Th42 - Next-generation Immunostimulatory Antibody-drug Conjugate (iADC) Combines Direct Tumor Killing and Innate Immune Stimulation to Provide Protective Anti-Tumor Immunity

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Abstract Text: In recent years, combination therapies of antibody-drug conjugates (ADCs) and immune system activators have garnered much interest due to their potential to unlock greater durable clinical benefit. Recently, we demonstrated that STRO-002, our novel anti-folate receptor alpha (FolRα) ADC currently in Phase I clinical trials, can engage the immune system through induction of immunogenic cell death (ICD). We further showed that by complementing the ICD-inducing property of STRO-002 with combination treatment with Avelumab, we could enhance infiltration of CD8+ T cells into the tumor and generate potent anti-tumor immunity. To develop the combination concept further, we leveraged Sutro's breakthrough XpressCF+TM cell-free technology, which utilizes precise site-specific conjugation to generate complex molecules, to engineer the immunostimulatory ADC (iADC), a next-generation ADC molecule that combines tumor-targeted cell killing and immune activation in a single modality. Using murine MC38 tumors engineered to express human FolRα, we demonstrated that delivery of a hemiasterlin/TLR agonist dual-conjugate anti-FolRα iADC resulted in a more robust anti-tumor response compared to either modality administered alone. This improved response was associated with innate immune cell activation and increased CD8+ T cell infiltration in the tumor. Moreover, a greater number of complete responses was also observed following treatment with the anti-FolRα iADC, and complete responders developed broad and robust immune memory that was able to reject MC38-hFolRα rechallenge in a CD8+ T cell-dependent manner and parental MC38 rechallenge. Thus, the iADC concept unites two complementary mechanisms of tumor control in a single molecule to attain greater therapeutic benefit.