First-in-human, phase I study of CBP-1008, a bi-specific ligand drug conjugate, in patients with advanced solid tumors

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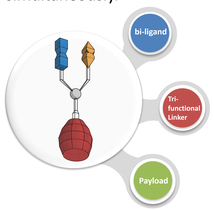
Bi-XDC's Synergies

Bi-XDC technology generates bi-ligand synergies on multiple dimensions by targeting to two receptors simultaneously.



Synergies:

- Pairing 2 undruggable targets to form a druggable target pair
- Overcome competition from endogenous ligands
- Fast penetration and enrichment in tumor cells

Bi-XDC's synergies come from the bi-ligand system. It deliver the conjugated payload into target cells highly efficient and specifically.

Theoretical explanation

Once Bi-XDC anchored on 2D cell membrane by one receptor , binding of 2nd receptor becomes a 2-dimensional cell surface event instead in a 3-D space, leading to higher binding affinity and overcoming of competition by endogenous ligands

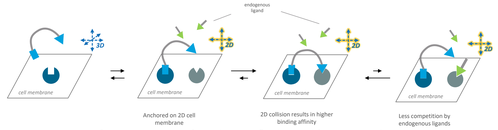


Figure 1. Mechanism of Bi-XDC's synergies

Strengthen binding affinity & Overcome competition

In the cell based binding experiments, More Bi-XDC bound than sum of 2 mono-ligand drug conjugates (Figure 2 left). After spiking endogenous ligands, Bi-XDC keep ~80% receptor binding, while mono-ligand lost >90% (Figure 2 right).

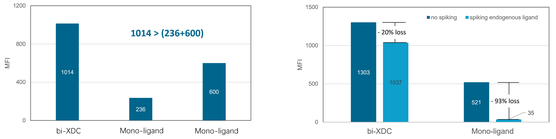


Figure 2. left: Cell surface receptor binding; right: after spiking endogenous ligand

Fast penetration and enrichment in tumor cells

bi-XDC penetrates into tumor tissues much faster than antibody. In receptor positive tumor model, it is enriched and sustained for long time.

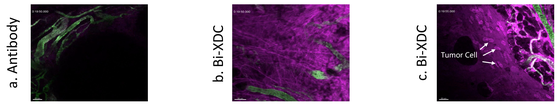


Figure 3. in-vivo a)Antibody

Background

- CBP-1008 is a first-in-class bi-specific ligand drug conjugate targeting **FRα** and **TRPV6** carrying monomethyl auristatin E (**MMAE**) as payload.
- CBP-1008 shows good anti-tumor activity in various PDX models. (Figure 4)
- Folate receptor α (FRα)[1] and vanilloid subfamily member 6 of transient receptor potential channels (TRPV6)[2,3] are overexpressed in many solid tumors including ovarian cancer hence could be promising therapeutic targets.

Tumor	PDX	FOLR1	TRPV6	TGI
Gastric Carcinoma	GA6844	8.4	2.8	67%
	GA0055	8.2	-2	69%
	GA2157	2.8	2.3	86%
	GA6212	0.6	6.8	76%
	GA0098	-1.6	-0.2	25%
	GA0074			100%
Esophageal Cancer	ES0136	1.4	3.3	95%
				100%
	ES0219	1.9	2.5	100%
				57%
Breast Cancer	BR2014	5.8	4.4	51%
	BR1115	3.4	2.3	100%
				71%
	BR1458	3.2	-2	94%
				54%
	BR1282	-1.6	-1.8	45%
				22%
Colorectal Cancer	CR0126	2.5	1.4	31%
	CR6222	7.5	-2	63%
	CR0205	-2	2.7	41%
Ovarian Cancer	OV0243	9.5	-2	24%
	OV0276	5.9	4.2	54%
	OV0250	4.9	-2	43%
Pancreatic Cancer	PA1644	5.2	4.2	43%
	PA6259	2.3	3.1	20%
				54%
				66%
Lung Cancer	LU6419	6.3	-1	54%
	LU1206	3.7	2.1	18%
	LU6421	-2	5.7	60%
				44%

Figure 4. Efficacy in various PDX models

Methods

CBP-1008 was administered by intravenous infusion.

The primary objective was to assess the safety and preliminary efficacy. (Figure 5)

Phase Ia:

- A dose-escalation period initiated by accelerated titration (0.015, 0.03mg/kg d1,15; q28d) and then switched to 3+3 scheme (0.12, 0.15, 0.17, 0.18mg/kg d1,15; q28d)
- A dose expansion period

Phase Ib/IIa: clinical expansion study included 3 cohorts

- Platinum-resistant ovarian cancer (PROC)
- Metastatic triple negative breast cancer (TNBC)
- Other solid tumors

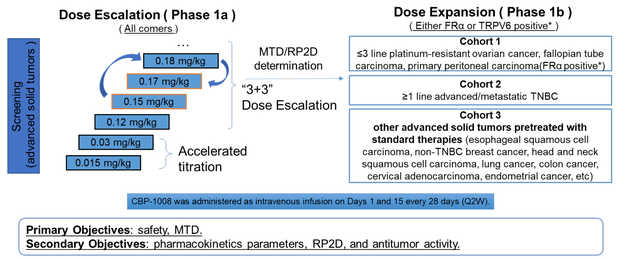


Figure 5. An open-label, multi-center, first-in-human phase 1 clinical study (NCT04740398).

