436P

Preliminary Results of the First-in-Human, Dose-Finding PROCLAIM-CX-072 Trial Evaluating the PD-L1 Probody Therapeutic CX-072 in Combination With Ipilimumab in Patients With Advanced Solid Tumors

Ruth Plummer,[1] Rachel E. Sanborn,[2] Elisabeth de Vries,[3] Patricia LoRusso,[4] Hendrik-Tobias Arkenau,[5] Nataliya Uboha,[6] Jerzy Wydmanski,[7] Mary Josephine Fidler,[8] Valentina Boni,[9] Javier Garcia-Corbacho,[10] Rachel Humphrey,[11] Matthias Will,[11] Karen A. Autio,[12] Anthony El-Khoueiry,[13] C. Willemien Menke-van der Houven van Oordt,[14] Fiona Thistlethwaite[15]

[1]Northern Centre for Cancer Care, Newcastle, United Kingdom; [2]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [3]University Medical Center Groningen, Groningen, Netherlands; [4]Yale University School of Medicine–Yale Cancer Center, New Haven, CT, USA; [5]Sarah Cannon Research Institute UK Limited, London, United Kingdom; [6]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [7]NZOZ Vegamed, Katowice, Poland; [8]Rush University Medical Center, Chicago, IL, USA; [9]START Madrid-CIOCC HM Hospital Sanchinarro, Madrid, Spain; [10]Hospital Clinic Barcelona, Barcelona, Spain; [11]CytomX Therapeutics, South San Francisco, CA, USA; [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [13]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [14]VUMC Cancer Centre Amsterdam, Amsterdam, Netherlands; [15]The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom

BACKGROUND

- Antibodies targeting the programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) pathway demonstrate deep and durable cancer treatment responses when administered as monotherapy regimens[1,2]
- Antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) also demonstrate deep and durable remissions, particularly in patients with advanced melanoma[3]
- Combination regimens with PD-1 and CTLA-4 inhibitors have improved efficacy considerably at the expense of toxicity, leading to a disproportionately high rate of immune-related toxicities compared with each agent alone[4-7]
- To date, this combination is the only immuno-oncology inhibitor doublet approved by the US Food and Drug Administration and the European Medicines Agency
- The most common immune-related adverse events (irAEs) observed with CTLA-4 and PD-pathway inhibitors (both in monotherapy and in combination) are serious, sometimes fatal, inflammation of the skin, liver, lung, and/or colon[8]
- Probody™ therapeutics are fully recombinant antibody prodrugs that are designed to remain relatively inactive systemically and in healthy tissue, minimizing binding to the target antigen, and to be activated specifically in the tumor microenvironment by tumor-associated protease activity[8,10]
- CX-072 is an investigational Probody therapeutic directed against PD-L1, designed to have anticancer activity with potentially reduced irAEs
- The combination of Probody CX-072 and ipilimumab in immunotherapy-naive patients with solid tumors for whom no other immunotherapy is approved or available (Part B1)[11] is presented here (ClinicalTrials.gov identifier, NCT03013491). See poster 435P for data from Probody CX-072 monotherapy (Parts A and A2)

OBJECTIVES AND END POINTS

- Primary objectives of Part B1 of the study are to assess the safety and tolerability and to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity of CX-072 when administered in a concomitant combination schedule with ipilimumab
- Secondary objectives are to obtain preliminary evidence of anticancer activity in patients treated with CX-072 combined with ipilimumab using
  - Response rate (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)
  - Time to response and duration of response
  - Progression-free survival

