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

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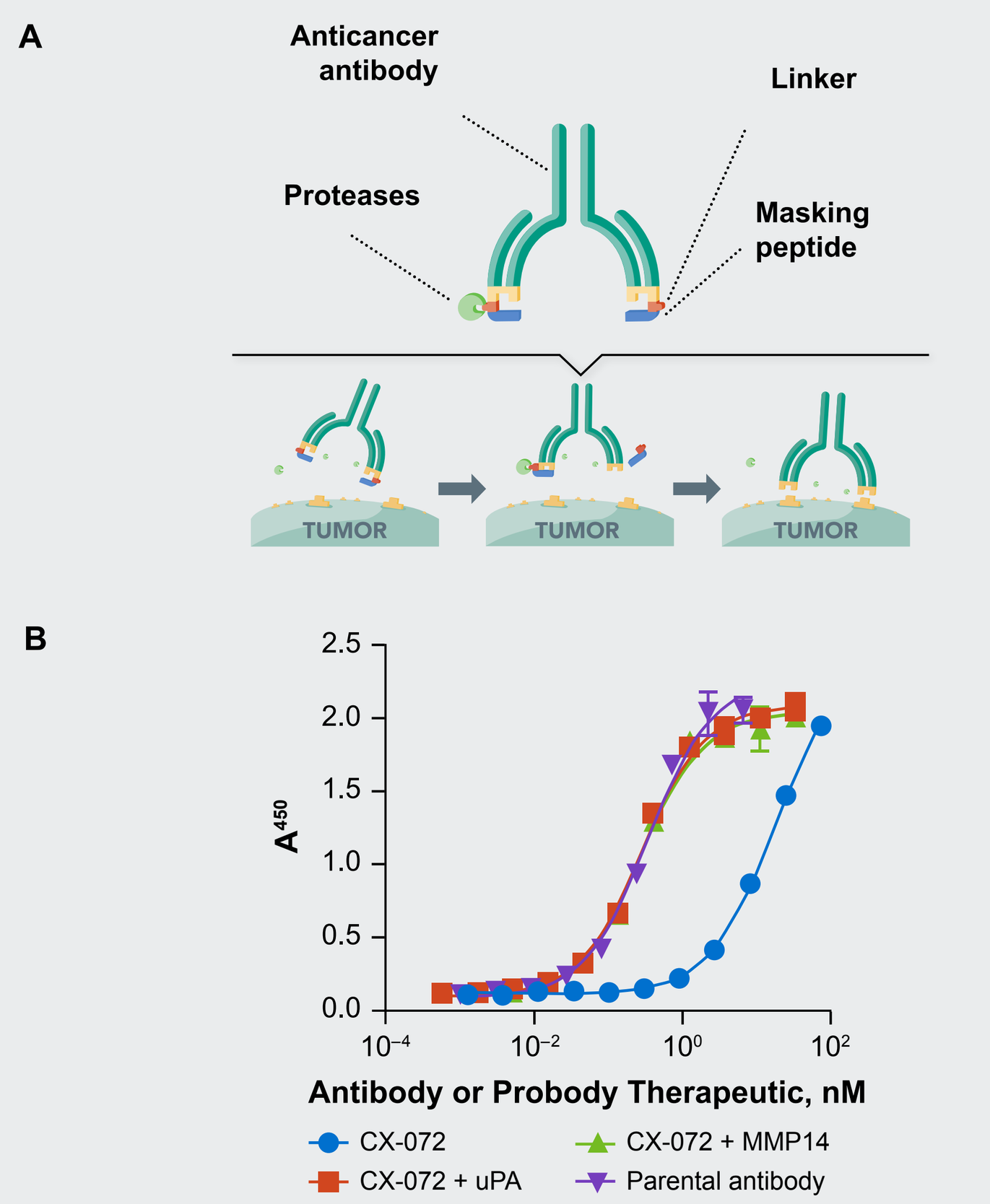
BACKGROUND

