OBI-904, a next-generation nectin-4-targeting exatecan ADC, demonstrates enhanced cytotoxicity and overcomes enfortumab vedotin resistance

Yuan-Liang Wang, Chi-Huan Lu, Woan-Eng Chan, Shin-Jin Lin, Ting-Yu Chang, Hong-Syuan Lin, Wei-Jhen Huang, Ya-Chi Chen
OBI Pharma, Inc., Taipei, Taiwan

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Abstract

Nectin-4 is a validated therapeutic target for multiple epithelial cancers, and Enfortumab vedotin (EV), the first FDA-approved Nectin-4-directed antibody–drug conjugate (ADC), has demonstrated meaningful clinical benefit; however, its efficacy is limited by several factors, including P-glycoprotein (P-gp)–mediated drug efflux, the emergence of EV-resistant tumor cells that reduce cytotoxic activity, a short plasma half-life requiring frequent dosing, and off-target hematological toxicities potentially arising from suboptimal linker stability and premature payload release in circulation. To overcome these limitations, we developed OBI-904, a next-generation Nectin-4-targeting ADC comprising a novel anti-Nectin-4 antibody (10K06) conjugated to an exatecan payload via a stable, glycan-based site-specific linker platform, resulting in a homogeneous ADC. The 10K06 antibody binds to the IgV domain of Nectin-4 (amino acids 86–92) and demonstrates strong binding affinity and efficient internalization in cell-based assays, ensuring effective target engagement. Notably, OBI-904 exhibits reduced binding to keratinocytes compared with EV, suggesting a lower risk of skin toxicity, and 10K06 selectively recognizes human and cynomolgus but not murine Nectin-4, supporting its suitability for non-human primate toxicology studies. Functionally, OBI-904 shows superior cytotoxic potency in Nectin-4 low-expressing tumor cell lines under 3D spheroid culture conditions, consistent with the high potency and membrane permeability of its exatecan payload and mediates a robust bystander effect in co-culture systems containing Nectin-4-positive and -negative cells. Importantly, OBI-904 retains strong cytotoxic activity in P-gp-overexpressing and EV-resistant tumor models. Collectively, these results establish OBI-904 as a potent next-generation Nectin-4 ADC with reduced skin binding, enhanced cytotoxicity, a pronounced bystander effect, and the ability to overcome both P-gp-mediated and EV-acquired resistance, supporting its further clinical development for the treatment of Nectin-4-expressing cancers.

OBI-904: A Next-Generation Antibody–Drug Conjugate with a Unique Modular Design

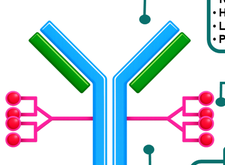
Limitations of EV

Antibody
- Keratinocyte binding may contribute to skin toxicity
- Boxed warning: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Payload
- Limited bystander effect of MMAE restricts activity in heterogeneous tumors
- Emerging MMAE resistance

Linker
Suboptimal linker–payload stability may lead to premature payload release, resulting in off-target toxicity and affecting dose frequency

Solutions



OBI-904

Antibody
10K06 (anti-Nectin-4 antibody)
- High affinity, tumor-specific targeting
- Low risk of skin toxicity
- Proprietary humanized anti-Nectin-4 Antibody

Payload
- Exatecan, DAR = 8
- High bystander effect
- Potential to overcome EV-resistance

Linker
- GlycOBI®, glyco-based site-specific conjugation enables homogeneous DAR
- HYPrOBI®, hydrophilic design enhances payload stability and enables controlled tumor release

Distinct binding epitopes of Enfortumab and 10K06 on the Nectin-4 IgV domain

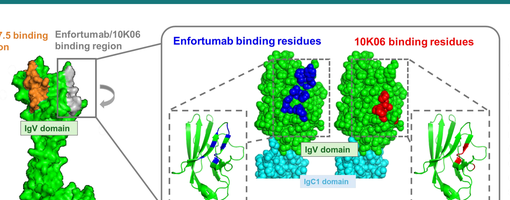


Figure 1. Epitope mapping of Enfortumab and 10K06 on Nectin-4 IgV domain. Structural modeling shows that both antibodies bind within the IgV domain of Nectin-4. The 15A7.5 binding region is highlighted in orange. Enfortumab-contact residues (blue) and 10K06-contact residues (red) are mapped onto the IgV surface, demonstrating distinct but partially overlapping epitopes. The IgC1 domain is shown in cyan for orientation.

10K06 exhibits higher specificity for human Nectin-4 than Enfortumab

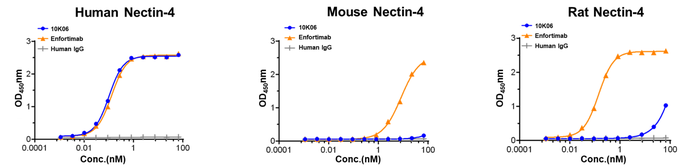


Figure 2. Dose–response binding of 10K06, Enfortumab, and control antibodies to human, mouse, and rat Nectin-4 was assessed by ELISA, with binding signals quantified by absorbance at 450 nm.

OBI-904 exhibits binding affinity comparable to EV, outperforms ETx-22

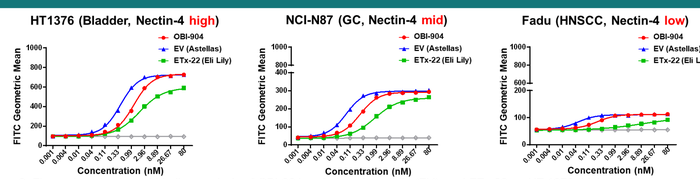


Figure 3. Flow cytometry–based binding analysis of OBI-904, enfortumab vedotin (EV), and ETx-22 on HT-1376 (high; bladder cancer), NCI-N87 (mid; gastric cancer), and FaDu (low; head and neck squamous cell carcinoma) cell lines with differential Nectin-4 expression. ETx-22 is an Eli Lilly-developed Nectin-4 ADC; the version used in this study is an in-house surrogate.