METHODS

Study Design

- This is a first-in-human, open-label, dose-escalation, multicenter, phase 1/2a study of CX-072 in combination with ipilimumab (Part B1)
- Patients are ≥18 years of age and have Eastern Cooperative Oncology Group performance status 0 to 1
- To be included in Part B1, patients are required
  - To have any metastatic or advanced unresectable solid tumor or lymphoma (excluding thymic epithelial tumor, thymoma, and thymic carcinoma) (measurable or nonmeasurable disease)
  - To be naive to immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitor therapy, and to have a tumor type for which a checkpoint inhibitor is not available for therapy
- CX-072 (0.3, 1, 3, and 10 mg/kg) in combination with ipilimumab (3 mg/kg or 10 mg/kg* for the highest CX-072 dose level) is administered intravenously every 21 days for 4 cycles, followed by CX-072 monotherapy every 14 days
- Initiation of cohort enrollment required successful completion of the CX-072 monotherapy dose level evaluated in Part A

Safety Assessments

- Adverse events (AEs) are assessed and reviewed before each infusion and at any other visit that includes a physical examination. AEs are coded using MedDRA v19.1 and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03
- irAEs were defined as treatment-related AEs (TRAEs) that were on a predefined list of >300 preferred terms, were related to CX-072 or ipilimumab treatment, and required treatment with systemic steroids within 30 days of the onset of the relevant AE

Tumor Response and Translational Evaluation

- Imaging for tumor response assessment using RECIST v1.1 is performed every 8 weeks for the first 12 months, then every 12 weeks thereafter
- After the last dose of study medication, patients who do not discontinue because of progressive disease will be evaluated every 3 months for disease progression
- All patients will be evaluated for overall survival until study withdrawal or death
- Archival tissue or fresh biopsy samples are provided at baseline
- Serial blood samples for pharmacokinetic (PK) analysis are collected to characterize the PK profile of CX-072 in combination with ipilimumab
- Participating patients provide serial blood samples for measurement of exploratory biomarkers of immune modulation

*The protocol has been amended to enroll patients receiving CX-072 in combination with ipilimumab 6 mg/kg; 1 patient was dosed with ipilimumab 10 mg/kg before amendment.

RESULTS

Patients

- As of August 3, 2018, a total of 20 patients were enrolled; the MTD was not reached, and 6 patients (30%) were still receiving treatment
  - 14 patients discontinued because of radiologic or clinical disease progression. No patients discontinued because of AEs
  - The median number of ipilimumab doses received was 3. For patients who did not experience disease progression during the combination period, the median number of ipilimumab doses received was 4
- The CX-072 10 mg/kg + ipilimumab 3 mg/kg cohort was selected for additional enrollment to further evaluate this dose level
- Baseline characteristics are presented in **Table 1**

Table 1. Baseline Characteristics of Patients Treated With CX-072

Baseline Characteristics	All Patients N = 20
Median age, years (range)	58 (28-70)
Sex, n (%)	
Female	12 (60)
Male	8 (40)
Race, n (%)	
White	16 (80)
Asian	1 (5)
Not reported/unknown/other	3 (15)
ECOG performance status, n (%)	
0	7 (35)
1	13 (65)
No. of previous cancer treatments, median (range)	3 (1-12)
Cancer types, n (%)	
Pancreatic carcinoma	3 (15)
Cancer of unknown primary	2 (10)
Other[a]	15 (75)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor.
[a]One patient each had anal squamous cell carcinoma, breast (ER+) carcinoma, cervix carcinoma, colon carcinoma, gastric cancer, glioblastoma, head and neck squamous cell carcinoma, osteosarcoma, ovarian carcinoma, prostate non-adeno carcinoma, salivary gland carcinoma, small cell lung cancer, testicular carcinoma, triple-negative breast cancer, or uterine carcinoma.

Duration of Treatment

- Median (range) durations of treatment are reported in **Table 2**

Table 2. Duration of CX-072 + Ipilimumab Treatment

CX-072 + Ipilimumab Dose, mg/kg	0.3 + 3 n = 6	1 + 3 n = 3	3 + 3 n = 3	10 + 3 n = 7	10 + 10 n = 1	All Patients N = 20
Median treatment duration (range), months	1.8 (1-14)	5.2 (3-9)	2.9 (1-8)	1.3 (0-7)	1.2 (1-1)	2.0 (0-14)

