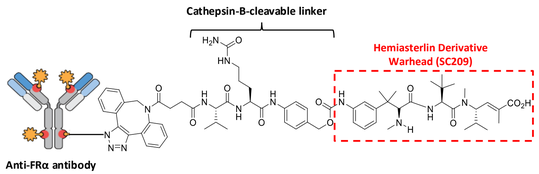
Abstract #3299:
Anti-FRα antibody-drug conjugate luveltamab tazevibulin for the treatment of FRα-expressing non-small cell lung cancer

Robert Yuan, Andrew McGeehan, Sihong Zhou, Mark Armanini, Jennifer Smith, Millicent Embry, Rhoneil Pena, Danielle K Lewis, Krishna Bajjuri, Cuong Tran, Gang Yin, Xiaofan Li, Hans-Peter Gerber, Alice Yam, Helena Kiefel, Genevive Hernandez

SCAN ME

SUTRO BIOPHARMA

Introduction



- Luveltamab tazevibulin (Luvelta, STRO-002) is a novel ADC composed of an anti-FRα-targeting antibody conjugated to a tubulin-targeting 3-aminophenyl hemiasterlin payload (SC209) via a cathepsin B-cleavable val-cit linker.
- Luveltamab tazevibulin utilizes Sutro's XpressCF+® cell-free expression system for site-specific conjugation of the linker-payload, yielding a homogenous ADC with a drug-antibody ratio of four.
- Phase I and II/III clinical trials of luveltamab tazevibulin in ovarian cancer and endometrial cancer (NCT03748186 and NCT05870748) demonstrate that it has promising clinical activity and a manageable safety profile as a monotherapy and in combination with bevacizumab.

The anti-FRα ADC luveltamab tazevibulin demonstrates target-specific cell killing

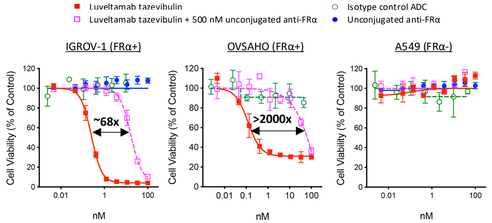
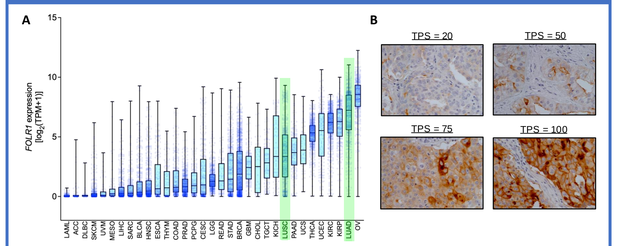


Figure 1. Cell killing curves of FRα+ (IGROV-1, OVSAHO) and FRα- (A549) cell lines after incubation with luveltamab tazevibulin, luveltamab tazevibulin + unconjugated anti-FRα, isotype control ADC, or unconjugated anti-FRα.

FRα is expressed in lung cancer patient tissue



C

FRα expression (TPS)	NSCLC Squamous	NSCLC Non-squamous
TPS = 0/<1%	84.3%	52%
1% ≤ TPS < 25%	11.6%	19.2%
25% ≤ TPS < 75%	1.4%	15.2%
TPS ≥ 75%	2.7%	13.6%

Figure 2. (A) Expression of *FOLR1* across tumor types from the TCGA database. LUAD = lung adenocarcinoma; LUSC = lung squamous cell carcinoma. (B) Representative images of FRα staining (brown) with hematoxylin counterstaining (blue) of human lung cancer tissues. Scale bar = 50 mm. (C) Table of FRα prevalence in NSCLC tumor microarrays. TPS = tumor proportion score.

Luveltamab tazevibulin demonstrates robust anti-tumor activity in patient-derived xenograft models of non-small cell lung cancer