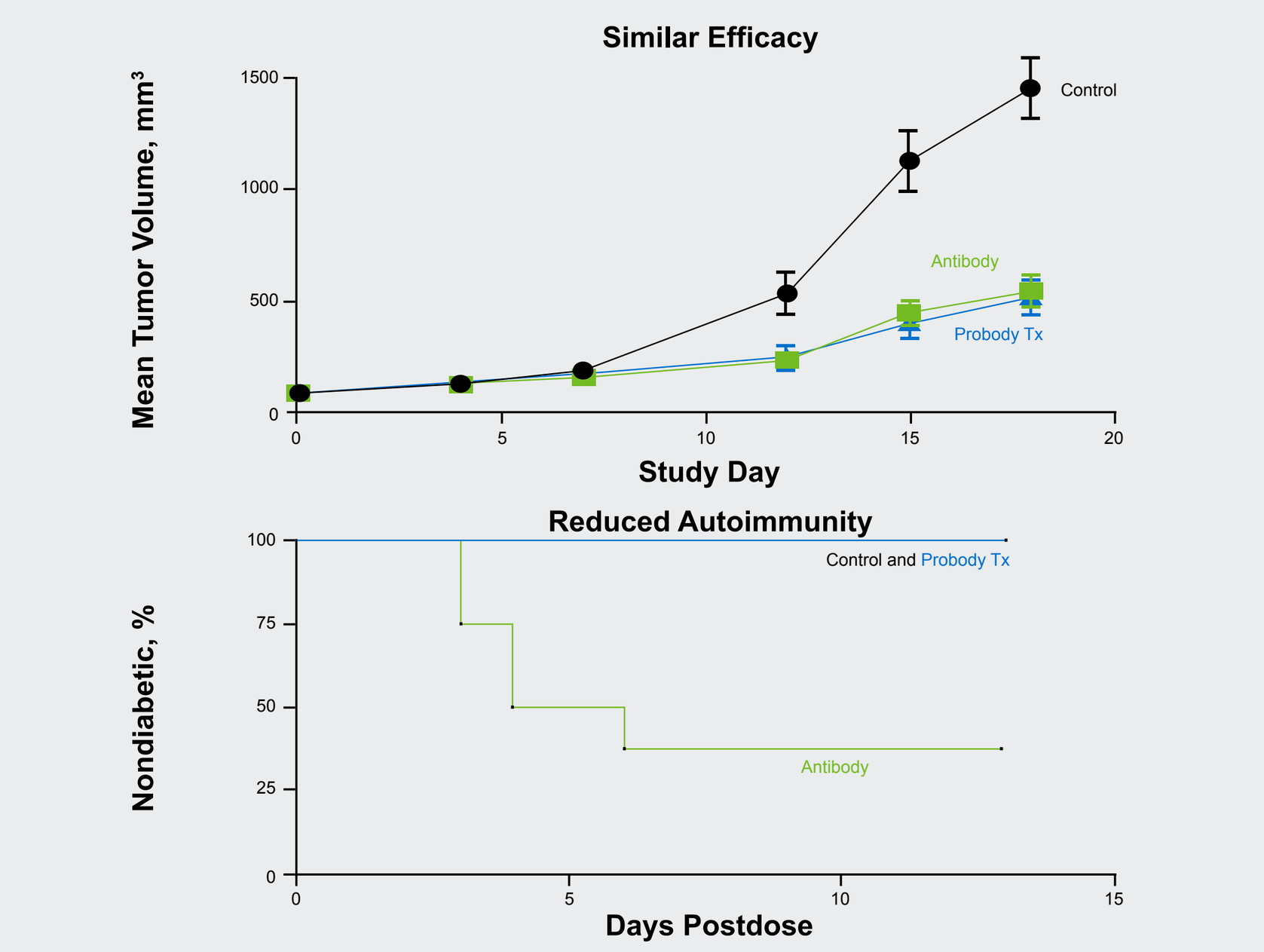
- Programmed cell death ligand 1 (PD-L1) is expressed on many cancer and immune cells; by binding the receptor programmed cell death 1 (PD-1), a negative regulator of T-lymphocyte activation, it can block cancer immune detection[1]
- Monoclonal antibodies targeting the PD-pathway and other immune-checkpoint inhibitors have shown anticancer activity in different tumor types[2]
- Immune-related adverse events (AEs), including interstitial pneumonitis, colitis, and transaminitis, are known toxicities of PD-1/PD-L1 axis-blocking antibodies. These toxicities are considerably higher when dual checkpoint inhibition is implemented[2-6]
- Probody™ therapeutics are fully recombinant antibody prodrugs that are designed to remain relatively inactive, both systemically and in healthy tissue, thereby avoiding binding to target antigen in healthy tissue. Probody therapeutics are designed to be activated specifically in the tumor microenvironment by tumor resident proteases (**Figure 1**)[7,8]
- CX-072 is a Probody therapeutic directed against PD-L1 for the treatment of patients with cancer
- In preclinical studies, a surrogate for CX-072 displayed potent antitumor activity[9]
  - Tumor-associated protease activation was required for CX-072 to bind to PD-L1 *in vitro*
  - A surrogate for CX-072 demonstrated efficacy equivalent to that of the parental antibody while minimizing the induction of autoimmune diabetes in nonobese diabetic mice (**Figure 2**)
  - A surrogate for CX-072 also exhibited reduced peripheral binding compared with the parental antibody
- The PROCLAIM-CX-072 (PRObody CLinical Assessment In Man) study is evaluating the tolerability and preliminary antitumor activity of multiple doses and expansion of CX-072 as monotherapy (Parts A, A2, and D) or as combination therapy with ipilimumab (Parts B1 and B2) or vemurafenib (Part C) in patients with advanced, unresectable solid tumors or lymphoma (ClinicalTrials.gov identifier, NCT03013491)

Figure 1. Probody therapeutics are protease-activatable antibody prodrugs. (A) Schematic representation of Probody therapeutic activation in the tumor microenvironment. (B) CX-072 exhibits protease-dependent binding to PD-L1 *in vitro* based on ELISA.



