Phase 1/2 study of the next-generation Nectin-4-targeting antibody–drug conjugate CRB-701 (SYS6002) in patients with urothelial and non-urothelial solid tumours

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BACKGROUND

- CRB-701 (also known as SYS6002) is a next-generation Nectin-4-targeted antibody–drug conjugate (ADC) with transglutaminase linker technology that is specifically designed to reduce the dose-limiting toxicities reported with monomethyl auristatin E (MMAE)-coupled Nectin-4-targeted ADCs such as enfortumab vedotin.[1,2]
- CRB-701-01 (NCT06265727) is an ongoing phase 1/2 study in Europe and the USA investigating the safety, tolerability, efficacy and pharmacokinetics of CRB-701 in participants with advanced solid tumours.
  - As reported at the 2025 ASCO Genitourinary Cancers Symposium, CRB-701 was well tolerated during the dose-escalation phase. The maximum tolerated dose was not reached and no dose-limiting toxicities were reported.[3]
  - The most common treatment-emergent adverse events (TEAEs) reported in more than 15% of participants were dry eye/keratitis, dysgeusia, fatigue, alopecia and nausea.[3]
  - Preliminary evidence of efficacy was also observed in participants with head and neck squamous cell carcinoma (HNSCC), bladder cancer and cervical cancer.[3]
- This poster presents updated safety and efficacy data from up to 167 participants enrolled in the dose escalation and optimization phases of the CRB-701-01 study, including anti-tumour responses in HNSCC, bladder cancer and cervical cancer.

METHODS

- Please see the **supplementary appendix** (accessible via QR code) for further information, including the methods for part A (dose escalation).
- In part B (dose optimization), the pharmacologically active dose range determined from part A was evaluated in a time-to-event Bayesian optimal phase 2 design.
- Separate cohorts of adults with HNSCC, cervical cancer, or locally advanced or metastatic urothelial cancer (laUC/mUC) with no previous exposure to Nectin-4-targeted or MMAE-based therapies were randomized 1:1 to receive CRB-701 2.7 mg/kg or 3.6 mg/kg every 3 weeks.
- Tumour types were confirmed from previous diagnostic records based on histology and/or cytology. Nectin-4 positivity was retrospectively assessed using immunohistochemistry-derived H-scores. Human papillomavirus (HPV) status was also collected retrospectively.
- Anti-tumour activity, safety, tolerability and pharmacokinetics were assessed.

RESULTS

Baseline characteristics, safety, tolerability and pharmacokinetics

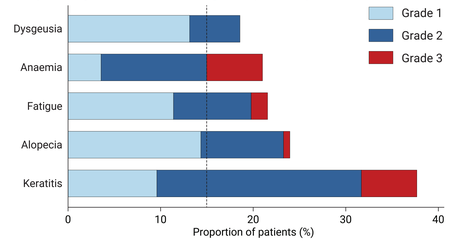
- As of 1 September 2025, 167 participants had enrolled in the safety population. Key participant baseline characteristics are presented in **Table 1**.
- Data for cumulative TEAEs reported in more than 15% of participants across all doses are shown in **Figure 1**.
  - Keratitis was the most frequently reported TEAE, with incidence increasing in a dose-dependent manner.
- Ocular TEAEs were reported in 101 (60.5%) of participants (**Supplementary Table S1**).
  - Grade 3 ocular TEAEs were reported in fewer than 10% of participants and no grade 4 or 5 events were reported.
- Peripheral neuropathy TEAEs were reported in 14 (8.4%) of participants based on the broad Standardized Medical Dictionary Regulatory Activities (MedDRA) Query category. No incidences of grade 3 or above were reported.
- Most rash or skin disorder TEAEs were reported in small proportions of participants, including: pruritus (24, 14.4%); dry skin (17, 10.2%); rash (15, 9.0%); rash maculo-papular (8, 4.8%); dermatitis acneiform (6, 3.6%); erythema (3, 1.8%); dermatitis bullous and rash pustular (each 2, 1.2%); and rash erythematous, rash macular, rash pruritic, skin disorder, skin reaction and skin ulcer (each 1, 0.6%).

