OBI-904 is a Nectin-4–targeted ADC conjugated with the topoisomerase I inhibitor Exatecan (DAR 8) via OBI's GlycOBI® glycan conjugation platform and dual-action EndoSymeOBI® enzymatic technology, designed to provide homogeneous DAR, improve ADC stability, and enable optimal payload delivery.

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OBI-904, a glycan-based site-specific Nectin-4–targeted ADC, demonstrates potent and durable antitumor activity with an improved PK profile and overcomes EV-resistance in non-clinical studies

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BACKGROUND

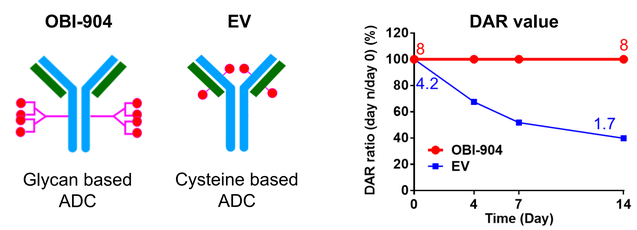
- Nectin-4 is a type I transmembrane adhesion molecule with low expression in normal tissues but is highly overexpressed in multiple cancers, including urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and triple-negative breast cancer (TNBC). Its expression is associated with tumor proliferation, metastasis, and poor prognosis, making it a clinically validated target for ADC development.
- Although Padcev® (enfortumab vedotin, EV) has demonstrated meaningful clinical benefit, safety concerns, suboptimal dosing schedules, and emerging resistance highlight the need for next-generation Nectin-4–targeted ADCs.
- OBI-904 is a Nectin-4–targeted ADC conjugated with the topoisomerase I inhibitor Exatecan (DAR 8) via OBI's GlycOBI® glycan conjugation platform and dual-action EndoSymeOBI® enzymatic technology, designed to provide a homogeneous DAR, improve ADC stability, and enable optimal payload delivery, with the aim of addressing key limitations of EV.

METHODS

- **In vitro stability** of OBI-904's linker-payload was assessed after 14-day incubation with human serum albumin, followed by LC-MS analysis.
- **Pharmacokinetics (PK)** of OBI-904 were evaluated over 28 days in a HNSCC, Fadu cell line–derived xenograft (CDX) model following a single IV dose.
- **Antitumor activity** of OBI-904 was assessed in multiple CDX models, including HNSCC, Colorectal Cancer (CRC), TNBC, prostate cancer (PC-3 with human Nectin-4 overexpression), cholangiocarcinoma, and an EV-resistant UC CDX model, as well as in patient-derived xenograft (PDX) models of cervical cancer (CrownBio) and squamous NSCLC (WuXi). Treatment was initiated when tumors reached volumes of 150–200 mm³.
- **EV-resistant** models were established by subcutaneous implantation of HT-1376 UC cells in BALB/c nude mice, followed by repeated EV treatment until resistance developed. Resistant tumors were harvested and re-implanted into naïve mice, which were then treated with OBI-904 or EV.
- **Immunohistochemistry (IHC)** represents variant Nectin-4 expression level in different tumor sections.

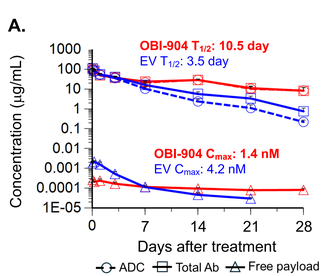
RESULTS

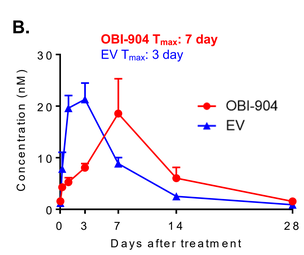
OBI-904 desplays enhanced linker-payload stability



- OBI-904 conjugated via site-specific glycan linkers maintains a homogeneous DAR in serum albumin offering enhanced stability.

OBI-904 demonstrates enhanced stability in circulation and prolonged payload delivery to tumors

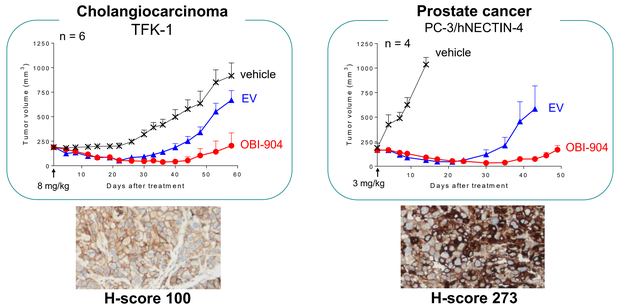




(HNSCC, Fadu CDX model, 6 mg/kg, n = 3)

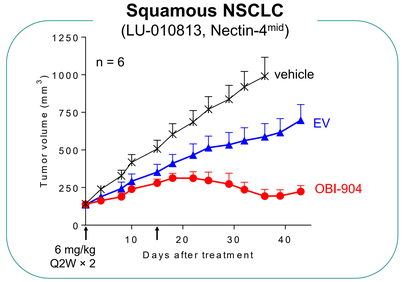
- A. OBI-904 shows a favorable PK profile with improved therapeutic index, high stability, and minimal payload release.
- B. OBI-904 demonstrated efficient and more controlled payload release at the tumor site relative to EV.

