5], Ann Ranger[5], Francis Payumo[5], Greg Motz[5], Veronika Bachanova[6]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Winship Cancer Institute, Emory University, Atlanta, GA; [3]Indiana Blood and Marrow Transplantation, Indianapolis, IN; [4]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [5]Unum Therapeutics Inc., Cambridge, MA; [6]University of Minnesota, Minneapolis, MN

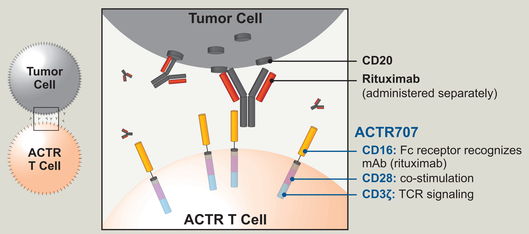
Introduction

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 a CD3ζ signaling domain 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. 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 solid tumor indications. ACTR T cell products are currently in clinical development in combination with rituximab (NCT02776813, NCT03189836), with SEA-BCMA (NCT032666926; ASH2018 abstract #1997), and with trastuzumab (NCT03680560).

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 (R/R) CD20+ B-cell lymphoma previously treated with anti-CD20 monoclonal antibody (mAb) therapy. Here, we present data from all subjects in the first 2 dose levels of ACTR707, through at least the first response assessment time point. All subjects were treated with ACTR707 in combination with rituximab.

ACTR T Cell Therapy

- ACTR T cells are used in combination with therapeutic antibodies (mAb)
  - *Ex vivo* autologous T cell culture, activation, and gene transduction manufacturing process; similar to other adoptive T cell therapies
- Tumor-directed antibodies provide ACTR T cell tumor specificity
- Disconnecting ACTR T cell activation and proliferation from direct tumor targeting facilitates optimization of therapeutic index via mAb dosing



- ACTR T cells and mAb administered separately to subjects
- Study ATTCK-20-03 uses rituximab as mAb to target CD20 on tumor cells

ATTCK-20-03 Study Design

First-in-human, multicenter, Phase 1, adaptive-design, dose escalation study of a single infusion of escalating dose levels of ACTR707 in combination with rituximab (375 mg/m^2 in 3-week cycles) following 3 days of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 and cyclophosphamide 400 mg/m^2)

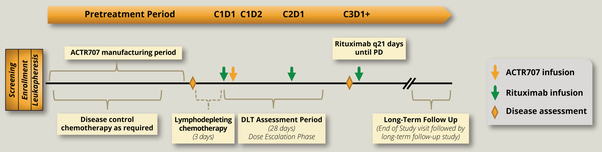
Primary objective: Evaluate the safety of ACTR707 in combination with rituximab (DLTs, AEs, and lab abnormalities)

Secondary objectives:

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

Key subject eligibility criteria:

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



Demographics & Baseline Characteristics

Characteristic	DL1 (n = 6)	DL2 (n = 3)
Diagnosis: DLBCL, n (%)	5 (83)	3 (100)
Diagnosis: Gr3b FL, n (%)	1 (17)	0
Median age, years (range)	61 (57-76)	58 (47-77)
Age ≥ 65 years, n (%)	2 (33)	1 (33)
Men, n (%)	5 (83)	2 (67)
≥ 3 prior therapies, n (%)	3 (50)	2 (67)
Refractory* to prior therapy, n (%)	5 (83)	3 (100)
Received ASCT, n (%)	2 (33)	3 (100)
Received optional bridging therapy, n (%)	5 (83)	1 (33)
Median baseline SPD of target lesion, cm^2 (range)	24 (6-112)	14 (12-134)

* Refractory defined as PD as best response to any line of chemotherapy or relapse ≤ 12 months post ASCT

Safety

TEAEs In ≥ 1 Subject, Regardless of Causality

Term, n (%)	TEAEs (Any Grade)		TEAEs ≥ Grade 3	
	DL1 (n = 6)	DL2 (n = 3)	DL1 (n = 6)	DL2 (n = 3)
Neutropenia	2 (33)	3 (100)	2 (33)	3 (100)
Thrombocytopenia	2 (33)	2 (67)	2 (33)	2 (67)
Anemia	1 (17)	2 (67)	1 (17)	2 (67)
Febrile neutropenia	2 (33)	1 (33)	2 (33)	1 (33)
Nausea	2 (33)	1 (33)	0	0
Vomiting	2 (33)	0	0	0
Arthralgia	2 (33)	0	0	0
Decreased appetite	2 (33)	0	0	0
Neurologic event*	2 (33)*	0	0	0
Disorientation (Gr 1)	1 (17)*	0	0	0
Muscle weakness (Gr 1)	1 (17)*	0	0	0

