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Phase I dose-escalation study of the next-generation nectin-4 targeting antibody—drug conjugate CRB-701 (SYS6002) in US and UK patients with urothelial cancer and other solid tumors

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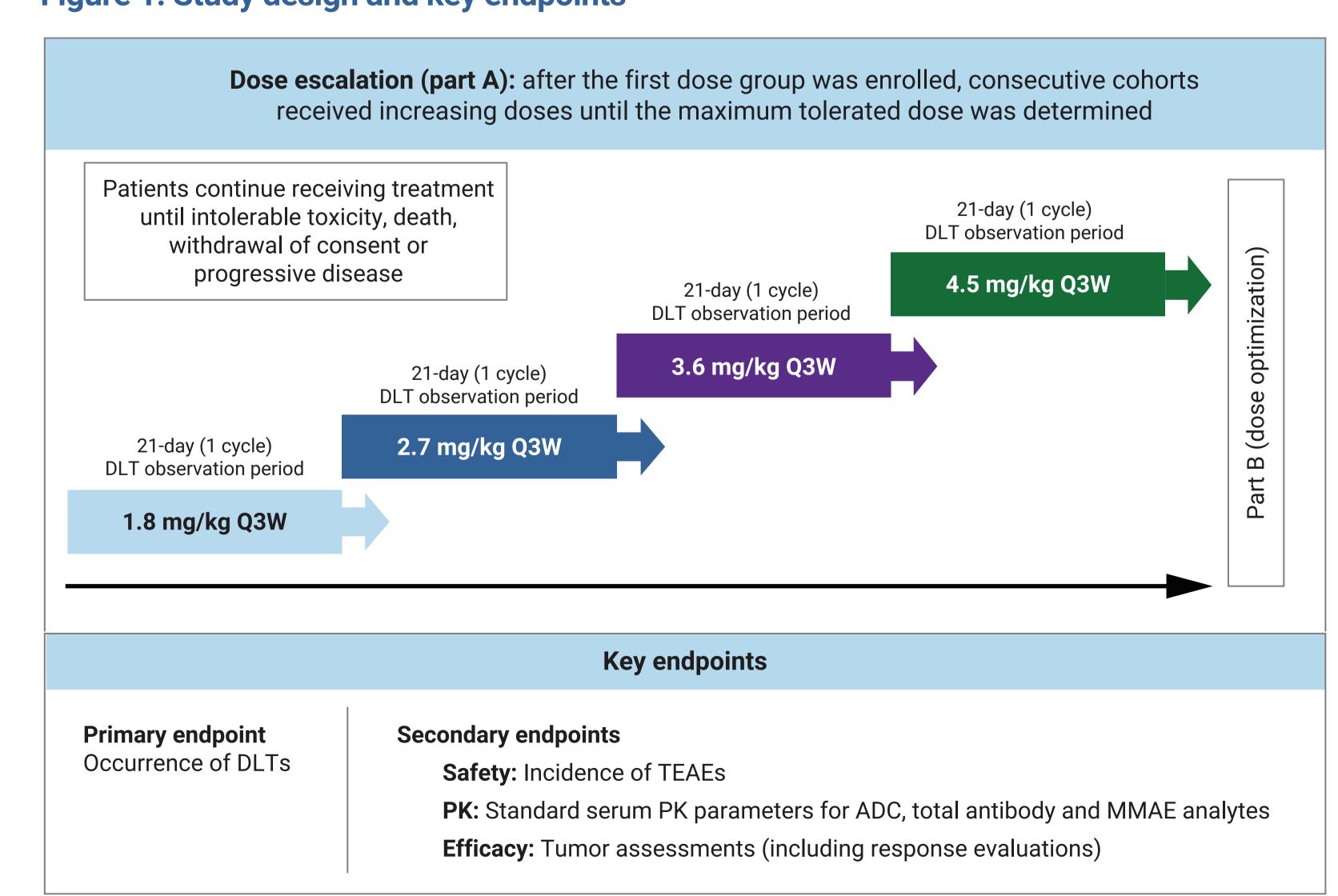
BACKGROUND