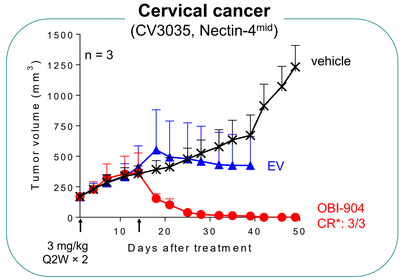
OBI-904 exhibits increased durability in CDX models



- OBI-904 demonstrates superior and durable antitumor activity versus EV across CDX models, independent of Nectin-4 expression.

OBI-904 outperforms EV in PDX models

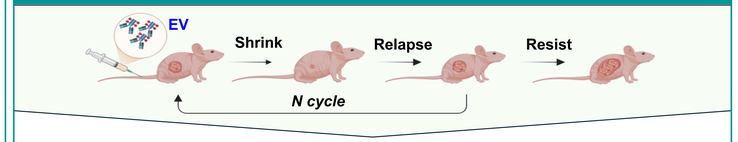


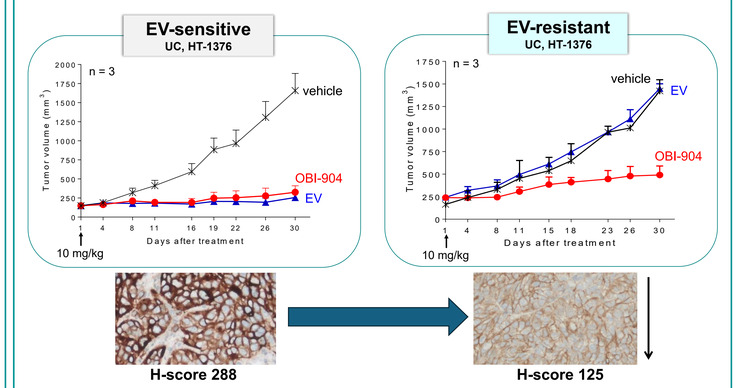


- OBI-904 demonstrated superior antitumor activity in squamous NSCLC and cervical cancer PDX models.

**CR: Complete response*

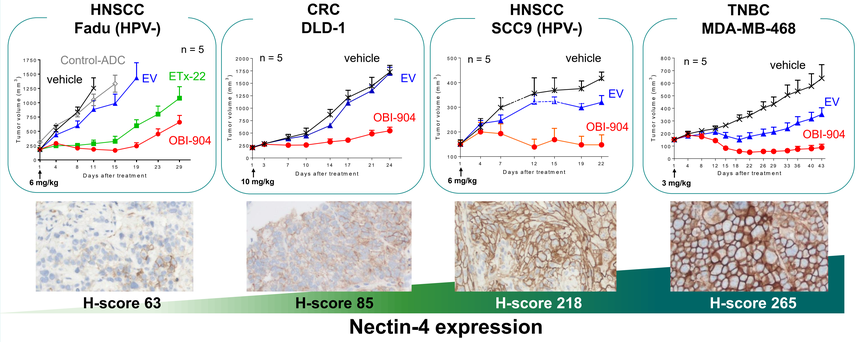
OBI-904 effectively overcomes EV-resistant urothelial carcinoma model





- EV resistance in UC model is associated with marked downregulation of Nectin-4 expression.
- OBI-904 retains antitumor activity in EV-resistant UC models, demonstrating efficacy despite reduced Nectin-4 expression.

OBI-904 demonstrates superior antitumor activity across CDX models with varying Nectin-4 expression levels



- OBI-904 exhibited strong antitumor efficacy across multiple preclinical models, including CDX models of HNSCC, CRC and TNBC, demonstrating therapeutic activity independent of Nectin-4 expression levels. Notably, OBI-904 showed greater differentiation from EV in models with low Nectin-4 expression.

CONCLUSIONS

OBI-904 is a next-generation Nectin-4–targeted ADC engineered for optimized stability and payload delivery, demonstrating potent and broad antitumor activity—including in EV-resistant models—independent of Nectin-4 expression. In vitro studies show strong cytotoxic activity across models with heterogeneous and low Nectin-4 expression, consistent with a payload-driven bystander effect, along with reduced binding to keratinocytes, suggesting a potentially improved safety profile, as demonstrated in Poster #1729. Collectively, these attributes position OBI-904 as a potential best-in-class Nectin-4–targeted ADC.

DISCLOSURE

This study was funded by OBI Pharma, Inc. All authors are employees of OBI Pharma, Inc.

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