Phase 1 Dose-Escalation of SYS6002 (CRB-701)
A next-generation Nectin-4 Targeting Antibody Drug Conjugate (ADC)

DingWei Ye[1], Jian Zhang[1*], Hua Yang[2], Jin Yang[3], Tongsen Zheng[4], Hongmei Sun[5], Yuping Su[6], Guiling Li[7], Ian Hodgson[8], Rachael Brake[8] Xueyuan Zhang[9], Ge Lan[9], Guilan Sun[9], Xiao Zhang[9]*

1. Fudan University Shanghai Cancer Center, 2. Clinical Trial Institution of Affiliated Hospital of Hebei university 3. The First Affiliated Hospital of Xi'an Jiaotong University 4. Harbin Medical University Cancer Hospital 5. Jiamusi Cancer Hospital 6. Shandong Provincial Institute of Cancer Prevention and Treatment 7. Union Hospital Tongji Medical College Huazhong University of Science and Technology 8. Corbus Pharmaceuticals 9. CSPC Pharmaceutical Group Co., Ltd. *Corresponding authors that contributed equally to this work dwyeli@163.com & syner2000@163.com

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Background

- Linker-conjugation of an ADC is a key feature in optimizing highly active and well tolerated agents
- For maximal intra-tumoral delivery, linkers need to be highly stable in the systemic circulation yet allow for efficient drug release at the target site
- SYS6002 (CRB-701) is a next generation Nectin-4 ADC that uses a novel site-specific, cleavable transglutaminase conjugation technology[1]
- It is designed to overcome dose-limiting toxicities associated with the maleimide conjugation (linker-payload) used by enfortumab vedotin (EV)
- Non-clinically, SYS6002 (CRB-701) demonstrates preferential internalization-mediated payload release and a longer half-life[2]
- Allometric scaling predicts an effective human dose ≥ 2.8 mg/kg
- Dose escalation of a Q3W schedule is ongoing and aims to reduce the concentration of free-MMAE and related dose limiting toxicities peripheral neuropathy (PN) and skin rash[3]
- These adverse events lead to dose interruptions (61%), reductions (34%), and discontinuations (17%) of EV [4]

Nonclinical validation

SYS6002 vs. EV in NHPs

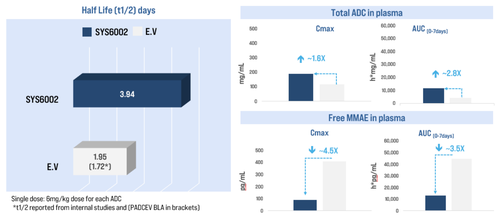


Figure 1: Comparison of SYS6002 (CRB-701) vs. enfortumab vedotin exposures over 7 days after a single dose in non-human primates. SYS6002 (CRB-701) is designed to increase the ADC half life and reduce circulating concentration of free-MMAE[2]

SYS6002 (CRB-701)

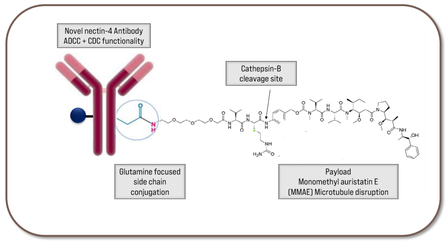


Figure 2: Design of SYS6002 (CRB-701) a next generation nectin-4 targeting ADC. With a site-specific cleavable linker, a homogenous DAR and a novel nectin-4 targeting monoclonal antibody

Method

SYS6002-001 Dose Escalation

KEY ELIGIBILITY

Age ≥18 years
Advanced urothelial carcinoma or Nectin-4 positive
Advanced solid tumors
ECOG 0-1
Adequate organ function
No uncontrolled diabetes
No active CNS metastasis

ESCALATION DESIGN

Bayesian Optimal Interval (BOIN) design with accelerated titration at DL-1
IV Q3W over a 21-day cycle
0.2 mg/kg
0.6 mg/kg
1.2 mg/kg
1.8 mg/kg
2.7 mg/kg
3.6 mg/kg
4.5mg/kg (recruiting)

KEY END POINTS

- Safety / tolerability
- Pharmacokinetics
- Anti tumor activity

NEXT STEPS

- Continue escalation
- PK expansion at 3.6mg/kg
- MTD or RP2D
- Specific expansion

Figure 3: SYS6002-001 first-in human study design and associated dose escalation schema

- Escalation has spanned 6 dose levels 0.2, 0.6, 1.2, 1.8, 2.7, 3.6mg/kg
- Dose escalation decisions were governed by a Bayesian Optimal Interval (BOIN) design with accelerated titration at DL-1
- The primary aim is to evaluate safety and tolerability of SYS6002 (CRB-701) and determine the Maximum Tolerated Dose (MTD) and/or the Phase II dose in patients with advanced solid tumors who have failed or were intolerant to standard treatment
- The pharmacokinetic (PK) and preliminarily anti tumor activity of SYS6002 (CRB- 701) has also been assessed

Results

Demographics & Key Characteristics

Characteristic	Value	Characteristic	Value
Median Age (Range)	58 (35-76)	Primary tumor type	n=18
Sex (M/F)	5/13	Urothelial	7
ECOG PS of 1	18 (100%)	Cervical	6
Weight in kg (Range)	55 (36-84)	Breast	4
Prior therapy (Range)	5 (1-10)	TNBC	3 of 4
Creatine Cl <60 µmol/L	7 (39%)	CRC	1
Visceral metastasis	15 (83%)	HbA1C levels ≤ 6.5%	18 (100%)