- Linker conjugation chemistry is a key determinant of antibody—drug conjugate (ADC) activity and tolerability.¹
- For maximal intra-tumoral drug delivery, linkers must be stable in systemic circulation and allow efficient drug release at the target site.¹
- CRB-701 (also known as SYS6002) is a next-generation nectin-4 targeted ADC employing site-specific transglutaminase linker technology, designed to reduce the toxicity reported with ADCs such as enfortumab vedotin (EV).²
- In the first-in-human study, conducted in Chinese patients (Study SYS6002-001), CRB-701 was associated with lower systemic free monomethyl auristatin E (MMAE) levels and had a longer half-life than EV (indirect comparisons), which may reduce toxicity and enable less frequent dosing.^{3,4}
- Following the first-in-human study, we report dose escalation results from a phase I/II clinical study conducted in the UK and USA (Study CRB-701-01; ClinicalTrials. gov identifier, NCT06265727).

METHODS

- Adults with locally advanced or metastatic solid tumors likely to express nectin-4 were eligible if disease had progressed despite the use of all available appropriate lines of therapy, or if no standard treatment options were available.
- Tumor types were confirmed by histology and/or cytology, and nectin-4 positivity was evaluated retrospectively using immunohistochemistry (IHC)-derived H-scores.
- A Bayesian Optimal Interval design with four dose groups (1.8, 2.7, 3.6 and 4.5 mg/kg; each administered intravenously once every 3 weeks) was used to determine the maximum tolerated dose and the pharmacologically active dose range for phase II evaluation (**Figure 1**).

Figure 1. Study design and key endpoints



Dose escalation/de-escalation decisions were made based on the occurrence of DLTs. If the rate of protocol-defined DLTs was below the threshold during the 21-day observation period, cohort enrollment could begin at the next dose level. A minimum of 3 evaluable patients were required to escalate to the next dose group.

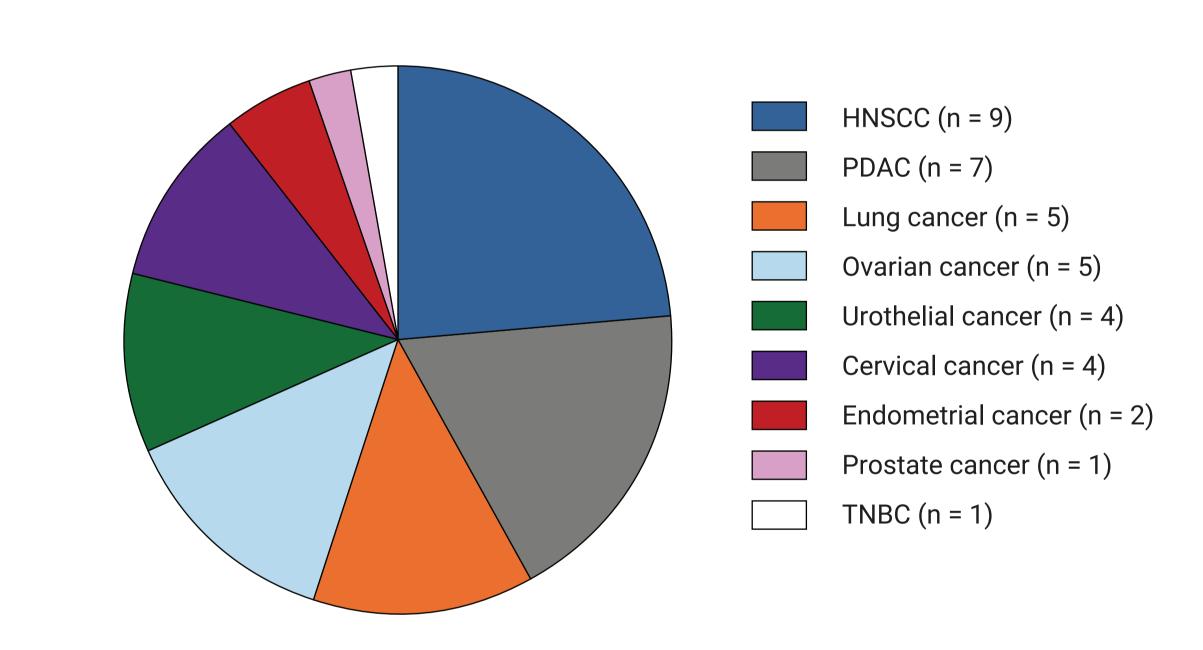
ADC, antibody—drug conjugate; DLT, dose-limiting toxicity; MMAE, monomethyl auristatin E; PK, pharmacokinetic; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

