Preclinical Activity and Safety of STRO-004, a Novel ADC Targeting Tissue Factor for Solid Tumors

Andrew McGeehan, Helena Kiefel, Sihong Zhou, Grace Lee, Mark Armanini, Brian Vuillemenot, Guifen Xu, Xiaofan Li, Krishna Bajjuri, Miao Wen, Jeff Hanson, Cuong Tran, Amandeep Gakhal, Daniel Calarese, Hans-Peter Gerber, Werner Rubas, Gang Yin, Alice Yam

Abstract #1572

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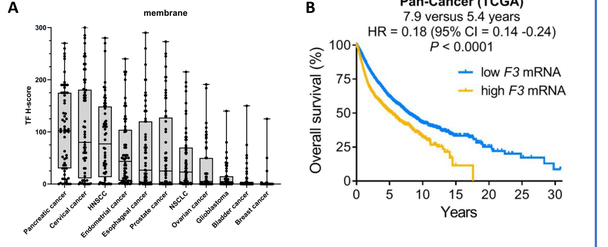
Introduction

- Tissue Factor (TF) is a type I transmembrane protein that is aberrantly expressed in multiple solid tumor indications including cervical, head and neck, non-small cell lung, and pancreatic cancers.
- TF expression is associated with poor prognosis and has been linked to pro-tumorigenic activities such as metastasis, inflammation, and angiogenesis.
- Under normal physiological conditions, TF plays an important role in blood clotting and, as such, is broadly expressed in many normal tissues, typically in the subendothelium. Upon endothelial damage, TF can combine with clotting factors in circulation to initiate a coagulation cascade, thus constituting a "hemostatic envelope".
- We have developed STRO-004, a novel TF-targeted ADC with a DAR8 β-glucoronidase-exatecan linker-payload, with enhanced potency and safety in preclinical models. STRO-004 is engineered for:
  - Reduced bleeding risk
  - Stability in circulation with stable, hydrophilic β-glucoronidase cleavable linker and site-specific conjugation
  - High potency against TF-expressing tumors
  - Improved safety and tolerability

Tissue Factor is Highly-Expressed Across Multiple Solid Tumor Indications

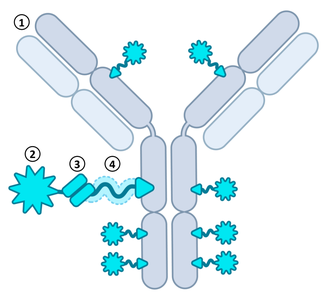


(A) TF is broadly expressed across multiple solid tumor indications (de Bono, et al. 2022 Cancer Reports). (B) An analysis of overall survival in the pan-cancer database (TCGA) suggests that high TF expression is associated with poor prognosis (Unruh and Horbinski (2020) J Hematology & Oncology. This article is licensed under a Creative Commons Attribution 4.0 International License: http://creativecommons.org/licenses/by/4.0/ No changes were made.)

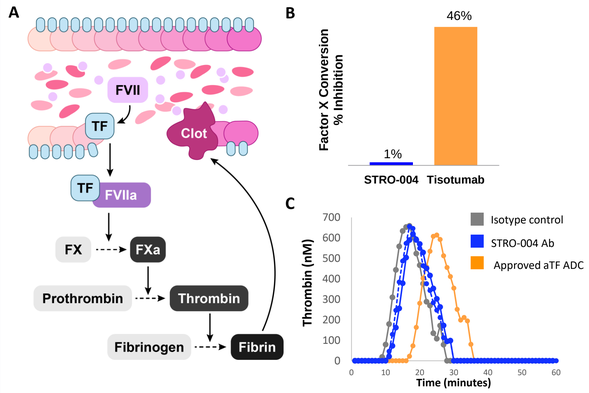
STRO-004 DAR8 Exatecan Payload ADC Designed for Enhanced Stability, Potency, and Tumor Selectivity

1. Anti-TF IgG with site-specific conjugation
2. Potent exatecan payload
3. Tumor-specific b-glu release
4. Improved hydrophilicity for PK

STRO-004 is a TF-targeted ADC, designed for optimal PK with stable drug linker, potent anti-tumor activity and reduced toxicity to ensure a wider therapeutic index.

