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

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Abstract

Background

GQ1001 was developed to overcome the current limitation of existing HER2 ADCs by using the next generation site-specific conjugation and a stable linker technology, coined **the intelligent ligase-dependent conjugation (iLDC) technology**. iLDC provides a robust platform for the generation of ADC with high homogeneity and excellent 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 with a larger therapeutic window in human.

Methods

In vitro and *in vivo* anticancer efficacy and the mechanism of action (MOA) of GQ1001 were assessed using several HER2+ cancer cell lines and animal models. Ex vivo linker stability was assessed by incubating GQ1001 with the plasma from different species. Pharmacokinetics in cynomolgus monkeys and safety profiles in rats and monkeys were evaluated.

Results

GQ1001 was generated by conjugating trastuzumab to DM1 via an unique open-ring containing linker and the enzymatic site-specific conjugation technology that significantly increases the stability of GQ1001. Optimal physiochemical property of GQ1001 was demonstrated from the long-term stability study in liquid formulation. GQ1001 demonstrated similar *in vitro* anti-cancer activities to T-DM1 in HER2+ tumor cells. However, T-DM1 showed significant non-specific cytotoxicity in HER2- cells while GQ1001 didn't. In animal studies, GQ1001 induced a robust dose-dependent tumor growth inhibition in multiple HER2-positive CDX and PDX models. From the combo treatment studies, GQ1001 showed synergistic anti-tumor response when combined with HER2-targeting tyrosine kinase inhibitors (TKIs) and chemotherapeutic agents in multiple HER2-positive models, including those resistant to anti-HER2 TKIs and/or mAbs. In ex vivo plasma stability assay, the DM1-shedding ratio of GQ1001 in human plasma was ~1/100th of that of T-DM1. This excellent linker stability was confirmed by the favorable pharmacokinetics in monkey with extremely low free DM1 exposure in circulation at a significantly lower level than T-DM1. The highest non-severely toxic dose (HNSTD) of GQ1001 in monkey was 45 mg/kg without any signs of peripheral neuropathy and interstitial lung disease, suggesting GQ1001 will demonstrate excellent tolerance in human. Consistent with this preclinical data, GQ1001 demonstrated superior tolerability profile in heavily pretreated HER2-positive advanced solid tumors patients in a global, open labeled multicenter phase Ia trial (Details were shown in abstract CT178).

Conclusion

GQ1001 is a unique HER2-targeting ADC that exhibits markedly-enhanced linker stability and safety profiles. Judging from preclinical data, GQ1001 demonstrates the potential to treat HER2-positive cancer patients, alone or in combination, who have progressed on previous HER2-targeting therapeutics with reduced toxicity.

Chemical structure, catabolism, and characterization

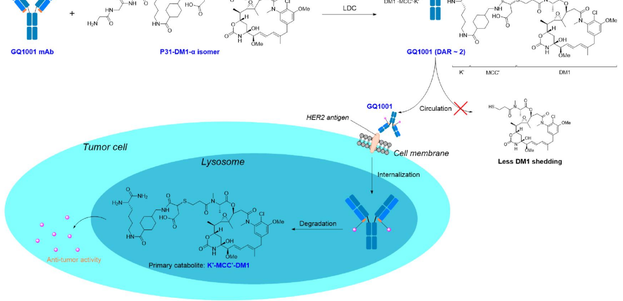

Figure 1. Design, production, and catabolism pathway of GQ1001. For overall design, the humanized anti-HER2 mAb (engineered trastuzumab) is connected with the cytotoxic payload DM1, via a uniquely-designed stable non-cleavable linker. The linker-payload internally named as P31-DM1-α is a key component of GQ1001, and its core structure, C-terminal-amidated K-MCC'-DM1, mimics T-DM1's linker-payload, but has undergone ring-opening modification, which further enhances its stability. After reaching the lysosome, GQ1001 is completely degraded and release the active ingredient K'-MCC'-DM1, thereby killing tumor cells.

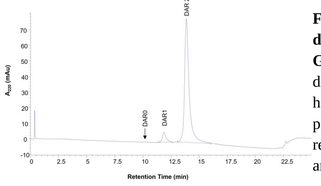

Figure 2. Drug-to-antibody ratio (DAR) distribution characterization by HIC of GQ1001. HIC analysis showed that drug distribution of GQ1001 was highly homogeneous, and that DAR1 and DAR2 peaks accounted for about 10% and 90%, respectively, with almost no unconjugated antibodies detected.

