CytomX Therapeutics, Inc. Logo

CytomX Therapeutics Announces Multiple Publications on Pacmilimab (CX-072), a Conditionally Activated Inhibitor of Programmed Death-Ligand 1 (PD-L1)

August 4, 2021

-Translational whole-body PET clinical imaging supports conditional activation in the tumor microenvironment-

-Pacmilimab demonstrated single-agent activity in advanced solid tumors, including metastatic triple-negative breast cancer-

-Combination of pacmilimab and ipilimumab illustrates potential for pacmilimab as a preferred checkpoint inhibitor for combination therapies-

SOUTH SAN FRANCISCO, Calif., Aug. 04, 2021 (GLOBE NEWSWIRE) -- CytomX Therapeutics, Inc. (Nasdaq: CTMX), a clinical-stage oncology-focused biopharmaceutical company pioneering a novel class of investigational conditionally activated therapeutics based on its Probody® technology platform, today announced the publication of three articles in peer-reviewed journals on pacmilimab (CX-072), the Company's wholly-owned conditionally activated antibody directed against PD-L1 currently being developed in combination with praluzatamab ravtansine (CX-2009) for the treatment of triple-negative breast cancer (TNBC).

"My colleagues and I are delighted to see our ground-breaking work on the CytomX Probody therapeutic platform being published in high quality journals as we continue to lead this emerging and important field," said Sean McCarthy, D.Phil., president, chief executive officer and chairman of CytomX Therapeutics. "These comprehensive first-in-human results with the first ever Probody therapeutic candidate evaluated in clinical studies provide robust evidence that Probodies function as designed, eliciting potent anti-tumor activity in the context of enhanced systemic tolerability. Our technology is enabling a wide range of potentially first-in-class therapies against previously undruggable targets and also new combination therapies, opening up different ways of thinking about cancer treatment."

Constructed using CytomX's industry-leading conditional activation Probody platform, each Probody therapeutic has a unique built-in mask that limits target binding in healthy tissues, while localizing its activation in the tumor microenvironment. This conditional activation is achieved by enabling mask removal by specific enzymes called proteases, which are activated in the tumor microenvironment, but tightly controlled in healthy tissues. Upon removal of the mask in the tumor microenvironment, Probody therapeutics engage their targets and destroy the cancer cells they were ultimately activated by.

While immune checkpoint inhibitor (ICI) therapies have transformed the landscape of cancer treatment, the limited response rates observed for cancer patients treated with single-agent PD-1/PD-L1 or cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) blocking antibodies leave significant room for improvement. Conventional anti-PD-1/PD-L1 therapies can be impaired by immune-related adverse events (irAEs), which have been reported in as many as 30% of patients in Phase 3 studies, and particulary in combination settings.[1]

Pacmilimab (CX-072) is a Probody therapeutic directed against PD-L1 designed and developed by CytomX. Pacmilimab is engineered to be conditionally activated in the tumor microenvironment by tumor-associated proteases and to remain predominantly masked in the circulation. In preclinical studies, pacmilimab induced anti-tumor responses comparable to those of the parental anti-PD-L1 antibody and demonstrated reduced toxicity. Pacmilimab is wholly owned by CytomX.

First-in-human PET Imaging Study of Pacmilimab Biodistribution Published in *Clinical Cancer Research*

To evaluate the effect of Probody modifications on biodistribution and pharmacokinetics, we, in collaboration with Elisabeth G.E. de Vries, MD, PhD., Professor of Medical Oncology at the University Medical Centre Groningen, Groningen, the Netherlands, studied the biodistribution of pacmilimab labeled with the positron emission tomography (PET) isotope, zirconium-89 (89Zr), in patients with locally advanced or metastatic malignancies.

89Zr-labeled pacmilimab was found to be intact in the blood for up to 7 days and predominantly in its masked form in circulation, consistent with Probody design. All patients showed uptake of radioactivity into tumor lesions. Tumor-to-blood ratio of radioactivity increased over time, indicating that tumor uptake of pacmilimab is specific and retained in the tumor.

"This is the first human imaging report of a Probody therapeutic candidate that is conditionally activated in the tumor microenvironment," stated Marcia P. Belvin, Ph.D., senior vice president and head of research of CytomX Therapeutics. "The findings of intact pacmilimab in the circulation, modest uptake in normal lymphoid organs, and accumulation in the tumor, all support mechanistic performance of the Probody therapeutic platform, with target engagement in the tumor and reduced target engagement in normal tissues."

First-in-human Study of Pacmilimab in Patients with Advanced Solid Tumors P**ublished in the *Journal for ImmunoTherapy of Cancer***

Patients with advanced solid tumors who were naïve to ICI therapies were eligible for this Phase 1/2 multicenter study. After the dose escalation (n=53) was complete and a recommended dose for future study defined, an additional 98 patients were enrolled into the dose expansion phase of the study, with pacmilimab administered intravenously at 10 mg/kg, the recommended Phase 2 dose (RP2D), every two weeks until confirmed disease progression or unacceptable toxicity. The tumor types evaluated included TNBC, anal squamous cell carcinoma (aSCC), cutaneous SCC (cSCC), undifferentiated pleomorphic sarcoma (UPS), small bowel adenocarcinoma (SBA), thymic epithelial tumor (TET), and high tumor mutational burden tumor (hTMB).

