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CBP-1018, a Bi-Ligand-Drug Conjugate treated in Patients with Advanced Solid Tumors: A Phase 1, Multi-Center, Open-Label, Dose-Escalation and Dose Expansion Study

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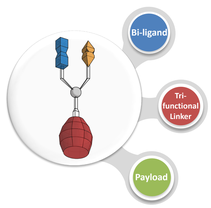
COHERENT BIOPHARMA

Introduction

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

Bi-XDC's Synergies

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

◆ **Theoretical explanation**

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

◆ **Strengthen binding affinity & Overcome competition**

In the cell based binding experiments, more Bi-XDC bound than sum of 2 mono-ligand drug conjugates (Figure 1 left). After spiking endogenous ligands, Bi-XDC kept ~80% receptor binding, while mono-ligand lost >90% (Figure 1 right).

◆ **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.

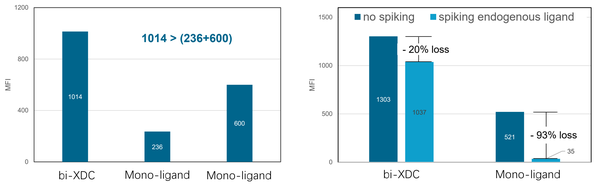


Figure 1. left: Cell surface receptor binding; right: after spiking endogenous ligand

TAG-Display Platform

Target **A**ctivated ligand-pair **G**eneration **Display** – technology for High-throughput screening of Bi-ligand pair.

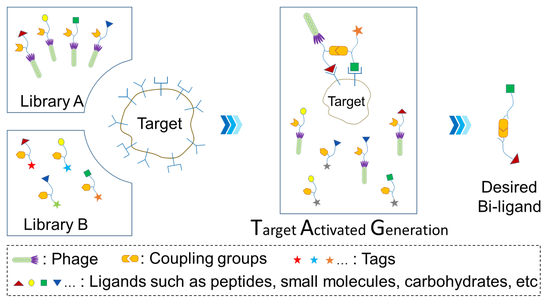


Figure 2. Diagram of TAG-Display platform

Background

Prostate-specific membrane antigen (PSMA) or folate hydrolase 1 (FOLH1) is highly expressed on prostate cancer and folate receptor α (FRα) overexpressed in various malignant tissues, which both related to tumor invasiveness. CBP-1018 is a first-in-class bi-ligand-drug conjugate targeting both PSMA and FRα with monomethyl auristatin E (MMAE) as payload.

Nonclinical Efficacy

- CBP-1018 shows good anti-tumor activity in various PDX&CDX models of lung cancer, ovarian cancer, prostate cancer, breast cancer and pancreatic cancer, up to 96% TGI.

Nonclinical toxicology

- Single-dose MTD of CBP-1018 is 4 mg/kg (SD rat) and 3 mg/kg (monkey).
- Repeat-dose MTD of CBP-1018 is 2 mg/kg (SD rat) and 3 mg/kg (monkey).
- Main toxicities are same as MMAE.
- No significant toxicity in cardiovascular, nervous, or respiratory system.

Nonclinical pharmacokinetics and pharmacodynamics

- CBP-1018 in plasma rapidly decreased, basically to the lower limit of quantitation (LOQ) at 1 to 2 hours.
- CBP-1018 fast distributed in several organs, and then fast cleared through kidney.
- Released MMAE mainly enriched and sustained in tumors.

Methods

This phase 1 study included both a dose-escalation stage and expansion stage.

- An accelerated titration was conducted in single patient at 0.03mg/kg and 0.06 mg/kg, followed by an i3+3 design for dose levels (DLs) ≥ 0.08 mg/kg, Q2W (IV.) in a 4-week cycle.
- Patients (pts) with metastatic castration resistant prostate cancer (mCRPC) which had experienced standard treatment failure or intolerance were enrolled.
- To evaluate the safety and tolerability, determine dose limiting toxicity (DLT) and maximum tolerated dose (MTD).
- Pharmacokinetics (PK) and preliminary efficacy will also be evaluated.

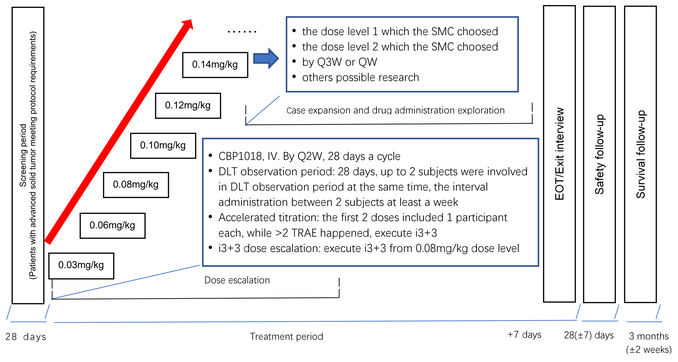


Figure 3. Dose escalation design of CBP-1018

Conclusions

CBP-1018 was well-tolerated at DLs of 0.03-0.14 mg/kg Q2W. Multiple SD and PSA decrease were observed at DLs of 0.06-0.14 mg/kg, conferred a promising preliminary antitumor activity in pts with mCRPC. No DLT observed in any DLs. MTD was not reached and dose-escalation to establish the RP2D is continuing.