Safety

- The MTD has not been reached (highest dose tested, CX-072 10 mg/kg + ipilimumab 10 mg/kg)
- AEs are summarized in **Table 3**
- irAEs occurred in 3 of 20 patients (15%); grade 3 irAEs occurred in 2 patients (10%)
- TRAEs were reported in 15 patients (75%); grade 3-4 TRAEs occurred in 4 patients (20%)
  - CX-072 0.3 mg/kg + ipilimumab 3 mg/kg: 2 patients (grade 3 colitis [n = 1] and grade 3 dyspnea/hypoxia/pneumonitis [n = 1])
  - CX-072 1 mg/kg + ipilimumab 3 mg/kg: 1 patient with grade 3 hyponatremia
  - CX-072 10 mg/kg + ipilimumab 3 mg/kg: 1 patient with both grade 3 amylase and grade 4 lipase increase
- No patients discontinued CX-072 because of AEs
- The most common treatment-emergent AEs (TEAEs) and all irAEs are reported in **Table 4** and **Table 5**, respectively

Table 3. Safety Summary by Dose, Patients Experiencing Event, n (%)

CX-072 + Ipilimumab Dose, mg/kg	0.3 + 3 n = 6	1 + 3 n = 3	3 + 3 n = 3	10 + 3 n = 7	10 + 10 n = 1	All Patients N = 20
TEAE						
All grades	6 (100)	3 (100)	3 (100)	6 (86)	1 (100)	19 (95)
Grade 3-4	4 (67)	2 (67)	0	3 (43)	1 (100)	10 (50)
SAE	3 (50)	3 (100)	0	1 (14)	0	7 (35)
TRAE						
All grades	5 (83)	3 (100)	2 (67)	5 (71)	0	15 (75)
Grade 3-4	2 (33)	1 (33)	0	1 (14)	0	4 (20)
SAE	2 (33)	2 (67)	0	0	0	4 (20)
irAE						
All grades	2 (33)	1 (33)	0	0	0	3 (15)
Grade 3-4	2 (33)	0	0	0	0	2 (10)
IRR						
All grades	1 (17)	0	0	2 (29)	0	3 (15)
Grade 3-4	0	0	0	0	0	0
TEAE leading to death						
All grades	0	0	0	0	0	0

AE, adverse event; irAE, immune-related adverse event; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related (to any study drug) adverse event.
Deaths due to disease progression (not considered related to study drug) were excluded from all safety analyses.
AEs were coded using MedDRA v19.1.

Table 4. Most Common TEAEs Occurring in ≥20% Patients, Patients Experiencing Event, n (%)

CX-072 + Ipilimumab Dose, mg/kg	0.3 + 3 n = 6		1 + 3 n = 3		3 + 3 n = 3		10 + 3 n = 7		10 + 10 n = 1		All Patients N = 20		
Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	Total
Nausea	4 (67)	0	3 (100)	0	0	0	1 (14)	0	1 (100)	0	9 (45)	0	9 (45)
Decreased appetite	2 (33)	0	1 (33)	0	1 (33)	0	2 (29)	0	0	0	6 (30)	0	6 (30)
Fatigue	3 (50)	0	2 (67)	0	0	0	1 (14)	0	0	0	6 (30)	0	6 (30)
Pruritus	1 (17)	0	0	0	1 (33)	0	4 (57)	0	0	0	6 (30)	0	6 (30)
Abdominal pain	1 (17)	1 (17)	0	0	0	0	1 (14)	1 (14)	1 (100)	0	3 (15)	2 (10)	5 (25)
Anemia	1 (17)	0	0	1 (33)	0	0	1 (14)	1 (14)	1 (100)	0	3 (15)	2 (10)	5 (25)
Constipation	1 (17)	0	1 (33)	0	1 (33)	0	0	0	1 (100)	0	4 (20)	0	4 (20)
Vomiting	2 (33)	0	1 (33)	0	0	0	1 (14)	0	0	0	4 (20)	0	4 (20)

TEAE, treatment-emergent adverse event.
Patients were grouped according to the most severe grade experienced for a particular AE. AEs were coded using MedDRA v19.1.

