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Abstract # 5556

First-in-human, phase I study of CBP-1008, a first-in-class bi-specific ligand drug conjugate (Bi-XDC), in patients with advanced solid tumors

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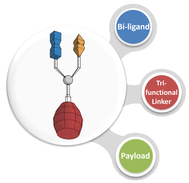
COHERENT BIOPHARMA

Background

Bi-XDC technology generates bi-ligand synergies on multiple dimensions by targeting 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

- Folate receptor α (FRα) and vanilloid subfamily member 6 of transient receptor potential channels (TRPV6) are potential promising therapeutic targets due to their high expression level in many solid tumors including ovarian cancer.
- **CBP-1008** is a first-in-class (FIC) bi-specific ligand drug conjugate targeting FRα and TRPV6 carrying monomethyl auristatin E (MMAE) as payload.

Method

- CBP-1008 was administered by intravenous infusion Q2W.
- The primary objective was to assess the safety and preliminary efficacy.
- Phase Ia: dose-escalation study:
  - The phase Ia started with accelerated titration (0.015, 0.03 mg/kg) and then switched to 3+3 design (0.12, 0.15, 0.17, 0.18, 0.20 mg/kg).
- Phase Ib: dose-expansion study included 4 cohorts:
  - HGSOC;
  - TNBC;
  - Other solid tumors;
  - Other sub-types of ovarian cancer such as OCCC and LGSOC.

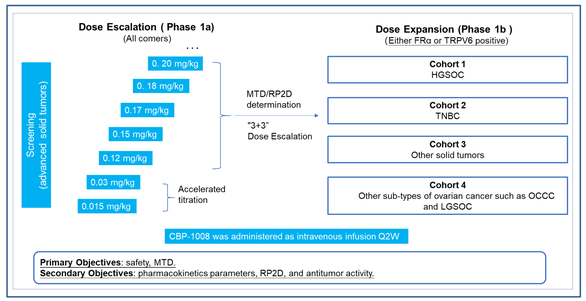


Figure 1. Phase 1 Clinical Study Design (NCT04740398)

MTD: Maximum tolerated dose; RP2D: Recommended phase 2 dose; TNBC: Triple-negative breast cancer; OCCC: Ovarian clear cell carcinoma; HGSOC: High-grade serous ovarian cancer; LGSOC: Low-grade serous ovarian cancer.

Results

Patients

- As of Mar 12, 2024, 267 patients (phase Ia: n=41; phase Ib: n=226) have been enrolled.

Table 1. Baseline Demographics and Characteristics (Ovarian Cancer)

	Ovarian Cancer[1]
Patient Numbers (N)	179
Age, Median (range)	54 (23-70)
Sex, n (%)	
Female	179 (100.0)
Male	——
ECOG, n (%)	
0	70 (39.1)
1	109 (60.9)
FRα expression (2+, and 3+), n (%)	
0% - 49%	84 (46.9)
50% -74%	46 (25.6)
≥75%	48 (27.1)
NE	1 (0.6)
Prior systemic therapy, n (%)	
1-3 Lines	128 (71.5)
≥ 4 Lines	51 (28.5)
Prior TIT[2] exposure, n (%)	
NO	2 (1.1)
prior 1L	44 (4.6)
prior 2L	67 (37.4)
prior ≥3L	66 (36.9)
Prior Bevacizumab exposure, n (%)	
Yes	98 (54.7)
No	81 (45.3)
Prior PARPi exposure, n (%)	
Yes	105 (58.7)
No	74 (41.3)

[1] Ovarian Cancer includes HGSOC and OCCC.
[2] TIT: Taxane-included treatments; Taxane includes Paclitaxel, Docetaxel, Paclitaxel Liposome for Injection, Albumin-Bound Paclitaxel.

Safety

- MTD has not yet reached at dose escalation.
- Most adverse events were mild to moderate without significant eye toxicity[1] (2.7%, Grade1) and peripheral neuropathy[2] (8.6%, Grades 1-2) which were often seen in ADCs with MMAE payload.
- The 0.15mg/kg dose cohort demonstrated favorable safety profile.
- Common treatment-related adverse events (TRAEs) were neutropenia, WBC decreased, AST increased, pyrexia, ALT increased and nausea.
- 16 pts (6.0%) appeared dose reduction due to TRAEs.
- 13 pts (4.9%) discontinued CBP-1008 due to TRAEs.

