PROCLAIM-CX-072: Monotherapy for Advanced Triple-Negative Breast Cancer With Skin Metastases in a Phase 1/2a Trial of the PD-L1 Probody Therapeutic CX-072

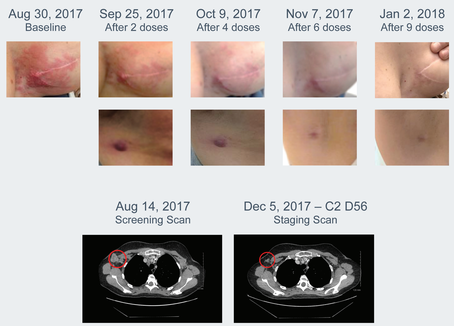
Sylvia Adams,[1] Erika Hamilton,[2] Patrick A. Ott,[3] Daniel Cho,[1] Kevin Kalinsky,[4] Patricia LoRusso,[5] Matthias Will,[6] Vanessa Huels,[6] Beverly Benson,[6] Carmen Murias,[7] Hendrik-Tobias Arkenau[7]

[1]Perlmutter Cancer Center, New York University School of Medicine, New York, NY, USA; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Columbia University Irving Medical Center, New York, NY, USA; [5]Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA; [6]CytomX Therapeutics, Inc., South San Francisco, CA, USA; [7]Sarah Cannon Research Institute UK Ltd, London, United Kingdom

BACKGROUND

- Triple-negative breast cancer (TNBC) lacks expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor 2 protein and accounts for 15%-20% of breast cancers; TNBC has an aggressive course and is associated with poor prognosis, especially when metastatic[1,2]
- Monoclonal antibodies targeting the programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) pathway have shown some clinical activity as monotherapy or as combination with chemotherapy in patients with TNBC; response to PD-1/PD-L1 has been observed primarily in those who are treatment naive[3-7]
- Immune-related adverse events, including interstitial pneumonitis, colitis, and transaminitis, are known toxicities of PD-1/PD-L1 axis-blocking antibodies and are commonly treated with steroids[8,9]
- Probody™ therapeutics are fully recombinant antibody prodrugs designed to remain relatively inactive systemically and to be activated specifically in the tumor microenvironment by tumor-associated protease activity[10,11]
- CX-072 is an investigational Probody therapeutic directed against PD-L1 and has demonstrated antitumor activity in TNBC patients in an ongoing phase 1/2a study
- In the phase 1 dose-escalation portion of the PROCLAIM-CX-072 (PRObody CLinical Assessment In Man) trial (NCT03013491), 3 of 20 evaluable patients (15%) had a partial response[12]
  - One of the patients with a partial response was a 39-year-old woman with stage IV TNBC whose disease had progressed after 8 cycles of chemotherapy (cisplatin) + ATR kinase inhibitor (VX-970) for metastatic disease (**Figure 1**).[12] Metastatic sites included extensive nodal disease and skin/chest wall lesions. The tumor was PD-L1 negative and microsatellite stable and had a low tumor mutational burden (4 mutations/megabase). The patient has continued to receive treatment with Probody CX-072 10 mg/kg for more than 12 months
- The potential efficacy of CX-072 observed in the patient with TNBC during the phase 1 dose-escalation portion of the study prompted additional exploration of Probody CX-072 monotherapy in TNBC during the phase 2a dose-expansion phase of the trial

Figure 1. Patient with stage IV triple-negative breast cancer treated with Probody CX-072 10 mg/kg monotherapy during the phase 1 dose-escalation portion of PROCLAIM-CX-072.[12]



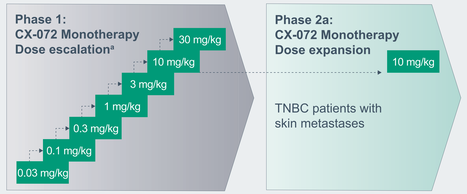
OBJECTIVE

- Phase 2a of the PROCLAIM-CX-072 study is evaluating the tolerability and preliminary antitumor activity of multiple doses of CX-072 as monotherapy in patients with TNBC and skin metastases

STUDY DESIGN

- PROCLAIM-CX-072 is a first-in-human, open-label, dose-escalation, multicenter, phase 1/2a study of CX-072 (**Figure 2**)
  - Phase 1 was designed to evaluate the safety and determine the maximum tolerated dose and/or maximum achieved dose of CX-072 as monotherapy
  - Phase 2a is the dose expansion of CX-072 monotherapy at 10 mg/kg every 2 weeks in specific tumor types, including TNBC with skin metastases

Figure 2. PROCLAIM-CX-072 phase 1/2a study design.



