2seventy bio Presents Late-Breaking Results for SC-DARIC33, an Investigational CD33-Targeting CAR T in Pediatric and Young Adults with Relapsed or Refractory Acute Myeloid Leukemia

May 19, 2023 10:00 AM EDT

Results of preliminary correlative analysis from the PLAT-08 study show rapamycin-regulated in vivo expansion and activation of SC-DARIC33 T cells as well as concurrent anti-CD33 activity

Enhanced anti-acute myeloid leukemia (AML) potency was obtained with the combination of regulated IL-15 production combined with rapamycin-controlled DARIC33 activation – a potential next generation approach

SC-DARIC33 is a potentially first-in-class CD33-targeting, regulatable CAR T therapy in development with Seattle Children's Therapeutics

CAMBRIDGE, Mass.--(BUSINESS WIRE)--May 19, 2023-- 2seventy bio, Inc. (Nasdaq: TSVT), a leading immuno-oncology cell therapy company, today announced late-breaking results from the ongoing Phase 1 PLAT-08 trial, in collaboration with Seattle Children's Therapeutics , evaluating SC-DARIC33 in relapsed or refractory pediatric and young adult AML patients, as well as an oral presentation evaluating regulated IL-15 production combined with DARIC33 activation for anti-AML potency. The data were presented at this year's American Society of Gene & Cell Therapy (ASGCT) Annual Meeting in Los Angeles, California.

"The treatment of patients with relapsed and refractory AML represents a tremendous unmet medical need, particularly for pediatric and young adult patients. Progressing the promise of CAR T therapy, while mitigating potentially dose-limiting toxicity, has the potential to be a meaningful advance," said Steven Bernstein, M.D., chief medical officer, 2seventy bio. "Together with Seattle Children's Therapeutics, we are pleased to share results that demonstrate three key steps toward clinically meaningful outcomes: rapamycin dosing optimization, rapamycin-regulated in vivo expansion and activation of SC-DARIC33 T cells as well as concurrent anti-CD33 activity. These data reinforce the potential of SC-DARIC333 as a new T cell therapy approach in AML."

SC-DARIC33 is an investigational CD33-targeted chimeric antigen receptor (CAR) T cell therapy that utilizes 2seventy bio's proprietary Dimerizing Agent Regulated Immunoreceptor Complex (DARIC) T cell platform, a drug regulatable CAR T cell technology. SC-DARIC33 has been shown to be activated by low non-immunosuppressive concentrations of rapamycin in the blood and, when rapamycin is removed, DARIC returns to an inactive state. SC-DARIC33 tests the hypothesis that a pharmacologically regulated CAR can enable potent AML targeting while limiting toxicities associated with normal myeloid and myeloid progenitor cell targeting.

Eligible patients in the ongoing Phase 1 PLAT-08 trial are 30 years of age or younger in first early relapse (less than 6 months), first relapse refractory to reinduction, or ≥ second relapse.

Following lymphodepletion (LD) with fludarabine/cyclophosphamide, patients received SC-DARIC33 T cells followed by rapamycin to activate SC-DARIC33. Primary objectives include assessment of safety and toxicity of SC-DARIC33, as well as the feasibility of manufacturing. Secondary objectives include assessment of efficacy, as well as engraftment, expansion, persistence, and activation states of SC-DARIC33 T cells.

As of March 17, 2023, three participants had received cell product infusion at 1 x 10^6 SC-DARIC33 T cells /kg (dose level 1) following LD chemotherapy. Infusions were generally well tolerated without occurrence of dose-limiting toxicities.

Preclinical studies predicted that DARIC33 dimerization, activation and expansion would occur at rapamycin trough levels in the range of ~1.5-3 ng/ml, well below the trough levels associated with immune suppression. Such levels were not achieved in the initial patient; however, after adjusting rapamycin monitoring and dosing algorithm, these levels were attained in the next two patients. As anticipated, attainment of such levels was associated with DARIC33 dimerization, activation, engagement of antigen and elicitation of CD33 expressing leukemic cell cytotoxicity. Of the two patients who achieved target rapamycin trough levels, the first one had extramedullary leukemia, and in this patient, we were able to infiltrate, activate and expand DARIC33 cells within an extramedullary leukemic infiltrate in the skin, resulting in hemorrhagic necrosis of this infiltrate. In the second patient, we saw DARIC33 expansion in the peripheral blood, peaking nine days after DARIC33 infusion, where 6.1% of the total lymphocytes were DARIC33 cells. The expansion of DARIC33 was associated with a significant transient reduction in the CD33 leukemic burden in the blood. Taken together, we believe this indicates at this very low cell dose that we can dose rapamycin to target levels resulting in the activation and expansion of DARICC33 cells which can then traffic to, engage, and kill leukemia cells.

