Preliminary Clinical Results from a Phase 1 Study of ACTR707 in Combination with Rituximab in Subjects with Relapsed or Refractory CD20⁺ Non-Hodgkin Lymphoma

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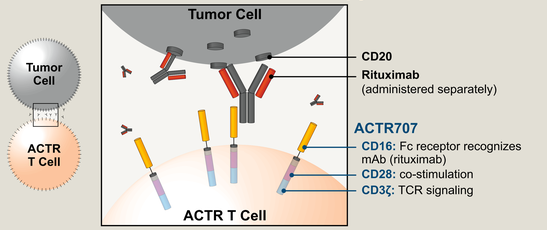
Introduction

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 antitumor 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 co-stimulatory domain. ACTR-expressing T cells are universal and can be flexibly paired with desired therapeutic antibodies to target tumor antigens. ACTR707, containing a CD28 co-stimulatory domain, is the lead ACTR candidate in clinical development. ACTR707 demonstrated robust activity and persistence in preclinical testing in combination with a broad range of tumor targeting antibodies for use in hematologic and solid tumor indications. In addition to this study in lymphoma, ACTR707 is currently being evaluated in combination with trastuzumab for the treatment of advanced HER2⁺ solid tumors (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 4 dose levels of ACTR707. All subjects were treated with ACTR707 in combination with rituximab.

ACTR T-Cell Therapy



- ACTR T cells are used in combination with separately administered therapeutic antibodies (mAb)
- Tumor-directed antibodies provide ACTR T cell tumor specificity
- 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 study of a single infusion of escalating dose levels of ACTR707 in combination with rituximab (375 mg/m² in 3-week cycles, up to 18 cycles) following 3 days of lymphodepleting chemotherapy (fludarabine 30 mg/m² and cyclophosphamide 400 mg/m²)

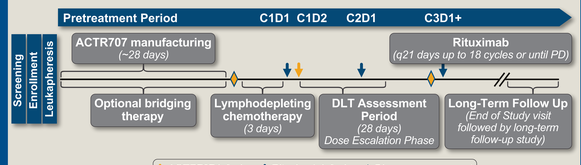
Primary objective: Evaluate the safety of ACTR707 in combination with rituximab (DLTs, AEs, and lab abnormalities)

Secondary objectives:

- Antitumor 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



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PosterCast

PDF

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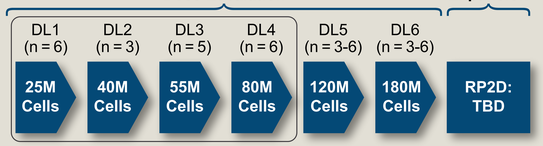
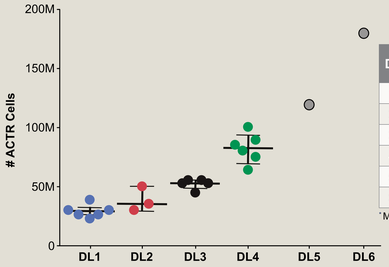
ATTCK-20-03 Trial Design



- Data from all subjects in the first 4 dose levels available (as of 1 November 2019)
- Dose escalation is ongoing:
  - Currently enrolling at DL5 at targeted dose of 120M ACTR⁺ T cells
  - DL6 (after DEC approval to continue) anticipated to be 180M ACTR⁺ T cells



DL	Target Dose*	Actual Dose,* median (range)
1	25	29 (23-38)
2	40	35 (30-50)
3	55	55 (45-55)
4	80	83 (65-100)
5	120	TBD
6	180	TBD

*Millions of ACTR⁺ T cells

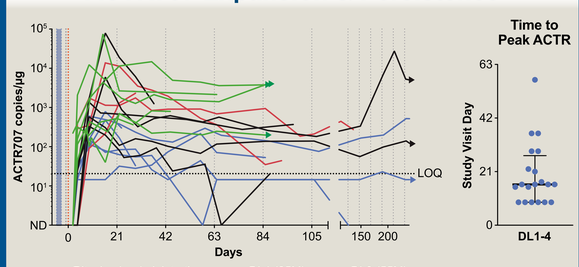
Demographics & Baseline Characteristics

Subjects were heavily pretreated; majority were refractory to prior therapy including rituximab

