Overcoming resistance with OBI-902: Preclinical evaluation of a next-generation TROP2 ADC

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ABSTRACT

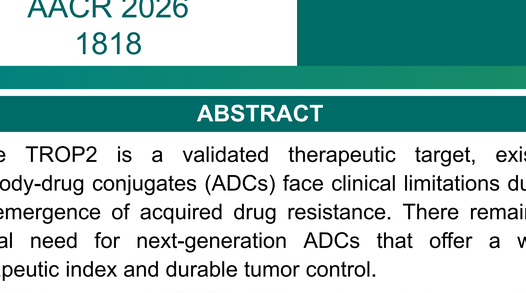
While TROP2 is a validated therapeutic target, existing antibody-drug conjugates (ADCs) face clinical limitations due to the emergence of acquired drug resistance. There remains a critical need for next-generation ADCs that offer a wider therapeutic index and durable tumor control.

OBI-902 is a novel TROP2 ADC engineered for exceptional stability through the integration of two proprietary technologies. It utilizes the GlycOBI® site-specific platform to conjugate a humanized anti-TROP2 antibody to a TOP1 inhibitor, producing a homogeneous ADC. Concurrently, it incorporates HYPrOBI® technology to optimize linker-payload stability, ensuring targeted payload delivery.

Here, we demonstrate the potent efficacy of OBI-902 across diverse preclinical models. OBI-902 successfully overcomes resistance to approved TOP1 ADCs and maintains continuous tumor suppression at extended dosing intervals. A Phase I clinical study (NCT07124117) is ongoing to evaluate OBI-902 in patients with advanced solid tumors.

Strong Target-Mediated Cytotoxicity: Precision targeting based on TROP2 expression

A Correlation between TROP2 expression and cytotoxicity



B IC_{50} heatmap across expression tiers

Expression Tier	Cell Line	TROP2 Levels (x 1000 molecules/cell)	OBI-902	Dato-DXd analog	SG	sac-TMT analog
High	BxPC3	3266	1.80	1.26	4.1	0.38
	NCI-N87	588.9	20.4	15.4	1.1	1.41
Middle	NCI-H1975-C797S	144.2	157	244	-	2.41
	DU-145	52.12	269	183	0.56	0.63
	MDA-MB-231	33.86	674	557	-	4.38
Low	NCI-H460	6.743	672	591	2.5	1.6
	ES-2	1.976	666	480	0.35	0.33

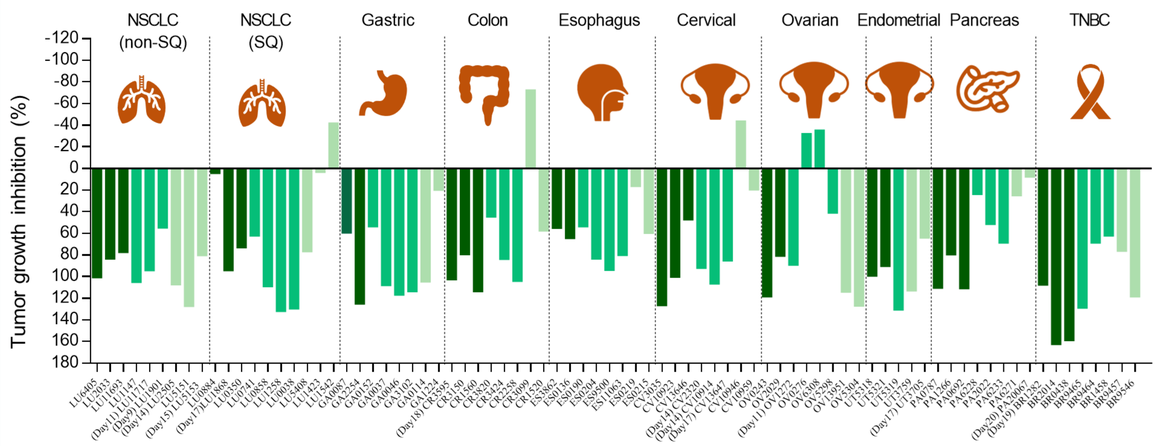
IC_{50} < 10 nM | 10 nM | 100 nM | > 100 nM
Active — Inactive

Figure 1. ***In vitro*** **cytotoxicity of OBI-902**

(A) OBI-902 exhibits a significant target-dependent profile, unlike the target-independent activity of SG and sac-TMT.

(B) OBI-902 demonstrates potent efficacy in high-expressing models but safely deactivates in low-expressing models, avoiding indiscriminate toxicity.

