WHITEPAPER

STRO-002 from Sutro Biopharma offers hope to patients with rare, otherwise fatal pediatric tumors

Sutro Biopharma's STRO-002 puts young leukemia patients into remission

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In an oral presentation at the American Society of Hematology's 64th (ASH) Annual Meeting in December, results of Sutro Biopharma's lead oncology product candidate STRO-002 will be reviewed, revealing the candidate's profound effect—including seven complete responses out of 16 evaluable patients—in children with a rare, genetically defined and often fatal form of leukemia. These results were seen in a pooled analysis of investigator-initiated studies carried out in a compassionate use setting, and are contained in an abstract titled *Anti-Leukemic Activity of STRO-002, a Novel Folate Receptor-α (FR-α)-Targeting ADC in Relapsed/Refractory CBF2AT3-GLIS2 AML* which was made available on November 3, 2022 in advance of the ASH meeting.

Young patients suffering from a specific, genetically defined form of leukemia, characterized by a genetic change referred to as the CBF2AT3-GLIS2 gene fusion, were treated with STRO-002, Sutro's antibody-drug conjugate (ADC) targeting folate receptor alpha (FolRα). The median age of patients at the time of treatment was two years, with a range of six months to seven years. Until these current results with STRO-002, this subtype of leukemia has been highly refractory to treatment and associated with a very poor prognosis.

For Sutro, the results, while heartwarming and very welcome, did not come as a complete surprise. Sutro, which is developing STRO-002 in Phase 1 clinical trials for ovarian and endometrial cancers, precisely designed STRO-002 to hit FolRα—a molecular target highly expressed on cells in many ovarian and endometrial cancers as well as on cells of this particular form of pediatric AML. Preclinical pharmacology research testing the effects of STRO-002 in relevant AML models, presented at the ASH Annual Meeting in 2021, showed compelling evidence of anti-leukemia activity. This preclinical work encompassed both *in vitro* studies and xenograft-based *in vivo* models. The promise of these preclinical data is further strengthened by these compelling clinical results, as the company explained in its press release issued in conjunction with the publication of its abstract. A more complete picture of the clinical results will be provided in an oral presentation at the 2022 ASH Annual Meeting.

The clinical testing of STRO-002 in pediatric AML patients came about based on the Company's collaboration with a leading academic investigator, Dr. Soheil Meshinchi of the Fred Hutchinson

Cancer Center in Seattle. Dr. Meshinchi is an expert in the biology and treatment of acute myeloid leukemia patients.[1] The role of the CBFA2T3-GLIS2 genetic change in driving the development of leukemia in this subtype was first identified by Gruber TA *et al.* and published in Cancer Cell 22(5):683-697, 2012. Dr. Meshinchi and his colleagues then identified that FOLR1, the gene encoding FolRα, was highly expressed in these leukemic cells, but not in other AML cells or in healthy blood cells.

They then confirmed that FolRα was overexpressed in myeloid leukemia cells obtained from patients with the CBFA2T3-GLIS2 genetic fusion. Dr. Meshinchi notified Sutro of the possible relevance of STRO-002 and Sutro shared the STRO-002 preclinical data obtained in ovarian and endometrial cancer models. Following the science, a collaboration on the CBF-GLIS2 AML preclinical *in vivo* and xenograft models was begun. Based on the promising results of the preclinical pharmacology studies, Dr. Meshinchi and the Sutro clinical team discussed the possibility that Sutro could provide STRO-002 on a compassionate use basis to physicians around the United States treating pediatric patients with AML expressing FolRα.

The CBFA2T3-GLIS2 genetic fusion uniformly leads to the development of an aggressive leukemia in children less than three years old. Patients with this fusion are often refractory to conventional therapy and frequently relapse after hematopoietic stem cell transplantation. The goal of most treatment regimens for these patients is to reduce their tumor burden through the use of chemotherapy and then replace their diseased bone marrow cells with those from a healthy donor. Although similar procedures can lead to cures in other pediatric AML cases, the majority of patients with CBFA2T3-GLIS2 are either refractory to initial rounds of chemotherapy or relapse following bone marrow transplantation. Some patients who were treated with STRO-002 had previously progressed or had persistent leukemia after six or seven rounds of previous treatments. The five-year survival of patients with CBFA2T3-GLIS2 ranges between 15% and 30%.

While the engagement of a biopharmaceutical company providing investigators with drug product candidate for compassionate use is not an infrequent occurrence in the industry, results of this type are unusual. Sutro had to decide to commit its drug candidate to these single patient IND studies and to do so in an indication different from the ones in which it is developing the same candidate. But the decision to do so, says Bill Newell, CEO of Sutro, was driven by the science. Given that STRO-002 is already a very promising candidate in treating ovarian and endometrial cancers, he said, it was a compelling opportunity to test STRO-002 in leukemias expressing the same target as these other cancers. “We were following the science and we saw a chance to make an impact in a super rare form of cancer where the patient prognosis is extremely poor. This is, to us, what the term ‘compassionate use’ is all about.

