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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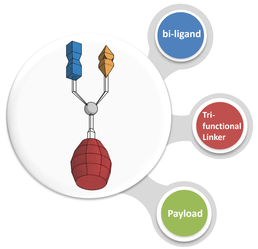
Introduction

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

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 with the 2nd receptor becomes a 2-dimensional cell surface event instead of a 3-D space, leading to higher binding affinity and overcoming of competition by endogenous ligands.

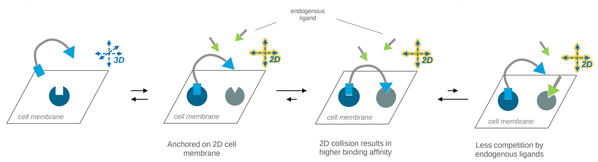


Figure 1. Mechanism of Bi-XDC's synergies

Strengthen binding affinity & Overcome competition

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

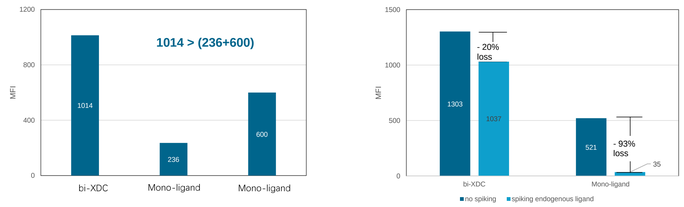
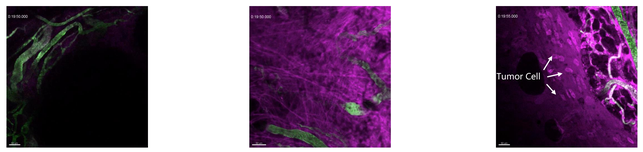


Figure 2. left: Cell surface receptor binding; right: after spiking endogenous ligand

Fast penetration and enrichment in tumor cells

Bi-XDC penetrates into tumor tissues much faster than antibody or ADC. In receptor positive tumor model, it is enriched and retained in cell for long time.



a. Antibody b. Bi-XDC c. Bi-XDC

Figure 3. in-vivo drug penetration and enrichment: a. Slow antibody penetration , b. Fast Bi-XDC penetration, c. Enrichment of Bi-XDC in receptor expressing tumors

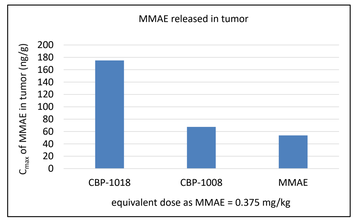
Background

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 pharmacology

- For FRα/PSMA positive tumor, CBP-1018 deliver more MMAE than CBP-1008 (CBP's first Bi-XDC) and MMAE itself do at the same molar dose. (Figure 4a)
- In-vivo PDX model, CBP-1018 shows superior efficacy than MMAE, through targeting delivery of payload into tumor cells provided by bi-ligand synergy. (Figure 4b)
- CBP-1018 shows good anti-tumor activity in various PDX & CDX models. (Figure 5)

a)



b)

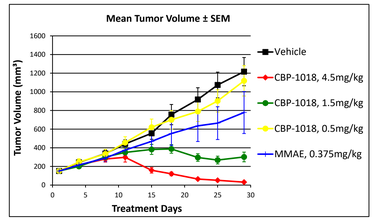


Figure 4. Efficacy in PDX model comparing to MMAE, a) delivery of MMAE into tumor of PDX model b) efficacy in lung cancer PDX models

Cancer	Model	TGI
Lung Cancer	LU0367	71%
	LU1160	88%
	LU1380	33%
	LU1480	20%
	LU2514	89%
	LU6412	94%
Ovarian Cancer	OV2015	57%
	OV2017	66%
	OV2546	52%
Prostate Cancer	LNCAP	96%
Breast Cancer	BR0438	71%
	BR1283	96%
Pancreatic Cancer	PA1644	52%

Figure 5. Efficacy in other PDX & CDX models

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 the same as MMAE.
- No significant toxicity in cardiovascular, nervous, or respiratory system.

Nonclinical pharmacokinetics and pharmacodynamics

- CBP-1018 in plasma rapidly decreased, basically below the LOQ at 1 to 2 hours.
- CBP-1018 distributed fast in several organs, and then rapidly cleared through kidney. (Figure 6)
- Released MMAE mainly enriched and sustained in tumor. (Figure 7)

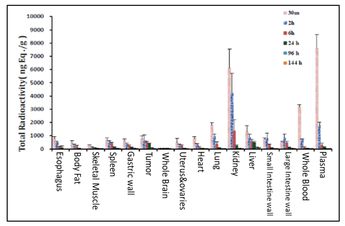


Figure 6. Distribution (radio labelled CBP-1018)

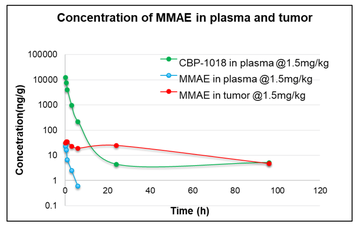


Figure 7. Concentration of MMAE in plasma and tumor

Methods

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

- An accelerated titration was conducted in single patient at 0.03 mg/kg followed by an i3+3 design for dose levels (DLs) ≥ 0.06 mg/kg, Q2W in a 4-week cycle.
- Mainly enrolled patients (pts) with metastatic castration resistant prostate cancer (mCRPC) received a median 3.5 prior lines of treatment.
- The primary objectives were to evaluate the safety and tolerability, determine dose limiting toxicity (DLT) and maximum tolerated dose (MTD).
- Pharmacokinetics (PK) and preliminary efficacy.

Results

- 14 pts (12 mCRPC, 1 bladder cancer and 1 ureteral carcinoma) were enrolled at 5 DLs (1 pt at 0.03 mg/kg, 3 pts each at 0.06, 0.08, 0.10 mg/kg, 4 pts at 0.12 mg/kg).
- No DLTs or drug-related deaths were observed.
- For 9 pts (64.3%) experienced treatment-related adverse events (TRAEs) ≥ grade 3
  - Neutrophil decrease (35.7%)
  - WBC decrease (28.6%)
  - Lymphocyte decrease (14.3%)
  - Elevated GGT (14.3%)
  - Hypertriglyceridaemia (14.3%)
- Among 10 efficacy evaluable pts with mCRPC
  - 3 SD were observed at DLs of 0.08, 0.10, and 0.12 mg/kg
  - 4 non-PD at 0.06, 0.10, and 0.12 mg/kg
  - 3 PD at 0.06 and 0.08 mg/kg
  - Decrease of prostate-specific antigen (PSA) was detected in 3 pts at 0.10 mg/kg.
- Overall median PFS was 7.2 months (95%CI, 1.7-9.3) and not reached in mCRPC pts.
- For PK profile of CBP-1018 and free MMAE, $t_{1/2z}$ was ranged 0.54-1.15 h and 40.28-57.27 h, respectively, no accumulation of both substances after multiple doses.

Conclusions

CBP-1018 was well-tolerated at DLs of 0.03-0.12 mg/kg Q2W with no DLTs. Multiple SD were observed at DLs of 0.08-0.12 mg/kg, conferred a promising preliminary antitumor activity in pts with mCRPC. MTD was not reached and dose-escalation to establish the RP2D is continuing.

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