RESULTS

Patient baseline characteristics, safety and tolerability

- As of the data cutoff on December 16, 2024, we had enrolled 38 patients with primary tumors of nine different types (**Figure 2**); the median patient age was 62 years and 57.9% were female (**Table 1**).
- All dose groups were enrolled, no dose-limiting toxicities (DLTs) were reported, and the maximum tolerated dose was not reached.
- At data cutoff, mean CRB-701 exposure was 88.7 days (**Table 2**); treatment was ongoing in 20/38 patients (52.6%).
- Most patients (34/38, 89.5%) had treatment-emergent adverse events (TEAEs) that were grade 3 or lower in severity; no grade 5 safety events were reported.
- A grade 4 treatment-related TEAE of increased blood bilirubin associated with obstructive jaundice and disease progression was reported in a patient with pancreatic ductal adenocarcinoma who received the 4.5 mg/kg dose.

Figure 2. Proportion of patients by primary tumor type (N = 38)



HNSCC, head and neck squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; TNBC, triple-negative breast cancer.

Table 1. Patient demographics and key baseline clinical characteristics

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HbA_{1c}, glycated hemoglobin.

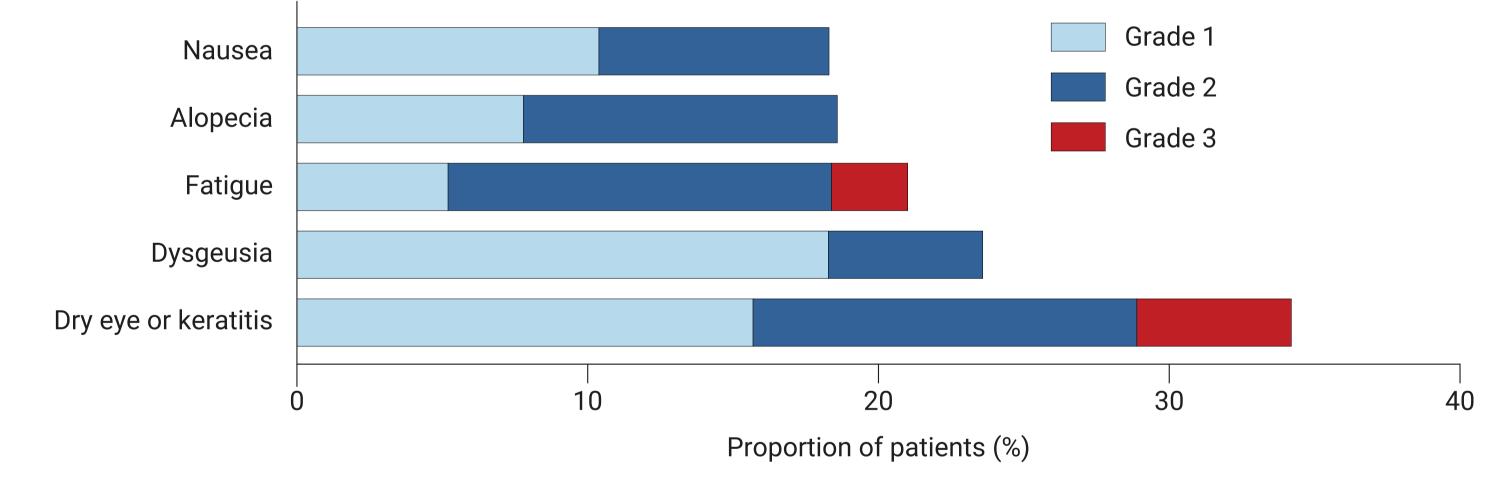
Demographic or characteristic	All dose groups (N = 38)		
Female, n (%)	22 (57.9)		
Median age, years (range)	62 (34–90)		
Median weight, kg (range)	64.8 (32.1-111.8)		
ECOG PS, n (%)			
0	9 (23.7)		
1	27 (71.1)		
2	2 (5.3)		
Median previous therapies, n (range)	3 (1-8)		
Creatinine clearance, n (%)			
30-60 mL/min	12 (31.6)		
> 60 mL/min	26 (68.4)		
HbA _{1c} , n (%)			
< 6.5%	23 (60.5)		
≥ 6.5%	6 (15.8)		
Missing	9 (23.7)		