In a separate oral presentation, researchers evaluated whether regulated IL-15 production combined with drug-controlled DARIC33 activation could enhance anti-AML potency without driving uncontrolled T cell growth or severe toxicity in the preclinical setting. Genetic modules were designed in which a novel synthetic promoter (iSynPro or iSP) transiently drove transcription of a modified IL-15 variant that further restricts IL-15 signaling to cells expressing IL-15Ra. The DARIC33 and iSP-IL-15 DARIC33 CAR T cells had similar expansion and phenotype characteristics during initial manufacturing and T cell activation with tumor cells resulted in rapamycin-dependent secretion of IL-15 in vitro and robust T cell expansion. When IL-15 was omitted from the culture media, iSP-IL-15 DARIC33 demonstrated enhanced expansion following tumor exposure but normal contraction kinetics, suggesting that iSP transcription may enhance T cell function through tightly regulated IL-15 production without promoting unrestrained T cell growth. Further, when AML tumor bearing mice were treated with DARIC33 with or without iSP-IL-15, we observed that both controlled tumor growth, but only iSP-IL-15 DARIC33 CAR T cells controlled tumor growth at a limiting cell dose.

These results demonstrate that Seattle Children's proprietary iSynPro-regulated expression combined with rapamycin-controlled DARIC33 activation has the potential to enhance T cell function while preventing unrestrained T cell outgrowth.

About PLAT-08

PLAT-08, the Phase 1 study of SC-DARIC33 in relapsed/refractory pediatric AML, led by Seattle Children's Therapeutics, couples 2seventy bio's DARIC T cell platform with Seattle Children's world-class bench-to-bedside expertise in oncology cell therapies. This study is a first-in-human investigation of the DARIC T cell platform and is now open for enrollment at Seattle Children's.

PLAT-08 is enrolling pediatric and young adult patients with relapsed or refractory CD33+ leukemia with and without prior history of allogeneic hematopoietic cell transplantation, to examine the safety and feasibility of administering an autologous T cell product that has been genetically modified to express a Dimerizing Agent Regulated Immunoreceptor Complex (DARIC).

For more information visit: clinicaltrials.gov using identifier NCT05105152.

About SC-DARIC33

2seventy bio is collaborating with Seattle Children's Therapeutics to rapidly accelerate development of potential new therapies for patients with acute myeloid leukemia (AML). This research collaboration is investigating potential solutions to two challenges in treating AML: disease heterogeneity and toxicity due to shared expression of targets between tumor and normal tissue.

SC-DARIC33 is an investigational, pharmacologically controlled CD33-targeted autologous T cell product that utilizes 2seventy bio's proprietary Dimerizing Agent Regulated Immunoreceptor Complex (DARIC) T cell platform, a regulatable CAR T cell technology. DARIC T cells are intended to be switched from "OFF" to "ON" in the presence of rapamycin, such that while in the "ON" state the T cell is poised to be activated upon encounter with its target antigen.

SC-DARIC33 is not approved for any indication in any geography.

About 2seventy bio

Our name, 2seventy bio, reflects why we do what we do - TIME. Cancer rips time away, and our goal is to work at the maximum speed of translating human thought into action – 270 miles per hour – to give the people we serve more time. We are building the leading immuno-oncology cell therapy company, focused on discovering and developing new therapies that truly disrupt the cancer treatment landscape.

With a deep understanding of the human body's immune response to tumor cells and how to translate cell therapies into practice, we're applying this knowledge to deliver next generation cellular therapies that focus on a broad range of hematologic malignancies, including the first FDA-approved CAR T cell therapy for multiple myeloma, as well as solid tumors. Our research and development is focused on delivering therapies that are designed with the goal to "think" smarter and faster than the disease. Importantly, we remain focused on accomplishing these goals by staying genuine and authentic to our "why" and keeping our people and culture top of mind every day.

For more information, visit www.2seventybio.com.

Follow 2seventy bio on social media: Twitter and LinkedIn.

Cautionary Note Regarding Forward-Looking Statements of 2seventy bio

This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to: statements about our plans, strategies, timelines and expectations with respect to the research, development, manufacture or sale of our product candidates, including the results of ongoing and planned pre-clinical studies and clinical trials; statements about the safety, efficacy and perceived therapeutic benefits of our product candidates and the potential dosing and indications thereof, market opportunities and demand therefor; statements about the strategic plans for 2seventy bio and potential corporate development opportunities; and statements about our ability to execute our strategic priorities. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation; the risk that our plans with respect to the research, pre-clinical and clinical development and regulatory approval of our product candidates may not be successfully achieved on the planned timeline, or at all , and that the collaboration with Seattle Children's Therapeutics may not continue or be successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect 2seventy bio's business, particularly those identified in the risk factors discussion in 2seventy bio's Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, 2seventy bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

View source version on businesswire.com: https://www.businesswire.com/news/home/20230519005091/en/

2seventy bio

Investors:
Jenn Snyder, 617-448-0281
jenn.snyder@2seventybio.com

Media:
Morgan (Adams) Shields, 774-313-9852
morgan.adams@2seventybio.com

Source: 2seventy bio