OBI-904 demonstrates internalization comparable to EV and ETx-22

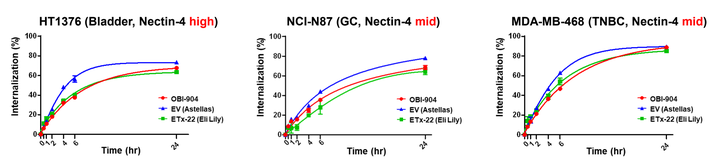


Figure 4. The internalization kinetics of OBI-904, enfortumab vedotin (EV), and ETx-22 were assessed by flow cytometry in HT-1376 (high; bladder carcinoma), NCI-N87 (mid; gastric carcinoma) and MDA-MB-468 (mid; triple-negative breast cancer) cells. ETx-22 is an Eli Lilly-developed Nectin-4 ADC; the version used in this study is an in-house surrogate.

OBI-904 retains cytotoxic activity under low Nectin-4 expression compared with EV

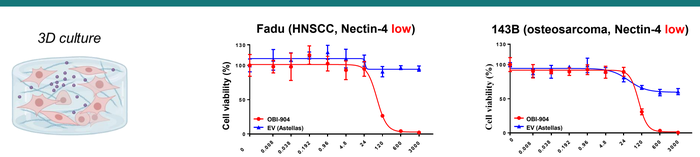


Figure 5. OBI-904 and enfortumab vedotin (EV) were evaluated in 3D cytotoxicity assays using two Nectin-4–low–expressing cell lines: FaDu (head and neck squamous cell carcinoma) and 143B (osteosarcoma).

OBI-904 demonstrates superior bystander effect compared to EV

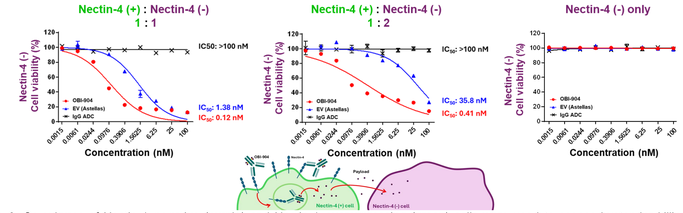


Figure 6. Co-cultures of Nectin-4–negative (purple) and Nectin-4–overexpressing (green) cells were used to assess bystander killing. OBI-904 (red) and enfortumab vedotin (EV) (blue) were compared for cytotoxicity. OBI-904 consistently showed lower IC_{50} values than EV across all co-culture ratios, indicating enhanced bystander killing and potential activity in Nectin-4–low tumor cells.

OBI-904 shows minimal keratinocyte binding, suggesting a lower risk of cutaneous toxicity

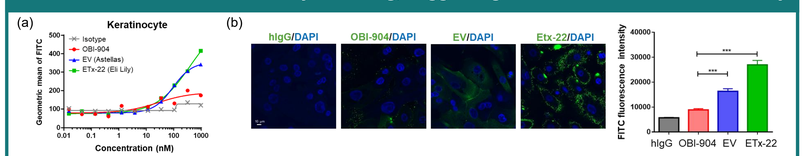
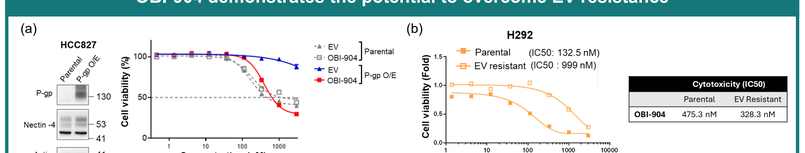


Figure 7. Reduced binding of OBI-904 to human keratinocytes. (a) Cell-surface binding of IgG control, OBI-904, enfortumab vedotin (EV), and ETx-22 in human keratinocytes was assessed by flow cytometry. (b) Antibody/ADC binding was examined by immunofluorescence, showing reduced signal intensity for OBI-904 compared with EV and ETx-22. Scale bar, 10 μm. ETx-22 is an Eli Lilly-developed Nectin-4 ADC; the version used in this study is an in-house surrogate.

OBI-904 demonstrates the potential to overcome EV resistance



Cytotoxicity (IC50)		
	Parental	EV Resistant
OBI-904	475.3 nM	328.3 nM

Figure 8. OBI-904 demonstrates activity in EV-resistant models. (a) EV resistance driven by P-gp overexpression in HCC827 cells. (b) EV resistance induced by prolonged EV exposure in H292 cells. Both resistant models remain sensitive to OBI-904.

Conclusion

OBI-904 delivers a differentiated profile compared to Enfortumab Vedotin and other Nectin-4 ADCs, with strong in vitro cytotoxic activity across models spanning heterogeneous and low Nectin-4 expression. This is enabled by the exatecan payload through its bystander effect, supporting tumor cell killing beyond antigen-positive populations. Reduced binding to keratinocytes further supports improved selectivity. Consistent with these findings, OBI-904 demonstrates robust and durable in vivo antitumor activity and a favorable pharmacokinetic profile in Poster #1819, supporting its potential to overcome EV resistance while maintaining a favorable safety profile.

Disclosure

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

Corresponding author: Ya-Chi Chen, yachichen@obipharma.com