SGN-35T: A Novel CD30-Directed Antibody-Drug Conjugate for the Treatment of Lymphomas

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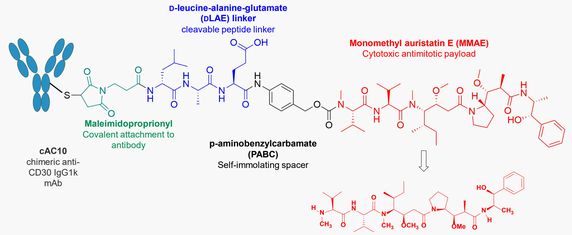
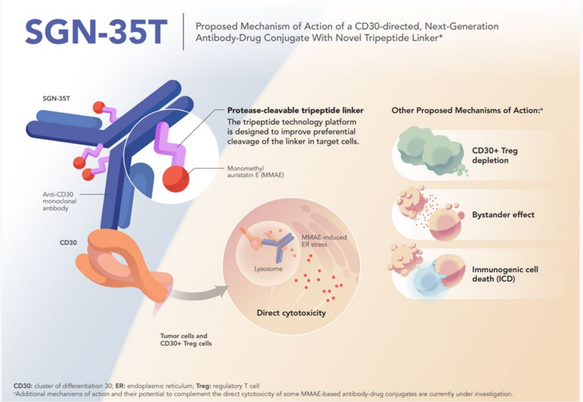
Background

- **CD30** (TNFRSF8), a member of the TNF receptor superfamily, is the target of the antibody drug conjugate brentuximab vedotin (BV) approved for use in multiple CD30-expressing lymphomas.
- **Antibody-drug conjugates (ADCs)** employing the vedotin drug linker are effective anti-cancer agents in a wide variety of solid and hematologic cancers. While vedotin ADCs are efficacious, side effects such as dose-limiting neutropenia and other toxicities may be observed[1].
- A **novel cleavable linker** containing a tripeptide molecule comprised of D-leucine-alanine-glutamate (DLAE) was designed to decrease bone marrow toxicity and potentially widen the therapeutic window (Poster C113).
- **SGN-35T** is a CD30-directed ADC with the same mAb backbone and cytotoxic monomethyl auristatin E (MMAE) payload as BV and utilizes the novel cleavable tripeptide DLAE linker.

Chemical structure of SGN-35T



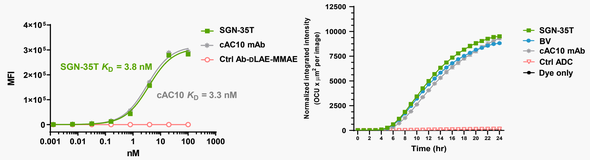
Proposed Mechanism of Action



Results

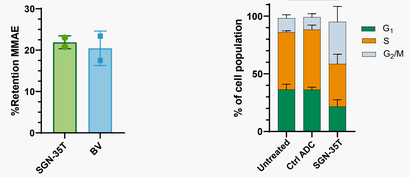
SGN-35T Exhibits Similar CD30-Directed Activity as BV

SGN-35T binds CD30+ cells and internalizes similar to BV



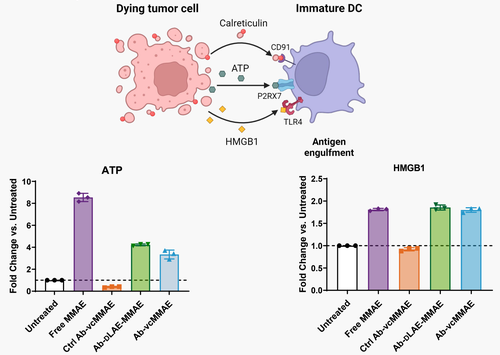
Saturation binding of SGN-35T, parental mAb cAC10, and non-binding control ADC Control Ab-DLAE-MMAE to CD30-expressing Karpas-299 lymphoma cells, measured by flow cytometry (N=2) (left). Error bars represent SEM. Right, fluorescent intensity reflecting internalization of a reporter (N=3). Data were normalized to the percent confluency per well. Error bars represent SD. Ctrl ADC = Non-binding control Ab-DLAE-MMAE.

Following internalization MMAE is released from SGN-35T and induces cell cycle arrest



Released MMAE was quantified in L540cy cells incubated with 100 ng/mL of SGN-35T or BV for 24 hours. Intracellular MMAE was calculated as a percentage of total free drug measured in the cell pellet plus supernatant (N=2) (left). Karpas-299 cells were treated with test articles and the percentage of cells in each phase of the cell cycle are depicted (right). Two-way ANOVA with Tukey's multiple comparisons test was performed between treatment groups. Error bars denote SD. ***P≤0.001. Ctrl ADC = non-binding control Ab-DLAE-MMAE.

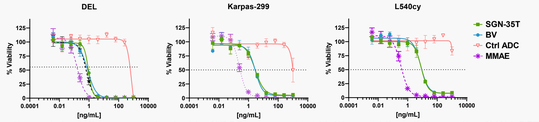
SGN-35T linker-payload induces markers of immunogenic cell death (ICD)



ICD markers including ATP and HMGB1[2] were measured after treating co-cultures of immune cells with MIA-PaCa2 pancreatic carcinoma cells treated with test articles. Levels of ATP and HMGB1 are reported as fold change versus untreated (dotted line). Top, created with BioRender.com.