ELISA, enzyme-linked immunosorbent assay; MMP14, matrix metalloproteinase 14; PD-L1, programmed cell death ligand 1; uPA, urokinase-type plasminogen activator.
CX-072 (blue) shows reduced binding to recombinant PD-L1 by ELISA, whereas proteolytic activation of CX-072 with uPA or MMP-14 (red, green) restores binding to levels comparable to that of the parental antibody (purple).

Figure 2. In preclinical studies, Probody therapeutics displayed efficacy similar to that of parental antibodies (comparable reduction in tumor growth) with improved safety (reduced autoimmunity) at equivalent doses.



Tx, therapeutic.

OBJECTIVES AND END POINTS

- The primary objectives of Part A 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 as monotherapy
- Secondary objectives are to obtain preliminary evidence of anticancer activity in patients treated with CX-072 using
  - Response rate (Response Evaluation Criteria in Solid Tumors [RECIST] v 1.1)
  - Time to response and duration of response
  - Progression-free survival
- Secondary objectives also include characterization of the single-dose and multidose pharmacokinetic (PK) profiles of CX-072 when administered alone
- Exploratory objectives include investigation of the immunomodulatory activity of CX-072 in on-treatment biopsy specimens

METHODS

Study Design

- This is a first-in-human, open-label, dose-escalation, multicenter, phase 1/2a study of CX-072 designed to evaluate the safety and to determine the MTD and/or maximum achieved dose of CX-072 as monotherapy (Part A, dose escalation)
- Patients are ≥18 years of age with Eastern Cooperative Oncology Group performance status 0-1
- To be included in Part A, patients (n ≤ 33) are required
  - To have any metastatic or advanced unresectable solid tumor or lymphoma (measurable or nonmeasurable disease)
  - To be naive to immunotherapy, including to PD-1/PD-L1 and CTLA-4 inhibitor therapy, and to have a tumor type not approved for immune checkpoint inhibitors
- CX-072 monotherapy (0.03, 0.1, 0.3, 1, 3, 10, 30 mg/kg) is administered intravenously every 14 days without any premedication

Assessments by RECIST v1.1

- Imaging for tumor response assessment is performed every 8 weeks for the first 12 months, then every 12 weeks thereafter
- After the last dose of study medication, patients will be evaluated every 3 months for disease progression and overall survival until study withdrawal or death
- Archival tissue or fresh biopsy samples are provided at baseline. On-treatment biopsy is optional
- Data snapshot for this analysis was taken on April 20, 2018

INTERIM RESULTS

Patients

- Baseline characteristics are presented in **Table 1**
- As of April 20, 2018, Part A had enrolled 22 patients, among them 2 patients still receiving treatment
  - 20 patients discontinued treatment for the following reasons: radiological or clinical disease progression (n = 16), investigator withdrawal (n = 2), or AE (n = 2)

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

	All Patients N = 22
Median age, years (range)	65 (32-81)
Sex, n (%)	
Female	13 (59.1)
Male	9 (40.9)
Race, n (%)	
White	18 (81.8)
Black or African American	1 (4.5)
Not reported/unknown	3 (13.6)
ECOG performance status score, n (%)	
0	9 (40.9)
1	13 (59.1)
No. of previous cancer treatments, median (range)	3 (1-13)
Cancer type, n (%)	
Uterine carcinoma	3 (13.6)
Esophageal carcinoma	2 (9.1)
Pancreatic carcinoma	2 (9.1)
Castration-resistant prostate cancer	2 (9.1)
Rectal carcinoma	2 (9.1)
Thymoma or thymic cancer	2 (9.1)
Triple-negative breast cancer	2 (9.1)
Other[a]	7 (31.8)
PD-L1 expression status,[b] n (%)	
None (<1%)	10 (45.5)
Low (1-49%)	7 (31.8)
High (≥50%)	2 (9.1)
Unknown	3 (13.6)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PD-L1, programmed death-ligand 1.
[a]One patient each had breast (ER+) carcinoma, cervical carcinoma, colon carcinoma, peritoneal carcinoma, salivary gland carcinoma, head and neck squamous cell carcinoma, and uterine sarcoma.
[b]Assessed with clone 22c3 using archival tissue.