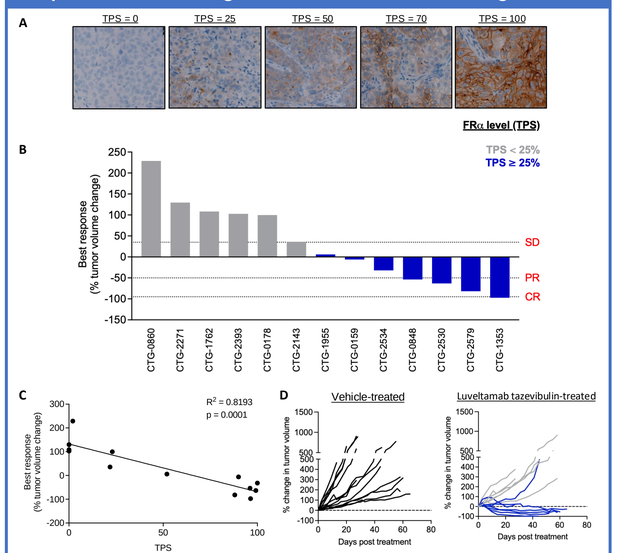


Figure 3. (A) Representative images of FRα staining (brown) with hematoxylin counterstaining (blue) of NSCLC PDX tumors showing the range of FRα expression. Scale bar = 20 µm. (B) Best response following luveltamab tazevibulin treatment (10 mg/kg, qwx4) in multiple NSCLC PDX models, categorized by FRα TPS <25% or ≥25%. SD = stable disease, PR = partial response, CR = complete response. (C) Scatterplot of best response and FRα TPS for NSCLC PDX models with best-fit linear regression line. (D) Individual tumor growth curves of vehicle-treated (left) and luveltamab tazevibulin-treated (right) NSCLC PDX models. For luveltamab tazevibulin-treated tumors, colors represent levels of FRα TPS, as outlined in panel (B).

Luveltamab tazevibulin induces hallmarks of immunogenic cell death (ICD) *in vitro*

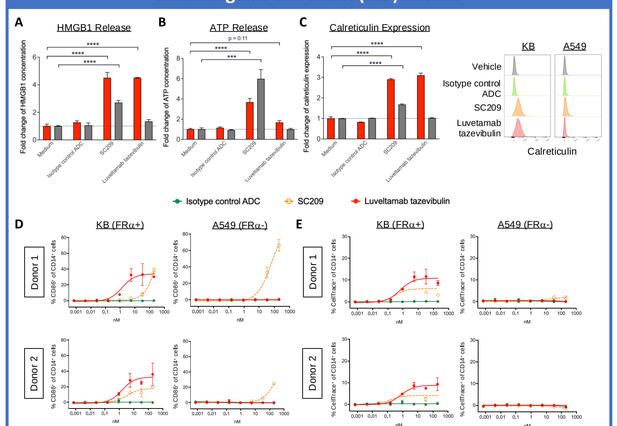


Figure 4. Fold change in (A) HMGB1 release, (B) ATP release, and (C) calreticulin expression in KB (FRα+) and A549 (FRα-) tumor cell cultures with medium only or isotype control ADC, SC209, or luveltamab tazevibulin. Fold change over the medium-only group is depicted. For calreticulin expression, representative histograms are shown to the right. Dose-response curves of proportion of (D) CD86+ cells or (E) CellTrace+ cells among CD14+ immune cells in tumor cell-PBMC co-cultures incubated with isotype control ADC, SC209, or luveltamab tazevibulin for 48 hours with two donors.

Vaccination with luveltamab-tazevibulin-treated tumor cells protects mice from tumor cell rechallenge

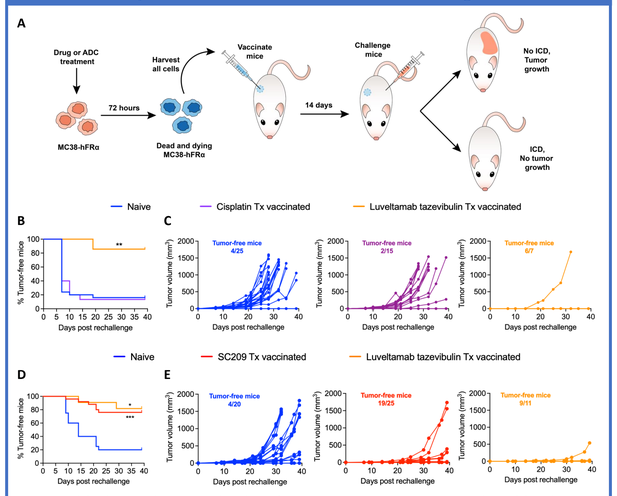


Figure 5. (A) Schematic depicting methodology of *in vivo* vaccination assays using MC38-hFRα. (B) Kaplan-Meier curves of tumor-free mice or (C) individual tumor growth curves following vaccination with cisplatin- or luveltamab tazevibulin-treated MC38-hFRα cells and subsequent MC38-hFRα challenge. (D) Kaplan-Meier curves of tumor-free mice or (E) individual tumor growth curves following vaccination with SC209- or luveltamab tazevibulin-treated MC38-hFRα cells and subsequent MC38-hFRα challenge.

