A Phase 1 Study of Two Investigational Agents, ACTR087, an Autologous T Cell Product Expressing an Antibody-Coupled T Cell Receptor, in Combination with SEA-BCMA, a Novel Non-Fucosylated Monoclonal Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma

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The James
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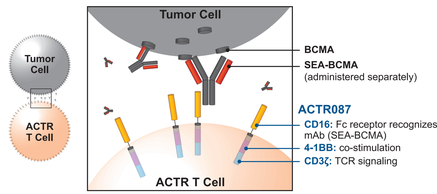
Introduction

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 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. ACTR T cell products are currently in clinical development in combination with rituximab (NCT02776813, NCT03189836; ASH abstract 2966), with SEA-BCMA (NCT03266692), and with trastuzumab (NCT03680560).

Study ATTCK-17-01 (NCT03266692) is the first clinical trial of ACTR087 in combination with SEA-BCMA. SEA-BCMA is an investigational non-fucosylated IgG1 mAb targeting BCMA that was created using Seattle Genetics' proprietary Sugar Engineered Antibody (SEA) technology. In preclinical studies, SEA-BCMA in combination with ACTR T cells resulted in T cell activation and cytotoxicity against multiple myeloma (MM) tumor target cells in a dose-dependent and target-specific manner *in vitro* and anti-tumor efficacy *in vivo* [AACR 2017, poster #4605]. ACTR087 in combination with SEA-BCMA is being studied in subjects with relapsed or refractory MM. Here, we present data from the first three cohorts, where 7 subjects have been enrolled and treated with ACTR087 in combination with SEA-BCMA. As of the database cut, safety data and some M protein data are available for all 7 enrolled subjects across Cohorts 1-3; PK data following ACTR administration are available for 6 subjects (Cohort 1, Cohort 2, and 4 of 5 in Cohort 3); response data (disease assessments per the investigator) and ACTR expansion data are available for 5 subjects (Cohort 1, Cohort 2, and 3 of 5 in Cohort 3); and inflammatory cytokine data following ACTR administration are available for Cohorts 1 and 2.

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
- Disconnecting ACTR T cell activation and proliferation from direct tumor targeting facilitates optimization of therapeutic index via mAb dosing

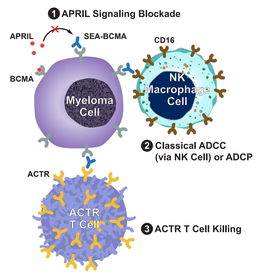


- ACTR T cells and mAb administered separately to subjects
- ATTCK-17-01 uses SEA-BCMA as mAb to target BCMA on tumor cells

SEA-BCMA: Novel, Non-Fucosylated IgG1 mAb Targeting BCMA

SEA-BCMA in combination with ACTR may exert anti-tumor effects through several potential mechanisms:

1. SEA-BCMA antibody blocks binding of the BCMA ligands, APRIL and BAFF, preventing multiple downstream events including proliferation of MM cells.
2. SEA-BCMA can induce NK-mediated ADCC and macrophage-mediated ADCP.
3. ACTR expressed on autologous T cells encode a high-affinity variant of the Ig Fc receptor CD16 (V158) which binds to SEA-BCMA opsonized onto BCMA-expressing myeloma cells to induce T cell activation pathways and proliferation and drive MM target cell cytotoxicity.



ATTCK-17-01 Study Design

Multicenter, Phase 1, dose-escalation study of ACTR087 in combination with SEA-BCMA. Dose escalation of 2 investigational agents, ACTR087 and SEA-BCMA, is determined according to adaptive design principles. Dose escalation cohorts have two DLT assessment periods: DLT 1 period to assess safety of SEA-BCMA as a single agent, and DLT 2 period to assess the safety of SEA-BCMA in combination with ACTR087.

Primary objectives:

- To characterize the safety and to determine the recommended Phase 2 dose of ACTR087 in combination with SEA-BCMA in subjects with relapsed/refractory MM.

Secondary objectives:

- Anti-myeloma activity, ACTR T cell expansion and persistence, cytokines, and SEA-BCMA PK

Key subject eligibility criteria:

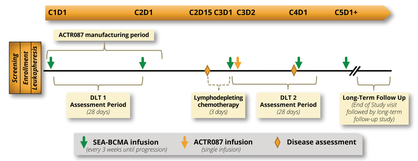
- Measurable disease
- Received at least 3 prior lines of therapy including treatment with a proteasome inhibitor and an immunomodulatory agent, and HSCT for HSCT-eligible subjects
- BCMA expression on MM cells **was not** a condition of eligibility

Cohorts

Single subject cohorts (with opportunity to expand based on safety experience) implemented at first 2 SEA-BCMA dose levels to limit treatment at SEA-BCMA dose levels unlikely to yield significant anti-tumor activity. All subjects received ACTR087 at the first dose level (target 30 x 10^6 ACTR$^+$ T cells) after 3 days of lymphodepleting chemotherapy (fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day).