[1] The biographical information on Dr. Meshinchi has been adapted from the biographical page on him found on the Fred Hutch website: https://www.fredhutch.org/en/faculty-lab-directory/meshinchi-soheil.html.

When we learned that we had a chance to treat infants and toddlers who had no other alternative and potentially treat them effectively, it tugged at our heartstrings."

The journey to the strong outcomes to be presented at ASH took over a year. The very first outcomes were disappointing. The initial, heavily pretreated patients were very sick with very advanced disease and did not ultimately respond to therapy in a way that changed the course of their disease. But even within the disappointment, the initial patient data delivered a positive signal. Several of these initial patients responded to treatment with STRO-002 such that they could go home with their families for at least a brief period of time. This response was directly attributable to STRO-002. These preliminary results offered a glimmer of hope that less heavily pretreated patients with less advanced disease and less pretreatment might indeed respond to STRO-002 more favorably. The Sutro team and the treating clinicians worked to optimize both the treatment regimen for STRO-002 and the logistics of obtaining institutional approval to expedite access of STRO-002 to other pediatric AML patients with this genetic signature, resulting in the remarkable clinical outcomes beginning to emerge after treatment of a handful of patients.

The results for these subsequent patients have been gratifying on at least three levels:

- **Meaningful Patient Benefit.** There have been seven complete responses. Several of these patients have recovered to the point where they could undergo a bone marrow or stem cell transplant—a treatment that has potential to provide long-term disease control in patients healthy enough to tolerate it. Of the seven patients who achieved a complete response, three had experienced primary, treatment-refractory disease or had residual leukemia after standard induction chemotherapy and four had relapsed after an allogeneic or unrelated donor stem cell transplant. Six of these seven patients with significant disease had what is considered a deep response to STRO-002 in the sense that no residual disease was observed following treatment. One patient, for example, had no remaining leukemia cells in their blood and a rapid decline in leukemia cells observable in their bone marrow after just three doses of STRO-002 administered as a single agent every other week. A second patient had a similarly rapid response to single-agent STRO-002 with clearance of all detectable disease after a second three-dose cycle of STRO-002 two weeks after the first cycle. The Sutro team, along with the independent treating physicians, have been learning over time that treatment outcomes are better for patients treated earlier in the course of their disease.

- **Tolerability.** STRO-002 has been observed to be well tolerated over the course of these treatments. Investigators are monitoring potential therapy-related adverse events very closely, especially in these very young and heavily pretreated children. These were described in the ASH abstract and will be described in greater detail at the conference.

- **Efficacy.** The clinical results point to the potential for meaningful efficacy for STRO-002; Sutro-sponsored clinical trials are ongoing in ovarian and endometrial cancer. The efficacy of STRO-002 in these AML patients provides strong evidence that STRO-002's effects are mechanism-related, that is, that the drug is engaging its molecular target and thereby selectively eliminating leukemia cells in the blood and bone marrow that express this target on their surface. Although it is too early to say whether this result might be reflected in other tumors, it is very encouraging to see such broad and deep effects already for patients with this molecular subtype of pediatric AML.

About Sutro Biopharma

Sutro Biopharma, Inc., headquartered in South San Francisco, is a clinical-stage oncology company pioneering site-specific and novel-format antibody drug conjugates (ADCs). Sutro has two wholly owned ADCs in the clinic—STRO-002, a folate receptor alpha (FolRα)-targeting ADC, in clinical studies for ovarian and endometrial cancers; and STRO-001, a CD74-targeting ADC, in clinical studies for B-cell malignancies. Additionally, Sutro is collaborating with Bristol Myers Squibb (BMS) on CC-99712, a BCMA-targeting ADC in the clinic for patients with multiple myeloma; with Merck KGaA, Darmstadt, Germany, known as EMD Serono in the U.S. and Canada (EMD Serono), on M1231, a MUC1-EGFR bispecific ADC in clinical studies for patients with solid tumors, particularly non-small cell lung cancer (NSCLC) and esophageal squamous cell carcinoma; with Merck, known as MSD outside of the United States and Canada, on MK-1484, a selective IL-2 agonist in clinical studies as a monotherapy and in combination with pembrolizumab for the treatment of solid tumors; and with Astellas Pharma (Astellas) on novel modality, immunostimulatory antibody-drug conjugates (iADCs). Sutro's platform technology also enabled the spin out of Vaxcyte (Nasdaq: PCVX) and the creation of VAX-24, a 24-valent pneumococcal conjugate vaccine in clinical studies for the prevention of invasive pneumococcal disease. Sutro's rational design and precise protein engineering has enabled six product candidates in the clinic. Follow Sutro on Twitter, @Sutrobio, and at www.sutrobio.com to learn more about our passion for changing the future of oncology.