* Defined as preferred term (PT) contained in standardized MedDRA query (SMQ) of "noninfectious encephalopathy delirium" or PTs of "neurotoxicity" or "ataxia" reported post ACTR707 treatment

ACTR707-Related SAEs

Preferred Term, n (%)	Subjects with SAE	
	DL1 (n = 6)	DL2 (n = 3)
Febrile neutropenia	1 (17)	1 (33)
Pancytopenia	0	1 (33)

AESIs

AESI, n (as defined in clinical study protocol)	Subjects with AESI	
	DL1 (n = 6)	DL2 (n = 3)
New malignancy	0	0
CRS	0	0
Use of therapeutic plasma exchange for any non-disease related AE	0	0
Clinically significant* neurologic disorder	0	0
Clinically significant* rheumatologic/ autoimmune disorder	0	0
Clinically significant* hematologic disorder	0	0

* Clinically significant = in the opinion of the Investigator, is clinically meaningful, requires medical intervention, and is medically important within the context of study treatment; cytopenias related to LD chemotherapy are excluded

Table data snapshots: 1 November 2018. **Graph Data snapshots:** 2 November 2018.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ASCT = autologous stem cell transplant; C#D# = cycle number, day number; CR = complete response; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma, DL = dose level; DLT = dose-limiting toxicity; DoR = duration of response; FL = follicular lymphoma; Gr = grade; IR = indeterminate response; LD chemo = lymphodepleting chemotherapy; LLN = lower limit of normal; LLOQ = lower limit of quantitation; MCL = mantle cell lymphoma; ORR = overall response rate; PD = progressive disease; PK = pharmacokinetic; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; q21 days = once every 21 days; SAE = significant adverse event; SD = stable disease; SPD = sum of product diameters; TCR = T cell receptor; TEAE = treatment-emergent adverse event; ULN = upper limit of normal

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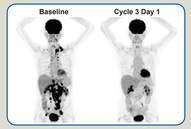
Anti-Tumor Activity

Term	DL1 (n = 6)	DL2 (n = 3)
CR	3	1
DoR (days)	85, 180+, & 207+	71+
PR	0	0
SD	0	0
IR	1	1
PD	2	1



Representative image of CR in subject with DLBCL treated with 5 prior therapies including ASCT

DL	Diagnosis	Baseline SPD (cm^2)	Optional Bridging Therapy	# Prior Therapies	ASCT	Refractory* to Prior Therapy	Response	DoR (Days)
1	Gr3b FL	24	No	2	No	No	Complete	207+
1	DLBCL	23.4	Yes	5	Yes	Yes	Complete	180+
1	DLBCL	11.9	Yes	3	No	Yes	Complete	85
2	DLBCL	14	Yes	3	Yes	Yes	Complete	71+

* Refractory defined as PD as best response to any line of chemotherapy or relapse ≤ 12 months post ASCT

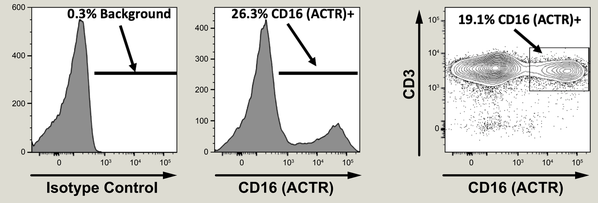
Manufacturing

Analytical Improvement Affects ACTR707 Dose Calculation

- Analytical method via flow cytometry to calculate ACTR+ T cell dose changed from isotope control gating (ICG) to population gating (PG)
- PG method takes into consideration variability in starting material and more consistently represents ACTR+ T cells
- This change to the analytic method affects the calculation of ACTR+ T cells and ACTR+ T cell dose targets in the ACTR707 drug product:

ATTCK-20-03 Dose Level	Dose Calculation (number of ACTR+ T cells)	
	by ICG	by PG
1	40 x 10^6	25 x 10^6
2	60 x 10^6	40 x 10^6

- Representative drug product analyzed by ICG (left and center panel) and PG (right panel):

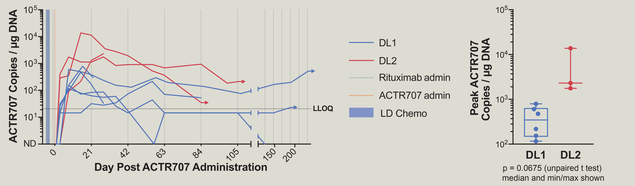


Summary of Manufacturing in DL1 and DL2

- There were no manufacturing failures in either DL1 (n = 6) or DL2 (n = 3). Across both dose levels, the average time from leukapheresis to drug product release was 26.6 days, which included release testing.