Table 5. irAEs, Patients Experiencing Event, n (%)

CX-072 + Ipilimumab Dose, mg/kg	0.3 + 3 n = 6		1 + 3 n = 3		3 + 3 n = 3		10 + 3 n = 7		10 + 10 n = 1		All Patients N = 20		
Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	Total
Any irAE	0	2 (33)	1 (33)	0	0	0	0	0	0	0	1 (5)	2 (10)	3 (15)
Endocrine	0	0	1 (33)	0	0	0	0	0	0	0	1 (5)	0	1 (5)
Hypophysitis	0	0	1 (33)	0	0	0	0	0	0	0	1 (5)	0	1 (5)
Gastrointestinal	0	1 (17)	0	0	0	0	0	0	0	0	0	1 (5)	1 (5)
Colitis	0	1 (17)	0	0	0	0	0	0	0	0	0	1 (5)	1 (5)
Lung	0	1 (17)	0	0	0	0	0	0	0	0	0	1 (5)	1 (5)
Dyspnea[a]	0	1 (17)	0	0	0	0	0	0	0	0	0	1 (5)	1 (5)
Pneumonitis[a]	0	1 (17)	0	0	0	0	0	0	0	0	0	1 (5)	1 (5)

irAE, immune-related adverse event.
[a]Dyspnea and pneumonitis occurred in the same patient.
irAEs were defined as treatment-related AEs that were on a predefined list of >300 preferred terms and that required treatment with systemic steroids within 30 days of the onset of the relevant AE.
Patients were grouped according to the most severe grade experienced for a particular AE. AEs were coded using MedDRA v19.1.

Tumor Response

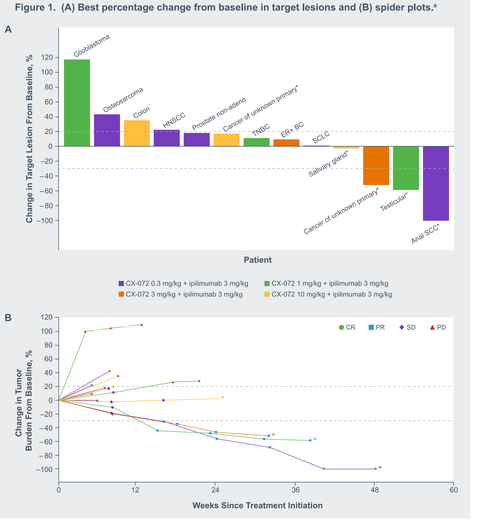
- Among evaluable patients (n = 14) who had ≥1 postbaseline tumor assessment, best tumor response was (**Table 6**)
  - Confirmed complete response (n = 1): anal squamous cell carcinoma (CX-072 0.3 mg/kg + ipilimumab 3 mg/kg); PD-L1 unknown, microsatellite-stable, intermediate tumor mutational burden (9 mutations/megabase), human papillomavirus (HPV) positive
  - Confirmed partial response (n = 2): testicular cancer (CX-072 1 mg/kg + ipilimumab 3 mg/kg) and cancer of unknown primary (CX-072 3 mg/kg + ipilimumab 3 mg/kg)
- Target lesions decreased from baseline in 4 of 13 evaluable patients (31%) with measurable disease at baseline and postbaseline (**Figure 1A**)
- Percentage change in tumor burden over time is presented in **Figure 1B**

Table 6. Best Tumor Response in Evaluable Patients[a] per RECIST v1.1, n (%)

CX-072 + Ipilimumab Dose, mg/kg	0.3 + 3 n = 5	1 + 3 n = 3	3 + 3 n = 2	10 + 3 n = 4	All Evaluable Patients n = 14
Objective response rate[b]	1 (20)	1 (33)	1 (50)	0	3 (21)
Complete response	1 (20)	0	0	0	1 (7)
Partial response	0	1 (33)	1 (50)	0	2 (14)
Stable disease	0	1 (33)	0	2 (50)	3 (21)
Disease control rate[c]	1 (20)	2 (67)	1 (50)	2 (50)	6 (43)
Progressive disease	4 (80)	1 (33)[d]	1 (50)	2 (50)	8 (57)

RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Evaluable patients are those with ≥1 postbaseline tumor assessment. No patients in the 10 + 10 cohort were evaluable.
[b]Objective response rate is the proportion of patients with complete response or partial response on 2 consecutive tumor assessments at least 4 weeks apart.
[c]Disease control rate = complete response + partial response + stable disease.
[d]One patient with glioblastoma was assessed per RANO criteria.

Figure 1. (A) Best percentage change from baseline in target lesions and (B) spider plots.[a]

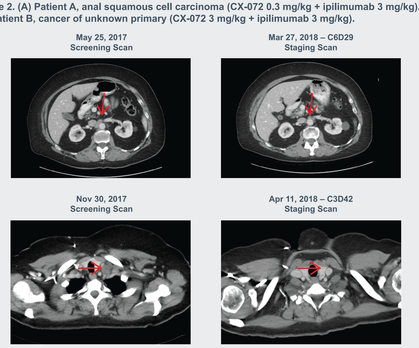


CR, complete response; ER+ BC, breast (ER+) carcinoma; HNSCC, head and neck squamous cell carcinoma; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SD, stable disease; TNBC, triple-negative breast cancer.
*Patient is still receiving treatment as of data cutoff.
One patient (glioblastoma) had increases up to 392.6%, which have been adjusted with broken lines in order to maintain readability.
One evaluable patient had PD, as evidenced by a new lesion, and did not have a postbaseline target lesion assessment.
[a]As evaluated per RECIST v1.1. Plots include evaluable patients with measurable disease at baseline and postbaseline.

Sample Case Studies

- Patient A has anal squamous cell carcinoma with intermediate tumor mutational burden (9 mutations/megabase) (microsatellite-stable, HPV-positive, and PD-L1 status unknown). The patient was treated with CX-072 0.3 mg/kg + ipilimumab 3 mg/kg and has been on treatment for 13.5 months. Patient A achieved a partial response at 3.7 months with a slow and steady decrease in tumor burden that continued to a complete response at 9.3 months which was confirmed on a follow-up scan 1.8 months later. The patient remains on study drug as of data cutoff (**Figure 2A**)
- Patient B has cancer of unknown primary location and PD-L1 negative status. The patient was treated with CX-072 3 mg/kg + ipilimumab 3 mg/kg and has been on treatment for 7.9 months. Patient B had a partial response on a follow-up scan at 3.2 months and remains on study drug as of data cutoff (**Figure 2B**)

Figure 2. (A) Patient A, anal squamous cell carcinoma (CX-072 0.3 mg/kg + ipilimumab 3 mg/kg). (B) Patient B, cancer of unknown primary (CX-072 3 mg/kg + ipilimumab 3 mg/kg).



CONCLUSIONS

- The MTD has not been reached
- Preliminary data suggest that concomitant dosing of Probody CX-072 and full-dose ipilimumab is well tolerated and compares favorably with historical data for non–Probody based PD-1 pathway inhibitors combined with ipilimumab (grade 3-4 TRAEs: 20% vs 55%-59%)[4,5]
- No new safety signals were observed with the combination of the anti–PD-L1 Probody CX-072 + ipilimumab 3 mg/kg; the overall rate of irAEs was 15%
- No patients to date have discontinued treatment because of toxicity
- Preliminary clinical activity has been evidenced by 3 objective responses, including 1 complete response
  - All responses are ongoing, with a maximum duration of response of 7.4 months
- As of August 3, 2018, 6 patients were still on treatment, including 3 receiving Probody CX-072 10 mg/kg + ipilimumab 3 mg/kg
- These data merit further exploration at ipilimumab doses >3 mg/kg; enrollment to a cohort receiving ipilimumab 6 mg/kg ipilimumab and Probody CX-072 10 mg/kg has been initiated

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