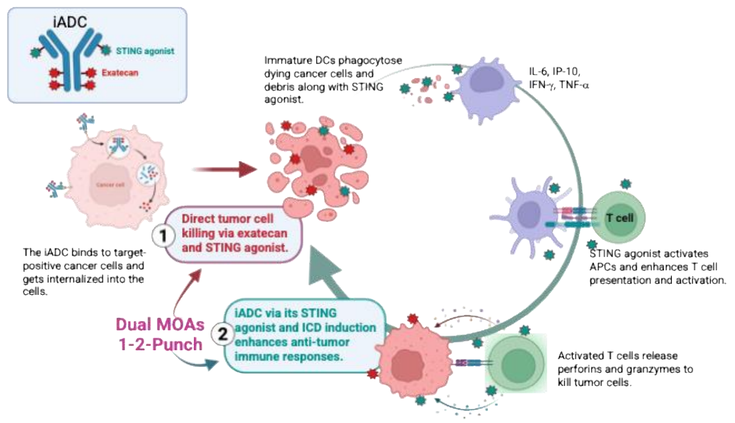
Next-Generation Immunostimulatory Antibody-Drug Conjugates (iADCs) Combine Tumor Cell Killing with Immune Activation to Induce Durable Antitumor Immunity

Gang Yin, Robert Yuan, Brian Vuillemenot, Wadie Mahauad-Fernandez, Wenjia Gu, Stephanie Armstrong, Miao Wen, Jeff Hanson, Cuong Tran, Garrett Gross, Werner Rubas, Xiaofan Li, and Hans-Peter Gerber
Sutro Biopharma Inc, 111 Oyster Point Blvd, South San Francisco, CA 94080

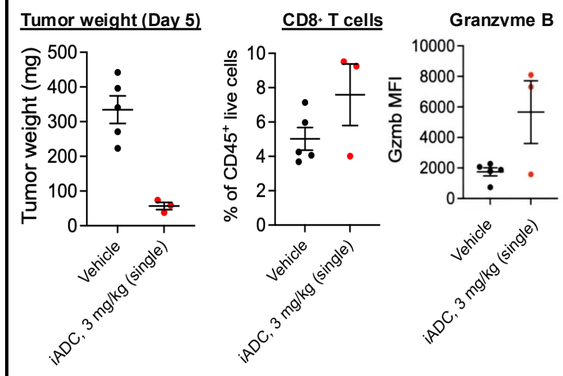
Introduction

- There is a critical need to safely enhance the potency of antibody-drug conjugates (ADCs) for targeting of low-target antigen and heterogeneous tumors and to overcome acquired resistance.
- Dual-payload immunostimulatory ADCs (iADCs) are designed to simultaneously deliver both a cytotoxin and an immune stimulator directly to the tumor cells.
- Dual-payload ADCs combine two payloads with different mechanisms of action (MOA) into a single ADC, offering the potential to enhance ADC efficacy and to overcome drug resistance.
- This dual-action approach aims to enhance therapeutic potency by debulking tumors via the cytotoxic payload while engaging the immune system with the immune stimulator payload.
- Sutro Biopharma's cell-free platform enables the precise and efficient development of high-DAR, dual-payload ADCs.

Immunostimulatory Antibody Drug Conjugate (iADC)



HER2 iADC Treatment Increases Proportion of CD8+ T cells Infiltrating the Tumor



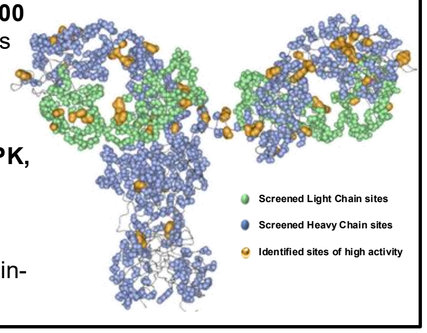
HER2 iADC was Well Tolerated in Exploratory NHP Toxicity Study

Findings:

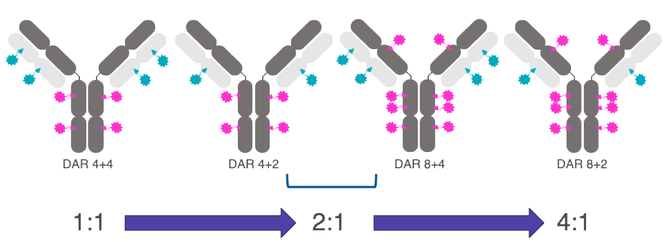
- 12.5 and 25 mpk Q3 wks x2 was well tolerated with no abnormal clinical signs.
- No increases in cytokines indicative of potential for cytokine release syndrome.
- Exhibited low clearance, long half-life (T1/2=9.5d), DAR stability, and negligible ADA formation.
- MTD = 25 mg/kg; toxicity profile similar to other exatecan containing ADCs and to HER2-exatecan DAR8 single conjugate.