Treatment Duration

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

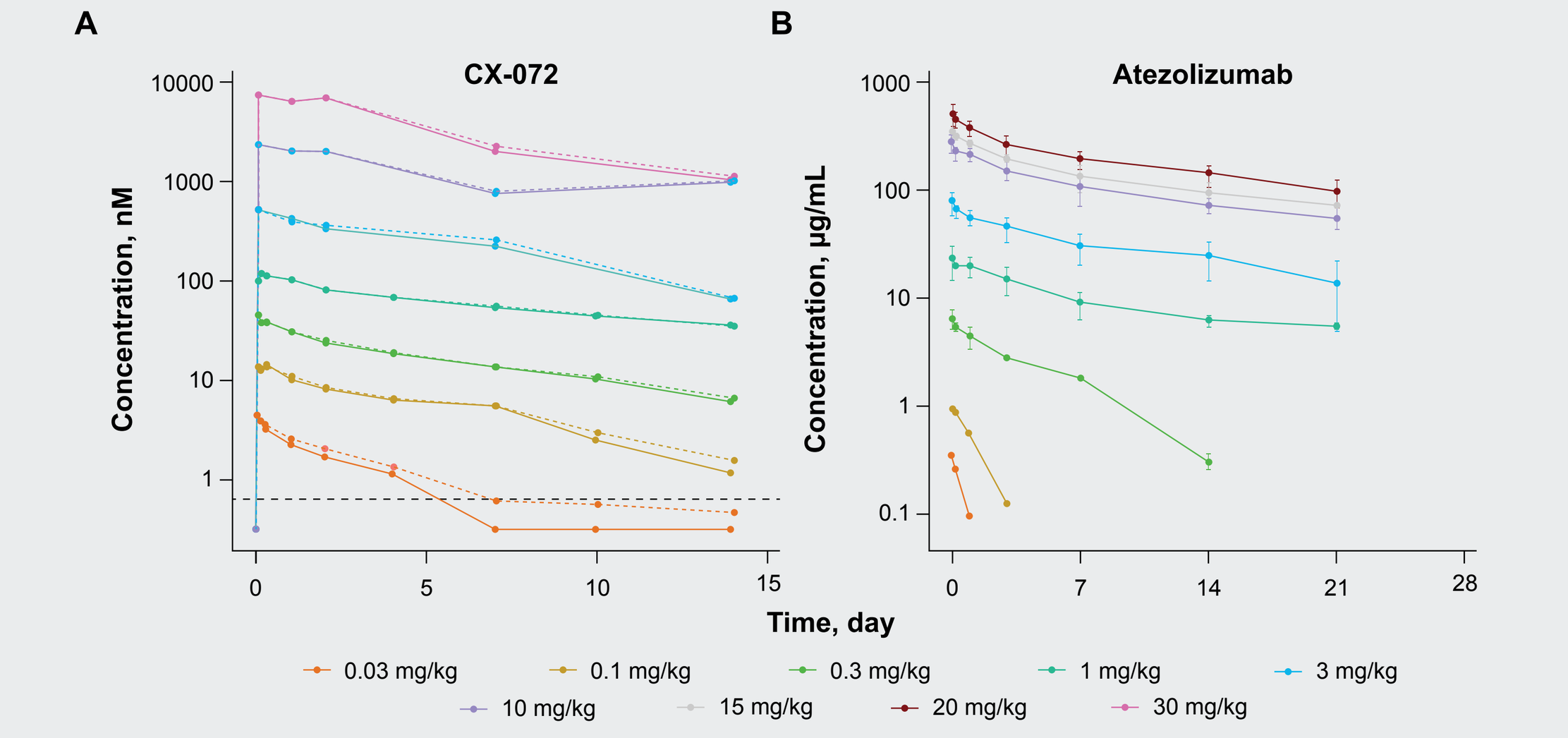
Table 2. Duration of CX-072 Treatment

CX-072 Dose, mg/kg	0.03 n = 2	0.1 n = 2	0.3 n = 2	1.0 n = 3	3.0 n = 7	10.0 n = 3	30.0 n = 3	All Patients N = 22
Mean treatment duration (range), months	5.6 (4-7)	3.5 (1-6)	1.8 (2-2)	4.4 (4-6)	2.5 (0-9)	5.9 (2-8)	2.5 (2-4)	3.5 (0-9)

Pharmacokinetic Analysis

- Preliminary single-agent, single-dose CX-072 PK data (**Figure 3A**) suggest that CX-072
  - Circulates predominantly as the intact prodrug species (96% intact at 30 mg/kg)
  - Is likely only minimally influenced by target-mediated drug disposition at low doses
- In contrast, the PD-L1 inhibitor atezolizumab exhibited nonlinear PK below the 1 mg/kg dose level (**Figure 3B**)

Figure 3. (A) Dose 1 median concentration of intact (solid colored lines) and total CX-072 (dashed colored lines) versus time after administration of up to 30 mg/kg CX-072 every 2 weeks.[a,b] (B) Dose 1 mean serum concentrations of atezolizumab.



LOQ, limit of quantitation.
[a]Gray dashed line represents LOQ for CX-072 assay, and data below the LOQ are assigned a value of LOQ/2.
[b]Cohort A, cycle 1, dose 1.
Figure 3B is reprinted by permission from Springer Nature. Herbst RS et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515:563-567. Copyright © 2014.

