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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Final publication number: 967P

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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

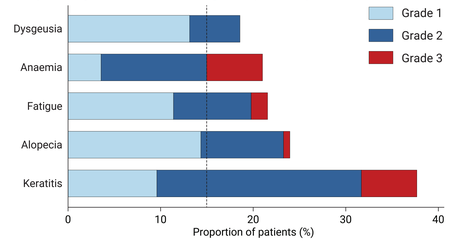
- As of 1 September 2025, 167 participants had enrolled in the safety population. Key participant baseline characteristics are presented in **Table 1**.
- Data for cumulative TEAEs reported in more than 15% of participants across all doses are shown in **Figure 1**.
  - Keratitis was the most frequently 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**).

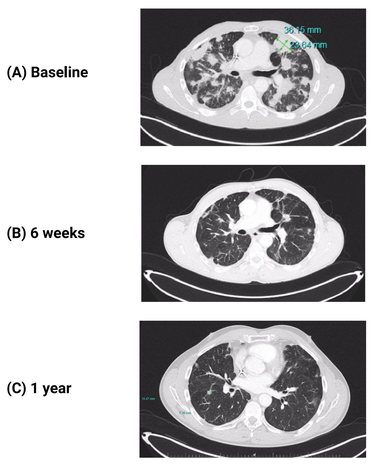
Table 3. ORRs and DCRs of CRB-701 Q3W by tumour type for the 2.7 mg/kg and 3.6 mg/kg doses (n = 84)

	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**.

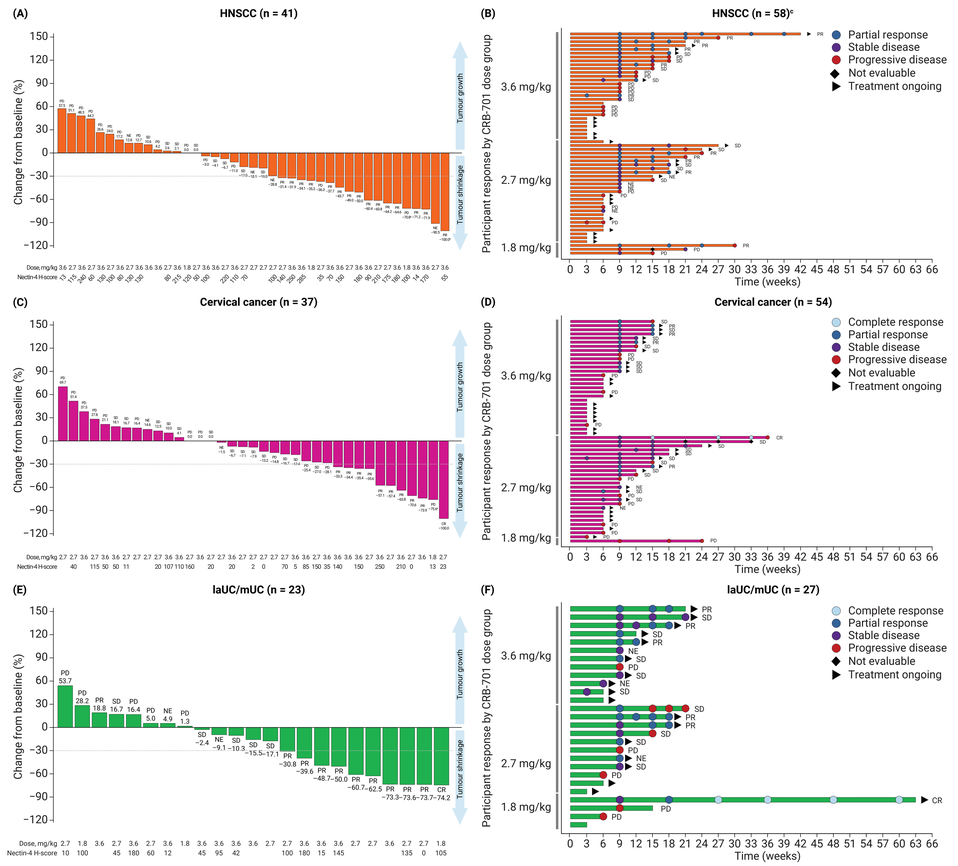
Figure 3. Axial chest CT scans at baseline (A), 6 weeks (B) and 1 year (C) from a patient with HPV-positive HNSCC receiving 3.6 mg/kg CRB-701



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

CAP has received steering committee, personal and other fees from BeiGene; travel, personal and other fees from Corbus Pharmaceuticals; advisory and personal fees from EMD Serono; consultancy, personal and other fees from Ipsen; and personal and advisory board fees from Pfizer. He has received institutional fees from, is a principal investigator for, or has a financial interest in Bayer, BeiGene, BMS, Corbus Pharmaceuticals, Deciphera, Duality Bio, Elevation Oncology, Elucida Oncology, Genentech, Inc., Jazz Pharmaceuticals, Kinnate Biopharma, Kumquat, Kura Oncology, LG Chem, Loxo Oncology, MediLink Therapeutics, Menarini-Stemline, Merus, Mirati Therapeutics, Multitude Therapeutics, Relay Therapeutics, Seagen Inc., SystImmune Inc., Tallac Therapeutics, TORL Bio, Xilio Therapeutics and Zhuhai Yufan Biotechnologies Co.

