AMB302/GQ1011, an antibody-drug conjugate (ADC) with TopoIx shows therapeutic potency in orthotopic glioblastoma PDX and bladder cancer models with FGFR3-TACC3 fusion

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Abstract # 2634

1 ABSTRACT

Background: FGFR3-TACC3 (F3-T3) fusion leads to constitutive FGFR3 kinase activation and acts as a driver mutation in several solid tumors. AMB302/GQ1011 is a novel FGFR3-targeting ADC that was developed using intelligent Ligase-Dependent Conjugation (iLDC) technologies from GeneQuantum (GQ), which provide high homogeneity, excellent druggability, high linker stability, and contain a topoisomerase 1 inhibitor as a payload. Based on preclinical characterization, AMB302/GQ1011 shows impressive anti-tumor activities against glioblastoma (GBM) and bladder cancer (BC) models with either FGFR3 alterations or F3-T3 fusion, and demonstrates the potential as a first-in-class FGFR3 ADC against FGFR3-active solid tumor indications.

Methods: In vitro anti-tumor effects and mechanism of action for AMB302/GQ1011 were assessed on patient-derived cells (PDCs) and cancer cell lines with F3-T3 using a 3D-spheroid high-throughput assay. In vivo anti-tumor effects of AMB302/GQ1011 were assessed on F3-T3 fusion GBM orthotopic PDX models and several FGFR3 alterations or F3-T3 fusion BC models.

Results: AMB302/GQ1011 was generated by linking FGFR3-targeting antibody (Aimedbio inc.) with TopoIx (GeneQuantum Healthcare), a next-generation Topoisomerase 1 inhibitor, via a cleavable linker using iLDC technologies. In a 3D-spheroid high-throughput assay system, AMB302/GQ1011 showed significant anti-tumor activity against GBM PDCs and BC cells in an F3-T3 dependent manner, which was superior to ADC conjugated using the same antibody and DXd payload. Additionally, AMB302/GQ1011 prolonged the survival in GBM orthotopic PDX models with F3-T3 fusion by >150% in combination with TMZ and achieved complete tumor regression in RT112 BC model with F3-T3 fusion. AMB302/GQ1011 treatments were well-tolerated up to 330 mg/kg in a mouse safety study and up to 80 mg/kg in a non-human primate toxicology study.

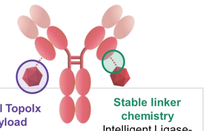
Conclusion: AMB302/GQ1011 showed robust anti-tumor efficacies in F3-T3 fusion and FGFR3 alterations models derived from GBM and BC in vitro and in vivo. In addition, AMB302/GQ1011 was well-tolerated with no adverse effects in rodent and NHP models. Our data suggest AMB302/GQ1011 has potential as a therapeutic option as a first-in-class FGFR3-targeting ADC for GBM, BC, and other solid tumors with FGFR3 overexpression or alterations.

2 INTRODUCTION

AMB302/GQ1011, a novel anti-FGFR3 ADC with TopoIx

Potential indication
- Bladder cancer with FGFR3 alteration (> 20 %), overexpression (> 40 %)
- GBM with FGFR3-TACC3 fusion (3~10 %)

AIMEDBIO
FGFR3 mAb
Fully human Immunoglobulin G1



Novel TopoIx payload
Strong bystander killing effect

Stable linker chemistry
Intelligent Ligase-Dependent site-specific drug conjugation

GeneQuantum Healthcare 启德医药

Core technology
- High affinity and specificity to FGFR3 domain I (500 pM)
- Robust target internalization & degradation in F3-T3 PDCs
- Enzymatic site-specific conjugation
- Modular, stable and hydrophilic cleavable linker
- TopoIx payload: excellent in vitro efficacy and bystander killing effect
- CMC: time/cost effective process and robust scalability

Current stage
- IND enabling study including preclinical tox study & CMC
- IND submission (1Q, 2024)

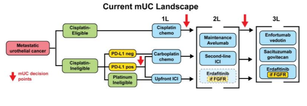
Target antigen	FGFR3
mAb isotype	fully human IgG1
Linker type	Cleavable
Payload	TopoIx (CPTs)
DAR	4

Unmet medical needs for FGFR3 alteration and overexpressed patients

- **Fibroblast growth factor receptor-3 (FGFR3)** plays a crucial role in regulating cell proliferation, differentiation, angiogenesis, and migration.
- FGFR3 alterations are commonly observed in various solid tumors, including bladder cancer and GBM.