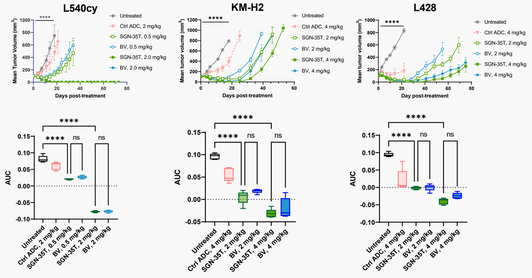
SGN-35T Demonstrates Anti-tumor Efficacy

CD30+ Lymphoma cell lines were sensitive to SGN-35T *in vitro*



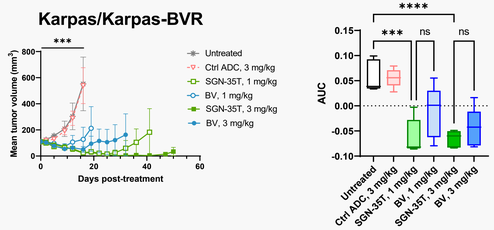
In vitro cytotoxicity was evaluated in CD30-expressing ALCL and HL cell lines after SGN-35T treatment, shown as mean percent viability versus untreated cells. The horizontal dotted line indicates 50% viability versus untreated. Error bars represent SD. CD30 expression on the cell surface was quantified by QFACS: DEL=285,000, Karpas-299=318,900, and L540cy=408,500. Ctrl ADC = Non-binding control Ab-DLAE-MMAE.

SGN-35T demonstrates efficacy in xenograft models



Human xenografts were subcutaneously implanted into female SCID mice. After tumors were established, mice were treated once by i.p. (N=5 mice/group). Mean tumor volumes were compared by two-way ANOVA through the last day control groups remained on study. AUC for tumor volume was compared by one-way ANOVA followed by Dunnett's post-hoc test. Select pairwise comparisons are shown. Error bars indicate SEM (tumor volume) or SD (AUC). ****P<0.0001; ***P<0.001; **P<0.01; ns, not significant. Ctrl ADC = Non-binding control Ab-DLAE-MMAE.

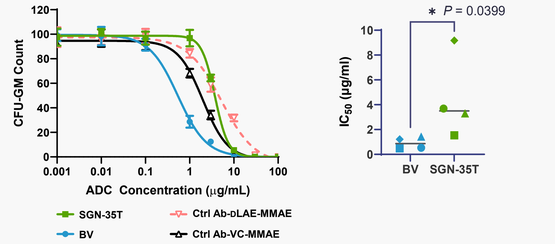
SGN-35T elicits bystander killing in a mixed model of CD30 expression



CD30-expressing Karpas-299 cells (318,900 CD30 surface molecules per cell) were mixed with a daughter line without CD30 surface expression, Karpas-BVR (0 CD30 surface molecules per cell), at a 1:1 ratio, then subcutaneously implanted into female SCID mice. After tumors were established, mice were treated once by i.p. (N=5 mice/group). Mean tumor volumes were compared by two-way ANOVA and AUC was compared by one-way ANOVA followed by Dunnett's. Error bars indicate SEM (tumor volume) or SD (AUC). ****P<0.0001; ***P<0.001; ns, not significant. Ctrl ADC = non-binding control Ab-DLAE-MMAE.

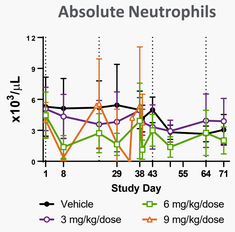
SGN-35T Displays an Improved Non-clinical Safety Profile Versus BV

Reduced in vitro potency against human bone marrow cells in a CFU-GM assay



The cytotoxic effects of SGN-35T on human bone marrow progenitor cells were assessed using human granulocyte-monocyte colony-forming units (CFU-GM). Left, one representative donor normalized dose response (N=4 donors total). Right, IC_{50} of BV and SGN-35T. Each dot represents the IC_{50} value calculated from one of four individual donors. Mean IC_{50} values were compared using an unpaired Student's t-test. *P<0.05.

SGN-35T is better tolerated than BV in non-human primates



Molecule	HNSTD
SGN-35T	6 mg/kg
BV[3]	3 mg/kg

Non-human primates were dosed with either vehicle or SGN-35T at 3, 6, or 9 mg/kg Q3WX4 (N=5/sex/group). Blood was periodically collected for clinical pathology assessment. Tissues were collected one week following the last dose to assess histopathology and determine the highest-non severely toxic dose (HNSTD). Left, Absolute neutrophils for SGN-35T. Right, HNSTD comparison of SGN-35T and BV.

Summary

- **SGN-35T** utilizes the same mAb backbone and cytotoxic MMAE payload as BV with similar binding, internalization, cytotoxicity, and efficacy compared to BV.
- SGN-35T demonstrates **reduced** hematopoietic toxicity compared to BV. Introduction of the novel DLAE linker led to a **two-fold improvement in tolerability** in non-human primates.
- A Phase 1, first-in-human study is planned to evaluate the safety and antitumor activity of SGN-35T in lymphoid malignancies.

References

1. Saber H and Leighton JK. An FDA oncology analysis of antibody-drug conjugates. Regul Toxicol Pharmacol. 2015 Apr;71(3):444-52.
2. Fucikova, J., Kepp, O., Kasikova, L. *et al.* Detection of immunogenic cell death and its relevance for cancer therapy. *Cell Death Dis* **11**, 1013 (2020).
3. Data on file

Poster No. C132
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