Background} Trodelvy® (sacituzumab govitecan-hziy, SG) is approved as second-line therapy for patients with locally advanced or metastatic bladder cancers (BC). SG is a TROP-2-directed ADC that delivers an active metabolite of irinotecan (SN-38) to tumors. SG binds to Trophoblast cell-surface antigen 2 (TROP-2), a cell-surface glycoprotein overexpressed in various solid tumors, including non-muscle invasive bladder cancers (NMIBC), and is also expressed in normal epithelial bladder cells. SG cytotoxic payload, SN-38, forms a ternary complex with Topoisomerase 1 (TOP1)-DNA complex. Most BC are diagnosed as NMIBC and treatment options remain limited for BCG-unresponsive patients with high-risk papillary tumors or with carcinoma in-situ. We hypothesize that local instillation of SG could offer an alternative to radical cystectomy for the treatment of high-risk NMIBC patients.

Methods} Human TROP-2 expression was evaluated in cell lines by flow cytometry and in a bladder cancer tissue panel by IHC and compared to TROP-2 quantification by LC-MS/MS. Normal cynomolgus monkey bladder tissue was similarly analyzed. Human TOP1 RNA expression was quantified and compared across TCGA normal, tumor-adjacent, and tumor tissue panels. SG toxicity for normal epithelial bladder cells and tumor cells was assessed after pulse exposure for apoptosis (annexin V) and DNA damage (p-gH2AX). SN-38 release from SG in human and monkey urine was determined under various pH conditions. Following two (once weekly) bladder instillations of SG to cynomolgus monkeys, urine cytology and histopathology of uroepithelial tissues were assessed, along with urine and plasma SG exposures.

Results} TROP-2 protein detection (IHC) and quantification (LC-MS/MS) were consistent across human bladder cell lines, and human and monkey normal bladder tissues. TROP-2 distribution was differentially localized in normal bladder compared to tumor tissues. TOP1 RNA expression was upregulated in various TCGA tumors compared with normal tissues, consistent with increased SG sensitivity of bladder cancer cell lines compared to normal epithelial bladder cells. Minimal increases in free SN-38 levels in human or monkey urine following 1-hour incubation under physiological conditions with SG were noted. SG was well-tolerated in monkeys with no in-life or histopathological changes following two weekly instillations of 1 hour each, and SG and SN-38 plasma exposures were minimal.

Conclusions} Overall, in vitro and in vivo data suggest that SG intravesicular instillation may provide a favorable safety risk benefit for high-risk NMIBC patients. SG instillation in naïve monkey bladder showed no toxicity at a localized exposure margin of approximately 2.5-fold higher than the projected efficacious dose for NMIBC patients.

Ethics Approval} All animal experiments were approved by the Institutional Animal Care and Use Committee of Gilead Sciences Inc. and carried out by certified staff in an Association for Assessment and Accreditation of Laboratory Animal Care International (AAALACi) accredited facility, in compliance with the institution’s Guide for the Care and Use of Laboratory Animals and applicable laws (including the Animal Welfare Act of 1966 and, if applicable, the California Laboratory Animal Use Approval Program).