ACTR707 Expansion and Persistence

Dose-Dependent ACTR T Cell Expansion and Sustained Persistence in the Presence of Rituximab

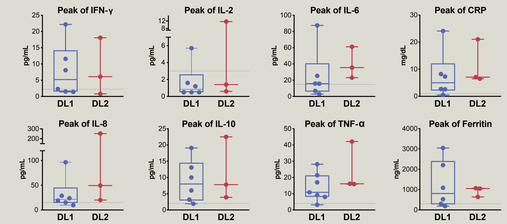


- ACTR T cells demonstrate expansion post-infusion and durable persistence
  - The median peak expansion in Dose Level 2 > 6x Dose Level 1, suggesting dose-dependent ACTR expansion
  - Persistence observed through 233 days (C12D1) post ACTR administration

Biomarkers

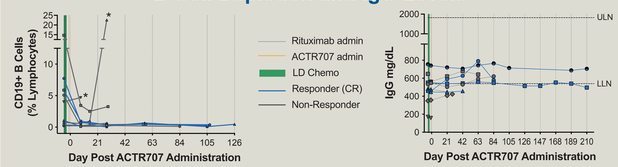
Inflammatory Markers and Cytokines

- Despite the increased ACTR expansion observed in DL2 relative to DL1, peak levels of inflammatory markers and cytokines did not increase, consistent with the observed safety profile



Peak values calculated between C1D3 (1 day post ACTR) and C2D8 (28 days post ACTR). Bar at median with whiskers at min and max. Dotted lines indicate upper limit of normal for each analyte.

B Cell Depletion and IgG Levels

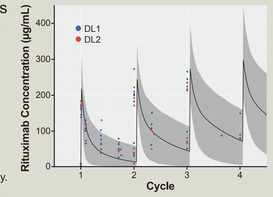


* Subjects with rapid disease progression. CD19+ cells detected by flow cytometry exhibited an unusually low CD19 level; circulating B cell lymphoma cannot be excluded

- Majority of subjects exhibit sustained depletion of B cells in the blood.
- Despite the lack of circulating B cells, IgG levels remain stable up to 210 days following initiation of ACTR707 in combination with rituximab, and no IVIG therapy was required.
- No meaningful impact on IgG levels between responders and non-responders

Rituximab PK

- Graph shows rituximab plasma concentrations from subjects overlaid on simulated rituximab 375 mg/m^2 q21d concentration-time data (simulation based on 1000 rituximab-treated subjects).
- Across the first 2 dose levels of ACTR707, rituximab PK is consistent with published models



Individual points = Observed concentration-time data from 20-03 study.
Black line = median simulated concentration data.
Shaded region = 2.5-97.5th percentile of simulated concentration data.

Conclusions

- Safety profile of ACTR707 + rituximab in first two dose cohorts supports further dose escalation
  - No DLTs or AESIs have been reported in DL1 or DL2
  - No serious or severe neurological events or CRS observed in either dose level
  - No meaningful elevations in inflammatory cytokines
- Pharmacodynamic evidence of activity of ACTR707 in combination with rituximab supports proof of mechanism
  - Dose-dependent peak ACTR707 expansion observed
  - ACTR707 persistence detectable > 200 days in the peripheral blood
- No impact of ACTR707 on rituximab PK
- Evidence of anti-tumor activity in both dose levels is encouraging with CRs reported in both dose levels
  - CR in 3 of 6 subjects in DL1, and in 1 of 3 subjects in DL2
  - DoR of 85 to 207+ days in DL1 and 71+ days in DL2
- These data support the continued evaluation of ACTR707 in combination with rituximab in subjects with CD20+ R/R aggressive lymphoma
  - Enrollment in DL3 is ongoing at a dose of 55 x 10^6 ACTR+ T cells (by PG)