Results

As of 30 June 2023, 24 pts (22 mCRPC, 1 bladder cancer and 1 ureteral carcinoma) were enrolled at 6 dose levels (DLs). No DLTs were observed in any dose level. Most common treatment-emergent adverse events (TEAEs) ≥ grade 3 were neutrophil decrease (45.8%), WBC decrease (37.5%), Lymphocyte count decreased (25.0%), Gamma-glutamyltransferase increased (16.7%), and hypertriglyceridaemia (12.5%). Among 18 evaluable mCRPC pts, 1 PR，8 SD and 5 Non-PD were observed. Prostate-specific antigen (PSA) 50% decrease was detected in 2 pts. The median PFS was 7.2 months (95%CI, 1.9-NE) in mCRPC pts.

Table 1. Summary of Demographic and Baseline Characteristics

Analysis variables / Classification	0.03 mg/kg N=1	0.06 mg/kg N=3	0.08 mg/kg N=3	0.10 mg/kg N=3	0.12 mg/kg N=6	0.14 mg/kg N=7	0.16 mg/kg N=1	Total N=24
Sex, N(%)								
Male	0(0.0)	2(66.7)	3(100.0)	3(100.0)	6(100.0)	7(100.0)	1(100.0)	22(91.7)
Female	1(100.0)	1(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
Age (year)								
Median (range)	57.0(57.0,57.0)	69.0(67.0,77.0)	73.0(69.0,75.0)	73.0(72.0,78.0)	71.0(60.0,74.0)	67.0(60.0,74.0)	66.0(66.0,66.0)	69.5(57.0,78.0)
BMI (kg/m^2)								
Median (range)	27.3(27.3,27.3)	24.7(24.3,25.9)	25.8(16.3,26.8)	23.0(22.8,23.4)	25.2(22.8,32.3)	24.0(21.1,27.8)	22.9(22.9,22.9)	24.7(16.3,32.3)
Tumor type, N(%)								
Prostate cancer	0(0.0)	2(66.7)	3(100.0)	3(100.0)	6(100.0)	7(100.0)	1(100.0)	22(91.7)
Non-prostate cancer	1(100.0)	1(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
Clinical stage, N(%)								
Stage I-III	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Stage IV	1(100.0)	3(100.0)	3(100.0)	3(100.0)	6(100.0)	7(100.0)	1(100.0)	24(100.0)
ECOG, N(%)								
0	0(0.0)	1(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
1	1(100.0)	2(66.7)	3(100.0)	3(100.0)	6(100.0)	7(100.0)	1(100.0)	23(95.8)
Prior treatment with chemotherapy, N (%)								
Yes	1(100.0)	3(100.0)	2(66.7)	2(66.7)	4(66.7)	3(42.9)	0(0.0)	15(62.5)
No	0(0.0)	0(0.0)	1(33.3)	1(33.3)	2(33.3)	4(57.1)	1(100.0)	9(37.5)

Table 2. Analysis of adverse events

Analysis variables / Classification	0.03 mg/kg (N=1) n (%)	0.06 mg/kg (N=3) n (%)	0.08 mg/kg (N=3) n (%)	0.10 mg/kg (N=3) n (%)	0.12 mg/kg (N=6) n (%)	0.14 mg/kg (N=7) n (%)	0.16 mg/kg (N=1) n (%)	Total (N=24) n (%)
DLT*1	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
TEAE*2	1(100.0)	3(100.0)	3(100.0)	3(100.0)	6(100.0)	7(100.0)	1(100.0)	24(100.0)
≥Grade 3 TEAE	1(100.0)	2(66.7)	2(66.7)	2(66.7)	6(100.0)	4(57.1)	0(0.0)	17(70.8)
TEAE led to dose reduction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	1(4.2)
TEAE led to treatment interruption	1(100.0)	1(33.3)	1(33.3)	0(0.0)	2(33.3)	1(14.3)	0(0.0)	6(33.3)
TEAE led to treatment discontinuation	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
TEAE led to death	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Serious adverse events (SAE)	1(100.0)	0(0.0)	0(0.0)	2(66.7)	2(33.3)	0(0.0)	0(0.0)	5(20.8)
Drug-related ≥Grade 3 TEAE*3	1(100.0)	2(66.7)	2(66.7)	2(66.7)	6(100.0)	4(57.1)	0(0.0)	17(70.8)
Drug-related TEAE led to dose reduction*3	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	1(4.2)
Drug-related TEAE led to treatment interruption*3	1(100.0)	1(33.3)	0(0.0)	0(0.0)	0(0.0)	1(14.3)	0(0.0)	3(12.5)
Drug-related TEAE led to treatment discontinuation*3	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Drug-related TEAE led to death*3	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Drug-related SAE*3	1(100.0)	0(0.0)	0(0.0)	0(0.0)	2(33.3)	0(0.0)	0(0.0)	3(12.5)

*1: Dose-limiting toxicity.
*2: Treatment emergent adverse event.
*3: Drug-related TEAE: Includes definitely、likely or possibly drug related TEAE.

