OBI-992, a Novel TROP2-Targeting Antibody-Drug Conjugate, Demonstrates Superior In Vivo PK/PD Properties and a Favorable Safety Profile

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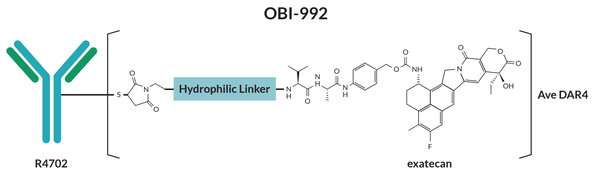
BACKGROUND

- Trophoblast cell surface antigen 2 (TROP2)-targeting antibody-drug conjugates (ADCs) have demonstrated promising clinical responses for the treatment of various solid tumors.[1,2]
- Even so, these ADCs have been associated with safety issues, such as hematologic toxicities and interstitial lung disease.[3]
- OBI-992 is a novel TROP2-directed ADC with an anti-TROP2 antibody conjugated to exatecan, a topoisomerase I inhibitor, via an enzyme-cleavable linker; OBI-992 is designed to have high stability in circulation and a broad therapeutic index (**Figure 1**).
- Additional in vitro and in vivo findings with OBI-992 are presented elsewhere at this meeting (see AACR 2024 posters 1893 and 3130).

Figure 1. Structure of OBI-992



DAR, drug to antibody ratio.

OBJECTIVE

- To provide a preclinical evaluation of OBI-992, including in vitro and in vivo stability, off-target toxicity, the pharmacokinetics/pharmacodynamics (PK/PD) profile, and initial safety findings.

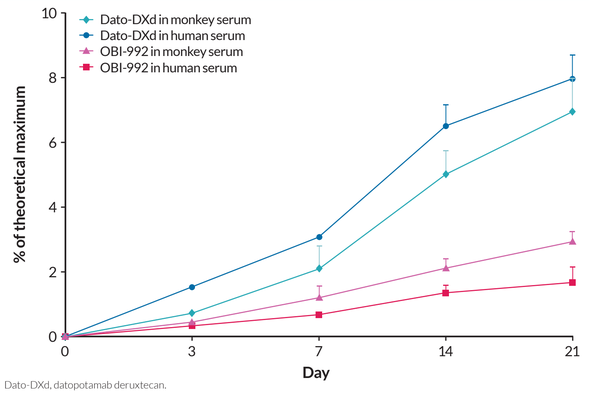
METHODS

- To assess linker stability, OBI-992 and datopotamab deruxtecan (Dato-DXd, a benchmark TROP2-targeting ADC) were incubated in monkey and human serum at 37°C for 0, 3, 7, 14, and 21 days. Released exatecan and DXd levels in the serum samples were quantified using liquid chromatography with tandem mass spectrometry, and the percentage of released payloads with respect to the theoretical maximum was calculated.
- To evaluate potential off-target toxicity, the association of TROP2-directed ADCs with peripheral blood leukocytes (PBLs) was assessed by an ex-vivo assay.
  - FcγR-mediated toxicity was evaluated using human monocyte THP-1 cells.
  - ADC-associated toxicity of neutropenia was tested on differentiating neutrophils.
- PK characterization was conducted in Sprague-Dawley rats following a single intravenous injection of OBI-992 or Dato-DXd at a dose of 10 mg/kg.
- PK/PD and receptor occupancy of OBI-992 were evaluated in a human NCI-H1975 lung cancer xenograft model (female BALB/c nude mice) following a single intravenous injection of OBI-992 or Dato-DXd at various doses.
- A 6-week repeat dose toxicity study in cynomolgus monkeys (0, 20, 40 and 60 mg/kg Q3W x 3 with a recovery period of 6 weeks) was conducted to evaluate the safety and toxicokinetics of OBI-992.

RESULTS

- OBI-992 exhibited better linker stability than the benchmark Dato-DXd (**Figure 2**).

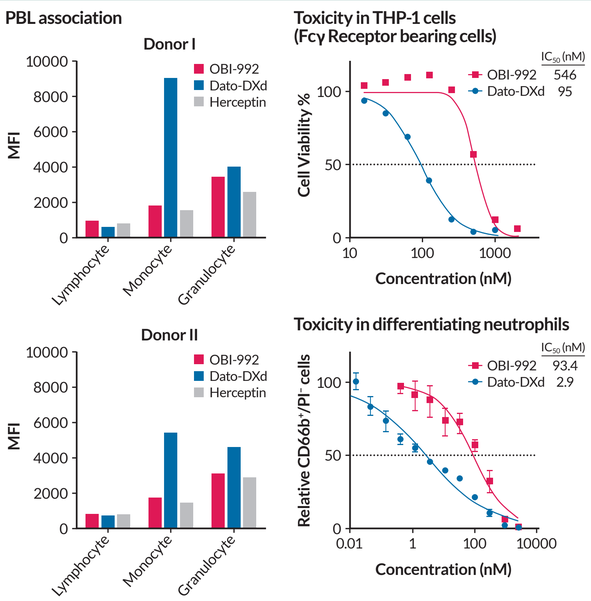
Figure 2. Ex Vivo Serum Stability of OBI-992 and Dato-DXd



Dato-DXd, datopotamab deruxtecan.

- OBI-992 had lower binding activity with monocytes and reduced cytotoxicity in both THP-1 cells and differentiating neutrophils compared with Dato-DXd, suggesting that OBI-992 may cause less off-target toxicity (**Figure 3**).