Table 2. Mean duration of CRB-701 exposure and summary of dose modifications

Parameter	1.8 mg/kg Q3W (n = 13)	2.7 mg/kg Q3W (n = 11)	3.6 mg/kg Q3W (n = 10)	4.5 mg/kg Q3W (n = 4)	All doses (N = 38)		
Mean (standard deviation) CRB-701 exposure, days	106.5 (74.0)	100.8 (59.2)	60.3 (60.8)	68.8 (29.4)	88.7 (64.1)		
Dose modification, n (%)							
Discontinuation	2 (15.4)	0	2 (20.0)	2 (50.0)	6 (15.8)		
Reduction	0	1 (9.1)	1 (10.0)	0	2 (5.3)		
Interruption	7 (53.8)	4 (36.4)	4 (40.0)	2 (50.0)	17 (44.7)		
Q3W, every 3 weeks.							

- TEAEs reported in more than 15% of patients are shown in **Figure 3**; treatment-related TEAEs reported in more than 15% of patients were dysgeusia (10 events in 9 patients), fatigue (9 events in 8 patients), alopecia (8 events in 7 patients) and dry eye (7 events in 6 patients).
- Rash was reported in 4/38 patients (10.5%), maculopapular rash was reported in an additional 2/38 patients (5.3%), and peripheral sensory neuropathy was reported in 2/38 patients (5.3%).
- Eye disorders were reported in 18/38 patients (47.4%); two patients experienced grade 3 keratitis and one patient experienced grade 3 watery eye.
- Blood and lymphatic system disorders were reported in 3/38 patients (7.9%), including grade 2 and grade 3 anemia in 2/38 patients (5.3%) and grade 3 leukocytosis in 1/38 patients (2.6%).
- No cases of pneumonitis were reported.

Figure 3. Summary of TEAEs reported in more than 15% of patients, by maximum CTCAE grade (N = 38)



CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

- In total, 15 serious TEAEs were recorded in 9/38 patients (23.7%); one event of photophobia was the only serious TEAE deemed related to treatment.
- Five patients (13.2%) discontinued treatment owing to adverse events (small bowel obstruction, obstructive jaundice, sepsis, increased ascites combined with elevated liver enzymes, acral bullous rash; only the rash was deemed treatment related; **Table 2**).
- The reason for dose discontinuation was unavailable for one patient.
- Just under 50% (8/17) of dose interruptions were due to eye disorders, including three events of keratitis, two events of photophobia, two events of blurred vision and one event of watery eyes.
- There were no discontinuations due to eye events, and most eye disorders improved over time.