- Cohort 1 (n = 1): SEA-BCMA 0.03 mg/kg + ACTR087
- Cohort 2 (n = 1): SEA-BCMA 0.1 mg/kg + ACTR087
- Cohort 3 (n = 5): SEA-BCMA 0.3 mg/kg + ACTR087

ATTCK-17-01 Subject Treatment Schema



Demographics & Baseline Characteristics

	Cohorts 1-3 (n = 7)
Median Age, years (range)	56 (42 - 68)
Men, n (%)	4 (57)
Time from diagnosis to study start, years (range)	6.3 (1.3 - 9.2)
ECOG, n (%)	
0	1 (14)
1	6 (86)
Number of prior lines, median (range)	8 (3 - 15)
Selected Prior Therapies, n (%)	
Immunomodulatory Drugs	7 (100)
Lenalidomide	7 (100)
Pomalidomide	6 (86)
Thalidomide	2 (29)
Proteosome Inhibitors	7 (100)
Bortezomib	6 (86)
Carfilzomib	6 (86)
Ixazomib	3 (43)
Monoclonal antibodies	6 (86)
Daratumumab	6 (86)
Elotuzumab	2 (29)
Prior autologous stem cell transplant	6 (86)

Safety Overview

DLTs

Across Cohorts 1-3, no DLTs have been reported after SEA-BCMA single-agent dosing (DLT 1 period) or after ACTR087 in combination with SEA-BCMA (DLT 2 period).

Adverse Events of Special Interest (AESIs)

AESI	n (%) *(Cohorts 1-3; n = 7)*
New malignancy	0
Cytokine release syndrome (CRS)	1 (14)[§]
Use of therapeutic plasma exchange for any non-disease related AE	0
Clinically significant* neurologic disorder	1 (14)[‡]
Clinically significant* rheumatologic/ autoimmune disorder	0
Clinically significant* hematologic disorder	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

§ Event of CRS was Grade 1 in severity and resolved without therapeutic intervention.

‡ Event of neurotoxicity was Grade 1 in severity and resolved without therapeutic intervention.

Treatment-Emergent AEs* ≥ Grade 3 in ≥ 2 Subjects

Preferred Term	n (%) *(Cohorts 1-3; n = 7)*
Anemia	4 (57)
Neutropenia	4 (57)
Lymphocyte count decreased	4 (57)
WBC count decreased	4 (57)

* AEs following treatment with any of the study medications ie, ACTR087, SEA-BCMA, fludarabine or cyclophosphamide

Related SAEs

- ACTR087-related SAEs:

Preferred Term	n (%) *(Cohorts 1-3; n = 7)*
Cytokine release syndrome (CRS)*	1 (14)

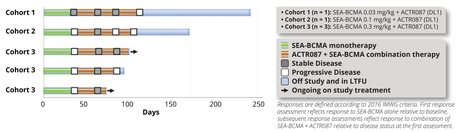
* Serious event of Grade 1 CRS that resolved without therapeutic intervention

- There were no SEA-BCMA-related SAEs reported.

Response Data

Response Assessments per Investigators

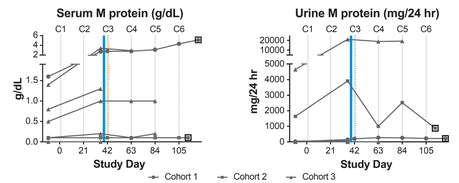
(Includes subjects with available response assessments post ACTR087 infusion)



Responses are defined according to 2016 IMWG criteria. First response assessment reflects response to SEA-BCMA alone relative to baseline, subsequent response assessments reflect response to combination of SEA-BCMA + ACTR087 relative to disease status at the first assessment.

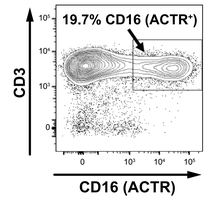
M Protein Levels

- Addition of ACTR087 stabilizes or decreases levels of M protein.
- M protein levels increase from Screening to C2D16 (SEA-BCMA monotherapy period), then decline or stabilize following infusion of ACTR087.



ACTR087 Manufacturing

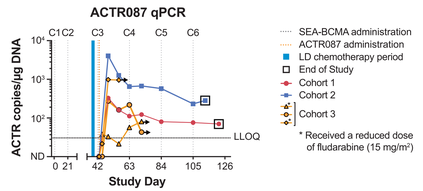
- There were no manufacturing failures in Cohorts 1-3 (n = 7), with a mean of 26 days between leukapheresis and drug product release, inclusive of release testing.



Representative example of ACTR T cell staining in ACTR087 drug product

ACTR087 Expansion & Persistence

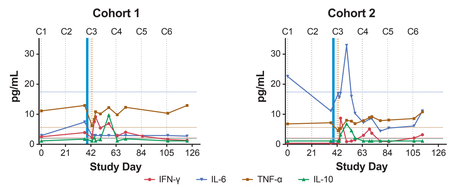
- ACTR087 expansion observed in the peripheral blood of all subjects in Cohorts 1-3 (first dose level ACTR$^+$ T cells).
- Persistence observed up to 86 days post ACTR087 administration.