Table 1. Key participant baseline characteristics (safety population)

Baseline characteristic	Part A (n = 62)	Part B (n = 105)	Overall (N = 167)
Female, n (%)	24 (38.7)	59 (56.2)	83 (49.7)
Median age, years (range)	62 (35–90)	59 (32–83)	60 (32–90)
Primary tumour type, n (%)			
HNSCC	29 (46.8)	31 (29.5)	60 (35.9)
Cervical cancer	3 (4.8)	51 (48.6)	54 (32.3)
laUC/mUC	4 (6.5)	23 (21.9)	27 (16.2)
NSCLC	7 (11.3)	0	7 (4.2)
Pancreatic cancer	7 (11.3)	0	7 (4.2)
Ovarian cancer	4 (6.5)	0	4 (2.4)
Endometrial carcinoma	3 (4.8)	0	3 (1.8)
Other[a]	4 (6.5)	0	4 (2.4)
Missing	1 (1.6)	0	1 (0.6)
ECOG PS, n (%)			
0	19 (30.6)	53 (50.5)	72 (43.1)
1	42 (67.7)	50 (47.6)	92 (55.1)
2	1 (1.6)	2 (1.9)	3 (1.8)
Median number of previous therapies (range)	3.0 (1–8)	3.0 (1–9)	3.0 (1–9)

[a]Other includes TNBC, prostate and penile cancer. ECOG PS, Eastern Cooperative Oncology Group Performance Status; HNSCC, head and neck squamous cell carcinoma; laUC/mUC, locally advanced or metastatic urothelial cancer; NSCLC, non-small cell lung cancer; TNBC, triple negative breast cancer.

Figure 1. Distribution of TEAEs reported in more than 15% of participants by maximum CTCAE grade (N = 167)



Participants with multiple events of the same type are counted once at the highest grade. CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

- Anaemia was the most frequently reported treatment-related cytopenia, reported in 21 participants (12.6%). Treatment-related hyperglycaemia was reported in 4 participants (2.4%).
- Treatment-related adverse events (TRAEs) of grade 3 or above in severity were reported in 30 participants (18.0%; 49 events). The most frequently reported TRAEs were eye disorders (**Supplementary Table S2**).
- No grade 4 or 5 TEAEs were deemed treatment-related.
- Serious TEAEs were reported in 31 participants (18.6%; 62 events), of these, three events occurring in 3 participants (1.8%) were deemed treatment-related: abnormal general physical condition (2.7 mg/kg dose; not resolved), hypercalcaemia (3.6 mg/kg dose; resolved) and tumour haemorrhage (2.7 mg/kg dose; resolved).
- Dose interruptions resulting from TRAEs were frequent, but dose discontinuations were uncommon (6% of participants; **Table 2**). The majority of dose modifications were due to eye disorders.
- The geometric mean ADC half-life of CRB-701 was 133 hours (5.6 days); pharmacokinetic parameters are presented in **Supplementary Table S3**.

Table 2. Summary of dose modifications resulting from TRAEs

Dose modification, n (%)	1.8 mg/kg (n = 13)	2.7 mg/kg (n = 74)	3.6 mg/kg (n = 76)	4.5 mg/kg (n = 4)	Total (N = 167)
Discontinuation	2 (15.4)	1 (1.4)	5 (6.6)	2 (50.0)	10 (6.0)
Reduction	0	5 (6.8)	10 (13.2)	2 (50.0)	17 (10.2)
Interruption	5 (38.5)	20 (27.0)	33 (43.4)	3 (75.0)	61 (36.5)

Q3W, every 3 weeks; TRAE, treatment-related adverse event.

Efficacy in participants with HNSCC, cervical cancer or laUC/mUC

- Of the 122/167 participants evaluable for efficacy analysis, 41 had HNSCC, 37 had cervical cancer and 23 had laUC/mUC (**Figure 2A, 2C and 2E**).
  - Participants with other tumour types (n = 21) and those who had not yet received their first post-baseline radiological evaluation are not presented in waterfall plots.
- Notable efficacy was observed in participants with HNSCC, cervical cancer and laUC/mUC (**Table 3** and **Figure 2**).