Acknowledgements

The authors would like to thank all of the patients and support staff involved in the study. Medical writing support was provided by Kayleigh Dodd PhD of PharmaGenesis Cardiff, Cardiff, UK, and funded by Corbus Pharmaceuticals, Inc., in accordance with Good Publication Practice (GPP 2022) guidelines (www.ismpp.org/gpp-2022).

Funding

Study sponsored by Corbus Pharmaceuticals, Inc.

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SUPPLEMENTARY APPENDIX

Presented at the European Society for Medical Oncology Congress 2025
17–21 October 2025, Berlin, Germany

Supplementary methods

Part A (dose escalation) study design

- Adults were eligible to participate if they had advanced or metastatic solid tumours known to express Nectin-4 and if disease had progressed despite the use of all appropriate lines of therapy.
- 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 further evaluation.

Study endpoints (parts A and B)

- The primary endpoint for part A was the occurrence of protocol-defined dose-limiting toxicities. Safety, pharmacokinetics and preliminary anti-tumour activity were assessed as secondary endpoints.
- The primary endpoint for part B was the objective response rate based on complete and partial responses determined according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. Safety, disease control rate and pharmacokinetic parameters were assessed as secondary endpoints.

Additional information related to 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)

The following participants were excluded from ORR and DCR calculations

- HNSCC
  - Participants who were NE due to their scan occurring < 42 days after baseline (n = 4)
  - Participant who received CRB-701 and pembrolizumab, assessed as having PD and change from baseline of +24.0 (n = 1)
  - Participants who received CRB-701 1.8 mg/kg (n = 3)
- Cervical cancer
  - Participants who were NE due to their scan occurring < 42 days after baseline (n = 2)
  - Participant who received CRB-701 1.8 mg/kg (n = 1)
- laUC/mUC
  - Participant with confounded data, assessed as having a PR and change from baseline of −60.7 (n = 1)
  - Participants who were NE due to their scan occurring < 42 days after baseline (n = 2)
  - Participants who received CRB-701 1.8 mg/kg (n = 3)

Table S1. Ocular TEAEs by maximum CTCAE grade and dose for CRB-701 Q3W

TEAE, 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)
Participants with ≥ 1 eye toxicity TEAE, n (%)	8 (61.5)	40 (54.1)	50 (65.8)	3 (75.0)	101 (60.5)
Grade 1	5 (38.5)	17 (23.0)	9 (11.8)	0	31 (18.6)
Grade 2	3 (23.1)	16 (21.6)	33 (43.4)	2 (50.0)	54 (32.3)
Grade 3	0	7 (9.5)	8 (10.5)	1 (25.0)	16 (9.6)

Data are summarized based on dose group assigned at enrolment. Participants with multiple events of the same type are counted once.
CTCAE, Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

Table S2. TRAEs of grade 3 or above in severity listed by system organ class and preferred term for CRB-701 Q3W

	1.8 mg/kg (n = 13)	2.7 mg/kg (n = 74)	3.6 mg/kg (n = 76)	4.5 mg/kg (n = 4)	Overall (N = 167)
Patients with ≥ 1 TRAE grade 3 or above in severity, n (%) [events, n]	1 (7.7) [2]	13 (17.6) [22]	13 (17.1) [20]	3 (75.0) [5]	30 (18.0) [49]
Eye disorders	0	6 (8.1) [8]	8 (10.5) [14]	1 (25.0) [1]	15 (9.0) [23]
Keratitis	0	4 (5.4) [4]	5 (6.6) [6]	1 (25.0) [1]	10 (6.0) [11]
Vision blurred	0	1 (1.4) [1]	1 (1.3) [1]	0	2 (1.2) [2]
Visual impairment	0	1 (1.4) [1]	1 (1.3) [1]	0	2 (1.2) [2]
Corneal epithelial microcysts	0	0	1 (1.3) [3]	0	1 (0.6) [3]
Keratopathy	0	1 (1.4) [1]	0	0	1 (0.6) [1]
Lacrimation increased	0	1 (1.4) [1]	0	0	1 (0.6) [1]
Ocular discomfort	0	0	1 (1.3) [1]	0	1 (0.6) [1]
Ulcerative keratitis	0	0	1 (1.3) [2]	0	1 (0.6) [2]
Blood and lymphatic system disorders	1 (7.7) [2]	4 (5.4) [7]	1 (1.3) [1]	0	6 (3.6) [10]
Anaemia	1 (7.7) [2]	4 (5.4) [5]	1 (1.3) [1]	0	6 (3.6) [8]
Lymphopenia	0	1 (1.4) [1]	0	0	1 (0.6) [1]
Thrombocytopenia	0	1 (1.4) [1]	0	0	1 (0.6) [1]
Investigations	0	3 (4.1) [4]	1 (1.3) [2]	1 (25.0) [3]	5 (3.0) [9]
ALT increased	0	1 (1.4) [1]	0	0	1 (0.6) [1]
AST increased	0	0	0	1 (25.0) [1]	1 (0.6) [1]
Blood ALP increased	0	0	0	1 (25.0) [1]	1 (0.6) [1]
Blood bilirubin increased	0	0	0	1 (25.0) [1]	1 (0.6) [1]
GGT increased	0	1 (1.4) [1]	0	0	1 (0.6) [1]
General physical condition abnormal	0	1 (1.4) [1]	0	0	1 (0.6) [1]