Cytokine Levels

Modest elevations in serum cytokines associated with T cell activation:

- Subjects in Cohort 1 (n = 1) and Cohort 2 (n = 1) exhibit early increases in IFN-γ (1 day following ACTR087 administration) and additional elevations following subsequent SEA-BCMA administrations, suggestive of antibody-dependent T cell activation
- Cytokine levels are only modestly above upper limits of normal, consistent with the safety profile



Dotted horizontal lines indicate upper limit of normal for cytokine with corresponding color

Safety & Response Data snapshots: 1 November 2018. Graph Data snapshots: 2 November 2018.

Abbreviations: ADCC = antibody-dependent cellular toxicity; ADCP = antibody-dependent cellular phagocytosis; AE = adverse event; APRIL = a proliferation inducing ligand; BAFF = B cell activating factor; C#D# = cycle number, day number; DL = dose level; DLT = dose-limiting toxicity; HSCT = hematopoietic stem cell transplant; IFN-γ = interferon gamma; IR = indeterminate response; LLOQ = lower limit of quantitation; LTFU = long-term follow-up; NK = natural killer; PK = pharmacokinetics; qPCR = quantitative polymerase chain reaction; SAE = serious adverse event; SD = stable disease; TCR = T cell receptor; TNF-α = tumor necrosis factor alpha; WBC = white blood cell

Disclosures: DB Nothing to disclose; HH Consultancy/Speakers Bureau: Bayer, Gilead, Rigel, Seattle Genetics; Research Funding: Gilead, Celgene, Genentech, Novartis, Seattle Genetics, Unum. PH Consultancy/Honoraria: Celgene, Bristol-Myers Squibb, Janssen, Kite, Takeda, Spectrum, Sanofi; Research Funding: Amgen, Celgene, Bristol-Myers Squibb, Takeda, Spectrum, Sanofi. JS, BE, AR, TC, IS: Employees of Unum Therapeutics. MOM: Employee and Equity Ownership:Seattle Genetics; DS: Employee of Seattle Genetics. LA Speakers Bureau: Bristol-Myers Squibb, Celgene, Gilead, Novartis, Takeda.

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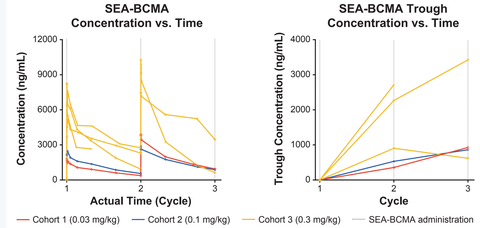
SEA-BCMA Pharmacokinetics

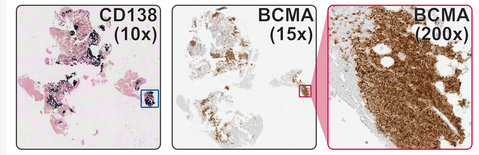
Preliminary PK data for SEA-BCMA indicate:

- A bi-phasic exponential decay within the dosing period
- Minimal accumulation of antibody during Cycles 1-3 for 3 of 4 subjects evaluable
- A half-life of 13.0 days (0.03 mg/kg), 11.5 days (0.1 mg/kg) and 13.9 days (geometric mean of 0.3 mg/kg dose cohort)



BCMA Expression on MM Tumor Cells

- All evaluable bone marrow biopsies received to date have demonstrated BCMA$^+$ MM cells.



- Representative images for CD138 and BCMA staining in bone marrow from a subject enrolled in Cohort 3. At this Screening visit, 95% of MM cells (CD138$^+$) were BCMA$^+$ with an intensity score of 2+ (moderate staining above background).

Conclusions

- First-in-human dosing of SEA-BCMA well-tolerated with expected pharmacological profile
  - No SAEs related to SEA-BCMA reported
  - Bi-phasic exponential decay within the dosing period with accumulation during Cycles 1-3
- Pharmacodynamic evidence of ACTR087 + SEA-BCMA activity supports proof of mechanism
  - ACTR087 demonstrates expansion and persistence in Cohorts 1-3 ongoing at up to 12 weeks in the peripheral blood
  - Modest increases in IFN-γ following ACTR087 administration is suggestive of T cell activation
- Safety profile of ACTR087 + SEA-BCMA in first three dose cohorts supports further dose escalation of the combination
  - No DLTs post SEA-BCMA single-agent dosing period (DLT 1) or post ACTR087 + SEA-BCMA (DLT 2)
  - No severe CRS or neurological events reported
- Disease assessments suggest combination activity of SEA-BCMA + ACTR087.
  - At the first dose levels tested, serum and urinary M protein levels increased during SEA-BCMA single-agent dosing and stabilized or decreased following ACTR087 administration
- Enrollment in Cohort 4 (dose level SEA-BCMA 2 mg/kg; ACTR target dose 30x10^6 ACTR$^+$ T cells) is ongoing