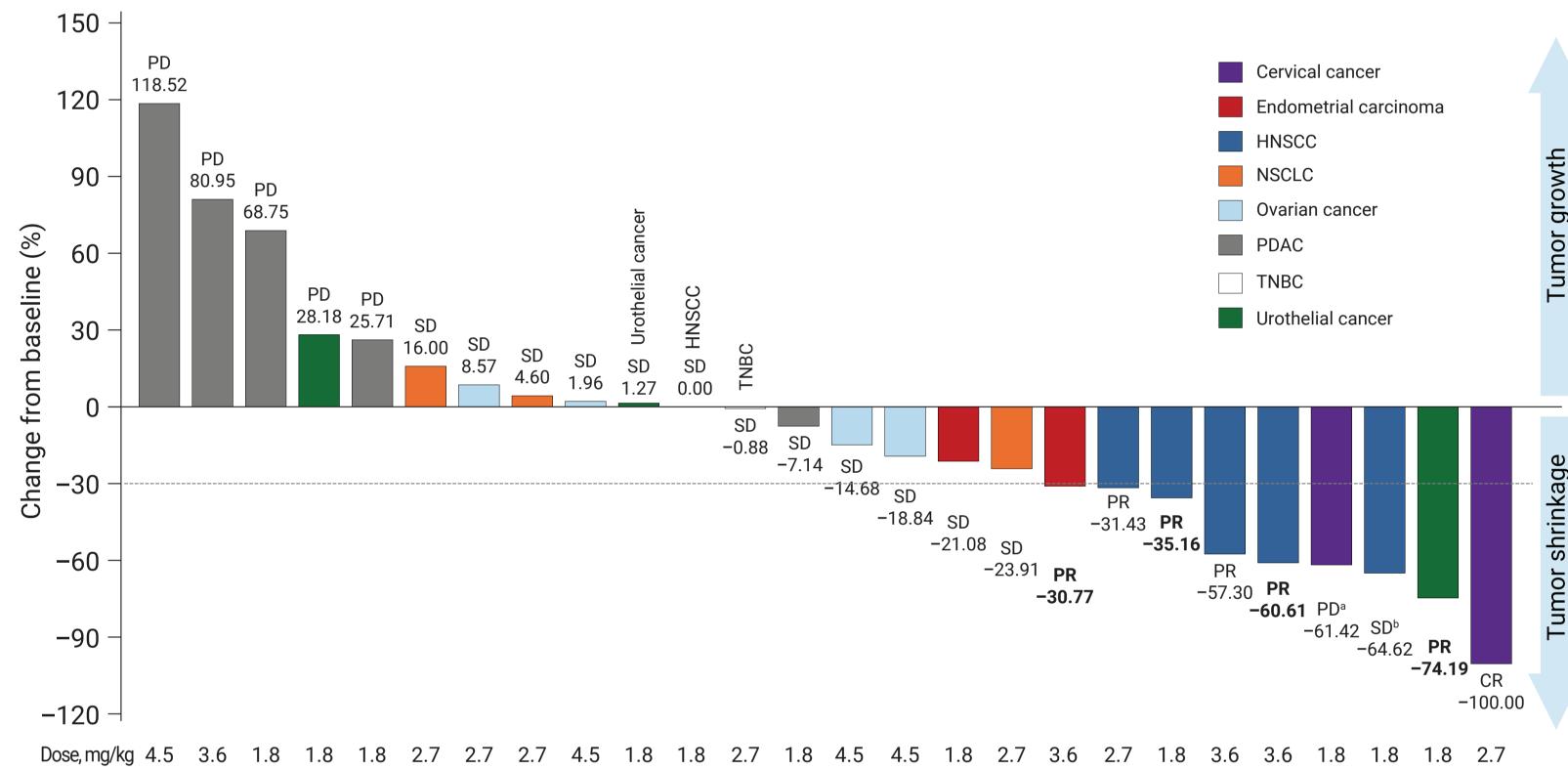
Serum pharmacokinetic parameters

• Emerging serum pharmacokinetic (PK) parameters for participants in the 1.8 mg/kg (n = 11), 2.7 mg/kg (n = 7) and 3.6 mg/kg (n = 5) dose groups revealed similar mean values to those previously reported in Chinese patients for ADC and MMAE exposure (area under the concentration—time curve from time 0 to time to last measurable concentration [AUC_{last}] and maximum concentration [C_{max}]; data not shown).^{3,4}

Preliminary efficacy data

- Antitumor responses based on Response Evaluation Criteria in Solid Tumors (RECIST)
 were observed across multiple doses and in multiple tumor types, with confirmed cases
 of partial response at the lowest dose, 1.8 mg/kg (Figures 4 and 5).
- Of the four patients with urothelial cancer who had response evaluations, one patient had a confirmed partial response and one patient had stable disease.
- Two cases of progressive disease (including one patient who had clinical progression without scans) were also observed; both patients had previously received EV.
- One unconfirmed complete response was observed in a patient with cervical carcinoma who had received the 2.7 mg/kg dose.

Figure 4. Percentage change from baseline in sum of diameters with best overall response (n = 26) and nectin-4 expression H-scores for CRB-701 Q3W (n = 22)



Dose, mg/kg 4.5 3.6 1.8 1.8 1.8 2.7 2.7 2.7 4.5 1.8 1.8 2.7 1.8 4.5 4.5 1.8 2.7 3.6 2.7 1.8 3.6 3.6 1.8 1.8 1.8 2.7 Nectin-4H-score 80 30 260 195 100 300 35 295 210 5 20 45 200 300 250 165 280 25 205 165 210 20

Each bar represents one patient. Best overall response is indicated at the end of each bar. **Bold** text indicates confirmed responses, all other responses are unconfirmed, no minimum duration was required for SD. Dotted line indicates threshold for PR according to RECIST criteria (> 30% reduction in the sum of diameters).