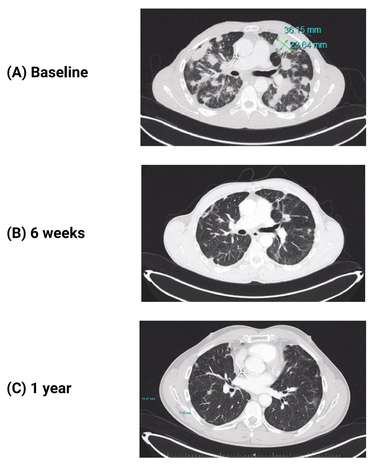
Table 3. ORRs and DCRs of CRB-701 Q3W by tumour type for the 2.7 mg/kg and 3.6 mg/kg doses (n = 84)

	HNSCC		Cervical cancer		laUC/mUC	
	2.7 mg/kg (n = 12)	3.6 mg/kg (n = 21)	2.7 mg/kg (n = 18)	3.6 mg/kg (n = 16)	2.7 mg/kg (n = 8)	3.6 mg/kg (n = 9)
ORR, n (%)	4 (33.3)	10 (47.6)	4 (22.2)	6 (37.5)	4 (50.0)	5 (55.6)
DCR, n (%)	9 (75.0)	13 (61.9)	12 (66.7)	11 (68.8)	6 (75.0)	8 (88.9)

ORRs and DCRs are based on the best unconfirmed overall response recorded post-baseline, up to first PD or initiation of alternative therapy (no confirmatory scan required; ORR: PR or CR; DCR: CR, PR or SD). Non-evaluable participants were excluded (HNSCC, n = 4; cervical cancer, n = 2; laUC/mUC, n = 2). In those receiving the 2.7 mg/kg dose, confirmed PRs were reported in 4/12 participants with HNSCC, 1/18 participants with cervical cancer and 2/8 participants with laUC/mUC. One participant with cervical cancer receiving the 2.7 mg/kg dose had a confirmed CR. For those receiving the 3.6 mg/kg dose, confirmed PRs were observed in 7/21, 3/16 and 3/9 participants with HNSCC, cervical cancer and laUC/mUC, respectively. See **Supplementary Table S4** for all confirmed best overall responses. CR, complete response; DCR, disease control rate; HNSCC, head and neck squamous cell carcinoma; laUC/mUC, locally advanced or metastatic urothelial cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease.

- Anti-tumour responses were observed in participants with both HPV-negative and -positive HNSCC.
- Representative chest computed tomography (CT) scans illustrating the anti-tumour response to CRB-701 over time in a participant with HPV-positive HNSCC are shown in **Figure 3**.

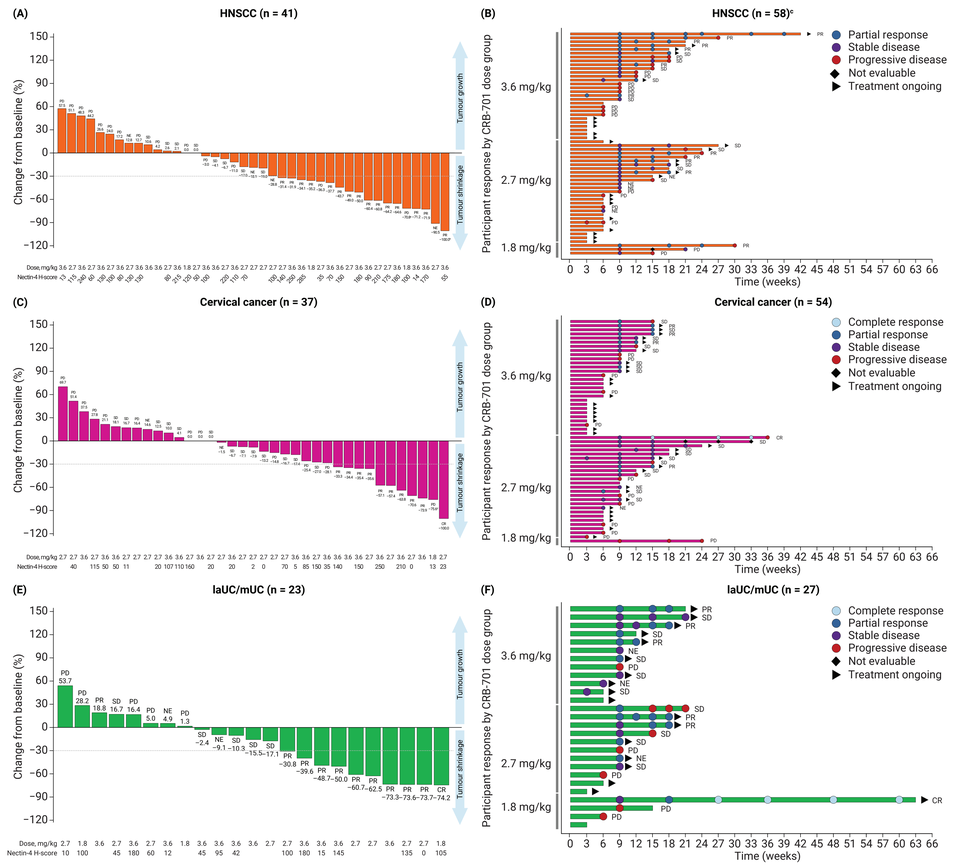
Figure 3. Axial chest CT scans at baseline (A), 6 weeks (B) and 1 year (C) from a patient with HPV-positive HNSCC receiving 3.6 mg/kg CRB-701



