Anti-leukemic Activity of Luveltamab Tazevibulin (LT, STRO-002), a Novel Folate Receptor-α (FR-α)-targeting Antibody Drug Conjugate (ADC) in Relapsed/Refractory CBFA2T3::GLIS2 AML

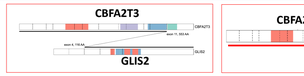
Dr. Soheil Meshinchi[1], Dr. Robin Williams[2], Dr. Lane Miller[3], Dr. Stephanie Massaro[4], Dr. Elizabeth Krieger[5], Dr. Melinda Pauly[6], Dr. Catherine Nelson[7], Dr. Rebecca Johnson[8], Dr. Jennifer Welch[9], Dr. Deepa Bhojwani[10], Dr. Babak Moghimi[10], Dr. Philip Neff[11], Dr. Terzah Horton[12], Dr. Hamayun Imran[13], Dr. Raul Ribeiro[14], Dr. Jeffrey Rubnitz[14], Dr. Terri Guinipero[15], Dr. Felipe Bautista[16], Dr. Matthew Kutny[17], Dr. Amy Johnson[18], Dr. Karen Lewing[18], Dr. Alan Gamis[18], Dr. Julienne Brackett[12], Dr. David McCall[19], Dr. Teena Bhatla[20], Dr. Maria Luisa Sulis[21], Dr. Amy Tellinghuisen[22], Dr. Jill Beck[23], Mike Loken[24], Laura Pardo[24] and Andrew Menssen[24]

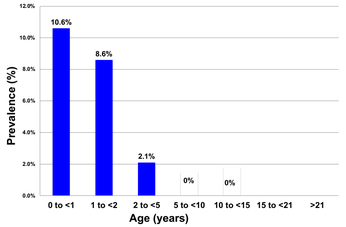
[1]Fred Hutch Cancer Research Center; [2]University of Minnesota Masonic Children's Hospital; [3]Children's Minnesota; [4]Yale University; [5]Virginia Commonwealth University; [6]Children's Healthcare of Atlanta; [7]Sanford Health; [8]Mary Bridge Children's Hospital; [9]Hasbro Children's Hospital (Lifespan); [10]Children's Hospital Los Angeles; Dell Children's Hospital[11]; Baylor[12]; University of South Alabama (USA Health)[13]; St. Jude Children's Research Hospital[14]; Nationwide Children's Hospital[15]; Novant Health Hemby Children's Hospital[16]; University of Alabama Birmingham[17]; Children's Mercy Kansas City[18]; MD Anderson[19]; Newark Beth Israel Medical Center[20]; Memorial Sloan Kettering Cancer Center[21]; Seattle Children's Hospital[22]; Children's Hospital & Medical Center Omaha[23]; Hematologics[24]

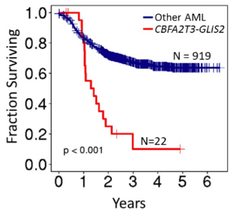
INTRODUCTION

- CBFA2T3::GLIS2 is a cryptic oncogenic fusion causing RAM phenotype AML
- Exclusively seen in infants and young children
  - Highly refractory to conventional chemotherapy (>80% induction failure)
- Near uniform mortality
- Fusion causes induction of FOLR1 on leukemic cell surface
  - No expression on normal hematopoiesis
- STRO-002 (FOLR1 ADC) shows high potency in pre-clinical models
- 25 relapsed/refractory CBF-GLIS AML patients received STRO-002 under SPIND.

CBFA2T3::GLIS2 AML

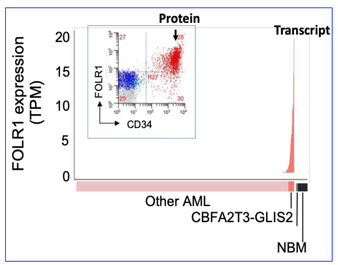


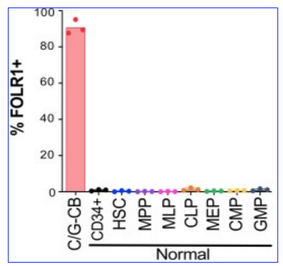




CBF-GLIS AML is uniquely expressed in infants and young children with a near uniform fatality and a 2-year survival of <15%.

