1157 GQ1007: THE NEXT GENERATION HER2-TARGETING ANTIBODY IMMUNE AGONIST CONJUGATE WITH ROBUST EFFICACY AND FAVORABLE SAFETY PROFILE

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Background Activation of professional antigen-presenting cells shows promise for overcoming limitations in PD1-based immunotherapy. Toll-like receptor 7/8 agonists have gained attention as potential partners for immune checkpoint inhibitors due to their potent APC activation. GQ1007 is a novel HER2 targeting immune agonist conjugate (AIAC) that was developed based on GeneQuantum's highly stable linker and enzymatic conjugation technologies. Through the fine tuning of TLR7/8 agonist potency and immune activation, here we report the unique attributes of GQ1007, demonstrating a favorable balance between efficacy and safety.

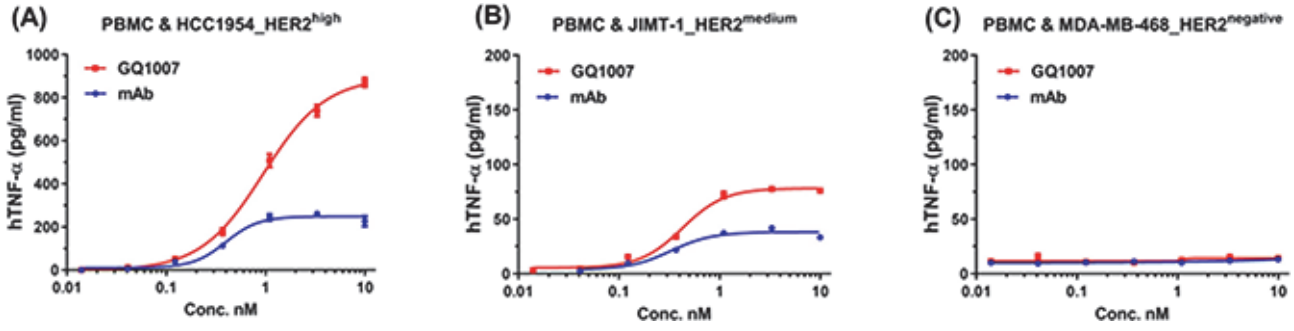
Methods We assessed *in vitro* immune activation and ADCP through PBMC/monocyte and tumor cell co-culture experiments. Non-specific release of proinflammatory cytokines was measured using a human whole blood assay, monitoring secretion of 13 different cytokines/chemokines. *In vivo* antitumor activity was evaluated in diverse mouse models. Serum cytokines secretion and TIL were analyzed in syngeneic model to understand the MOA. *Ex vivo* linker stability was determined using a sensitive LC-MS/MS method. The safety of GQ1007 was assessed in a toxicology study using cynomolgus monkeys.

Results GQ1007 selectively increased TNF-α secretion when co-cultured with HER2-positive cells, correlating with HER2 expression levels (figure 1). Treatment with GQ1007 enhanced phagocytosis specifically in HER2-positive cells, with no increase observed in HER2-negative cells (figure 2). GQ1007 demonstrated potent antitumor response in diverse HER2-expressing animal models (figure 3A). Combination therapy with GQ1007 and anti-mPD-1 showed improved efficacy compared to monotherapy (figure 3B). Tumor rechallenge experiments revealed immunological memory and epitope spreading in mice (figure 4). *In vivo* experiments demonstrated rapid tumor cell death, accompanied by infiltration of APCs and CD8+ T cells, and transient induction of key proinflammatory mediators (figures 5 and 6). Notably, compared to other clinical stage benchmark test articles, GQ1007 showed minimal cytokine induction in a whole blood assay, indicating a favorable safety profile (figure 7). No release of free agonist was observed in human plasma after 96 hours of incubation at 37°C, confirming the stability of GQ1007 (figure 8). The excellent safety profile of GQ1007 was further supported by the results of the GLP monkey toxicology study (table 1).