[a]During phase 1 (dose escalation), CX-072 monotherapy was administered intravenously every 2 weeks. Lower dose levels (0.03, 0.1, and 0.3 mg/kg) were single-patient cohorts to obtain adequate safety without exposure of patients to potentially subtherapeutic doses. Cohorts starting at the 1-mg/kg up to the 30-mg/kg dose followed a 3+3 design.

Patients

- Up to 14 patients with TNBC and skin metastases who meet defined criteria (**Table 1**) will be initially enrolled into phase 2a of the study and will receive CX-072 10 mg/kg every 2 weeks
- Based on prespecified response rates in the first 14 patients, the TNBC cohort may be expanded

Table 1. Key Eligibility Criteria for the TNBC Cohort

Phase 2a
Age ≥18 years
ECOG performance status 0-1
Histologically confirmed TNBC (ER negative [<1%], PR negative [<1%], and HER2 negative) per ASCO-CAP guidelines[a]
Locally advanced and recurrent skin or subcutaneous metastases not suitable for surgical resection or radiotherapy
Measurable disease
Willing to provide a fresh skin tumor biopsy from a nontarget lesion
Previous treatment with 1-3 lines of therapy for breast cancer, with documented progression on most recent therapy
Naive to immunotherapy (PD-1/PD-L1 and CTLA-4 inhibitors)
Approved PD-1/PD-L1 immunotherapy unavailable for patient's disease

ASCO-CAP, American Society of Clinical Oncology–College of American Pathologists; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PR, progesterone receptor; TNBC, triple-negative breast cancer. [a]Patients with weakly (<5%) ER- or PR-positive disease are eligible if the treating physician considers the patient not eligible for endocrine therapy.

END POINTS

Primary End Points

- Objective response rate according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Secondary End Points

- Objective response rate according to immune-related RECIST
- Duration of response
- Progression-free survival
- Incidence of antidrug antibodies
- Pharmacokinetic profile of CX-072
- Overall survival
- Safety and tolerability

Exploratory Objectives

- Protease activity and degree of CX-072 cleavage in tumors
- Immunomodulatory activity of CX-072 in on-treatment biopsy samples
- Potential predictive markers of CX-072 activity

SPECIFIC ASSESSMENTS

- Imaging for tumor response assessment will be 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 must be provided at baseline, and patients must consent to additional biopsies to aid in translational analyses

STUDY PROGRESS

- Sites in the United States and Europe are open for the enrollment of patients with TNBC and skin metastases to be treated with CX-072 monotherapy
- This study is registered with ClinicalTrials.gov, number NCT03013491
- For more information, please visit https://clinicaltrials.gov/ct2/show/NCT03013491 or contact clinicaltrials@cytomx.com

REFERENCES

1. Anders CK et al. *Clin Breast Cancer.* 2009;9(suppl 2):S73-S81.
2. Curigliano G et al. *J Natl Cancer Inst Monogr.* 2011;2011:108-110.
3. Nanda R et al. *J Clin Oncol.* 2016;34:2460-2467.
4. Dirix LY et al. *Breast Cancer Res Treat.* 2018;167:671-686.
5. Schmid P et al. *N Engl J Med.* 2018 October 20. doi: 10.1056/NEJMoa1809615.
6. Adams S et al. *Ann Oncol.* 2018 Nov 26. doi: 10.1093/annonc/mdy517.
7. Adams S et al. *Ann Oncol.* 2018 Nov 26. doi: 10.1093/annonc/mdy518.
8. Iwai Y et al. *J Biomed Sci.* 2017;24:26.
9. Baxi S et al. *BMJ.* 2018;360:k793.
10. Desnoyers LR et al. *Sci Transl Med.* 2013;5:207ra144.
11. Polu KR et al. *Expert Opin Biol Ther.* 2014;14:1049-1053.
12. Autio KA et al. *J Clin Oncol.* 2018;36(suppl). Abstract 3071.

ACKNOWLEDGMENTS

The authors thank the participating patients and their families and all staff at participating sites. This study was sponsored by CytomX Therapeutics, Inc. Medical writing assistance was provided by Andrew Occiano, PharmD (ApotheCom, San Francisco, CA, USA) and was funded by CytomX Therapeutics, Inc.