CT, computed tomography; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.

- Most participants in the laUC/mUC and cervical cancer cohorts were awaiting their confirmatory scan at the time of data cut (**Figure 2C–2F**).
  - Confirmed complete responses were observed in one participant with cervical cancer receiving 2.7 mg/kg and one participant with laUC/mUC receiving 1.8 mg/kg (**Figure 2C–2F**).
- Anti-tumour responses were observed in participants with high and low levels of Nectin-4 expression regardless of tumour type (**Figure 2**).
- Anti-tumour responses were observed as early as week 6, with the longest sustained response recorded from weeks 9 to 60 (**Figure 2**).

Figure 2. Percentage change from baseline in sum of diameters with unconfirmed best overall response (A, C and E) and participant-level confirmed best overall response by dose (B, D and F) for CRB-701 Q3W by tumour type and dose



Data are summarized based on the dose group assigned at enrolment. Each bar represents one participant. Anti-tumour activity was determined according to RECIST v1.1 criteria.[4] Best overall response is indicated at the end of each bar. A confirmation scan ≥ 4 weeks after the initial recorded response was required to confirm PR and CR. A minimum duration of 42 days was required to confirm SD; therefore, participants with only one post-baseline SD scan completed < 42 days after treatment initiation were deemed not evaluable. Dotted line on parts A, C and E indicates the threshold for PR according to RECIST v1.1 criteria (> 30% reduction in the sum of diameters). [b]Participant developed invasive aspergillosis and new lesions were not evaluable. [c]Participant presented with a 100% target response reduction from baseline in the sum of diameters; however, non-target lesions were still present. [d]Two participants were excluded because they were missing a baseline scan. [e]Participant had a PR based on target lesions, but new lesions developed in the bone and liver. CR, complete response; HNSCC, head and neck squamous cell carcinoma; laUC/mUC, locally advanced metastatic urothelial cancer; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

CONCLUSIONS

- The results presented here suggest that CRB-701 may be differentiated from other Nectin-4-targeted MMAE-coupled ADCs based on safety, efficacy and/or pharmacokinetics.[2,5–7]
- CRB-701 demonstrated evidence of efficacy in tumour types beyond urothelial cancer, including HNSCC and cervical cancer, with responses observed across a wide range of Nectin-4 expression levels.
- In this heavily pretreated population of participants with HNSCC, encouraging efficacy was observed with the 2.7 mg/kg and 3.6 mg/kg doses, indicating that CRB-701 may offer a promising single-agent therapeutic option for participants with HNSCC.
- CRB-701 demonstrated a favourable safety profile, with low incidence of MMAE-associated toxicities, for example, peripheral sensory neuropathy.[8]
  - Ocular toxicities were largely manageable through dose delays and modifications, as well as prophylactic measures. Overall dose discontinuations due to TRAEs were infrequent (6.6% of participants at the 3.6 mg/kg dose).
- The results of this dose optimization phase will inform the recommended dose for phase 2 evaluation.
- Collectively, these results support the continued development of CRB-701 in patients with HNSCC, cervical cancer and laUC/mUC.

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Disclosures

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