Extensive Pan-Tumor Activity: Demonstrating strong tumor growth inhibition across 80 PDX models

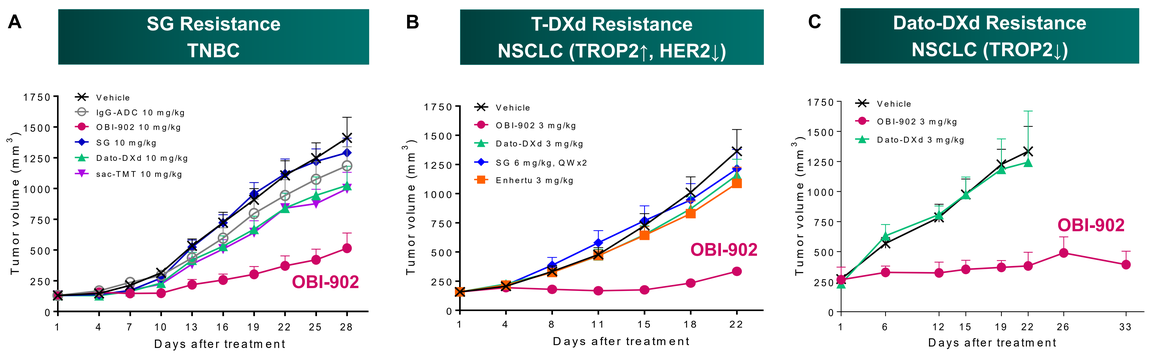


NSCLC: Non-small cell lung cancer, TNBC: Triple-negative breast cancer
OBI-902 was administered as a single 6 mg/kg dose.
TROP2 expression (high, medium, low) was classified based on Fragments Per Kilobase of transcript per Million mapped reads (FPKM) from CrownBio RNA-seq data across tumor models.
TGI (%) = [1 − (Ti − T1)/ (Ci − C1)] × 100%
(Ti and Ci refer to mean tumor volumes in the treatment and control groups at study end, while T1 and C1 represent mean tumor volumes at treatment start).

Figure 2. Antitumor activity of OBI-902 in 80 PDX models spanning 10 cancer types

A single dose of OBI-902 induces profound TGI% across a diverse panel of 80 PDX models spanning 10 distinct solid tumor indications. Notably, robust antitumor activity is maintained across high, medium, and low TROP2 expression profiles.

Potent Efficacy in Resistant Models: Overcoming TOP1 ADCs resistance in TNBC and NSCLC



The resistance models used in this study were established through multiple sources: (A) with support from the University of Hawai'i Cancer Center (UHCC), (B) acquired from a commercial CRO, and (C) generated through in-house development.

Figure 3. Antitumor activity of OBI-902 in resistant models

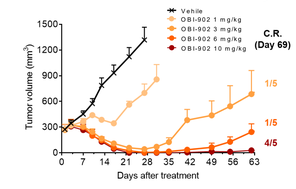
(A) OBI-902 drives deep TNBC regression where SG is inactive.

(B) OBI-902 outperforms Enhertu and Dato-DXd in TROP2↑/HER2↓ NSCLC.

(C) OBI-902 maintains robust control in TROP2↓ NSCLC, whereas Dato-DXd shows no benefit.

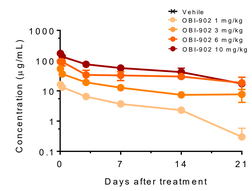
Favorable Exposure-Efficacy Correlation: Antitumor activity driven by systemic exposure

A Dose-dependent efficacy



Near-complete tumor eradication (4/5 C.R.) at 10 mg/kg

B ADC concentration profile



Mean $T_{1/2}$: 7.7 days (across all 4 doses)

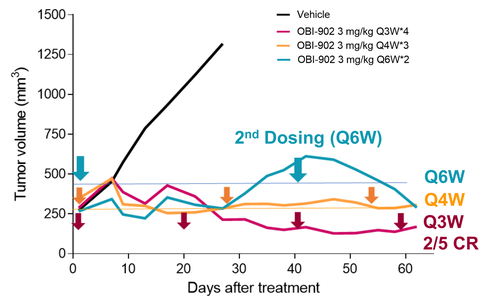
Figure 4. Exposure-efficacy correlation of OBI-902

(A) OBI-902 drives robust, dose-dependent tumor regression.

(B) Serum concentration profiles demonstrate proportional systemic exposure across all dose cohorts.

Sustained Antitumor Durability: Maintaining robust tumor control at extended dosing intervals

EGFR L858R/T790M-mutant NSCLC model



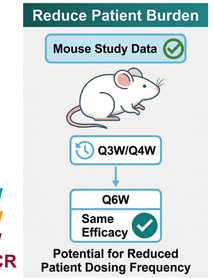


Figure 5. Antitumor durability of OBI-902

OBI-902 maintains sustained tumor suppression in TKI-resistant NSCLC at Q6W intervals, supporting a patient-friendly regimen that reduces hospital visits.

CONCLUSIONS

OBI-902 demonstrates potent antitumor activity across a broad range of PDX models, independent of TROP2 expression. Notably, robust efficacy has been observed in both NSCLC (non-squamous and squamous) and gastric cancer models. In addition, OBI-902 shows the potential to overcome emerging resistance to currently approved TOP1 ADCs. Nonclinical data further support the possibility of extended dosing intervals in the clinical setting, positioning OBI-902 as a next-generation therapeutic for solid tumors.

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