GQ1001 is a next generation HER2-targeting ADC with excellent druggability, safety and potency

**Abstract**

GQ1001 was developed to overcome the intrinsic limitations of existing HER2 ADCs by the next generation approach with improved druggability. A new linker-decoupled conjugation technology (LiDCT) technology; LiDCT provides a robust platform for the generation of ADC with high homogeneity and robust linker stability. Our data show that GQ1001 is highly homogeneous with strong anti-tumor potency, more importantly, markedly enhanced linker stability and reduced off-target toxicity, and points to a safer HER2 ADC platform than previously developed molecular conjugates.

**Methods**

Its in vivo anti-cancer efficacy and the mechanism of action (MOA) of GQ1001 were assessed using several HER2+ cancer cell lines and animal models. In vivo linker stability was assessed by incubating GQ1001 with cell-free plasma. Pharmacokinetics in cynomolgus monkeys and safety profiles in rats and monkeys were evaluated.

GQ1001 was generated by conjugating trastuzumab to DM1 via an unique coupling method involving linker and the LiDCT conjugation technology that significantly increased the stability of GQ1001. Typical physical-chemical property of GQ1001 was demonstrated from the long-term stability study in liquid formulation. Stability data in human plasma and PBMCs against catalase activity in GQ1001 is HER2+ tumor cell lines. Moreover, DM1 showed significant non-specific toxicity in HER2- cells while GQ1001 didn't. In animal models, GQ1001 induced a robust dose dependent tumor growth inhibition in multiple HER2+ positive tumors (semi) and PDX models. From the combined treatment studies, GQ1001 showed synergistic anti-tumor response when combined with HER2 targeting kinase inhibitors (TKIs) and chemotherapeutic agents in multiple HER2+ positive models, including those resistant or over-express HER2 TKIs and/or mutants. In vivo tumor stability assay, the DM1-stabilized GQ1001 in vitro anti-tumor activity in a TKI-sensitive (D) and TKI-resistant (C) HER2+ tumor models. GQ1001 demonstrated superior tumor volume inhibition profile in both TKI-resistant positive or TKI-sensitiv tumor models in a global, open-label multicenter phase I study (Saito et al., 2017).

**Results**

GQ1001 is a unique HER2-targeting ADC that exhibits markedly enhanced linker stability and safety profiles. From preclinical data, GQ1001 demonstrated the potential to treat HER2-positive carcinoma patients, alone or in combination, with improved expression of HER2-targeting biomarkers and drug resistance.

**Discussion**

High homogeneity based on LiDCT site-specific conjugation platform. Minimal free payload release based on highly stable linker. The only HER2 targeting ADC with the potential to be developed into a liquid formulation. Robust anti-tumor efficacy in diverse cancer types as a monotherapy. Significant synergistic anti-cancer activity when combined with TKI or chemotherapies. Excellent efficacy confirmed in NHP GLP study with HNSDT as 45 mg kg⁻¹.

**Summary**

**Figure 1.** Superior safety in HER2 negative cells.