Sutro's XpressCF+® Platform Allows for Empirical Evaluation to Identify the Best Conjugation Site Combinations for Dual-Payload ADCs

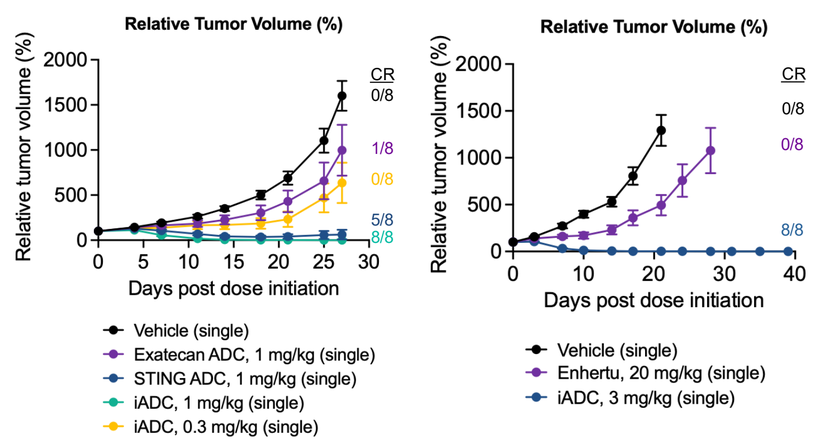
- Extensive screening of **~400** sites and site combinations conducted to identify sites that exhibit favorable characteristics: **stability, conjugation efficiency, PK, efficacy & safety**.
- A true **site-selective** approach to develop best-in-class dual-payload ADCs



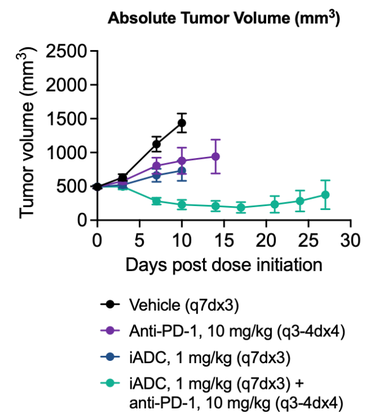
XpressCF+® Platform Facilitates Precise Tuning of the DARs and Ratios of Two Payloads Critical for Optimal Synergy

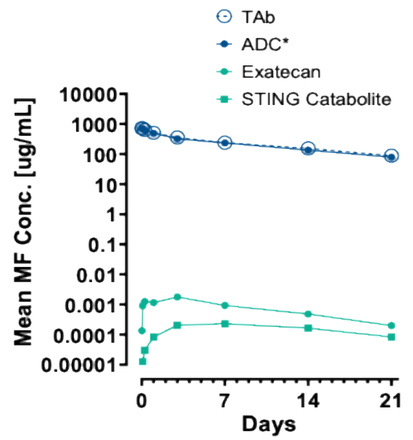


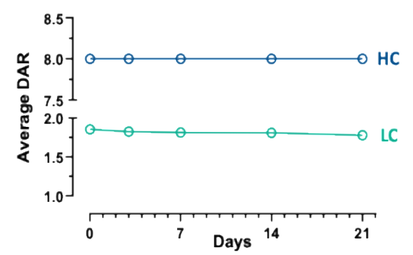
HER2 iADC Treatment Results in More Complete Responses Compared to Single Payload ADCs in the MC38-hHER2 Tumor Model



HER2 iADC Plus αPD-1 Enhances Therapeutic Response in Large MC38-hHER2 Tumors







CONCLUSION: iADCs have the potential to become a novel treatment option that integrates targeted cytotoxicity with immune engagement to address resistance and to improve long-term outcomes for cancer patients