Safety

- Escalation to 30 mg/kg was completed; MTD was not reached
- Treatment-emergent AEs (TEAEs) are summarized in **Table 3**
  - Most treatment-related AEs (TRAEs) were grade 1-2, with grade 3-4 TRAEs occurring in 9.1% (2/22) patients
    - 3 mg/kg: neutropenia, thrombocytopenia (thymic cancer)
    - 30 mg/kg: transaminase elevation (breast cancer)
- There were 4 deaths (all from disease progression) within 30 days of last study drug administration
- The most common TEAEs occurring in ≥3 patients are reported in **Table 4**

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

CX-072 Dose Level, mg/kg	0.03 n = 2	0.1 n = 2	0.3 n = 2	1.0 n = 3	3.0 n = 7	10.0 n = 3	30.0 n = 3	All Patients N = 22
Any TEAE	2 (100.0)	2 (100.0)	2 (100.0)	3 (100.0)	7 (100.0)	3 (100.0)	3 (100.0)	22 (100.0)
Grade 3-4	2 (100.0)	1 (50.0)	2 (100.0)	1 (33.3)	3 (42.9)	2 (66.7)	2 (66.7)	13 (59.1)
SAE	1 (50.0)	0	1 (50.0)	1 (33.3)	4 (57.1)	2 (66.7)	0	9 (40.9)
TRAE	0	0	1 (50.0)	1 (33.3)	4 (57.1)	2 (66.7)	3 (100.0)	11 (50.0)
Grade 3-4	0	0	0	0	1 (14.3)	0	1 (33.3)	2 (9.1)
SAE	0	0	0	0	1 (14.3)	0	0	1 (4.5)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related AE.
Adverse events were coded using MedDRA version 19.1.

Table 4. Most Common TEAEs Occurring in ≥3 Patients, n (%)

CX-072 Dose Level, mg/kg	<1.0 n = 6		1.0 n = 3		3.0 n = 7		10.0 n = 3		30.0 n = 3		All Patients N = 22	
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
Cough	0	0	1 (33.3)	0	4 (57.1)	0	2 (66.7)	0	1 (33.3)	0	8 (36.4)	0
Decreased appetite	2 (33.3)	0	1 (33.3)	0	1 (14.3)	1 (14.3)	1 (33.3)	0	0	0	5 (22.7)	1 (4.5)
Dyspnea	0	0	1 (33.3)	0	2 (28.6)	1 (14.3)	2 (66.7)	0	0	0	5 (22.7)	1 (4.5)
Constipation	2 (33.3)	0	1 (33.3)	0	1 (14.3)	0	1 (33.3)	0	0	0	5 (22.7)	0
Anemia	0	1 (16.7)	1 (33.3)	0	0	0	0	0	1 (33.3)	1 (33.3)	2 (9.1)	2 (9.1)
Arthralgia	1 (16.7)	0	0	0	0	1 (14.3)	0	0	2 (66.7)	0	3 (13.6)	1 (4.5)
Back pain	0	1 (16.7)	0	0	1 (14.3)	0	1 (33.3)	0	1 (33.3)	0	3 (13.6)	1 (4.5)
Fatigue	1 (16.7)	0	0	0	1 (14.3)	1 (14.3)	1 (33.3)	0	0	0	3 (13.6)	1 (4.5)
Nausea	1 (16.7)	0	0	0	2 (28.6)	0	1 (33.3)	0	0	0	4 (18.2)	0
Pyrexia	1 (16.7)	0	0	0	1 (14.3)	0	1 (33.3)	0	1 (33.3)	0	4 (18.2)	0
Blood alkaline phosphatase increased	0	0	1 (33.3)	0	1 (14.3)	0	0	0	0	1 (33.3)	2 (9.1)	1 (4.5)
Edema peripheral	2 (33.3)	0	0	0	0	0	1 (33.3)	0	0	0	3 (13.6)	0
Neuropathy peripheral	0	0	1 (33.3)	0	1 (14.3)	0	1 (33.3)	0	0	0	3 (13.6)	0
Pain in extremity	0	0	0	0	2 (28.6)	0	0	1 (33.3)	0	0	2 (9.1)	1 (4.5)
Pruritus	1 (16.7)	0	0	0	1 (14.3)	0	0	0	1 (33.3)	0	3 (13.6)	0

TEAE, treatment-emergent adverse event.
Patients were grouped according to the most severe grade experienced for a particular adverse event. Adverse events were coded using MedDRA version 19.1.