Stability of GQ1001 in liquid

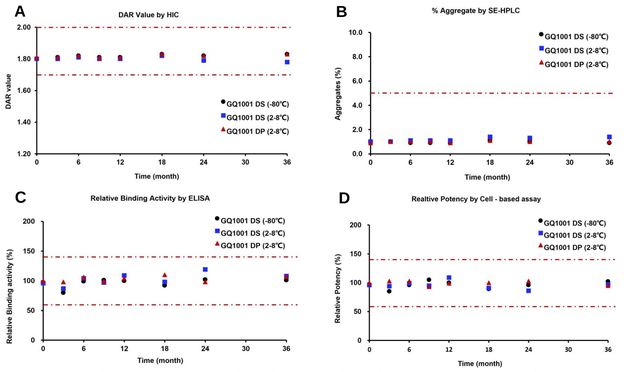

Figure 3. Stability of GQ1001 in liquid. Temporal trends of (A) drug-to-antibody ratio (DAR), (B) aggregates, (C) binding activity and (D) biological activity of GQ1001 were monitored in liquid at 2-8℃ for 36 months. The excellent stability of GQ1001 in solution allows it to be developed into liquid formulation for commercial use, which may simplify manufacturing processes, reduce costs, and increase convenience of clinical use.

Mechanisms of action and *in vitro* activity

Figure 4. Mechanisms of action and *in vitro* activity. GQ1001 demonstrated similar mechanisms as T-DM1 in HER2+ tumor cells such as binding (A), internalization (B), ADCC (C), and apoptosis (D). GQ1010 exhibited robust *in vitro* cytotoxicity in diverse cells including HCC1954 (E) and SK-BR-3 (F)

Superior safety in HER2 negative cells

Figure 5. Superior safety in HER2 negative cells. Up to 100 nM, GQ1001 had no significant effect on cytotoxicity (A) or apoptosis (B) against HER2-negative cells *in vitro*, as opposed to T-DM1 which showed significant non-specific *in vitro* cytotoxicity. This indicates GQ1001 is safer than T-DM1.

Dose-dependent *in vivo* anti-tumor efficacy

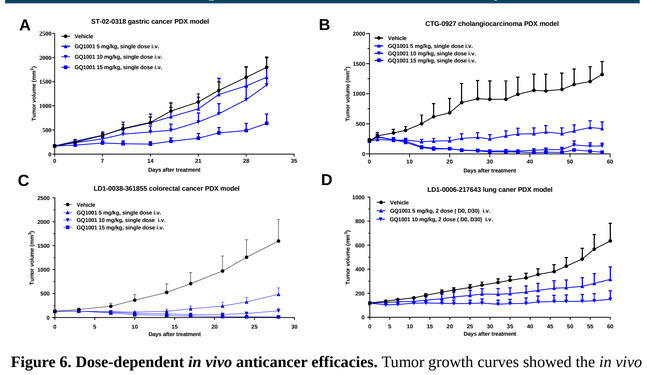

Figure 6. Dose-dependent *in vivo* anticancer efficacies. Tumor growth curves showed the *in vivo* anticancer efficacy of different concentrations of GQ1001 in HER2-positive human cancer PDX tumor models. GQ1001 demonstrates robust, dose-dependent anti-tumor efficacy in diverse PDX models.

Synergistic anti-tumor activity of GQ1001 with HER2-targeting TKIs

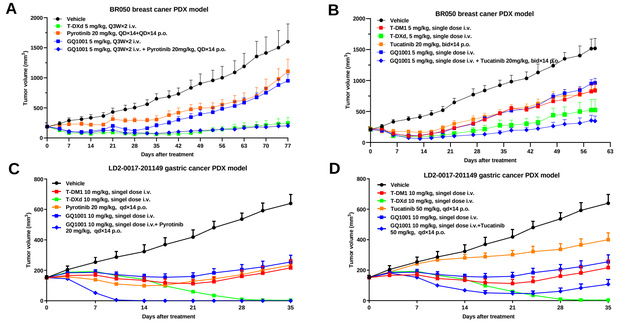

Figure 7. *In vivo* efficacies of GQ1001 combined with HER2-targeting tyrosine kinase inhibitors (TKIs). GQ1001 combined with tucatinib and pyrotinib demonstrates synergistical anti-tumor activity in breast cancer PDX model BR050 (A-B) and gastric cancer PDX modelLD2-0017-201149 (C-D), similar or superior to T-DXd.