Table 1: Baseline demographics of participants enrolled in SYS6002-001 and the associated clinical characteristics of interest

Safety and Dose Modifications

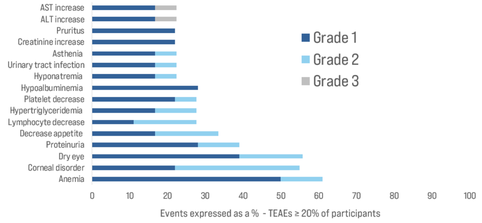


Figure 4: A summary of TEAEs ≥ 20% observed per CTCAE criteria as of December 18th 2023 cut off

- SYS6002 was well tolerated with mainly grade 1or 2 AEs
- No DLTs or Grade 4 or 5 AEs have been observed to date
- Anemia and eye related adverse events were the most common treatment emergent AEs (TEAE)
- Four subjects reported seven SAEs, of which 3 were considered probably related to SYS6002
- Two Grade 3 SAEs (ILD and pulmonary infection) were reported in a single participant, and 1 Grade 3 (ALT increase) in a separate participant
- To date no cases of rash or peripheral neuropathy have been observed

Dose Modifications (n=18)	Value
Discontinuations	0
Reductions	0
Interruptions	1 (5.5%)

Table 2: A summary of the dose modifications observed in the SYS6002-001 trial

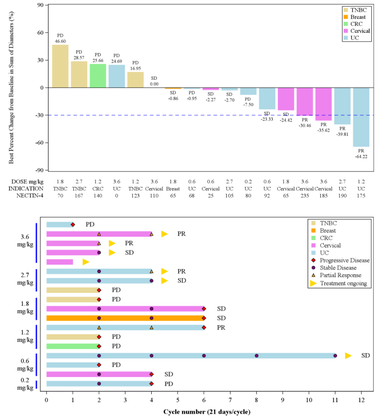
Clinical Pharmacology

- After single IV infusion of SYS6002, the exposure of TAb, ADC and MMAE generally increased in a dose proportional manner
- Clearance and volume of distribution were similar across doses
- The half-lives of TAb, ADC and MMAE were 4-6 days, 4-5 days and 5-10 days, respectively
- No obvious accumulation was observed on C3D1
- Time to peak conc of MMAE was approx. 3-7 days
- When compared to EV exposures SYS6002 (CRB-701) consistently demonstrates lower free MMAE

21 Day PK	Comparison	% ADC		% Free MMAE	
		Cmax	AUC tnf	Cmax	AUC tnf
Enfortumab vedotin (EV) 1.25 mg/kg Q1W x3	EV benchmark	100%	100%	100%	100%
SYS6002 (CRB-701) 1.2 mg/kg Q3W	Matched ADC dose	79%	106%	33%	29%
SYS6002 (CRB-701) 2.7 mg/kg Q3W	Matched MMAE dose	177%	183%	79%	68%

Table 3: SYS6002 (CRB-701) exposure relative to EV at 1.25 mg/kg Q1W over 21-day dosing

Efficacy



Note: Of the 4 PRS reported; 2 PRs are confirmed and 2 remain unconfirmed

Figure 5 (a) Waterfall plot of best percent change in sum of diameters (%) and (b) Best Overall Response and a Swimmers plot of duration of therapy by dose level and subject as of January 10th 2024

Discussion

- Participants spanned 5 tumor types and ranged from 35-76 years, with 72% being female
- 17/18 (94%) of patients were nectin-4 positive with a H-score rage of 25-235
- A single UC patient at 3.6mg/kg was nectin-4 negative
- SYS6002 (CRB-701) appears to be well tolerated
- The majority of AEs were grade 1 or 2 and reversible. Dose modifications were minimal, coinciding with the absence of skin rash and peripheral neuropathy
- Across the dose escalation SYS6002 (CRB-701) demonstrated approximately dose-proportional PK and minimal accumulation
- CRB-701 exhibited a longer ADC half-life and a lower free-MMAE exposure relative to EV at comparable dose levels
- Anti tumor responses across multiple doses were observed, with the first confirmed stable disease at 0.6 mg/kg and the first confirmed partial response, at 1.2 mg/kg
- Assessment of responses at or above 2.7mg/kg (n=7) suggests an emerging ORR of 43% and a DCR of 71%
- Responding populations include UC and cervical cancer
- 7 /18 (38%) of participants remain on SYS6002 therapy
- Dose escalation is ongoing at 4.5 mg/kg Q3W
- Dose expansion at 3.6 mg/kg Q3W to gain a deeper understanding of clinical pharmacology and safety

References

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2. Sun et al., 2023 Development of CRB-701 (SYS6002): *A novel site-specific, Nectin-4 targeting ADC*. AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics 2023
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4. Enfortumab vedotin prescribing information: https://astellas.us/docs/PADCEV_label.pdf
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Abbreviations

TNBC (triple-negative breast cancer), CRC (colorectal cancer), DLT (dose limiting toxicity), SAE (serious adverse event), ILD (interstitial lung disease), AE (adverse event), TEAEs (treatment emergent adverse events), UC (urothelial cancer), Tab (total antibody), DCR (disease control rate), ORR (objective response rate)