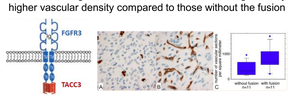
UC, Treatment Landscape

Current mUC Landscape



GBM, Treatment Landscape

GBMs exhibiting the F3-T3 fusion demonstrate a significantly higher vascular density compared to those without the fusion



FGFR3 Alteration and Urothelial Cancer (UC)
- Up to 50% of patients with mUC are ineligible for cisplatin-based treatment.
- A FGFR-targeted tyrosine kinase inhibitor (TKI), Erdafitinib, has been approved as a second-line treatment option for patients with FGFR3 alterations.
- Despite the availability of new therapies for advanced UC, there is still a need for better treatment options

FGFR3-TACC3 fusion in GBM
- Temozolomide (TMZ) is the only chemotherapeutic agent for GBM
- GBM with F3-T3 fusion shows abnormal extracranial metastasis pattern with high vascularization and disruption in BBB
- Targeting the F3-T3 fusion oncogene presents a promising avenue for antibody-based therapeutic approaches in a subset of glioblastoma patients.

3 RESULT

AMB302/GQ1011 specifically binds to FGFR3 and induces robust internalization and ADCC effect

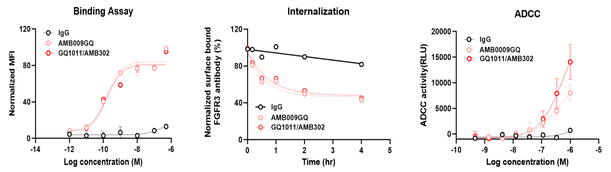
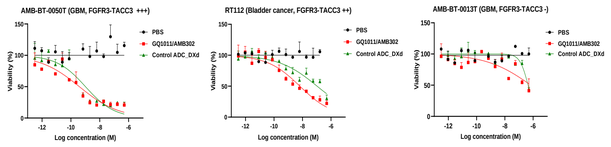


Figure 1. Binding, internalization and ADCC assay were evaluated for FGFR3 overexpressing cells (KMS11, multiple myeloma). **A. AMB302/GQ1011 shows a high affinity for FGFR3 overexpressing cells B. AMB302/GQ1011 shows rapid internalization efficiency on FGFR3 overexpression cells in a short time after treatment C. AMB302/GQ1011 exhibits a high ADCC effect depending on FGFR3 overexpression cells. AMB302/GQ1011 exhibits similar in vitro biological activities compared to AMB009GQ (mAb).**

AMB302/GQ1011 exhibits a superior cytotoxicity-killing effect depending on FGFR3 expression



Cell	FGFR3 expression	IC50 (nM)	
		AMB302/GQ1011	Control ADC_DXd
AMB-BT-0050T	+++	0.4	1.0
RT112	++	6.55	106.1
AMB-BT-0013T	-	NA	NA

Figure 2. To confirm the FGFR3 target-dependent cell cytotoxicity effect, AMB302/GQ1011 was evaluated by 3D-spheroid assay methods.

AMB302/GQ1011 demonstrates superior in vitro cytotoxicity compared to control ADC (same Ab with DXd) in FGFR3-TACC3 fusion cell lines with varying target expression. In vitro cytotoxicity mediated by AMB302/GQ1011 shows a strong correlation with target expression levels.