Results

As of September 30, 2022, 178 patients received at least one dose of study drug were enrolled (phase Ia: n=35; phase Ib: n=143) and received median 3 prior regimens.

Included tumor species were:

- PROC (n=101)
- TNBC (n=25)
- ER+/Her2+ breast cancer (BC) (n=17)
- colorectal cancer (n=6)
- pancreatic cancer (n=12)
- others (n=17)

In phase Ia study, DLTs were observed in 3 patients (0.12, 0.15, 0.18mg/kg, n=1 each), including grade 4 hypophosphatemia, neutropenia, febrile neutropenia, and grade 3 hyperglycemia, alanine aminotransferase (ALT) elevation.

MTD was not yet reached. Majority of adverse events were mild to moderate.

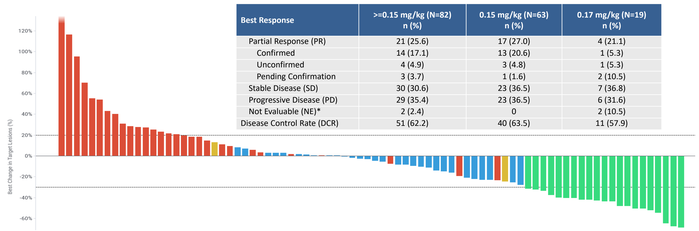
In phase Ib/IIa study, grade 3/4 treatment-emerging adverse events (TEAEs) occurred in ≥ 3% subjects were neutropenia (n=85), decreased leukocyte count (n=49), anaemia (n=10), AST elevation (n=7), ALT elevation (n=7). Drug-related death was observed in 1 patient.

Preferred Term, n (%)	Total (N=178)	
	Any grade (%)	Grade ≥3 (%)
Neutrophil count decreased	144 (80.9)	85 (47.8)
White blood cell count decreased	137 (77.0)	49 (27.5)
Pyrexia	127 (71.3)	0
Aspartate aminotransferase increased	116 (65.2)	7 (3.9)
Nausea	91 (51.1)	3 (1.7)
Alanine aminotransferase increased	90 (50.6)	7 (3.9)
Vomiting	83 (46.6)	1 (0.6)
Decreased appetite	70 (39.3)	2 (1.1)
Anaemia	67 (37.6)	10 (5.6)
Haemoglobin decreased	60 (33.7)	4 (2.2)
Diarrhoea	56 (31.5)	2 (1.1)
Blood glucose increased	51 (28.7)	3 (1.7)
Asthenia	49 (27.5)	2 (1.1)
Alopecia	48 (27.0)	0
Protein urine present	42 (23.6)	0

A total of 82 PROC patients at dose of 0.15mg/kg or above were evaluable for efficacy assessment. (Figure 6)

- 21 patients achieved partial response (PR); 30 patients achieved stable disease (SD).
- Objective response rate (ORR) was 25.6%; Disease control rate (DCR) was 62.2%.
- Median progression-free survival (mPFS) was 3.7 months (95% CI: 2.7-5.1).
- In 34 PROC patients with FRα expression ≥25% and ≤3 prior treatment regimens, ORR was 32.4% and mPFS was still 3.7 months (95% CI: 3.3-7.3).

Given the small sample size, efficacy data of breast cancer and other solid tumors will be analyzed after recruiting more patients.



Best Response	>=0.15 mg/kg (N=82) n (%)	0.15 mg/kg (N=63) n (%)	0.17 mg/kg (N=19) n (%)
Partial Response (PR)	21 (25.6)	17 (27.0)	4 (21.1)
Confirmed	14 (17.1)	13 (20.6)	1 (5.3)
Unconfirmed	4 (4.9)	3 (4.8)	1 (5.3)
Pending Confirmation	3 (3.7)	1 (1.6)	2 (10.5)
Stable Disease (SD)	30 (30.6)	23 (36.5)	7 (36.8)
Progressive Disease (PD)	29 (35.4)	23 (36.5)	6 (31.6)
Not Evaluable (NE)*	2 (2.4)	0	2 (10.5)
Disease Control Rate (DCR)	51 (62.2)	40 (63.5)	11 (57.9)

Figure 6. Efficacy assessment of 82 PROC patients at dose of 0.15mg/kg or above

Conclusion

The current result showed that CBP-1008 has manageable safety profile. Antitumor activity was observed in PROC patients at dose of 0.15mg/kg or above, especially in PROC patients with FRα expression ≥25% and ≤3 prior treatment regimens.

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