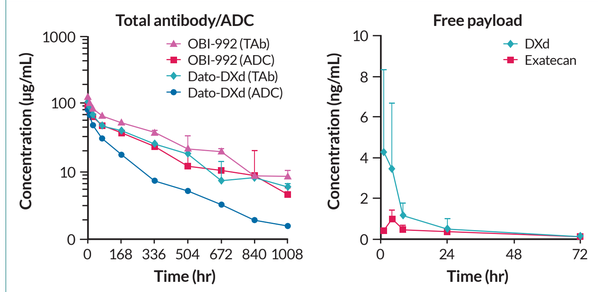
Figure 3. Off-Target Toxicity Evaluation of OBI-992 and Dato-DXd



Dato-DXd, datopotamab deruxtecan; IC_{50}, half-maximal inhibitory concentration; MFI, mean fluorescence intensity; PBL, peripheral blood leukocyte.

- OBI-992 demonstrated a favorable PK profile in rats, with a half-life of 11.6 days. Higher ADC and total Ab concentration as well as lower free payload were observed compared with Dato-DXd (**Figure 4**).

Figure 4. Pharmacokinetic Profiles of OBI-992 and Dato-DXd in Rats



Mean concentration vs time profiles of total antibody, ADC, and free payload in serum following a single dose of OBI-992 or Dato-DXd at 10 mg/kg in rats are shown.
ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; hr, hour; TAb, total antibody.

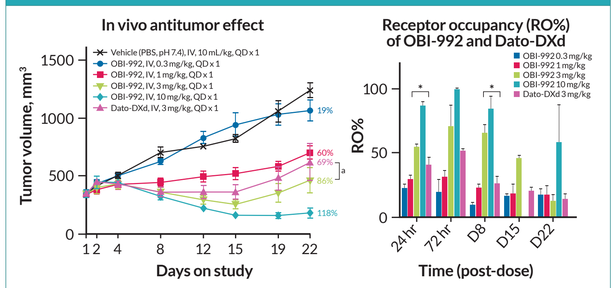
- A PK/PD study in tumor-bearing mice revealed that OBI-992 exhibited higher tumor exposure of free payload and higher serum exposure of ADC compared to Dato-DXd, resulting in more robust antitumor efficacy (**Table 1; Figure 5**).
- The antitumor effect positively correlated with receptor occupancy percentage in a dose-dependent manner (**Figure 5**).

Table 1. Mean Pharmacokinetic Parameters of Serum ADC and Tumor Free Payload in NCI-H1975 Tumor-Bearing Mice

ADC	Dose (mg/kg)	Serum ADC				Tumor free payload		
		C_{max} (μg/mL)	$AUC_{0\text{-}t}$ (hr*μg/mL)	CL (mL/hr/kg)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/g)	$AUC_{0\text{-}t}$ (hr*ng/g)
OBI-992	0.3	3.5	184	1.61	54	72	0.2	58
	1	13.4	1064	0.93	81	72	0.33	84
	3	42.0	3858	0.76	93	24	0.66	209
	10	154.4	16978	0.54	145	72	1.59	402
Dato-DXd	3	26.9	1652	1.8	66	6	0.45	90

ADC, antibody-drug conjugate; AUC, area under the curve; CL, clearance; C_{max}, maximum serum concentration; Dato-DXd, datopotamab deruxtecan; $T_{1/2}$, half-life; T_{max}, time to maximum concentration.

Figure 5. An In Vivo PK/PD and Receptor Occupancy Study of OBI-992 in an NCI-H1975 Tumor Model



In vivo antitumor effect and receptor occupancy percentage (RO%) of OBI-992 and Dato-DXd following a single intravenous injection of OBI-992 and Dato-DXd at various doses are shown.
Dato-DXd, datopotamab deruxtecan; IV, intravenous; PBS, phosphate-buffered saline; QD, daily.
[a]Statistically significant difference on tumor volume was observed at Day 15 ($P \leq .05$)
*$P \leq .05$

- Toxicokinetics of OBI-992 in cynomolgus monkeys revealed that the systemic exposure of ADC was similar to that of total antibody. Furthermore, the systemic exposure of ADC and total antibody were found to increase in a dose-proportional manner (data not shown).
- Major toxicities in monkeys were target-related skin lesions. The highest non-severely toxic dose (HNSTD) was determined to be 60 mg/kg (**Table 2**).

Table 2. OBI-992 Safety Evaluation in Cynomolgus Monkeys

OBI-992 toxicities in cynomolgus monkeys		
Tissue/organ	**Major findings**	**Reversibility**
Skin	Scaly skin, pigmentation	Yes
Hematology	Reduced reticulocytes counts; Reduced RBC counts; Reduced hemoglobin	Yes

RBC, red blood cell.

CONCLUSIONS

- OBI-992 exhibited better linker stability and lower systemic exposure of free payload compared with Dato-DXd.
- OBI-992 had lower association with human monocytes and lower toxicity in differentiating neutrophils and THP-1 cells compared with Dato-DXd, suggesting that OBI-992 may cause less off-target toxicity.
- OBI-992 demonstrated a superior PK profile and a robust antitumor effect that was better than that observed with the benchmark Dato-DXd.
- The HNSTD was determined to be 60 mg/kg, which is higher than that reported for Dato-DXd and Trodelvy.
- Initial safety findings in cynomolgus monkeys showed limited toxicity, supporting further clinical development of OBI-992.

References

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2. Marei HE, et al. *Cancer Cell Int*. 2022;22(1):255.
3. Nguyen TD, et al. *Cancers (Basel)*. 2023;15(3):713.

Disclosures

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