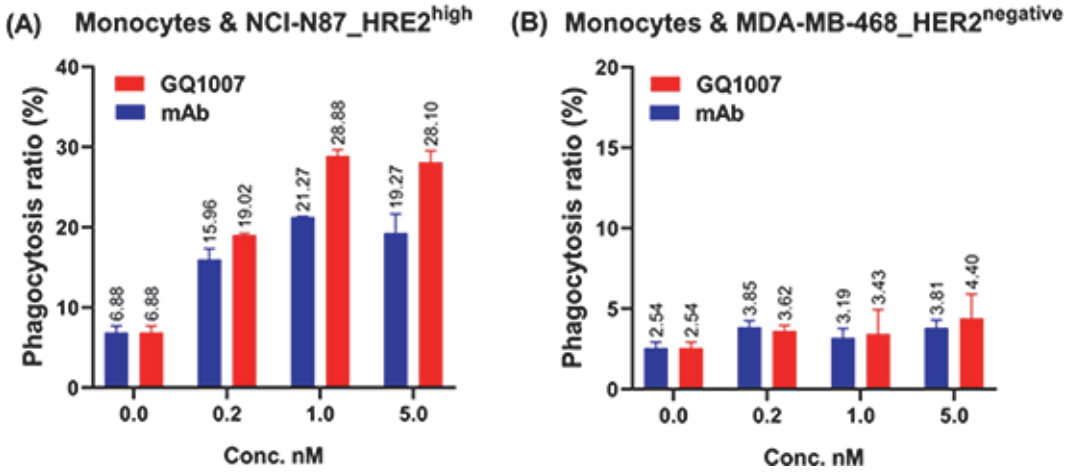
Conclusions GQ1007 demonstrates potent antitumor activities and robust tumor-specific immune activation. Importantly, our data strongly indicate a high potential for a favorable safety profile for GQ1007, highlighting its suitability for clinical exploration as a monotherapy or as a combination treatment with the existing ICI therapies. In conclusion, GQ1007 holds a great promise as a novel and effective treatment option for advanced HER2-expressing patients.

Abstract 1157 Table 1 Summary of repeat dose toxicity studies in monkey

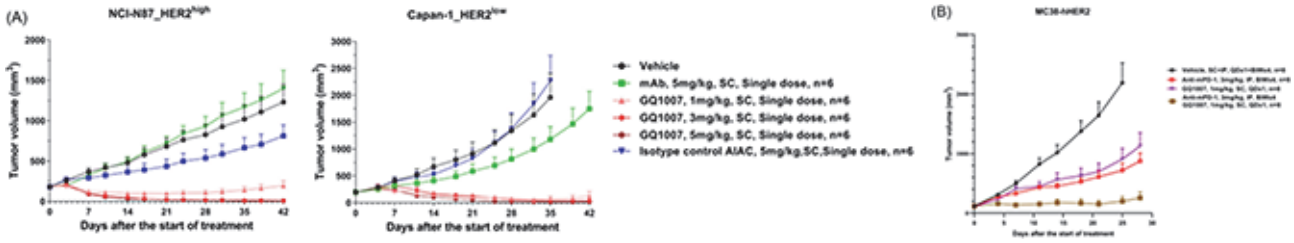
Species	Cynomolgus monkeys
Doses	0, 2, 6, 12 mg/kg
Regimens	IV injection, every 2 weeks; Days 1, 15, 29, 43 (4 times in total)
No. of animals	3 monkeys per sex for 0 and 12 mg/kg groups, 5 monkeys per sex for 2 and 6 mg/kg groups
Body weight	No GQ1007 related body weight change was noted
Hematology	≥ 2 mg/kg: Decreases in RBC, HGB, HCT and MCHC; Increases in PLT; ≥ 6 mg/kg: Decrease in WBC, Neut, and Lymph
Target organs and tissues	≥ 2 mg/kg: Colorectum and colon glands, thymus



