Background Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a cell-surface, oncofetal protein whose expression is correlated with oncogenic properties such as enhanced proliferation, survival, and chemoresistance. Despite its prevalence across many cancer indications, ROR1 has restricted expression in adult tissues, making it an ideal target for targeted therapies.

Methods We have designed a novel ROR1-targeted ADC, STRO-003, which is composed of an anti-ROR1 human IgG1 antibody (SP11285) conjugated to an exatecan warhead via a stable, β-glucuronide linker (SC3417) with a drug-to-antibody ratio (DAR) of 8. SP11285 was discovered using Fab ribosome display as a selective and high affinity ROR1 antibody that exhibits favorable internalization activity upon cell binding, consistent with an ADC mechanism of action. The exatecan payload is a potent topoisomerase I inhibitor of the camptothecin class and has anti-proliferative activity against a variety of cancer cell lines in vitro. The SC3417 linker-payload releases exatecan upon glucuronidase linker cleavage and is site-specifically conjugated using strain promoted alkyne-azide cycloaddition (SPAAC) to form a stable, homogeneous ADC.

Results The anti-Ror1 antibody SP11285 binds with high affinity to the ROR1 immunoglobulin domain and is cross-reactive to both rodent and monkey ROR1. Unlike other camptothecin analogs, exatecan is resistant to overexpression of Pgp, and therefore has reduced risk of multi-drug resistance. Exatecan also induces immunogenic cell death, thereby providing an avenue for engaging the immune system and enriching the anti-tumor response. STRO-003 has exhibited potent and specific activity in xenograft models for TNBC and lung cancer, and importantly, elicited significant anti-tumor suppression in a panel of NSCLC PDx models, including those with low ROR1 expression. In nonclinical safety studies conducted in cynomolgus monkeys, STRO-003 was tolerated up to 45 mg/kg without signs of hematological toxicity or tissue-specific lesions. By comparison, a similar exatecan-ADC with a cathepsin-sensitive linker was more poorly tolerated and elicited signs of inflammation in the lung.

Conclusions Our data suggests that STRO-003 is a promising clinical candidate for solid tumor indications and we have initiated IND-enabling studies.

Ethics Approval All in vivo procedures were conducted in compliance with the guidelines of the Institutional Animal Care and Use Committee (IACUC) at Sutro Biopharma or commissioned contract research organization (CRO).