Combining all patients treated at 10 mg/kg, the overall objective response rate (ORR) in 114 evaluable patients who had at least one post-baseline disease assessment was 12 percent, with a disease control rate of 42 percent. Best responses per RECIST 1.1 in each tumor type are summarized in the table below:

	TNBC (n=15)	aSCC (n=15)	cSCC (n=14)	UPS (n=20)	SBA (n=14)	TET (n=10)	hTMB (n=14)	Others (n=12)	Total (N=114)
ORR, %	7	13	36	5	0	0	29	8	12

CR, n (%)	0	0	1 (7)	0	0	0	1 (7)	0	2 (2)
PR, n (%)	1 (7)	2 (13)	4 (29)	1 (5)	0	0	3 (21)	1 (8)	12 (11)
SD, n (%)	7 (47)	6 (40)	5 (36)	4 (20)	2 (14)	5 (50)	2 (14)	3 (25)	34 (30)
DCR, n (%)	8 (53)	8 (53)	10 (71)	5 (25)	2 (14)	5 (50)	6 (43)	4 (33)	48 (42)

ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate (defined as CR, PR or SD of at least 8 weeks duration)

"These early results are very encouraging when compared with historical data from conventional ICIs," remarked Amy C. Peterson, M.D., executive vice president and chief development officer of CytomX Therapeutics. "The activities in TNBC and aSCC are particularly noteworthy given that single-agent atezolizumab had a 6% ORR in second or higher-line metastatic TNBC and the ORR for single-agent pembrolizumab in recurrent, PD-L1-positive aSCC was 17%, both of which are similar to our findings with pacmilimab in patients with more advanced disease," added Dr. Peterson.

At the RP2D of 10 mg/kg, pacmilimab displayed a favorable tolerability profile. Grade 3 or higher treatment-related adverse events (TRAEs) were reported in 10 patients (9%) and serious TRAEs in six patients (5%). The discontinuation rate due to TRAEs was a low 2%. Grade 3 or higher irAEs occurred in two patients, one each for rash and myocarditis. Additionally, pneumonitis and colitis, irAEs commonly seen in patients receiving conventional anti-PD-1/PD-L1 agents (2.2% and 0.7%, respectively),[2] were reported only once for pneumonitis (0.7%) and there were no reports of colitis (0%). Collectively, these adverse event data indicate that pacmilimab is an attractive candidate for combination therapy.

First-in-human Study of Pacmilimab in Combination with Ipilimumab in Advanced Solid Tumors Published in the *Journal for ImmunoTherapy of Cancer*

To maximize the benefits of immunotherapy for patients, the field has moved aggressively toward combination therapy. While many of these combinations have been shown to elicit improved response rates compared with monotherapy, their adverse event profiles are often worse. A notable example is the combination of nivolumab (anti-PD-1) at a dose of 1 mg per kilogram of body weight and 3 mg per kilogram of ipilimumab (anti-CTLA-4) every three weeks, which produced a 58% ORR in a cohort of 314 patients with previously untreated advanced melanoma. However, this improved efficacy came at the cost of safety and tolerability, with grade 3 or 4 TRAEs occurring in 59% of patients.[3]

The goal of this first-in-human dose-finding study was to evaluate the tolerability and preliminary antitumor activity of pacmilimab combined with ipilimumab in patients with advanced, unresectable solid tumors. Twenty-seven patients who had not been previously treated with an ICI were enrolled. Dose-escalation followed a standard 3+3 design and continued until the maximum tolerated dose (MTD) was determined. Pacmilimab+ipilimumab was administered intravenously every 3 weeks for four cycles, followed by pacmilimab administered every 2 weeks as monotherapy.

The ORR was 19%, including one patient with anal squamous cell carcinoma having a complete response and four partial responses in patients with leiomyosarcoma, mesothelioma, testicular cancer, and cancer of unknown primary. Moreover, these responses appeared durable, with four of five responses lasting for more than 1 year as of data cutoff on August 28, 2020, including the patient with a complete response maintaining for more than 24 months. Pacmilimab-related grade 3-4 AEs and grade 3-4 irAEs were reported in nine (33%) and six (22%) patients, respectively. Three patients (11%) discontinued treatment due to AEs. There were no treatment-related deaths and no new safety signals were identified. Based on these findings, the MTD and recommended Phase 2 dose was pacmilimab 10 mg/kg in combination with ipilimumab 3 mg/kg administered every 3 weeks.