Tumor Response

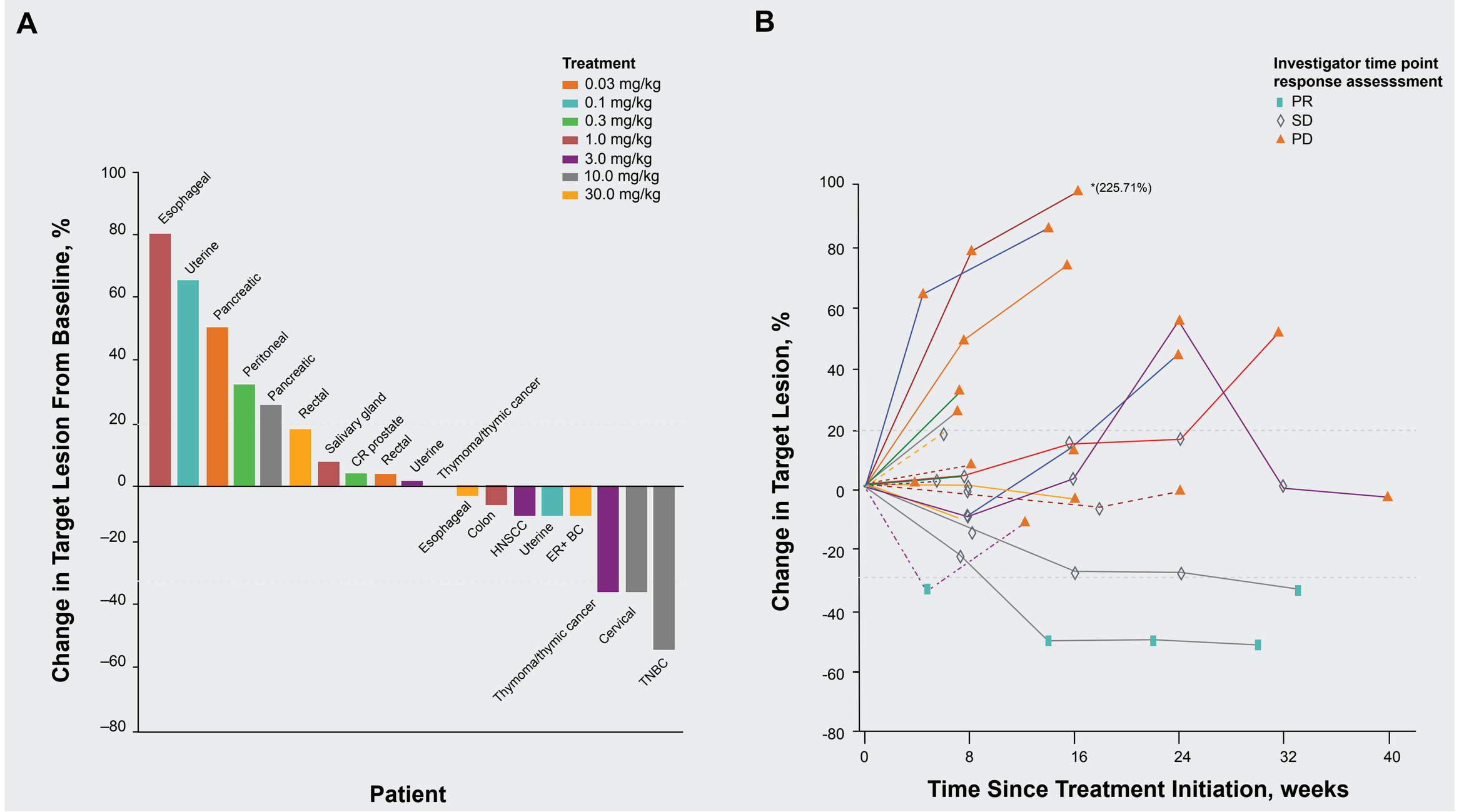
- Tumor response rates among evaluable patients (n = 20, including 1 patient with nonmeasurable disease) are provided in **Table 5**
- Target lesions decreased from baseline in 8 of 19 patients (42%) with measurable disease at baseline (**Figure 4A**)
  - Target lesions decreased from baseline at dose levels ≥3 mg/kg in 6 of 10 patients (60%)
- Percentage change in tumor burden over time is presented in **Figure 4B**

Table 5. Best Tumor Response in Evaluable Patients[a] per RECIST v1.1, n (%)

CX-072 Dose, mg/kg	0.03 n = 2	0.1 n = 2	0.3 n = 2	1.0 n = 3	3.0 n = 5	10.0 n = 3	30.0 n = 3	All Evaluable Patients N = 20
Best overall response, n (%)								
Partial response[b]	0	0	0	0	1 (20.0)	2 (66.7)	0	3 (15.0)
Stable disease	1 (50.0)	1 (50.0)	1 (50.0)	1 (33.3)	2 (40.0)[c]	0	2 (66.7)	8 (40.0)
Progressive disease	1 (50.0)	1 (50.0)	1 (50.0)	2 (66.7)	1 (20.0)	1 (33.3)	0	7 (35.0)
Inevaluable	0	0	0	0	1 (20.0)	0	1 (33.3)	2 (10.0)

RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Evaluable patients are those with an adequate disease assessment at baseline and ≥1 postbaseline tumor assessment.
[b]Includes 2 patients with unconfirmed partial response.
[c]Includes 1 patient with incomplete response/nonprogressive disease who did not have measurable disease at baseline.