Synergistic anti-tumor activity of GQ1001 with chemotherapy

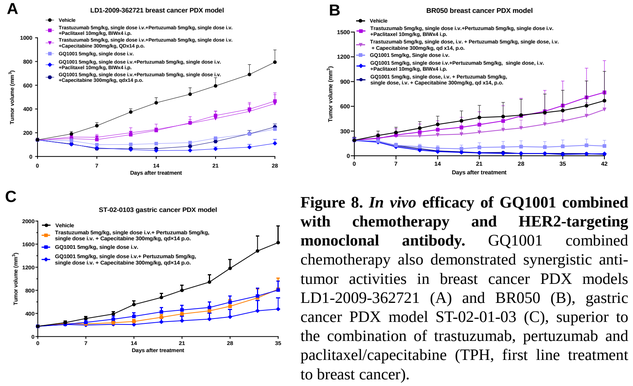

Figure 8. *In vivo* efficacy of GQ1001 combined with chemotherapy and HER2-targeting monoclonal antibody. GQ1001 combined chemotherapy also demonstrated synergistic anti-tumor activities in breast cancer PDX models LD1-2009-362721 (A) and BR050 (B), gastric cancer PDX model ST-02-01-03 (C), superior to the combination of trastuzumab, pertuzumab and paclitaxel/capecitabine (TPH, first line treatment to breast cancer).

Excellent linker stability confirmed by favorable pharmacokinetics

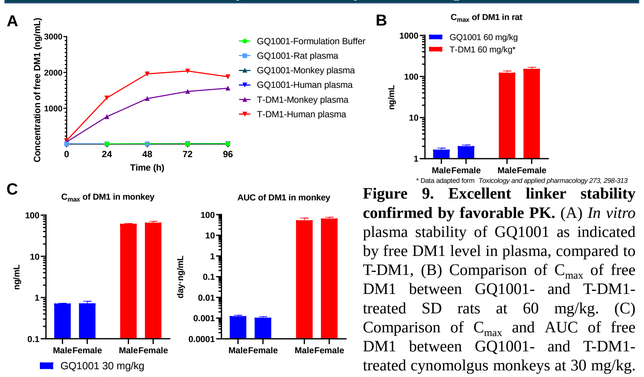

Figure 9. Excellent linker stability confirmed by favorable PK. (A) *In vitro* plasma stability of GQ1001 as indicated by free DM1 level in plasma, compared to T-DM1, (B) Comparison of C_{max} of free DM1 between GQ1001- and T-DM1-treated SD rats at 60 mg/kg. (C) Comparison of C_{max} and AUC of free DM1 between GQ1001- and T-DM1-treated cynomolgus monkeys at 30 mg/kg. The data demonstrates excellent linker stability for GQ1001.

GQ1001 shows excellent safety in NHP

Period	Organ	Histopathological finding	GQ1001 45 mg/kg (HNSTD)		T-DM1* 10 mg/kg (HNSTD)	
			Male	Female	Male	Female
Dosing period	Spinal cord	Axonal degeneration of dorsal funiculus	-	-	3/3	-
	Sciatic nerve	Axonal degeneration	-	-	2/3	1/3
	Lungs	Infiltrate of mononuclear cells in interstitium	-	-	1/3	1/3
	Kidney	Infiltrate of mononuclear cells	-	-	2/3	1/3
		Mitoses/arrested metaphase of tubular epithelial cells	-	-	1/3	-
	Liver	Hypertrophy of Kupffer cells	2/3	3/3	3/3	3/3
		Increased mitotic figure/mitoses/arrested metaphase	3/3	3/3	3/3	3/3
		Increased sinusoidal leukocytes	-	-	3/3	1/3
	Thymus	Lymphoid depletion	-	-	2/3	3/3
Recovery period	Spinal cord	Axonal degeneration, dorsal funiculus	-	-	1/2	1/2
	Sciatic nerve	Axonal degeneration	-	-	1/2	1/2
	Liver	Microgranuloma(s)	-	-	-	2/2

* Data adapted from FDA, Center for drug evaluation and research, Application number: 125427Orig1s000, Pharmacology Review(S)

Toxicity spectrum of GQ1001 was narrower and significantly milder than that of T-DM1. Nerve system toxicity was consistently observed after T-DM1 treatment leading to high level DM1 release in circulation, while such toxicity was not observed in any of the GQ1001 studies.

Summary

- High homogeneity based on iLDC 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 anticancer activity when combined with TKI or chemotherapies.
- Excellent safety confirmed in NHP GLP study with HNSTD as 45 mg/kg.
- Superior tolerability profile over T-DM1 and robust clinical efficacy demonstrated in early phase 1 study (Details shown in abstract CT178).