Pacmilimab is currently being evaluated in combination with praluzatamab ravtansine (CX-2009), the Company's wholly-owned conditionally activated antibody-drug conjugate targeting CD166, in a Phase 2 study in patients with TNBC. To learn more about this study, please go to www.ClinicalTrials.gov using the identifier: NCT04596150.

About CytomX Therapeutics

CytomX is a clinical-stage, oncology-focused biopharmaceutical company with a vision of transforming lives with safer, more effective therapies. We are developing a novel class of investigational conditionally activated therapeutics, based on our Probody® technology platform, for the treatment of cancer. CytomX has strategic drug discovery and development collaborations with AbbVie, Amgen, Astellas, and Bristol Myers Squibb.

Probody therapeutics are conditionally activated biologics designed to remain inactive until they are activated by proteases in the tumor microenvironment. As a result, Probody therapeutics are intended to bind selectively to tumors and decrease binding to healthy tissue, to minimize toxicity and potentially create safer, more effective therapies. As leaders in the field, our innovative technology is designed to turn previously undruggable targets into druggable targets and to enable more effective combination therapies. CytomX and its partners, comprised of leading biotechnology and pharmaceutical companies, have developed a robust pipeline of potential first-in-class therapeutic candidates against novel, difficult to drug targets and potential best-in-class immunotherapeutic candidates against clinically validated targets. The CytomX clinical-stage pipeline comprises five assets, four of which are in Phase 2 clinical studies. First-in-class product candidates against previously undruggable targets include a CD166-targeting conditionally activated antibody-drug conjugate wholly owned by CytomX (praluzatamab ravtansine, CX-2009) and a CD71-targeting conditionally activated antibody-drug conjugate partnered with AbbVie (CX-2029). CD166 and CD71 are among cancer targets that are considered to be inaccessible to conventional antibody-drug conjugates due to their presence on many healthy tissues. The CytomX clinical-stage pipeline also includes cancer immunotherapeutic candidates against validated targets such as the CTLA-4-targeting Probodies, BMS-986249 and BMS-986288, partnered with Bristol Myers Squibb, and our wholly-owned conditionally activated anti-PD-L1 antibody, pacmilimab (CX-072). For additional information about CytomX Therapeutics, visit www.cytomx.com and follow us on LinkedIn and Twitter.

CytomX Therapeutics Forward-Looking Statements

This press release includes forward-looking statements. Such forward-looking statements involve known and unknown risks, uncertainties and other important factors that are difficult to predict, may be beyond our control, and may cause the actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied in such statements. Accordingly, you should not rely on any of these forward-looking statements, including those relating to the potential benefits, safety and efficacy or progress of CytomX's product candidates, including pacmilimab (CX-072), as monotherapy or in combination with ipilimumab, the potential benefits or applications of CytomX's Probody platform technology, CytomX's ability to develop and advance product candidates into and successfully complete clinical trials, including the ongoing and planned clinical trials of praluzatamab ravtansine and pacmilimab, and the timing of the commencement of clinical trials and other

development milestones. Risks and uncertainties that contribute to the uncertain nature of the forward-looking statements include: the unproven nature of CytomX's novel Probody platform technology; CytomX's clinical trial product candidates are in the initial stages of clinical development and its other product candidates are currently in preclinical development, and the process by which preclinical and clinical development could potentially lead to an approved product is long and subject to significant risks and uncertainties, including the risk that the COVID-19 worldwide pandemic may continue to negatively impact the business, research and clinical operations of CytomX or its partners, including the development of preclinical drug candidates due to delays in and disruption of research activities and the development of clinical drug candidates due to delays in or disruption of clinical trials, including impacts on the enrollment of patients in clinical trials or other clinical trial disruptions; the possibility that the results of early clinical trials may not be predictive of future results; the possibility that CytomX's clinical trials will not be successful; the possibility that current preclinical research may not result in additional product candidates; CytomX's dependence on the success of praluzatamab ravtansine, CX-2029, BMS-986249, BMS-986288, and pacmilimab; CytomX's reliance on third parties for the manufacture of the company's product candidates; and possible regulatory developments in the United States and foreign countries. Additional applicable risks and uncertainties include those relating to our preclinical research and development, clinical development, and other risks identified under the heading "Risk Factors" included in CytomX's Quarterly Report on Form 10-Q filed with the SEC on May 6, 2021. The forward-looking statements contained in this press release are based on information currently available to CytomX and speak only as of the date on which they are made. CytomX does not undertake and specifically disclaims any obligation to update any forward-looking statements, whether as a result of any new information, future events, changed circumstances or otherwise.

References

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Management of Immunotherapy-Related toxicities, v1, 2020.
2. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018;360:k793.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381:1535-46.

Investor Contact:
Chau Cheng, PhD MBA
VP, Investor Relations & Corp. Communications
ccheng@cytomx.com
Direct: (650) 273-4999

Media Contact:
Bret Coons
Director, Corporate Communications
bcoons@cytomx.com
Direct: (650) 528 2929

Source: CytomX Therapeutics Inc.