Luveltamab tazevibulin activates CD8⁺ T cells and macrophages in the tumor microenvironment

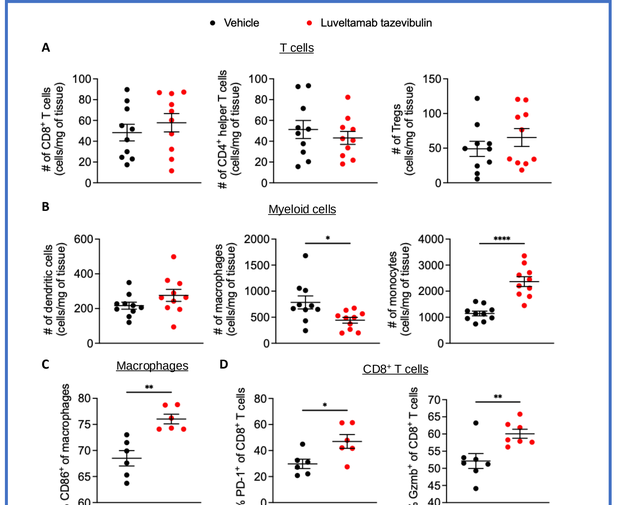


Figure 6. Cell density of (A) CD8⁺ T cells, CD4⁺ helper T cells, and Tregs or (B) dendritic cells, macrophages, and monocytes in MC38-hFRα tumors treated with luveltamab tazevibulin. (C) Frequency of CD86⁺ macrophages of total macrophages and (D) frequency of PD-1⁺ and granzyme B⁺ CD8⁺ T cells of total CD8⁺ T cells in MC38-hFRα tumors treated with luveltamab tazevibulin. Cell infiltration was analyzed at 5 days post treatment.

Luveltamab tazevibulin combines with immune checkpoint inhibitors to generate potent and durable anti-tumor immunity

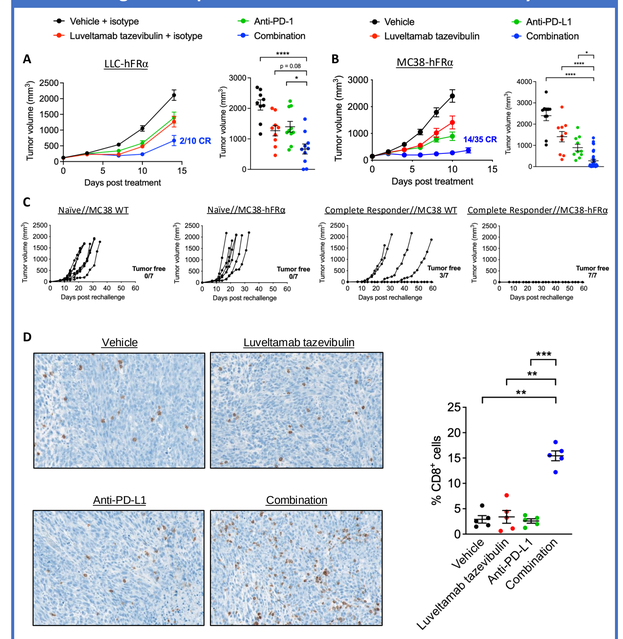


Figure 7. (A) Tumor growth curves of LLC-hFRα tumors treated with vehicle and isotype control (10 mg/kg, single dose), luveltamab tazevibulin (10 mg/kg, single dose) and isotype control (10 mg/kg, single dose), anti-PD-1 (10 mg/kg, q3-4dx4), or combination (left). Tumor volumes on Day 14 post treatment (right). (B) Tumor growth curves of MC38-hFRα tumors treated with vehicle, luveltamab tazevibulin (10 mg/kg, single dose), anti-PD-L1 (10 mg/kg, q3-4dx4), or combination (left). Tumor volumes on Day 10 post treatment (right). (C) Individual tumor growth curves of naïve or complete responder mice rechallenged with MC38 wild-type or MC38-hFRα cells. (D) Representative images of CD8 staining (brown) with hematoxylin counterstaining (blue) in tumors treated with vehicle, luveltamab tazevibulin (10 mg/kg, single dose), anti-PD-L1 (20 mg/kg, single dose), or combination therapy to the left. Quantification of percent CD8⁺ cells of total cells are shown to the right. Cell infiltration was analyzed at 7 days post treatment.

Conclusions

- FRα is expressed in NSCLC patient tumors, with non-squamous tumors exhibiting higher levels of FRα compared to squamous tumors.
- Luveltamab tazevibulin achieves objective responses (PR and CR) in FRα-positive NSCLC PDX tumors.
- Luveltamab tazevibulin induces immunogenic cell death and can activate immune cells in the tumor microenvironment.
- Luveltamab tazevibulin combination therapy with immune checkpoint blockade demonstrates greater anti-tumor efficacy than monotherapies alone.
- Altogether, the work presented here provides rationale for evaluating luveltamab tazevibulin in NSCLC either as monotherapy or in combination with immune checkpoint blockade
- REFRaME-L1 is a global Phase II study (NCT06555263) that is investigating the safety and efficacy of luveltamab tazevibulin in previously treated advanced or metastatic NSCLC patients with positive FRα expression.