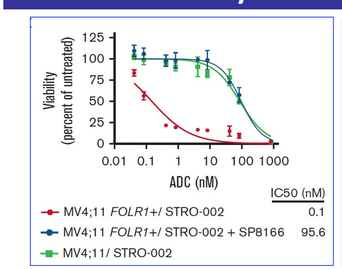
FOLR1 expressed on AML blast; Silent in Normal Hematopoiesis

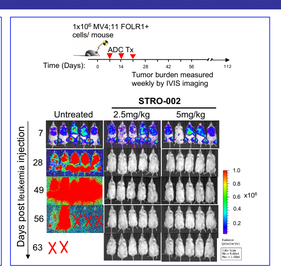




FOLR1 transcript and protein is uniquely expressed in CBF-GLIS AML and induced in cord blood stem cells transduced with the fusion. FOLR1 is not expressed in normal hematopoiesis.

Preclinical Efficacy of STRO-002 in CBF-GLIS AML

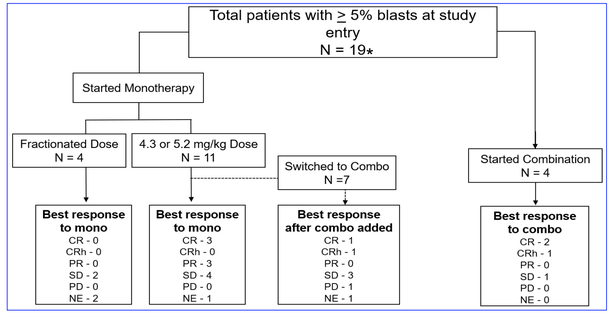


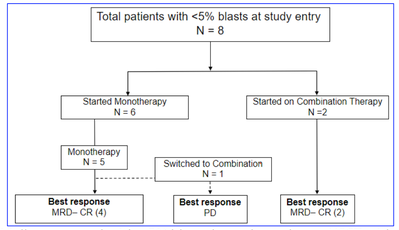


METHODS AND TREATMENT

All pts were required to demonstrate CBF-GLIS fusion by PCR or sequencing. Each investigator in consultation with Sutro Biopharma Inc. defined the treatment plan as to dose, schedule, and combination therapy administered. Between August 2021 and September 2023, 25 patients with relapsed/refractory CBF-GLIS AML were treated with STRO-002 at doses of 4.3 or 5.2mg/kg every 2-4 weeks (4 patients treated early on in 2021 received smaller fractionated doses on days 1, 3, 5 per cycle).

19 patients had ≥5% blasts at study entry and are evaluable for CR. 6 patients had <5% blasts at study entry and were evaluable for MRD negative CR. Fractionated dosing was not found to provide sufficient control of leukemic blasts and was not used further. These patients are not included in our analysis of safety and efficacy.





*Two children initially presented with <5% blasts but relapsed post-HSCT with ≥5% blasts and restarted STRO-002. They are included in the N for both diagrams.

ADVERSE EVENTS

STRO-002 was generally well tolerated. Observed cytopenias were often reported in patients with baseline cytopenia. There was 1 patient receiving monotherapy STRO-002 who reported a persistent asymptomatic AST increase that resulted in a temporary dose reduction. There were no other reported dose reductions. There were 4 patients receiving monotherapy STRO-002 who reported at least 1 drug delay due to an AE. In all cases, the AE resolved, and dosing resumed without modification.

Of the 25 patients treated with STRO-002 there were no grade 5 events considered related. There were 4 serious adverse events (SAEs) reported in patients receiving full dose monotherapy with STRO-002. These were reported in 4 separate patients and included 1 event of each pyrexia, bacteremia, sepsis and lung infection. All SAEs were assessed as unlikely or unrelated to STRO-002.