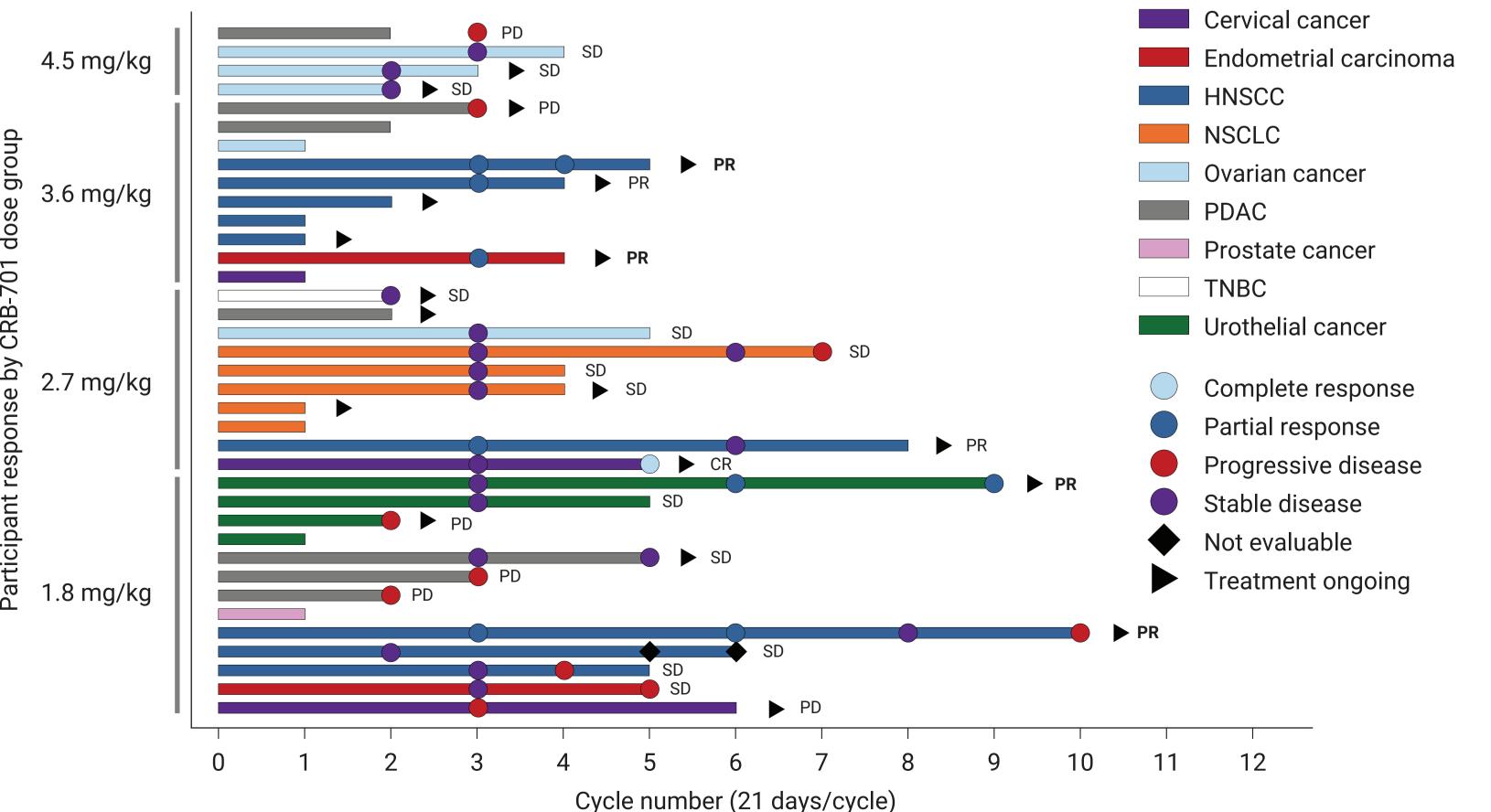
^aA new lesion was identified at first scan and PD was associated with significant target lesion shrinkage.

