2024 ASCO ANNUAL MEETING

Abstract # 5047

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

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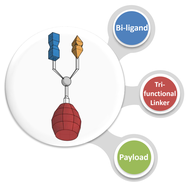
## Background

**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

CBP-1018 is a first-in-class (FIC) 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.

## Method

This is an ongoing, open-label, phase I study in advanced solid tumors, conducted in two stages: dose-escalation and dose-expansion.
- In the dose-escalation stage, an accelerated titration was initiated at 0.03 mg/kg Q2W, followed by a standard "3+3" from 0.06 to 0.18 mg/kg.
- In the dose-expansion stage, selected dose levels were further investigated.

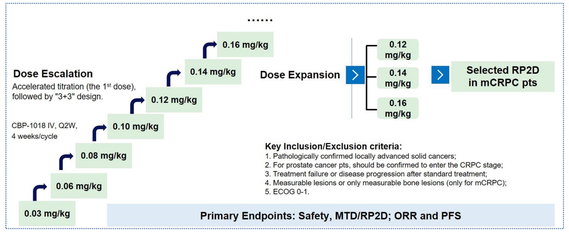



**Figure 1.** Study Design Schemes

## Results

### Patients
- By 31 Dec. 2023, 59 pts were enrolled. 21 pts in dose-escalation stage received dose levels 0.03 - 0.16 mg/kg, and 38 pts in dose-expansion stage received dose levels 0.12 and 0.14 mg/kg. The median age of all subjects was 67.5 years. 89.8% of them have an ECOG score of 1 at baseline. 44.1% of the subjects had visceral metastases, and 78.0% had bone metastases.
- Most of the subjects (96.6%, 57/59) were mCRPC, with a median PSA of 82.2 ug/L (range: 0.0, 2994.7) at baseline. All of them have been heavily treated, and the median number of prior lines of therapy is 6 (79.7% with chemotherapy, 94.9% with NHA and 76.3% with both).

**Table 1.** Summary of Demographic and Baseline Characteristics

| Analysis variables | 0.03-0.10 mg/kg N=10 | 0.12 mg/kg N=17 | 0.14 mg/kg N=29 | 0.16 mg/kg N=3 | Total N=59 |
|---|---|---|---|---|---|
| **Sex，N(%)** | | | | | |
| Male | 8 (80.0 ) | 17(100.0) | 29(100.0) | 3(100.0) | 57(96.6) |
| Female | 2 (20.0 ) | 0(0.0) | 0(0.0) | 0(0.0) | 2(3.4) |
| **Age (years)** | | | | | |
| Median (Min, Max) | 72.5(57.0 , 78.0 ) | 68.0(50.0,75.0) | 67.0(54.0,78.0) | 63.5(57.0,66.0) | 67.5(50.0,78.0) |
| **ECOG，N(%)** | | | | | |
| 0 | 1 ( 10.0 ) | 0(0.0) | 5(17.2) | 0(0.0) | 6(10.2) |
| 1 | 9 ( 90.0 ) | 17(100.0) | 24(82.8) | 3(100.0) | 53(89.8) |
| **Tumor type, N (%)** | | | | | |
| Prostate cancer | 8 ( 80.0 ) | 17(100.0) | 29(93.1) | 3(100.0) | 57(96.6) |
| Non-prostate cancer | 2 ( 20.0 ) | 0(0.0) | 0(0.0) | 0(0.0) | 2(3.4) |
| **Baseline PSA (ug/L)** | | | | | |
| Median | 34.5 | 170.0 | 58.7 | 89.0 | 82.2 |
| Min, Max | 8.1 , 759.0 | 0.0,1805.4 | 0.0,2994.7 | 5.7,201.0 | 0.0,2994.7 |
| **Metastases sites, N(%)** | | | | | |
| Visceral metastases* | 7(70.0) | 9(52.9) | 9(31.0) | 1(66.6) | 26(44.1) |
| Bone metastases | 8(80.0) | 14(82.4) | 21(72.4) | 3(100.0) | 46(78.0) |
| **Prior chemotherapy, N(%)** | 8(80.0) | 15(88.2) | 24(82.8) | 0(0.0) | 47(79.7) |
| **Prior NHA, N(%)** | 8(80.0) | 16(94.1) | 29(100.0) | 3(100.0) | 56(94.9) |
| **Prior chemotherapy & NHA, N (%)** | 6(60.0) | 15(88.2) | 24(82.8) | 0(0.0) | 45(76.3) |

*Visceral metastases include lungs, liver, bladder, adrenal glands, seminal vesicles.