Figure 4. (A) Best percentage change from baseline in target lesions and (B) spider plots.[a]

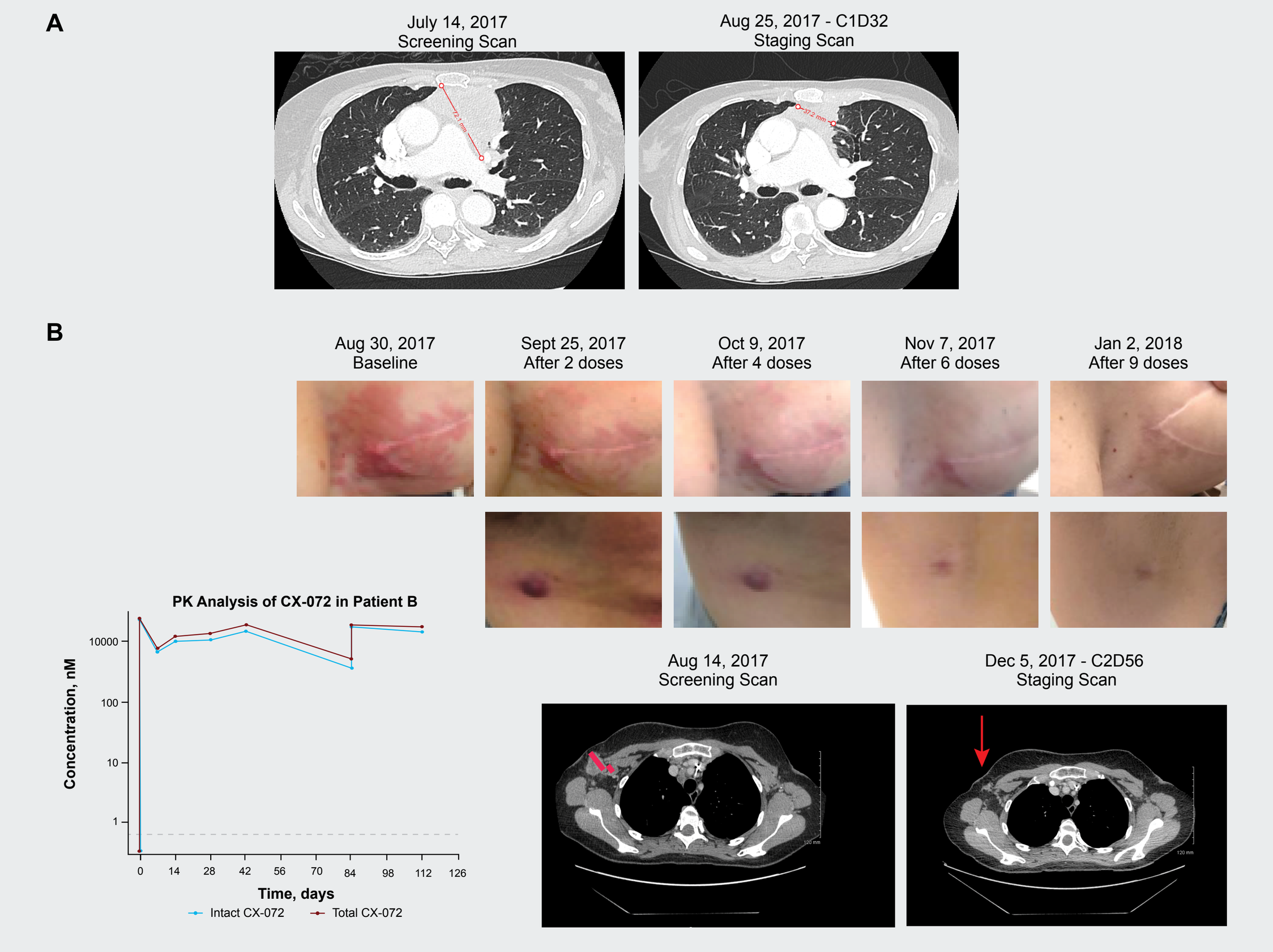


CR, castration-resistant; ER+ BC, estrogen receptor–positive breast cancer; HNSCC, head and neck squamous cell carcinoma; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TNBC, triple-negative breast cancer.
[a]As evaluated per RECIST v1.1. Plots include data from evaluable patients with measurable disease at baseline.

Sample Case Studies

- Patient A has thymic cancer with high baseline PD-L1 expression and received treatment with CX-072 3 mg/kg. The patient experienced a response to treatment after 2 weeks and had a 48% reduction in mediastinal mass. Patient discontinued treatment because of neutropenia (**Figure 5A**)
- Patient B has triple-negative breast cancer with microsatellite-stable low tumor mutational burden (4 mutations/megabase) and negative PD-L1 and received treatment with CX-072 10 mg/kg. As seen in **Figure 4B**, patient B has confirmed partial response (**Figure 5B**)

Figure 5. (A) Patient A: thymic cancer (CX-072 3 mg/kg). (B) Patient B: TNBC (CX-072 10 mg/kg).