** Control ADC_DXd: ADC prepared using same AMB000GQ (mAb), GQ technology and DXd as the payload*

AMB302/GQ1011 shows a superior bystander killing effect than Dxd conjugated ADC

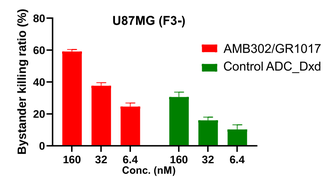


Figure 3. Evaluation of the bystander-killing effect of AMB302/GQ1011 on RT112 (FGFR3 positive cells) and U87MG (FGFR3 negative cells) through 1:1 co-culture and FACS analysis. **The AMB302/GQ1011 as payload TopoIX demonstrates a more effective bystander killing effect than the control ADC_Dxd as payload Dxd.**

Stable properties of AMB302/GQ1011 in plasma of various species

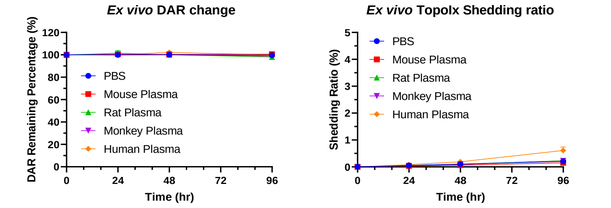


Figure 4. Ex vivo plasma stability study of AMB302/GQ1011 by incubation with plasma for 96 hrs. **AMB302/GQ1011 demonstrates excellent linker stability in various species. The stable DAR and extreme low shedding ration of payload, indicating the toxicity caused by shedding payload and/or linker-payload is minimal.**

AMB302/GQ1011 shows excellent anti-tumor efficacy in vivo CDX models with various FGFR3 alteration

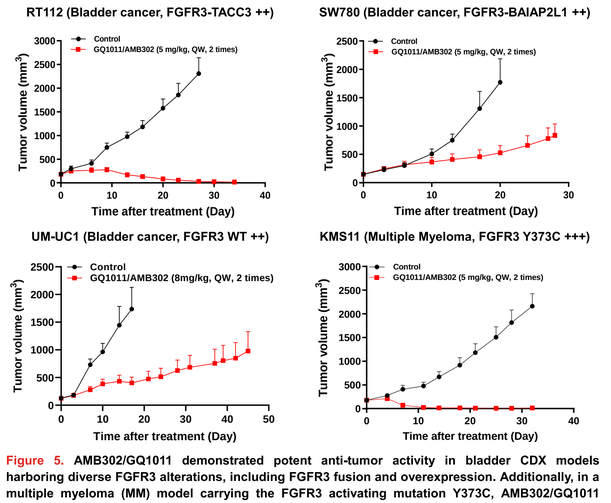
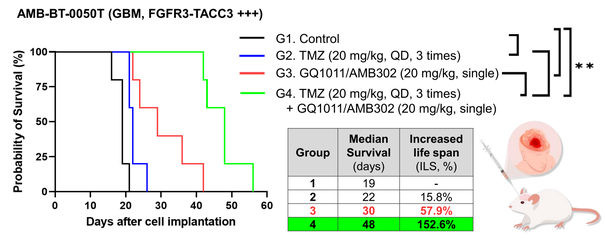


Figure 5. AMB302/GQ1011 demonstrated potent anti-tumor activity in bladder CDX models harboring diverse FGFR3 alterations, including FGFR3 fusion and overexpression. Additionally, in a multiple myeloma (MM) model carrying the FGFR3 activating mutation Y373C, AMB302/GQ1011 exhibited robust anti-tumor efficacy. Data were presented as mean ± SEM.

AMB302/GQ1011 significantly increases the probability of survival with TMZ combination treatment in vivo orthotopic GBM PDX models



Group	Median Survival (days)	Increased life span (ILS, %)
1	19	-
2	22	15.8%
3	30	57.9%
4	48	152.6%

Figure 6. In the GBM PDX orthotopic model, AMB302/GQ1011 shows a synergistic anti-tumor response when combined with TMZ. This combination treatment results in a remarkable increase in ILS from 15.8% to 152.6%.These results suggest that AMB302/GQ1011 has the potential to be an effective treatment option for GBM with F3-T3 fusion. Statistical comparison is made logrank (Mantel-Cox) test. *p<0.05, **p<0.01, ***p<0.001.