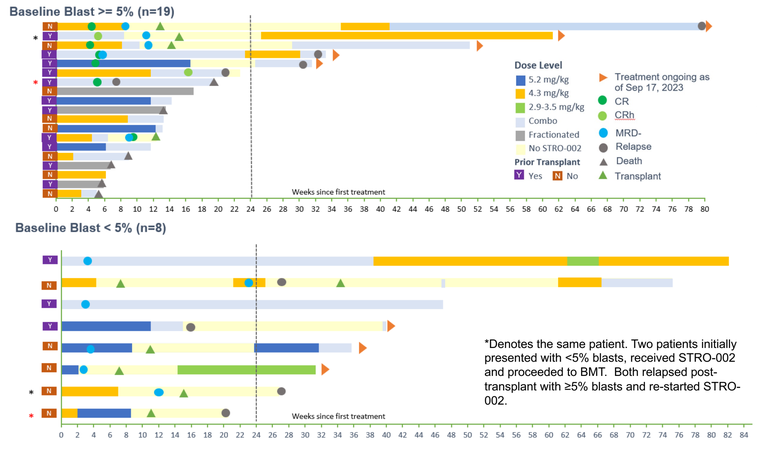
TEAs occurring in ≥10% of patients who received monotherapy with STRO-002

	Total (N=17)	≥ 3 Toxicity Grade
Neutrophil count decreased	11 (64.7%)	10 (58.8%)
Anaemia	9 (52.9%)	1 (5.9%)
Aspartate aminotransferase increased	8 (47.1%)	0
Platelet count decreased	7 (41.2%)	3 (17.6%)
White blood cell count decreased	7 (41.2%)	3 (17.6%)
Hyperglycemia	5 (29.4%)	0
Pyrexia	5 (29.4%)	0
Alanine aminotransferase increased	4 (23.5%)	1 (5.9%)
Diarrhoea	4 (23.5%)	0
Lymphocyte count decreased	4 (23.5%)	2 (11.8%)
Vomiting	4 (23.5%)	1 (5.9%)
Blood thyroid stimulating hormone increased	3 (17.6%)	0
Cough	3 (17.6%)	0
Decreased appetite	3 (17.6%)	1 (5.9%)
Hypokalemia	3 (17.6%)	0
Abdominal Pain	2 (11.8%)	0
Activated partial thromboplastin time prolonged	2 (11.8%)	0
Blood lactate dehydrogenase increased	2 (11.8%)	0
Constipation	2 (11.8%)	0
Dermatitis diaper	2 (11.8%)	0
Hypertriglyceridaemia	2 (11.8%)	0
Hyponatraemia	2 (11.8%)	0
Irritability	2 (11.8%)	0
Nasal congestion	2 (11.8%)	0
Nausea	2 (11.8%)	1 (5.9%)

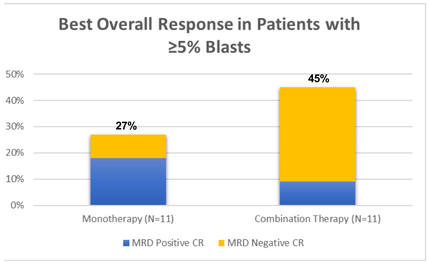
RESULTS

The median duration of STRO-002 treatment was 15.9 weeks (3-73.1) and 68% of patients received ≥5 doses. While the initial dose was typically delivered inpatient, approximately 80% of subsequent doses were delivered outpatient. Eight patients remain on treatment, with 5 of them in continued remission and on STRO-002 maintenance.

STRO-002 has enabled these children to receive potentially definitive therapy including bone marrow transplantation and donor lymphocyte infusions. Nine patients successfully underwent bone marrow transplant with some receiving STRO-002 as a maintenance agent post-transplant. The median event (leukemia) free survival after transplant during STRO-002 (mono/combo) treatment is 9.2 months with 95% CI (1.8, 15.65+).