Characteristic	DL1 (n = 6)	DL2 (n = 3)	DL3 (n = 5)	DL4 (n = 6)
Diagnosis: DLBCL, n (%)	5 (83)	3 (100)	5 (100)	3 (50)
Gr3b-FL, n (%)	1 (17)	0	0	0
MCL, n (%)	0	0	0	3 (50)
Double/Triple-hit* mutation status, n (%)	5 (83)	1 (33)	1 (20)	3 (50)
Median age, years (range)	61 (57-76)	58 (47-77)	77 (67-78)	68 (45-71)
Age ≥ 65 years, n (%)	2 (33)	1 (33)	5 (100)	4 (67)
Men, n (%)	5 (83)	2 (67)	4 (80)	3 (50)
≥ 3 prior therapies, n (%)	3 (50)	3 (100)	2 (40)	3 (50)
Refractory** to prior therapy, n (%)	5 (83)	3 (100)	2 (40)	3 (50)
Received ASCT, n (%)	2 (33)	3 (100)	1 (20)	4 (67)
Received optional bridging therapy, n (%)	5 (83)	1 (33)	1 (20)	3 (50)
Median baseline SPD of target lesion, cm² (range)	37 (6-112)	14 (12-134)	30 (1-65)	13 (0-218)

*Double hit defined as c-MYC and BCL2 and/or BCL6; Triple hit defined as c-MYC, BCL2, and BCL6
**Refractory defined as no response to prior therapy or relapse ≤ 12 months post ASCT

ACTR707 Expansion & Persistence



- Kinetics demonstrate gradual time to peak expansion (median 14 days)
- ACTR persistence observed up to 347 days post administration
- ACTR levels may be more sustained (beyond Day 42) in highest dose level (80M)
- No correlation detected between ACTR levels and response

Safety

Tolerable Safety Profile through 4 Dose Levels

- TEAEs occurring in >2 ACTR707-treated subjects, All Grades and Gr 3-4; no Gr 5 events

Preferred Term, n (%)	DL1 (n = 6)		DL2 (n = 3)		DL3 (n = 5)		DL4 (n = 6)		Overall (n = 20)	
	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4
Nausea	2 (33)	0	1 (33)	0	5 (100)	0	4 (67)	0	12 (60)	0
Neutropenia	2 (33)	2 (33)	3 (100)	3 (100)	2 (40)	2 (40)	3 (50)	3 (50)	10 (50)	10 (50)
Thrombocytopenia	2 (33)	2 (33)	2 (67)	2 (67)	2 (40)	2 (40)	3 (50)	2 (33)	9 (45)	8 (40)
Constipation	1 (17)	0	1 (33)	0	4 (80)	0	1 (17)	0	7 (35)	0
Diarrhea	0	0	1 (33)	0	3 (60)	0	3 (50)	0	7 (35)	0
Anemia	1 (17)	1 (17)	2 (67)	2 (67)	1 (20)	1 (20)	2 (33)	1 (17)	6 (30)	5 (25)
Febrile neutropenia	2 (33)	2 (33)	1 (33)	1 (33)	0	0	1 (17)	1 (17)	4 (20)	4 (20)
Headache	0	0	0	0	1 (20)	0	3 (50)	0	4 (20)	0
Fatigue	1 (17)	0	0	0	1 (20)	0	2 (33)	0	4 (20)	0
Pyrexia	2 (33)	0	0	0	2 (40)	0	0	0	4 (20)	0
Neurologic event*	2 (33)[a]	0	1 (33)[b]	0	0	0	1 (17)[c]	0	4 (20)	0
Cough	0	0	1 (33)	0	2 (40)	0	1 (17)	0	4 (20)	0
Vomiting	2 (33)	0	0	0	1 (20)	0	0	0	3 (15)	0
Decreased appetite	2 (33)	0	0	0	0	0	1 (17)	0	3 (15)	0

*Defined as PT contained in SMQ of noninfectious encephalopathy/delirium or PTs of "ataxia" or "neurotoxicity" reported post ACTR707 treatment.
[a]1 event Gr 1 disorientation; 1 event Gr 1 muscular weakness. [b]1 event Gr 2 confusional state. [c]1 event Gr 1 dysphagia.