Lymphocyte count decreased	0	1 (1.4) [1]	0	0	1 (0.6) [1]
WBC count decreased	0	0	1 (1.3) [2]	0	1 (0.6) [2]
Gastrointestinal disorders	0	0	2 (2.6) [2]	0	2 (1.2) [2]
Constipation	0	0	1 (1.3) [1]	0	1 (0.6) [1]
Diarrhoea	0	0	1 (1.3) [1]	0	1 (0.6) [1]
General disorders and administration site conditions	0	1 (1.4) [1]	1 (1.3) [1]	0	2 (1.2) [2]
Fatigue	0	1 (1.4) [1]	1 (1.3) [1]	0	2 (1.2) [2]
Metabolism and nutrition disorders	0	2 (2.7) [2]	0	0	2 (1.2) [2]
Hypokalaemia	0	2 (2.7) [2]	0	0	2 (1.2) [2]
Skin and subcutaneous tissue disorders	0	0	0	1 (25.0) [1]	1 (0.6) [1]
Dermatitis bullous	0	0	0	1 (25.0) [1]	1 (0.6) [1]

Data are summarized based on dose group assigned at enrolment. Patients with multiple events of the same type are counted once.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; Q3W, every 3 weeks; TRAE, treatment-related adverse event; WBC, white blood cell.

Table S3. Mean CRB-701 pharmacokinetic parameters during cycle 1 for CRB-701 (n = 94)

Parameter, mean (CV, %)	1.8 mg/kg (n = 13)	2.7 mg/kg (n = 36)	3.6 mg/kg (n = 41)	4.5 mg/kg (n = 4)
ADC				
C_{max}, µg/L	33 762 (19)	50 585 (20)	63 182 (77)	73 479 (24)
AUC_{last}, h*µg/L	3 757 663 (40)	6 737 092 (36)	8 729 295 (65)	11 980 010 (20)
$t_{1/2}$, h[a]	107 (34)	133 (24)	139 (57)	178 (24)
MMAE				
C_{max}, ng/L	1567 (139)	1676 (77)	2818 (99)	1988 (62)
AUC_{last}, h*ng/L	461 710 (126)	516 530 (72)	922 938 (94)	648 554 (25)
$t_{1/2}$, h[b]	164 (38)	212 (36)	234 (36)	N/A

Data are geometric mean and CV.

[a]n = 35 in the 2.7 mg/kg dose group and n = 39 in the 3.6 mg/kg dose group.

[b]n = 7 in the 1.8 mg/kg dose group, n = 9 in the 2.7 mg/kg group, n = 8 in the 3.6 mg/kg dose group and n = 0 in the 4.5 mg/kg dose group.

ADC, antibody–drug conjugate; AUC_{last}, area under the time–concentration curve from dosing to the time of the last measured concentration; C_{max}, maximum concentration; CV, coefficient of variation; MMAE, monomethyl auristatin E; N/A, not applicable; $t_{1/2}$, terminal half-life.

Table S4. Confirmed best overall responses in HNSCC, cervical cancer and laUC/mUC for the 2.7 mg/kg and 3.6 mg/kg doses (n = 84)

Response, n (%)	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)
CR	0	0	1 (5.6)	0	0	0
PR	4 (33.3)	7 (33.3)	1 (5.6)	3 (18.8)	2 (25.0)	3 (33.3)
SD	5 (41.7)	5 (23.8)	10 (55.6)	8 (50.0)	4 (50.0)	5 (55.6)
PD	3 (25.0)	9 (42.9)	6 (33.3)	5 (31.3)	2 (25.0)	1 (11.1)

Responses were determined according to RECIST v1.1 criteria. A confirmation scan ≥ 4 weeks after the initial recorded response was required to confirm PR and CR. SD was confirmed if sustained for at least 42 days. Non-evaluable participants were excluded (HNSCC, n = 4; cervical cancer, n = 2; laUC/mUC, n = 3).

CR, complete response; HNSCC, head and neck squamous cell carcinoma; laUC/mUC, locally advanced or metastatic urothelial cancer; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.