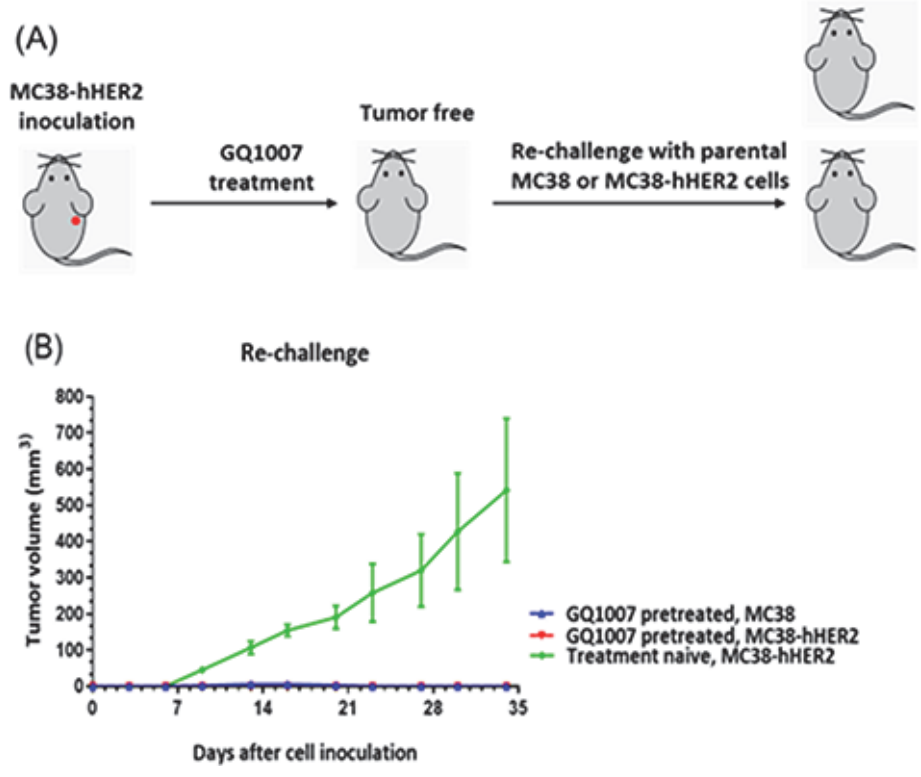
Abstract 1157 Figure 1 The induction of TNF-α release by GQ1007 is HER2 and dose-dependent. Human TNF-α secretion, serving as a marker of immune cell activation, was monitored in a co-culture experiment using PBMC and cancer cells with different levels of HER2 expression.



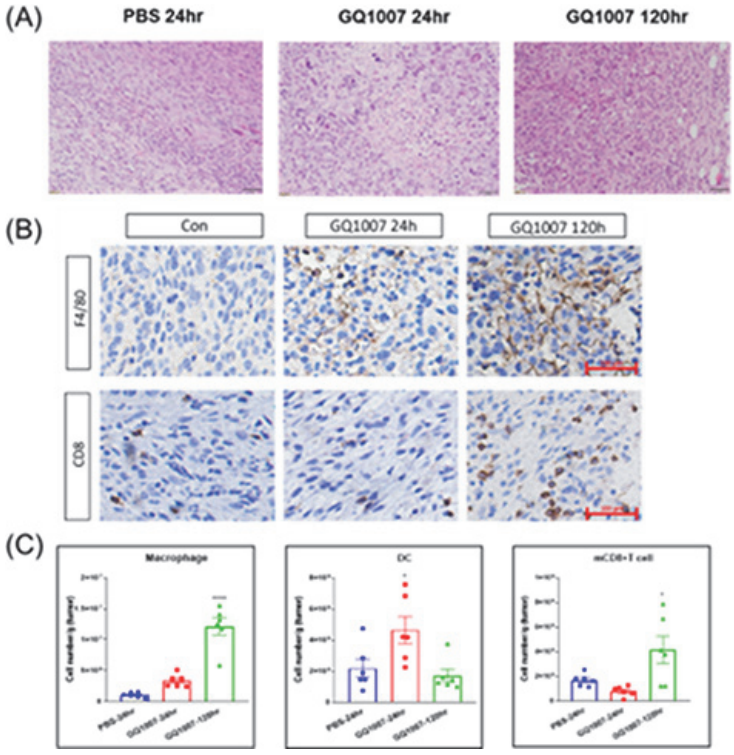
Abstract 1157 Figure 2 GQ1007 induces ADCP in a dose-dependent and HER2-dependent manner. CD14+ monocytes (effector cells) were isolated from fresh PBMCs and labelled with Cell Trace™ Far Red dye; and tumor cells (target cells) were labelled CFSE dye. The percentage of NCI-N87 and MDA-MB-468 cells that were engulfed by monocytes (double-positive cells) upon the treatment of GQ1007 and its parental antibody (mAb) were determined in a monocytes and tumor cells co-culture assay.



