#CT178

GQ1001: a next generation HER2-targeting ADC that exhibits promising early clinical efficacy, excellent safety and tolerability in a multi-center, phase Ia study

Charlotte Lemech[1], Chenfei Zhou[2], Xianbao Zhan[3], Yan Shi[2], Jieqiong Liu[4], Sarina A. Piha-Paul[5], Gary Richardson[6], Gang Qin[7], Paul Song[7], Lili Shi[7], Yajun Sun[7], Yi Xia[7]

[1]. Scientia Clinical Research Ltd; [2]. Ruijin Hospital; [3]. Changhai Hospital; [4]. Sun Yat Sen Hospital; [5]. MD Anderson; [6]. Cabrini; [7]. GeneQuantum Healthcare (Suzhou) Co., Ltd.;

GeneQuantum Healthcare 启 德 医 药

Abstract

Background: GQ1001 is a novel HER2-targeted antibody-drug conjugate (ADC) that was developed using innovative conjugation technologies known as intelligent Ligase-Dependent Conjugation (iLDC), which significantly improves homogeneity and stability of ADC. In preclinical studies, GQ1001 showed a robust anti-tumor activities in multiple HER2+ models alone or in combination with HER2 TKIs and chemotherapeutics, and excellent pharmacokinetics and safety profiles in rats and monkeys due to superior linker stability (**see abstract 2702**).

Methods: In phase Ia dose escalation, a modified 3+3 model was used to guide dose escalation and determine the maximal tolerable dose (MTD) or dose recommended for dose expansion (DRDE) of GQ1001. GQ1001 was administered intravenously as a monotherapy on Day 1 of 21-day cycles. The starting dose was 1.2 mg/kg, followed by subsequent doses of 2.4, 3.6, 4.8, 6.0, 7.2 and 8.4 mg/kg.

Results: As of Dec. 28th, 2022, 32 subjects with HER2-positive advanced solid tumors, predominantly in breast (9), gastric or gastro-esophageal junction (9) and salivary gland (4), were enrolled and received GQ1001 treatment. Patients had a median 3 (range, 0-11) prior lines of therapies, and 37.5% of those previously received ≥2 lines of anti-HER2 therapies. Median exposure time of GQ1001 was 18.5 weeks. The longest treatment duration exceeded 370 days. No DLT was observed in all doses, MTD was not reached up to 8.4 mg/kg, the highest dose tested. Treatment-related adverse events (TRAEs) occurred in 24 subjects (75%). The most common TRAEs (>10.0%) were aspartate aminotransferase (AST) increased (37.5%), thrombocytopenia (28.1%), alanine aminotransferase (ALT) increased (25.0%), pyrexia (21.9%), anemia (18.8%), alkaline phosphatase increased (12.5%), vomiting (12.5%) and nausea (12.5%). Grade ≥3 TRAEs occurred in 9 subjects (28.1%), including 5 myelosuppression, 2 abnormal liver function, 1 hypertension and 1 vomiting. There were no drug-related deaths. The pharmacokinetics analysis showed the concentration of GQ1001 and TAb generally peaked rapidly and declined in a roughly biphasic manner. Among 15 evaluable subjects who received ≥ 7.2 mg/kg, 6 cases achieved confirmed partial response, and 3 had stable disease, the median progression-free survival was 4.8 months.

Conclusions: GQ1001 demonstrates an excellent tolerability and promising antitumor activity in heavily pretreated HER2-positive advanced solid tumors, supporting further evaluation of the safety and efficacy of GQ1001 at DRDE of 8.4 mg/kg in the following phase Ib trial.

Study Design

Primary Outcome Measure:

- Dose Limiting Toxicities (DLTs)
- MTD or DRDE

Secondary Outcome Measures:

- Safety and Tolerability (AEs and pts with abnormal lab values)
- PK Parameters (AUC, C_{max}, T_{max}, $T_{1/2}$, MRT, V_d)
- Immunogenicity
- Preliminary Efficacy (ORR, DCR, DoR, PFS)

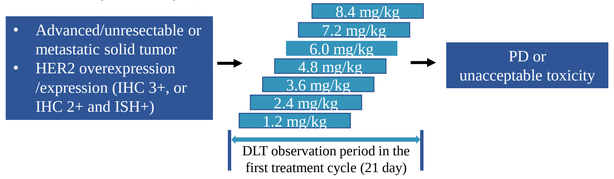


Figure 1. General Study Design.

Patient Characteristics

- As of Dec. 28th, 2022, 32 subjects with HER2-positive advanced solid tumors, predominantly in breast (9), gastric or gastro-esophageal junction (9) and salivary gland (4), were enrolled and received at least one dose of GQ1001 treatment.
- Patients had a **median 3 (range, 0-11) prior lines of therapies**, and 37.5% of those previously received ≥2 lines of anti-HER2 therapies.

Table 1. Demographics and Baseline Characteristics

Characteristics	Total (N=32)
Age (years)	
Median	58.0
Mean (SD)	58.3 (8.48)
Gender (n,%)	
Male	18 (56.3%)
Female	14 (43.8%)
Race (n,%)	
White	16 (50.0%)
Asian	16 (50.0%)
Tumor type (n,%)	
Breast	9 (28.1%)
Gastric or gastro-esophageal junction	9 (28.1%)
Salivary gland	4 (12.5%)
Prior system therapy	
Median	3
Min, Max	0, 11
Prior ≥2 lines of anti-HER2 therapies (n, %)	12 (37.5%)

Drug Exposure

- Median exposure time of GQ1001 was **18.5 weeks**. The longest treatment duration exceeded **370 days**.
- Intra-patient dose escalation was permitted after 3 cycles of treatment in low doses, 2 subjects in 2.4 mg/kg and 1 in 3.6 mg/kg elevated one dose level.
- One subject who received dose of 7.2 mg/kg had the dose reduced to 6.0 mg/kg due to AE.