^bPatient developed invasive aspergillosis and non-target lesions were not evaluable; SD was associated with significant target lesion shrinkage.

CR, complete response; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD, progressive disease;

PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TNBC, triple-negative breast cancer.

Figure 5. Patient-level best overall response by dose group for CRB-701 Q3W (n = 37)



Efficacy data were unavailable for one patient (infusion only, no duration data). Best overall response is indicated at the end of each bar. **Bold** text indicates confirmed responses, all other responses are unconfirmed, no minimum duration was required for SD.

CR, complete response; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Q3W, every 3 weeks; SD, stable disease; TNBC, triple-negative breast cancer.

• In head and neck squamous cell carcinoma (HNSCC), stable disease was observed in two patients and partial response was observed in four patients, suggesting an emerging objective response rate of 57% (4/7 patients) and an emerging disease control rate of 86% (6/7 patients; one patient had clinical progression without scans).

CONCLUSIONS

- In this dose-escalation study conducted in a Western population, CRB-701 safety, PK and efficacy observations were generally consistent with those from the first-in-human study in Chinese patients.^{3,4}
- This study enrolled patients with a wider range of tumor types than the previous study, which included a population enriched with nectin-4-positive urothelial and cervical cancers.^{3,4}
- Overall, CRB-701 was well tolerated, with no DLTs or grade 5 safety events reported to date.^{3,4}
- The incidence of rash and peripheral neuropathy was lower than expected for a nectin-4 targeted ADC with MMAE payload;⁵ however, as with other ADCs,⁶ prophylaxis for potential eye disorders is recommended.
- Hematological toxicities were reported in fewer than 10% of patients and no cases of interstitial lung disease (pneumonitis) were reported.
- Preliminary efficacy was observed at multiple doses in patients exhibiting a wide range of nectin-4 IHC-derived H-scores, and, for the first time, we report efficacy in patients with HNSCC and the first unconfirmed complete response in a patient with cervical carcinoma.
- These results support the continued development of CRB-701 in patients with solid tumors expressing nectin-4.
- Part B of the CRB-701-01 Study is continuing with dose optimization cohorts in HNSCC, cervical cancer and bladder cancer.

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Disclosures

CAP has received consultancy or advisory fees from BeiGene, EMD Serono and Pfizer and research funding from Accutar Biotech, ADANATE Biotechnology, Artios, Ayala Pharmaceuticals, BeiGene, Coherent Biopharma, Compass Therapeutics, Corbus Pharmaceuticals, DualityBio, Elevation Oncology, Elpiscience, Genentech Inc., HyaMab, Kinnate Biopharma, Kura Oncology, Merus, Mirati Therapeutics, Pfizer, Relay Therapeutics, Ribon Therapeutics, Seagen, SystImmune, Tachyon Therapeutics, Tallac Therapeutics, Inc., Xilio Therapeutics and Zhuhai Yufan Biotechnologies. **NG** is an employee of the Carolina BioOncology Institute and BioCytics Inc. **KM** has no relationships with companies to disclose. **CLC** has received consultancy or advisory fees from Iovance Biotherapeutics and research funding from Amgen, Array BioPharma, Bristol Myers Squibb, Celldex, EMD Serono, F. Hoffmann-La Roche, Genentech Inc., Merck, Novartis, Regeneron and Seagen. **IH** and **DS** are employees of Corbus Pharmaceuticals. **DJP** has received consultancy or advisory fees from Avammune, AstraZeneca, Da Volterra, Eisai, Exact Sciences, F. Hoffmann-La Roche, Incyte, Ipsen, LIfT BioSciences, MiNA Therapeutics, Mursla Bio and Starpharma; speaker fees from Bayer Healthcare Pharmaceuticals, Boston Scientific, Bristol Myers Squibb and Eisai; and research fees from Bayer Healthcare Pharmaceuticals, Bristol Myers Squibb, GlaxoSmithKline and MSD.

Acknowledgments

Medical writing support was provided by Kayleigh Dodd PhD of PharmaGenesis Cardiff, Cardiff, UK, and funded by Corbus Pharmaceuticals, in accordance with Good Publication Practice (GPP 2022) guidelines (www.ismpp.org/gpp-2022).