AMB302/GQ1011 exhibits a strong anti-tumor response in the GBM PDX s.c. models

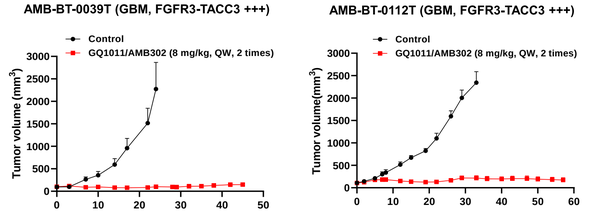


Figure 7. AMB302/GQ1011 shows a superior anti-tumor effect against GBM PDX subcutaneous models with F3-T3 (AMB-BT-0039T, AMB-BT-0112T). Data are presented as mean ± SEM.

AMB302/GQ1011 shows better *in vivo* anti-tumor efficacy than Competitor's ADC

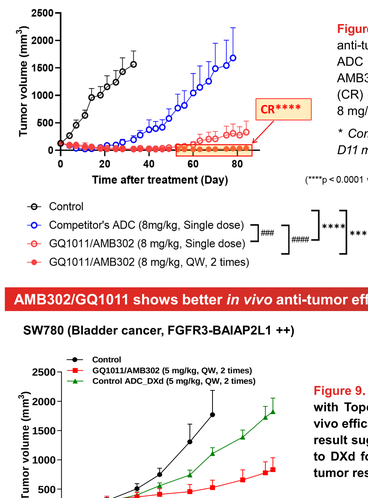


Figure 8. AMB302/GQ1011 demonstrates superior anti-tumor efficacy compared to Competitor's ADC in the RT112 bladder cancer model. In the AMB302/GQ1011 group, a complete response (CR) is achieved with two injections at a dose of 8 mg/kg.

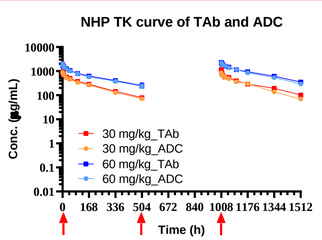
** Competitor's ADC: ADC prepared using IMC-D11 mAb, GQ technology and DM4 as the payload*

(****p < 0.0001 versus control; ###p < 0.001, ####p < 0.0001 versus Group 2.)

AMB302/GQ1011 shows better *in vivo* anti-tumor efficacy than Dxd-conjugated ADC

Figure 9. In a comparison study, AMB302/GQ1011 with TopoIx demonstrates significantly better in vivo efficacy than the control ADC with DXd. This result suggests that TopoIx is a superior payload to DXd for delivering a potent and durable anti-tumor response in vivo.

AMB302/GQ1011 exhibits high tolerability in cynomolgus monkey



NHP tolerability test

60 mg/kg (n=2) *(Q3W*5 times)*

80 mg/kg (n=2) *(Q3W*2 times)*

30 mg/kg (n=2) *(Q3W*3 times)*

Well-tolerable at 60 mg/kg, Q3W, 4 times (on going)

Figure 10. The monkey TK profile of the TAb and ADC completely overlap, indicating excellent stability in the cynomolgus monkey. AMB302/GQ1011 is well-tolerated by cyno-monkeys (given repeated doses of 60mg/kg) without any significant observed toxicity. These findings suggest that AMB302/GQ1011 has a large therapeutic window.

4 SUMMARY

- AMB302/GQ1011 is a potential first-in-class ADC that targets FGFR3. It utilizes a globally patented antibody, novel payload TopoIx, and stable linker technology.
- TopoIx has superior cytotoxicity, induces greater immunogenic cell death (ICD), and bystander killing compared to DXd and SN38.
- AMB302/GQ1011 has demonstrated a strong in vivo antitumor response against bladder tumors with diverse FGFR3 alterations.
- AMB302/GQ1011 has the potential for a combination therapy with TMZ, which is the standard of care (SOC) in GBM.
- There is a high potential for excellent synergy between AMB302/GQ1011 and anti-PD1 antibody treatment in the clinic.
- Preliminary safety data in monkeys suggest that AMB302/GQ1011 has the potential to be a safe FGFR3-ADC with a wide therapeutic window.
- AMB302/GQ1011 is expected to submit an IND in early 2024.

Acknowledgement
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