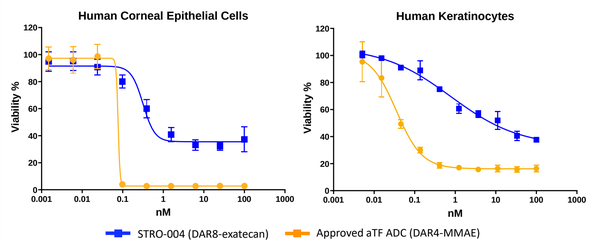


STRO-004 Antibody Does Not Interfere with Coagulation



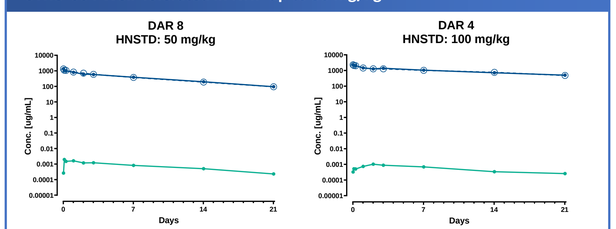
(A) Upon injury, Tissue Factor (TF) combines with circulating coagulation factors to initiate a coagulation cascade. Coagulation factors (like Factor X and prothrombin) are converted to activated enzymatic forms via cleavage of pro-polypeptide sequences. (B) STRO-004 antibody does not inhibit factor X conversion to Factor Xa compared to a clinical benchmark, Tisotumab. (C) Thrombin generation was measured over time in a thrombin generation assay. STRO-004 antibody and an isotype control had a similar rate of thrombin generation whereas a clinical benchmark antibody caused a delay in thrombin conversion.

STRO-004 Lowers Toxicities vs Approved aTF ADC



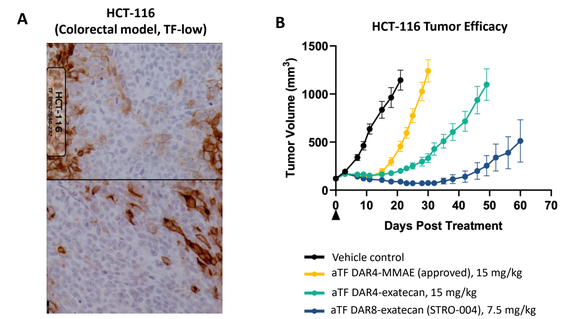
Tissue Factor is expressed in the eye and the skin, which may lead to on-target toxicity by TF ADCs. Primary human corneal epithelial cells and keratinocytes were used to assess the potential on-target toxicity of TF ADCs *in vitro*. In both assays, STRO-004 show significantly less cytotoxicity than a clinically approved benchmark (anti-TF DAR4-MMAE).

STRO-004 Well-Tolerated in NHP up to 50 mg/kg



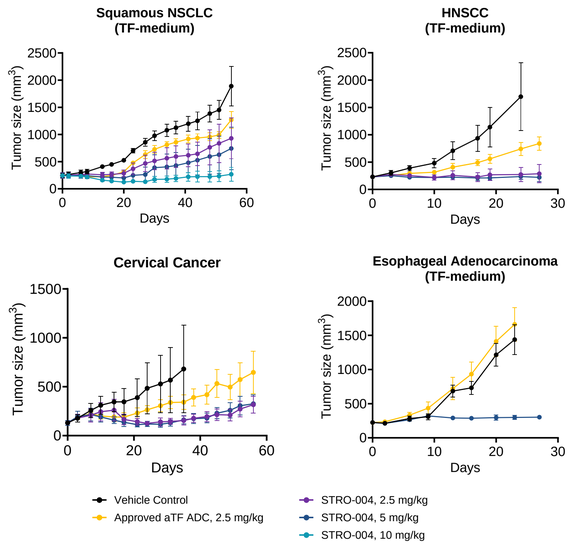
Exploratory toxicology studies in nonhuman primates show that STRO-004 has a favorable PK profile and was well tolerated up to 50 mg/kg, the highest dose tested. Study: Animals were dosed twice, three weeks apart, with either 25 or 50 mg/kg of STRO-004 (DAR8-exatecan) or with 50 or 100 mg/kg of an anti-TF DAR4-exatecan ADC and monitored over a six-week period. Findings: both test articles were well-tolerated with no evidence of eye toxicity and only mild signs of skin toxicity. Signs of myelosuppression, like neutropenia or lymphopenia, were not observed.

