2seventy bio Presents New Preclinical Data on bbT369, an Investigational Dual-Targeting Gene-Edited CAR T Cell Therapy, at the AACR Annual Meeting

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bbT369, 2seventy bio's investigational novel CD79a/CD20 dual targeting CBLB gene edited CAR T cell therapy demonstrates promising anti-lymphoma activity in preclinical models

bbT369 is the first novel cell therapy investigated in the clinic that uses 2seventy bio's proprietary highly specific megaTAL ™gene editing platform

CRC-403, a phase 1/2 dose-escalation study of bbT369 in relapsed and/or refractory B-NHL is currently enrolling patients

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 8, 2022-- 2seventy bio, Inc. (Nasdaq: TSVT), a leading immuno-oncology cell therapy company, will present preclinical data on bbT369, an investigational novel CD79a/CD20 dual-targeting *CBLB* gene edited CAR T cell therapy at the American Association for Cancer Research (AACR) Annual Meeting 2022 in New Orleans, LA. These data will be presented in a poster session (poster #581) on Sunday, April 10, 1:30-5:30 PM CT.

"While anti-CD19 CAR T cell therapies have improved outcomes for relapsed and/or refractory B cell non-Hodgkin lymphoma (B-NHL) patients, 60-70% of those treated with currently available CAR T cell therapies do not achieve a long-term remission, highlighting the need for more treatment options," said Philip Gregory, D.Phil., chief scientific officer at 2seventy bio. "bbT369 was purposefully designed to potentially address known mechanisms of anti-CD19 CAR T cell therapy failure. We are excited to present the results of preclinical studies that demonstrate the anti-lymphoma activity of bbT369 and suggest that bbT369 has the potential to overcome failure modes of anti-CD19 CAR therapies, supporting a first-in-human trial (CRC-403) to evaluate initial safety and efficacy in B-NHL patients."

bbT369 is an innovative therapeutic approach designed to address known limitations of anti-CD19 CAR T cell therapy

Emerging data[1-2] suggests several failure modes for anti-CD19 CAR T cell therapies, including loss or down-regulation of CD19 antigen, loss of co-stimulatory ligands on tumor cells, exhaustion of CAR T cells, and immunosuppressive microenvironments.

bbT369 was purposely designed with three layers of innovation to address the potential mechanisms of anti-CD19 CAR T cell therapy failure:

- First, bbT369 targets a novel combination of antigens highly expressed in B cell lymphomas, CD79a and CD20. CD79a, a novel target, is a critical signaling component of the B cell receptor and CD20 is a known clinical target for lymphoma. The dual targeting of bbT369 may limit antigen escape as a mechanism of lymphoma relapse.
- Second, bbT369 is designed with a combination of a traditional 2nd generation CAR and an investigative "chimeric co-stimulatory" architecture (CCR-CAR), a split co-stimulation signaling technology intended to drive more robust T cell activation in response to either antigen compared with dual CAR designs.
- Third, cells are gene-edited with megaTAL™ technology to remove the function of *CBLB*, a known negative regulator of T cells. Removal of *CBLB* function may enable robust antigen-dependent CAR T cell expansion and allow cells to resist anergy and maintain activity in sub-optimal conditions for T cell activation.

bbT369 demonstrates increased anti-lymphoma activity and duration of response in preclinical models

- Increased tumor control was seen with bbT369's CCR-CAR design compared to dual CAR designs, and cell killing was observed when bbT369 encountered either antigen.
- Compared with non-gene edited cells in different *in vitro* model systems, bbT369 demonstrated a lower threshold for stimulation, retained activity in the presence of the immunosuppressive factor TGFβ, reduced reliance on tumor cell co-stimulation, and exhibited increased capacity for multiple rounds of tumor cell killing.
- bbT369 resulted in three-fold increased cell expansion and prevention of late relapses in B-NHL mouse models compared with a non-gene edited control.

- bbT369 outperformed CD19 CAR T cells in cell-based and mouse models, with increased IL-2 secretion and prolonged duration of tumor remission, suggesting bbT369 may have enhanced functionality compared with the other constructs.

Results are detailed in an E-Poster here, available to registered attendees on the AACR website through Wednesday, July 13.

Infusion of first patients in Phase 1/2 study of bbT369 in B-NHL is anticipated in 2022

CRC-403 (NCT05169489), an open-label, multi-site Phase 1/2 dose-escalation study, is currently enrolling patients, and will assess the safety and potential efficacy of bbT369 in patients with relapsed and/or refractory B-NHL, including patients who relapsed after CD19 CAR T cell therapy as well as patients who are CAR-naïve. Initial assessment of feasibility of bbT369 drug product manufacturing and patient safety is expected in 2H 2022.

The study will also serve as a proof-of-concept assessment of 2seventy bio's proprietary megaTAL™ gene editing platform, dual-targeting strategies and split co-stimulation signaling technology.

About bbT369

bbT369 is an investigational dual-targeting CAR T cell therapy with a gene edit for patients with relapsed and/or refractory B-NHL.

bbT369 has three layers of innovation, purposely designed to address the potential mechanisms of anti-CD19 CAR T cell therapy failure: dual targeting (CD79a/CD20), split co-stimulation signaling technology, and a gene edit to remove the function of *CBLB.*

In December 2021, the FDA cleared the Investigational New Drug (IND) application for bbT369.

The clinical development program for bbT369 includes the Phase 1/2 CRC-403 study (NCT05169489). Safety and potential efficacy of bbT369 in patients with specific subtypes of relapsed and/or refractory B-NHL will be assessed, including patients who relapsed after CD19 CAR T cell therapy as well as patients who are CAR-naïve.

bbT369 is not approved for any indication in any geography.

About megaTAL™ technology

megaTALs are single-chain enzymes that combine the natural DNA recognition and cleavage processes of Homing Endonucleases (HEs) with the modular DNA binding properties of transcription activator-like (TAL) effectors. This protein fusion architecture allows the generation of highly specific and active nucleases in a compact format compatible with all current viral and non-viral cell delivery methods.

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.

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[1]Schuster et al, Lancet Oncology 2021
[2]Neelapuet. al., Blood 2019

Cautionary Note Regarding Forward-Looking Statements

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 development, manufacture or sale of our product candidates, statements about the efficacy and perceived therapeutic benefits of our product candidates and the potential indications, market opportunities and demand therefor; statements about the strategic plans for 2seventy bio; 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, our limited independent operating history and the risk that our accounting and other management systems may not be prepared to meet the financial reporting and other requirements of operating as an independent public company; the risk that dedicated financial and/or strategic funding sources may not be available on favorable terms or at all; the risk that our plans with respect to the preclinical and clinical development and regulatory approval of our product candidates may not be successfully achieved on the planned timeline, or at all. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in the information statement contained in our most recent Annual Report on Form 10-K and any other filings that we have made or will make with the Securities and Exchange Commission in the future. All information in this press release is as of the date of the release, and 2seventy bio undertakes no duty to update this information unless required by law.

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