Treatment-Emergent SAEs

Preferred Term, n	TESAEs, all causalities (ACTR707-related)			
	DL1 (n = 6)	DL2 (n = 3)	DL3 (n = 5)	DL4 (n = 6)
Febrile neutropenia	2 (1)	1 (1)	0	1 (1)*
Cytopenia	0	1 (1)	0	0
Pleural effusion	0	1	0	0

*Same subject with 2 events, 1 pre and 1 post ACTR707.

- Febrile neutropenia events occurred within median 16 days of lymphodepleting chemotherapy
- All SAEs resolved with median of 3 days to resolution
- Events were also all assessed as at least possibly related to lymphodepleting chemotherapy

DLTs & Adverse Events of Special Interest

- No events of cytokine release syndrome (CRS) or serious/severe neurotoxicity
- No DLTs reported through DL4

AESI, n (as defined in clinical study protocol)	Subjects with AESI			
	DL1 (n = 6)	DL2 (n = 3)	DL3 (n = 5)	DL4 (n = 6)
New malignancy	1**	0	1**	0
CRS	0	0	0	0
Use of therapeutic plasma exchange for any non-disease related AE	0	0	0	0
Clinically significant* neurologic disorder	0	0	0	0
Clinically significant* rheumatologic/autoimmune disorder	0	0	0	0
Clinically significant* hematologic disorder	0	0	1***	0

*Clinically significant = In the opinion of the Investigator, is clinically meaningful, requires medical intervention, and medically important within the context of study treatment; cytopenias related to LD chemotherapy are excluded. **Basal cell carcinoma (non-serious, resolved).
***Prolonged cytopenia (serious).

Safety Conclusions

- Favorable safety profile through 4 dose levels
  - No CRS or severe neurotoxicity
  - Grade 3-4 AEs were limited to hematologic toxicities
  - No Grade 5 AEs
- Limited requirement for supportive care
  - Protocol requirement for 2 nights of hospitalization post ACTR707 administration
  - Low rate of re-admission for SAEs following ACTR707 treatment: 5 of 20 patients (25%)
  - All SAEs resolved with a median of 3 days to resolution

Abbreviations: ACTR = Antibody-Coupled T-cell Receptor; AE = adverse event; AESI = adverse event of special interest; ASCT = autologous stem cell transplant; CD = Cluster of Differentiation; C#D# = cycle number, day number; CR = complete response; CRP = C-reactive protein; CRS = cytokine release syndrome; DEC = dose escalation committee; DLBCL = diffuse large B-cell lymphoma, DL = dose level; DLT = dose-limiting toxicity; DOR = duration of response; FL = follicular lymphoma; Gr = grade; IFN-γ = interferon-γ; IL = interleukin; IR = indeterminate response; LD = lymphodepleting [chemotherapy]; LOQ = limit of quantitation; M = million [cells]; mAb = monoclonal antibody; MCL = mantle cell lymphoma; ND = not detectable; ORR = overall response rate; PD = progressive disease; PK = pharmacokinetics; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; PT = preferred term; q21 days = once every 21 days; R/R = relapsed/refractory; SAE = serious adverse event; SD = stable disease; SMQ = standard MedDRA query; SPD = sum of product diameters; TCR = T cell receptor; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TNFα = tumor necrosis factor alpha; ULN = upper limit of normal