[1] Eye toxicity: Dry eye/ Periorbital edema/ Blurred vision/ Eyelid edema;
[2] Peripheral neuropathy: Decreased sensation/ Peripheral sensory neuropathy/ Neuralgia/ Neuromuscular pain.

Efficacy

Platinum-resistant Ovarian Cancer (PROC)

- Promising efficacy was observed in HGSOC patients (pts) who received prior 1-2L of TIT (if prior 2L, ≥12m of time interval between 2L; and ≥3m of time interval from the last TIT to CBP-1008 first dose).
- The ORR is 48.3%(14/29) and DCR is 82.8%(24/29), regardless of FRα expression.

Table 3. Clinical Efficacy in PROC

	0.15 mg/kg prior 1 or 2L TIT [1] (N = 29) n (%)
Best of Response	
Partial Response (PR)	14 (48.3)
Stable Disease (SD)	10 (34.5)
Progressive Disease(PD)	5 (17.2)
Objective Response Rate(ORR)	**14 (48.3)**
Disease Control Rate (DCR)	**24 (82.8)**

[1] Prior 1 or 2L TIT: interval between 2L TIT ≥12m; interval from the last TIT to CBP-1008 1st dose ≥3m

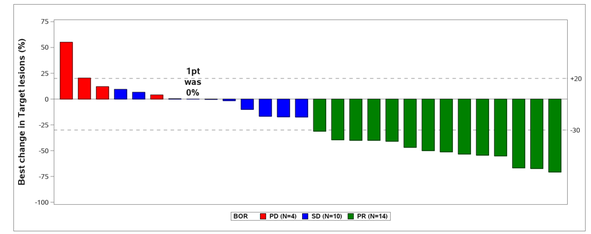


Figure 2. Best Changes of Target Lesions in Evaluated HGSOC Pts with Prior 1-2L of TIT[1].

[1] The target lesion in one pt was assessed as not evaluable (NE) due to effusion interference, and overallefficacy was deemed PD due to the emergence of new lesions, not deplcted in the waterfall plot.

Platinum Resistant OCCC

- OCCC accounts for 5% to 25% of OC[1], and current treatment options have very poor ORR of <10%[2-3].
- The ORR of CBP-1008 (0.15 or 0.17 mg/kg) for OCCC pts was 31.3% (5/16), regardless of FRα expression.

Table 4. Promising Efficacy in Platinum Resistant OCCC

	Platinum-resistant OCCC (N = 16) n, (%)
Best of Response	
PR	5 (31.3)
SD	5 (31.3)
PD	6 (37.4)
ORR	**5 (31.3)**
DCR	**10 (62.5)**

[1] Anglesio MS et al., Gynecologic Oncology 2011, 121: 407–415.
[2] Takano M et al., Int J Gynecol Cancer 2008, 18: 937–942.
[3] David RC et al, Gynecologic Oncology 2007, 105: 404-408.

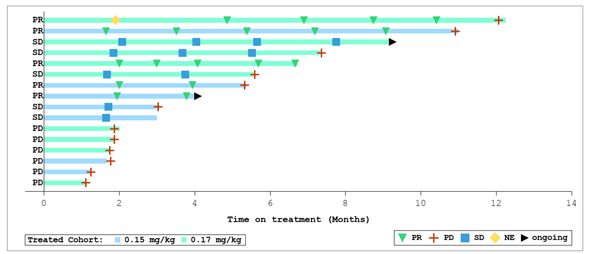


Figure 3. Treatment Duration and Response in Pts with OCCC (N=16)

Conclusions

- CBP-1008, as the FIC Bi-XDC globally, exhibits the characteristic of targeted supper chemotherapy:
  - Tolerable and manageable safety profile with less dose adjustment,
  - Without significant concern of ocular toxicity and peripheral neuropathy commonly seen in MMAE ADCs.
  - Promising antitumor activity was observed in ovarian cancer patients at dose of 0.15mg/kg, especially in platinum-resistant HGSOC patients who received prior 1-2L of TIT (if prior 2L , ≥12m of time interval between 2L ; and ≥3m of time interval from the last TIT to CBP-1008 first dose).
  - CBP-1008 showed the potential to be a better treatment option for ovarian cancer especially for OCCC regardless of FRα expression levels.
  - The remarkable efficacy and favorable safety profile in PROC will be further confirmed in the future pivotal trial.

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