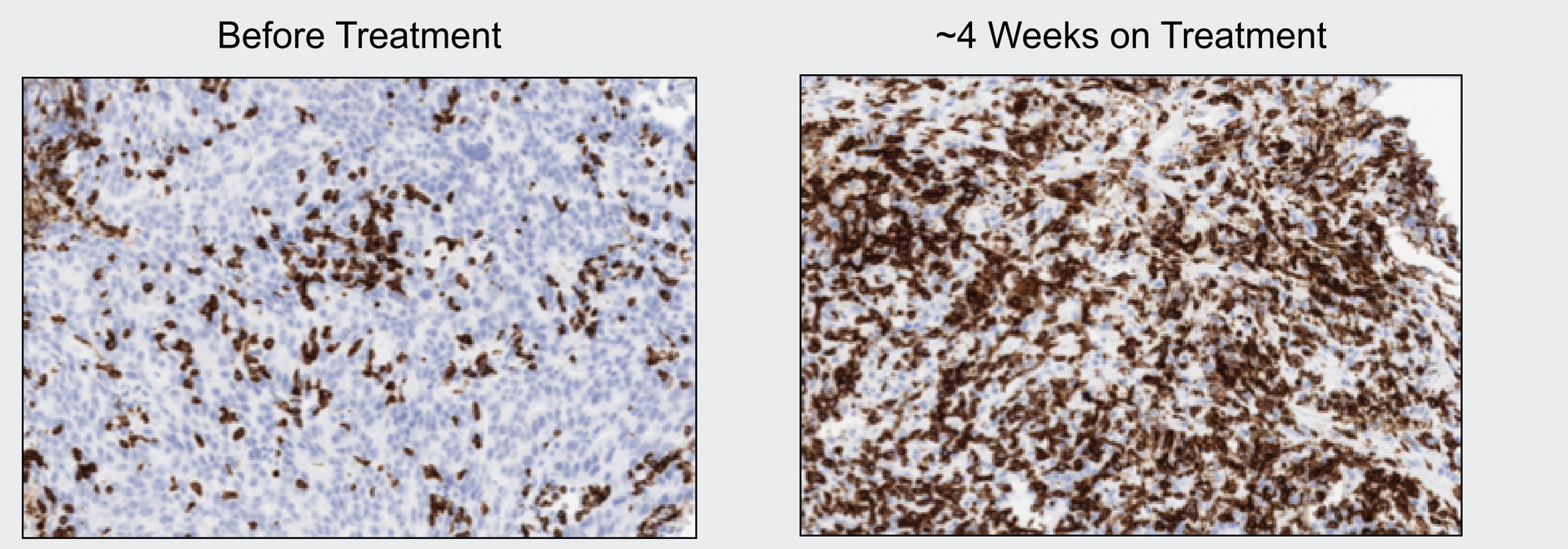


Node	Screening Aug 14, 2017	C2D56 Dec 5, 2017	C4D56 Mar 27, 2018
Right axillary	30 mm	12 mm	9 mm
Precarinal lymph	17 mm	9 mm	6 mm
Subcutaneous	25 mm	14 mm	19 mm

LOQ, limit of quantitation; PK, pharmacokinetic; TNBC, triple-negative breast cancer.
For PK analysis, the dashed line represents LOQ for CX-072 assay, and data below the LOQ are assigned a value of LOQ/2.

- Biomarker analysis of tumor biopsy pairs from Patient C (esophageal cancer; CX-072 30 mg/kg) demonstrated a 3-fold increase in $CD8^+$ T-cell infiltration after 4 weeks of treatment (**Figure 6**)

Figure 6. CD8 IHC staining from matched tumor biopsy samples collected before and during treatment with CX-072 (Patient C: esophageal cancer, CX-072 30 mg/kg).



IHC, immunohistochemistry.

INTERIM CONCLUSIONS

- This first-in-human Probody study with the anti–PD-L1 CX-072 used as monotherapy provides early evidence suggesting that CX-072 behaves as expected
  - MTD was not determined with doses up to 30 mg/kg
  - CX-072 is activated *in vivo* and exerts biological activity as evidenced by
    - 3 objective responses in 20 evaluable patients (15%), including those with negative PD-L1 expression
    - 3-fold increase in $CD8^+$ T-cell infiltration after 4 weeks of treatment in 1 patient with esophageal cancer
  - CX-072 exhibited reduced binding in peripheral tissue, as suggested by
    - Predominant circulation as the intact (masked) prodrug species (96% intact at 30 mg/kg)
    - Minimal influence of target-mediated drug disposition at low doses
    - Favorable safety profile, with only 2 patients experiencing a grade 3 TRAE
- These findings warrant further exploration of CX-072 monotherapy; research is ongoing in 8 expansion cohorts (10 mg/kg)
- Based on the safety profile, additional exploration is being conducted in combination therapy (Poster 3072)

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