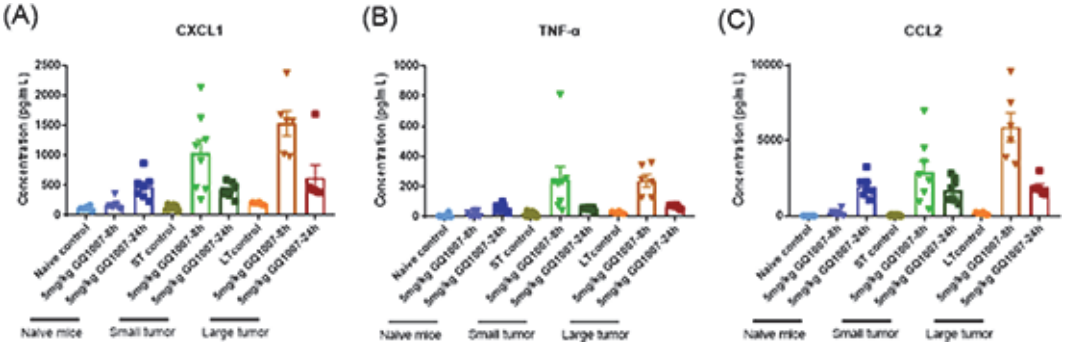
Abstract 1157 Figure 3 GQ1007 exhibits robust in vivo antitumor activity. (A) Tumor growth inhibition of GQ1007 in HER2 high expressing NCI-N87 and HER2 low expressing Capan-1 xenograft (CDX) mouse models. (B) Tumor growth inhibition of GQ1007 in combination of anti-mPD-1 in MC38-hHER2 syngeneic mouse model. The combination of different dosages of GQ1007 and anti-mPD-1 resulted in improved therapeutic efficacies in comparison with single agent treatments. Data points represent group mean, error bars represent SEM.



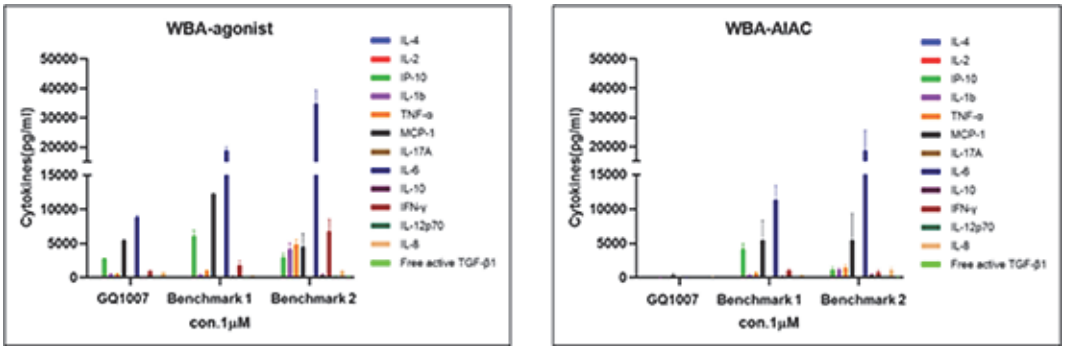
Abstract 1157 Figure 4 GQ1007 demonstrates a robust in vivo efficacy in the tumor rechallenge. Tumors growth was monitored after the inoculation of MC38-hHER2 or MC38 cell in mice that had cleared MC38-hHER2 tumors in response to GQ1007 treatment. Data points represent group mean, error bars represent SEM.