Selected DAR8 ADC Delivers More Payload to Low-TF Expressing Tumors Corresponding to Greater Anti-Tumor Response



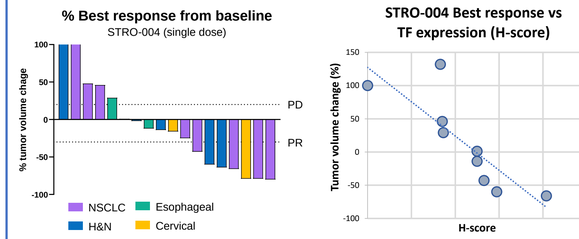
STRO-004 DAR8-ADC delivers more payload to low TF-expressing tumors compared to DAR4-ADCs at payload-matched doses. (A) Representative image of TF staining (brown) with hematoxylin counterstaining (blue) in HCT. HCT-116 tumors show heterogeneous membranous staining (0 to 3+) with the majority of the tumor showing minimal to no TF expression. (B) Tumor growth curves of HCT-116 tumors following treatment with STRO-004 DAR8-exatecan ADC (blue), anti-TF DAR4-exatecan ADC (green), TF MMAE (approved benchmark, yellow).

STRO-004 is Efficacious in PDX Models of NSCLC, Head and Neck Cancer, Cervical and Esophageal Cancers



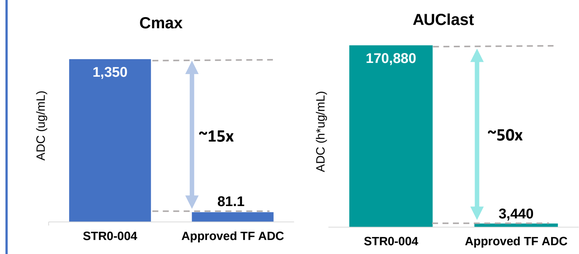
STRO-004 demonstrates long lasting anti-tumor activity in PDX models of esophageal carcinoma, NSCLC, and head and neck cancer. Tumor growth curves of STRO-004 DAR8-exatecan ADC (blue) and TF MMAE (approved benchmark, yellow)-treated PDX models of cervical carcinoma, esophageal adenocarcinoma, NSCLC squamous cell carcinoma, and HNSCC.

STRO-004 Shows Promising Anti-tumor Activity In TF Positive PDX Models of HNSCC, NSCLC, Cervical and Esophageal Cancer



STRO-004 induces an overall response rate of 39% and a disease control rate of 72% across PDX models of cervical cancer, NSCLC, esophageal cancer, and head and neck cancer. Best response from each PDX model is plotted as the greatest reduction in tumor volume observed (percent tumor volume change from start of treatment at time t ≥ d10). Models are sorted by increasing response to STRO-004. Response criteria were adapted from RECIST clinical criteria; Partial Response (PR): best response of <-30%, Progressive Disease (PD): best response > 20%. Correlation of best response based on tumor volume change (%) to TF expression (H score) determined by IHC of vehicle treated tumors.

STRO-004 Widens the Therapeutic Window Compared to First Generation TF ADCs



Metrics of drug exposure (Cmax or AUClast) at the HNSTD in NHPs were plotted for STRO-004 (HNSTD 50 mg/kg) compared to an approved TF ADC benchmark (HNSTD 3 mg/kg).

Key Findings

- STRO-004 is a TF-targeted ADC, engineered for a wider therapeutic index with reduced bleeding risk, stable drug-linker and ADC construction, and potent preclinical anti-tumor activity.
- In preclinical xenograft models, STRO-004 demonstrates potent, dose-dependent activity from 0.25-10 mg/kg, including in models with low and heterogeneous levels of TF expression.
- STRO-004 was evaluated in patient-derived xenograft (PDx) models of cancers with prevalent TF expression and demonstrated 50% overall response rate and 70% disease control rate across all models after single dose treatment.
- Exploratory toxicology studies show that STRO-004 has a favorable safety profile in cynomolgus monkeys up to 50 mg/kg, the highest dose tested.
- In circulation, STRO-004 demonstrated extended half-life, low clearance, and stable drug-linkage. Consistent with this finding, only low levels of free exatecan could be detected.
- Based on these promising preclinical observations, STRO-004 is advancing to IND enabling studies for the treatment of TF expressing malignancies.