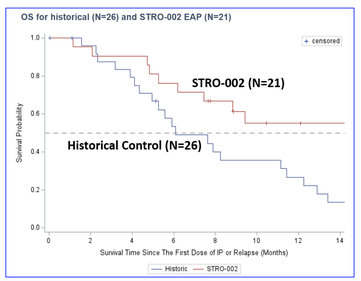
*Denotes the same patient. Two patients initially presented with <5% blasts, received STRO-002 and proceeded to BMT. Both relapsed post-transplant with ≥5% blasts and re-started STRO-002.



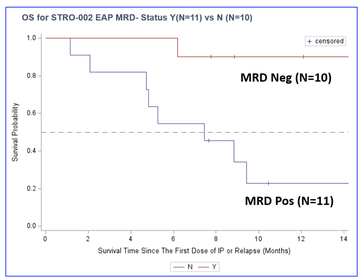
6 of 8 patients (75%) with <5% blasts achieved MRD negative CR (4 with monotherapy and 2 with combination)

Plot #1 demonstrates the median overall survival (OS) for all patients who received full/unfractionated dose of STRO-002; Available historical control data is provided. **Plot #2** shows the median OS for the same patients by MRD status.
Patients whose leukemia experienced an MRD-Neg CR had an improved outcome over those who did not experience an MRD-Neg CR.

Plot 1; All Patients



Plot 2; Survival by MRD Status



CONCLUSION

STRO-002 based therapy in CBF-GLIS AML results in clinical responses that are highly unusual in this refractory patient population with a dismal prognosis. The additional subjects treated with STRO-002 and longer follow-up confirm the previously reported potential of targeting FOLR1α in CBF-GLIS AML. The ability of STRO-002 to obtain a CR and MRD- CR, with an acceptable safety profile that does not require inpatient delivery is impressive. Importantly, STRO-002 enables these children to receive potentially definitive therapy. The improved survival observed in these patients compared to historical controls supports further characterization of this drug in pediatric CBF-GLIS AML. A prospective pivotal trial in relapsed/refractory CBF-GLIS AML is in operational startup with the COG PEP-CTN and ITCC networks.

References:
Targeting FOLR1 in high-risk CBF2AT3-GLIS2 pediatric AML with STRO-002 FOLR1-antibody-drug conjugate. Tang T, Le Q, Castro S, Pardo L, McKay CN, PerkLE, Loken MR, Tarlock K, Meshinchi S, Loeb KR.Blood Adv. 2022 Nov 22;6(22):5933-5937. doi: 10.1182/bloodadvances.2022008503.PMID: 36149945
CBFA2T3-GLIS2 model of pediatric acute megakaryoblastic leukemia identifies FOLR1 as a CAR T cell target.
Le Q, Hadland B, Smith JL, Leonti A, Huang BJ, Ries R, Hylkema TA, Castro S, Tang TT, McKay CN, Perkins L, Pardo L, Sarthy J, Beckman AK, Williams R, Idemmili R, Furlan S, Ishida T, Call L, Srivastava S, Loeb AM, Milano F, Imren S, Morris SM, Pakiam F, Olson JM, Loken MR, Brodersen L, Riddell SR, Tarlock K, Bernstein ID, Loeb KR, Meshinchi S.J Clin Invest. 2022 Nov 15;132(22):e157101. doi: 10.1172/JCI157101.PMID: 36136600
Comprehensive Transcriptome Profiling of Cryptic *CBFA2T3-GLIS2* Fusion-Positive AML Defines Novel Therapeutic Options: A COG and TARGET Pediatric AML Study.
Smith JL, Ries RE, Hylkema T, Alonzo TA, Gerbing RB, Santaguida MT, Eidenschink Brodersen L, Pardo L, Cummings CL, Loeb KR, Le Q, Imren S, Leonti AR, Gamis AS, Aplenc R, Kolb EA, Farrar JE, Triche TJ Jr, Nguyen C, Meerzaman D, Loken MR, Oehler VG, Bolouri H, Meshinchi S.Clin Cancer Res. 2020 Feb 1;26(3):726-737. doi: 10.1158/1078-0432.CCR-19-1800. Epub 2019 Nov 12.PMID: 31719049