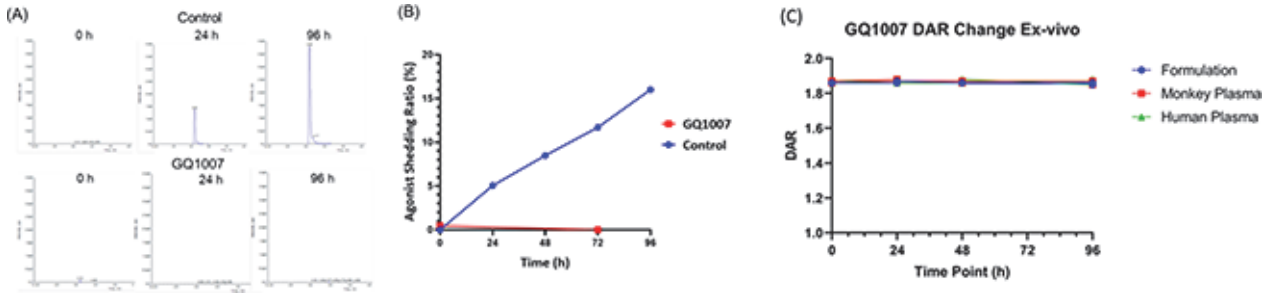
Abstract 1157 Figure 5 GQ1007 induces rapid and robust recruitment of immune cell subsets in tumor microenvironment. MC38-hHER2 tumor-bearing mice were dosed subcutaneously with GQ1007 at 5 mg/kg with tumor-infiltrating leukocytes(TIL) measured at 24 h or 120 h, respectively. Representative histology (A) and F4/80+ and CD8+ IHC (B) images were taken at 24 or 120 h after GQ1007 administration. The number of tumor-infiltrating macrophages, DCs and CD8+ T cells were quantified by FACS (C). Data points represent group mean, error bars represent SEM. P values were calculated by one-way with Tukey's correction for multiple comparisons, *p < 0.05 **** p < 0.0001.



Abstract 1157 Figure 6 The induction of pharmacodynamic markers of myeloid cell activation is rapid and HER2 tumor-dependent. CXCL1 (A), TNF-α (B) and CCL2 (C) were measured in plasma from naive C57BL/6N mice and MC38-hHER2 tumor-bearing mice treated subcutaneously with GQ1007 at 5 mg/kg for 8 h. The induction of cytokines was faster and stronger in tumor-bearing mice compared to naive C57BL/6N mice.



Abstract 1157 Figure 7 GQ1007 induces minimal off-target immune activation in the human blood and has a better safety profile than its small molecule agonist. Non-specific blood immune cell activation to GQ1007 and two benchmarks (right panel) or the corresponding small molecule agonists (left panel) was evaluated using a whole blood assay. The cytokines and chemokines including IL-4, IL-2, CXCL10 (IP-10), IL-lß, TNF-α, CCL2 (MCP-1), IL-17A, IL-6, IL-10, IFN-γ, IL-12p70, CXCL8 (IL-8) and TGF-ßl were detected using Cytometric Bead Array (CBA).



Abstract 1157 Figure 8 GQ1007 demonstrates excellent linker stability in ex vivo plasma stability studies. GQ1007 was incubated with human plasma at 37C for 96 h. Concentration of free agonist at 0 h, 24 h, 48 h, 72 h and 96 h was detected by LC-MS/MS. Chromatograms of free agonist at 0 h, 24 h and 96 h was shown (A) and agonist shedding ratio was calculated (B). Consistent data was obtained from DAR change analysis of GQ1007 using LC-MS/MS in monkey and human plasma (C).

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