### Safety
- No DLT was observed and MTD was not reached in dose-escalation stage.
- The majority of treatment-related adverse events (TRAEs) were grade 1 or 2.
- The most common ≥grade 3 TRAEs mainly included neutrophil count decreased (30.5%), WBC count decreased (20.3%), lymphocytes count decreased (13.6%), hypertriglyceridemia (11.9%), hypokalemia (8.5%), gamma-glutamyl transferase increased (6.8%) and anemia (5.1%). Most of them can be recovered in short days with supportive treatment.
- Only 2 (3.4%) subjects experienced TRAE leading to dose reduction or treatment discontinuation, without TRAEs resulted in death.

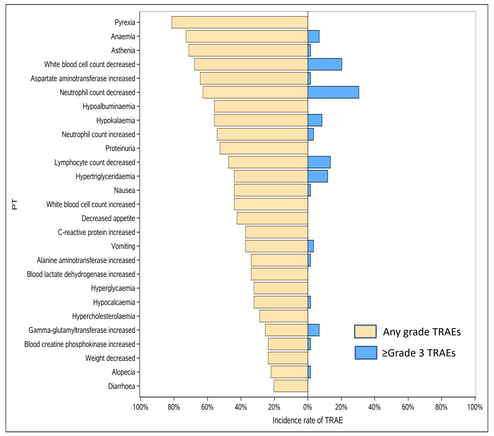



**Figure 2.** Any Grade TRAEs (≥20%) and ≥Grade 3 TRAEs in All Dose Levels

### Efficacy
- In all mCRPC subjects who received CBP-1018, better efficacy signals were observed in subjects with dose level ≥0.14 mg/kg: 52.0% of the subjects had PSA decreased after treatment. According to RECIST v1.1, the ORR was 33.3% and DCR was 100% based on 9 evaluable pts with target lesions.
- The median radiographic progression-free survival (rPFS) was 9.2 months in all mCRPC. Specifically, the median rPFS was 5.0 months for pts who previously treated by systematic chemotherapy per RECIST 1.1 and PCWG3.

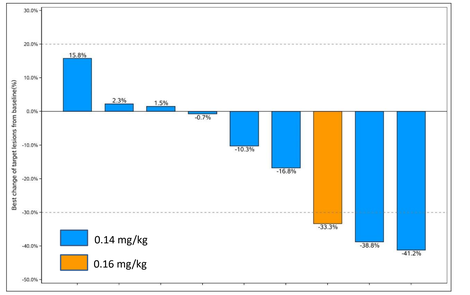



**Figure 3.** Target Lesions Changes (%) from Baseline per RECIST v1.1

**Table 2.** Best Overall Response per RECIST V1.1

| Analysis variables Classification | Cohort 6 0.14 mg/kg (N=8) | Cohort 7 0.16 mg/kg (N=1) | Cohort 6+7 0.14+0.16 mg/kg (N=9) |
|---|---|---|---|
| CR | 0 (0) | 0 (0) | 0 (0) |
| PR | 2 (25.0%) | 1 (100%) | 3 (33.3%) |
| SD | 6 (75.0%) | 0 (0) | 6 (66.7%) |
| PD | 0 (0) | 0 (0) | 0 (0) |
| **cORR, %** | 2 (25.0%) | 1 (100%) | 3 (33.3%) |
| **DCR, %** | 8 (100.0%) | 1 (100%) | 9 (100%) |

### Pharmacokinetics
- The exposure levels of CBP-1018 and MMAE increased with escalating doses;
- $T_{max}$ of CBP-1018 was reached by the end of administration;
- $C_{max}$ of MMAE in plasma was much lower than that of CBP-1018;
- Rapid clearance of MMAE reduces the probability of accumulation;
- PK profile indicates superior safety potential.

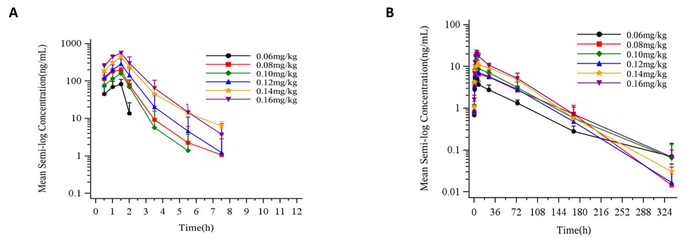



**Figure 4.** Mean Plasma Concentration-time Plot of CBP-1018 (A) and MMAE (B) after the First Administration

## Conclusions

- **The dose of CBP-1018, the FIC bi-XDC globally, was escalated from 0.03 mg/kg to 0.16 mg/kg. No DLT was not observed and the MTD has not yet been reached.**
- **CBP-1018, at dose level of ≥0.14 mg/kg Q2W, has showed a promising preliminary efficacy and a well-tolerated safety profile, supporting further investigation in mCRPC patients to determine the optimal dose and further confirmation in a large scale population.**

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