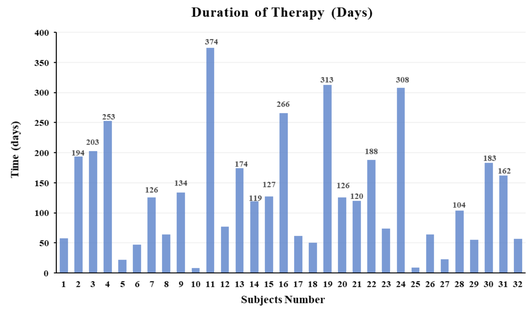


Figure 2. Duration of Therapy (Days).

Clinical Safety

- No DLT was observed in all doses, MTD was not reached up to 8.4 mg/kg, the highest dose tested.
- Treatment-related adverse events (TRAEs) occurred in 24 subjects (75%).
- **Grade≥3 TRAEs occurred in 9 subjects (28.1%),** including 5 myelosuppression, 2 abnormal liver function, 1 hypertension and 1 vomiting.
- There was no drug-related death.
- The same safety profile was observed in the dose of 8.4 mg/kg, with most common TRAEs as aspartate aminotransferase increased, alanine aminotransferase increased and platelet count decreased.

Table 2. Summary of Study Drug Related TEAEs by PT

All Study Drug Related TEAEs	Total (N=32) (n, %)
	24 (75.0%)
Aspartate aminotransferase increased	12 (37.5%)
Platelet count decreased	9 (28.1%)
Alanine aminotransferase increased	8 (25.0%)
Pyrexia	7 (21.9%)
Anemia	6 (18.8%)
Blood alkaline phosphatase increased	4 (12.5%)
Vomiting	4 (12.5%)
Nausea	4 (12.5%)
Blood cholesterol increased	3 (9.4%)
Chills	3 (9.4%)
Infusion related reaction	3 (9.4%)

Pharmacokinetics Analysis

- The pharmacokinetics analysis showed the concentration of GQ1001 generally peaked rapidly and declined in a roughly biphasic manner.
- The exposure of GQ1001 (C_{max} and AUC) increased in an approximate dose-proportional manner in the dose range of 1.2 mg/kg to 8.4 mg/kg.
- The extremely low exposure of free DM1 released by GQ1001 in blood circulation indicates the toxicity and side effects would be greatly reduced.

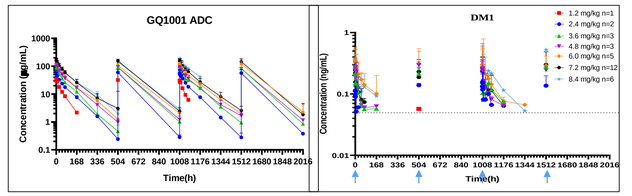
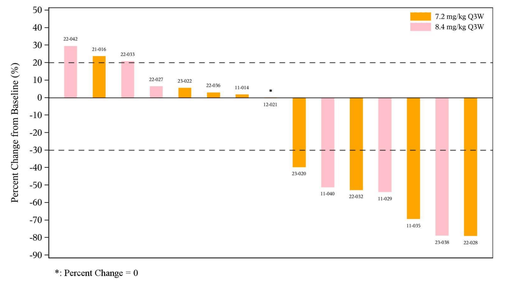


Figure 3. Pharmacokinetics of GQ1001 ADC (left) and DM1 (right).

Clinical Efficacy

- Among 15 evaluable subjects who received ≥ 7.2 mg/kg, 6 cases achieved confirmed partial response, 3 had stable disease (Figure 4).
- Among 27 evaluable heavily pre-treated subjects, the median progression-free survival (PFS) was 4.8 months (Cutoff date-Dec. 28th, 2022).



*: Percent Change = 0

Figure 4. Waterfall Graph of the Best Percentage Change from Baseline of Target Lesions in 7.2 and 8.4 mg/kg.

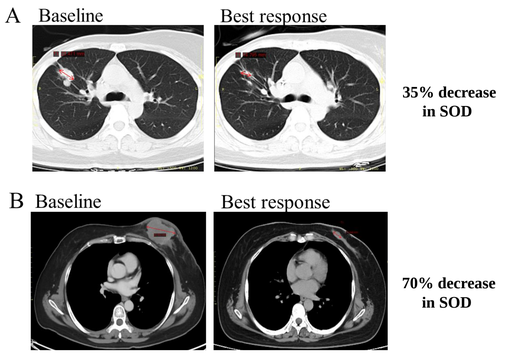


Figure 5. Representative CT Images of two BC subjects achieved a partial response (PR) with a best response of 35% (A) and nearly 70% (B) reduction in sum of diameters (SOD) , respectively.

Summary

- No DLT was observed in all explored doses from 1.2 mg/kg up to 8.4 mg/kg, MTD was not reach up to 8.4 mg/kg.
- The lower incidence of side effects compared to benchmark products suggests that GQ1001 has a better safety profile and an excellent tolerability.
- The pharmacokinetics analysis showed the concentration of GQ1001 generally peaked rapidly and declined in a roughly biphasic manner.
- GQ1001 demonstrates promising antitumor activity in heavily pretreated HER2-positive advanced solid tumors, supporting further evaluation of the safety and efficacy of GQ1001 at DRDE of 8.4 mg/kg in the following phase Ib trial (NCT04450732).