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Antitumor Activity

Best Response	DL1 (n = 6)	DL2 (n = 3)	DL3 (n = 5)	DL4 (n = 6)	Total (n = 20)
CR	3	1	2	2	8
Duration (days)	85, 295, 544+	43	131+, 264+	71+, 81+	range: 43-544+
PR	0	1	2	0	3
Duration (days)	n/a	32	44, 55	n/a	range: 32-55
SD	0	0	0	1	1
Duration (days)	n/a	n/a	n/a	81+	81+
IR	1	0	0	0	1
PD	2	1	1	3	7
Best ORR	**50% (3/6)**	**67% (2/3)**	**80% (4/5)**	**33% (2/6)**	**55% (11/20)**

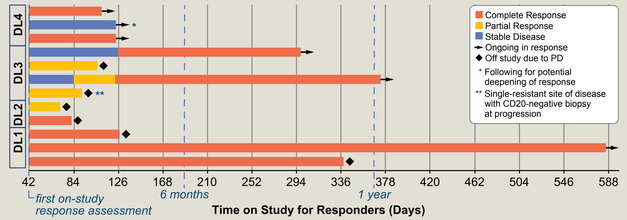
Characteristics of Subjects with CR

DL	Diagnosis	Age	Baseline* SPD (cm²)	Optional Bridging Therapy	# Prior Therapies	ASCT	Refractory** to Prior Therapy	Duration (Days)
1	Gr3b-FL	60	50.2	No	2	No	No	295
1	DLBCL	74	23.4	Yes	5	Yes	Yes***	544+
1	DLBCL	60	11.9	Yes	3	No	Yes***	85
2	DLBCL	77	14.0	Yes	3	Yes	Yes	43
3	DLBCL	77	11.1	No	3	No	No	264+
3	DLBCL	67	1.0	No	2	No	No	131+
4	MCL	71	0*	Yes	4	Yes	Yes	81+
4	MCL	57	0.9	No	2	Yes	No	71+

*Baseline SPD from scan performed post-bridging therapy (within 14 days prior to LD chemotherapy). *Patient with measurable disease at screening; no evidence of disease post-bridging therapy. **Refractory to prior therapy defined as no response to prior therapy or relapse ≤ 12 months post ASCT.
***Subject also rituximab refractory, defined as PD as best response to rituximab or rituximab-containing therapy.

Time on Study for Responders

- Short duration of follow-up for DL4 available to assess durability and potential deepening of response; deepening of responses noted in 2 patients in DL3

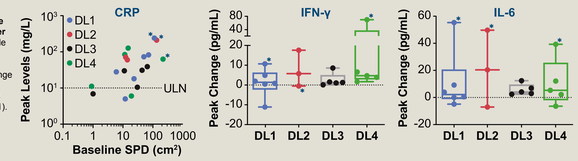


Inflammatory Markers & Cytokines

- Modest increases in inflammatory markers and cytokines observed post-ACTR administration
- Highest levels of CRP and increases in inflammatory cytokines IFN-γ, IL-6, TNFα, and IL-8 were largely associated with greater baseline tumor burden (SPD > 100 cm²), suggesting target-driven T-cell activity
- Changes in inflammatory markers and cytokines are not ACTR707 dose-dependent or correlated with response

Representative Cytokine and Inflammatory Marker Assessments: Each circle represents an individual subject in the study, for IFN-γ and IL-6, peak change as shown is the maximal change over first 4 weeks relative to baseline (C1D1).

•= subjects with baseline SPD > 100 cm²



Conclusions

Data from the ATTCK-20-03 study support proof-of-mechanism for the ACTR platform

- ACTR707 can combine with rituximab to mediate responses in patients with advanced CD20⁺ NHL
  - In a CD20 target-specific manner
  - In patients refractory to prior rituximab-containing therapy
  - Without associated T cell-mediated toxicities such as CRS and severe neurotoxicity
- Favorable safety profile and limited requirement for supportive care in Dose Levels 1-4
  - Supports the potential for broad applicability of this therapy
  - Provides possible path to outpatient administration
- Dose escalation continues, to drive improved response rates and durability
  - Enrollment in Dose Level 5 is ongoing at a dose of 120M ACTR⁺ T cells