Table 3. Analysis of tumor efficacy evaluation (Best of Overall Response*3 and PFS)

Analysis variables / Classification	0.03mg/kg N=1 n (%)	0.06mg/kg N=3 n (%)	0.08mg/kg N=3 n (%)	0.10mg/kg N=3 n (%)	0.12mg/kg N=4 n (%)	0.14mg/kg N=4 n (%)	Total N=18*2 n (%)
CR	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
PR	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0) *1	1(5.6)
SD	0(0.0)	1(33.3)	1(33.3)	1(33.3)	3(75.0)	2(50.0)	8(44.4)
Non-PD	0(0.0)	1(33.3)	0(0.0)	2(66.7)	1(25.0)	1(25.0)	5(27.8)
PD	1(100.0)	1(33.3)	2(66.7)	0(0.0)	0(0.0)	0(0.0)	4(22.2)
NE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
ORR（CR + PR）	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	1(5.6)
DCR（CR + PR+SD）	0(0.0)	1(33.3)	1(33.3)	1(33.3)	3(75.0)	3(75.0)	9(50.0)
PFS							
N	1	3	3	3	4	4	18
Median (95%CI)	/	7.2(1.7~NE)	1.6(1.4~NE)	6.5(5.0~NE)	NR*4	NR*4	7.2(1.9~NE)

*1: PR for one prostate cancer subject.
*2: As the cut-off date of June 30, 2023, 6 subjects out of ITT was not included in this tumor efficacy evaluation due to below reasons: 2 subjects (0.12 mg/kg group) were not evaluated after treatment due to early withdrawal, 3 subjects (0.14mg/kg group) and 1 subject (0.16mg/kg group) did not reach the tumor assessment time by the cut-off date.
*3: Based on RECIST version 1.1 and PCWG3 criteria.
*4: Have no PFS events by the cut-off date.

For PK profile of CBP-1018 and free MMAE, $t_{1/2z}$ was ranged 0.54-1.15 h and 38.27-57.27 h, respectively, no accumulation of both substances after multiple doses.

- T_{max} of CBP-1018 was at the end of administration, then decreased rapidly.
- PK exposure of CBP-1018 in plasma increased with the increase of dose.
- T_{max} of MMAE was at about 2 h after administration, then decreased slowly.
- C_{max} of MMAE in plasma was much lower than that of CBP-1018, indicating that the plasma MMAE was gradually, slowly and continuously released after drug administration, which was consistent with the mechanism of action of the coupled drug.
- No accumulation of CBP-1018 and MMAE after multiple dosing.

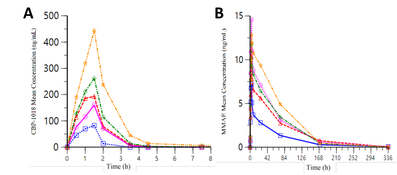


Figure 4. Mean plasma concentration-time plot of CBP-1018 (A) and MMAE (B) after the first administration

Table 4. PK parameters of CBP-1018 after the first administration

Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$T_{1/2}$* (h)	T_{max}* (h)
0.06 (n=3)	82.6±28.3	97.1±43.2	120.7±69.0	0.95 (0.61~1.40)	1.5 (1.5~1.5)
0.08 (n=3)	217±4.6	311.6±47.9	365.3±NA	1.15 (1.15~1.15)	1.5 (1.0~1.5)
0.10 (n=3)	160.3±49.7	218.5±120.1	360.1±NA	0.54 (0.54~0.54)	1.5 (1.5~1.5)
0.12 (n=6)	281.7±80.9	399.0±188.7	618.7±104.2	0.74 (0.46~1.02)	1.5 (1.5~1.5)
0.14 (n=4)	443.8±34.3	757.8±74.9	767.9±78.4	1.12 (0.97~1.16)	1.5 (1.5~1.5)

Table 5. PK parameters of MMAE after the first administration

Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$T_{1/2}$* (h)	T_{max}* (h)
0.06 (n=3)	7.4±0.9	271.7±57.0	283.4±51.3	57.27 (41.95~69.4)	3.5 (2.0~3.5)
0.08 (n=3)	10.4±1.2	516.8±123.8	537.7±128.3	43.72 (36.59~46.64)	3.5 (2.0~3.5)
0.10 (n=3)	14.6±5.3	622.8±110.8	635.3±106.7	44.57 (37.22~52.15)	3.5 (3.5~3.5)
0.12 (n=6)	11.9±6.7	560.8±234.8	582.3±252.4	38.27 (21.25~45.79)	3.5 (3.5~4.5)
0.14 (n=4)	12.9±1.2	737.5±179.4	932.4±407.0	43.31 (31.88~78.56)	3.5 (3.5~4.5)

*T_{max}、$T_{1/2}$: Median (Min-Max), intravenous infusion for 1.5h (0h=Start Infusion)

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