Anti-Leukemic Activity of Stro-002a Novel Folate Receptor-α (FR-α)-Targeting ADC in Relapsed/Refractory CBF2AT3-GLIS2 AML

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BACKGROUND: CBF2AT3-GLIS2 (CBF/GLIS) oncogenic fusion is the underlying genomic cause of "RAM" phenotype AML, a megakaryoblastic subtype exclusively seen in infants and young children. CBF/GLIS AML is a

highly refractory and uniformly fatal subtype of AML with limited response to conventional chemotherapy. We have demonstrated that FR-α, a known target in ovarian cancer, is expressed in CBF/GLIS AML cells and this expression is causally linked to the fusion oncogene. STRO-002 is currently under clinical investigation for the treatment of relapsed/refractory ovarian and endometrial cancer (NCT03748186). Preclinical studies have tested and confirmed the potent *in vitro* and *in vivo* anti-leukemia activity of STRO-002 in CBF/GLIS AML cell lines and xenograft models (Le et al. ASH 2021). Based on these compelling preclinical pharmacology observations, Sutro Biopharma evaluated patients on a case-by-case basis for consideration of a single patient IND (compassionate use) program for pediatric patients with CBF/GLIS AML.

METHODS: Key criteria for consideration of STRO-002 were CBF2AT3-GLIS2 oncogenic fusion and FR-α expression by flow cytometry in AML sample. Key exclusion criteria were co-existent acute/uncontrolled infection and compromised organ function (pulmonary, hepatic, renal, etc). Between August 2021 and July 2022, 16 patients received STRO-002. Median age at treatment was 2 years (range 6 months-7 years). Median number of prior therapies was 3 (range 1-8). Eight patients had relapsed after stem cell transplant (SCT) and the remaining 8 had primary refractory (induction failure) or relapsed AML.

RESULTS: In the 16 patients treated, 10 received STRO-002 as monotherapy, and 6 received combination with chemotherapy (fludarabine/cytarabine, decitabine, methotrexate (MTX), or dasatinib). All 16 pts were evaluable for response, best observed response included 7 CRs with 6 MRD negative remissions. Of these CRs, 3 occurred after monotherapy and 4 with combination therapy: MTX/fludarabine/cytarabine (n = 1), decitabine/DLI (n = 1), fludarabine/cytarabine/G-CSF (n = 1) and dasatinib/DLI (n = 1). The remaining 9 patients had stable disease or transient decrease in disease burden. Of the 7 patients who achieved a CR, 4 proceeded to SCT, 2 are receiving DLI and 1 will receive consolidation therapy. Ten (63%) of the 16 evaluable patients are alive and the other 6 died of progressive disease. Follow-up is limited for the surviving patients.

Of note were 6 patients who achieved an MRD negative CR, two with primary refractory disease, and four who had relapsed after an allogeneic SCT. These six patients with significant disease had deep response to STRO-002 with MRD negative remission. One patient had a rapid decline in marrow blasts and had no evidence of disease by flow after 3 single agent every other week (QOW) doses of STRO-002. A second patient had a similarly rapid response to single agent STRO-002 with clearance of all detectable

disease after a second QOW dose of STRO-002. ANC for both patients one week after last dose of STRO-002 was >1000. These patients were consolidated with allogeneic stem cell transplant or with DLI.

STRO-002 was generally well tolerated. Collection and review of treatment-emergent AEs (TEAEs) is ongoing. Treatment-related events ≥ grade 3 included neutrophil count decreased (n = 3), platelet count decreased (n = 3), anemia (n = 2), WBC decreased (n = 2), hyperbilirubinemia (n = 1), bacteremia (n = 1), febrile neutropenia (n = 1), urticaria (n = 1), generalized edema (n = 1), aspartate aminotransferase elevation (n = 1), alanine aminotransferase elevation (n = 1).

CONCLUSIONS: STRO-002 has promising activity in relapsed/refractory CBF2AT3-GLIS2 AML, a disease that tends to be highly refractory to all standard-of-care (SOC) therapies. Further, STRO-002 is well tolerated as a monotherapy agent and in combination with SOC therapies. Patients with low tumor burden were more likely to achieve CR and transition to SCT, DLI and CAR-T. Deep molecular and flow cytometric remission was achieved in a cohort of patients. Patients with primary refractory disease (no prior transplant), 1-3 prior lines of therapy, low disease burden, or without extramedullary disease appeared to have a more potent response to STRO-002.

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STRO-002 Expanded Access Patient Summaries:

Patient	Age	Disease status at time of treatment	Prior Therapies	Prior transplant	Cycles of STRO-002 received	Treatment Details	Best Response	Disposition	Survival status
1	2y	Stable disease on ruxolitinib + venetoclax	6 lines of therapy	Y (umbilical cord blood)	2	Fractionated dosing; cycles q2wk	Palliation of symptoms	Progressive disease	Dead
2	1y	Relapse Day 30-post transplant	6 lines of therapy	Y (UCB transplant)	3	Fractionated dosing; cycles q2wk	Stable Disease (from C1-C3)	Progressive disease	Dead
3	4y	Refractory disease	2 lines of therapy	N	5	Fractioned dosing; cycles q2wk	Stable Disease reported during C2	T cells collected for CAR-T trial. Progressed at C5 and proceeded to CAR-T without response.	Dead
4	2y	Relapse Day 154-post transplant	4 lines of therapy	Y (unrelated donor)	10	4.3mg/kg q2wk; MTX C6-10; DLI C8-10.	PR after C1	Achieved MRD – state; Progressed at C10 (transition to alternate therapy).	Dead
5	3y	Relapsed 6 months after BMT. Progressed on CAR-T	7 lines of therapy	Y (unrelated donor)	4	Fractionated dosing; cycles q3-4 wk.	Stable Disease (from C1-C4)	Progressive disease	Dead
6	11m (1y)	Refractory disease – induction failure	1 line of therapy	N	3 – pre-SCT 1—post SCT relapse	4.3mg/kg q2wk; MTX each cycle. Fludarabine/ Cytarabine added C3	CR at C3 (MRD negative)	Achieved CR and followed by SCT. Progressed Day +35 (marrow 12% blasts by flow), restarted STRO-002 Day +70 with plan to go to CAR-T	Alive
7	23m (2y)	Refractory – induction failure	2 lines of therapy	N	4	4.3mg/kg q2wk monotherapy	CR at C4 (MRD negative)	Achieved CR followed by SCT. Post-transplant Day +56 NED.	Alive
8	2y	Relapse – 270 days post SCT (low tumor burden 0.02% blasts in BM)	2 lines of therapy	Y (unrelated donor)	5	4.3mg/kg once monthly; Decitabine each cycle. DLI C2-5.	CR by Flow cytometry and PCR after C1 (MRD negative)	On-treatment	Alive
9	9m	Refractory – induction failure	3 lines of therapy	N	3	4.3mg/kg q2wk monotherapy	CR by morphology but MRD positive (0.083%)	Received SCT. Relapsed Day +75 post SCT. Restarting STRO-002.	Alive
10	2y	Relapse 6 months post-SCT	3 lines of therapy	Y (allogeneic sibling donor)	3	4.3mg/kg q2wk; FLAG added C3	CR after C3 (MRD negative)	Received 2nd SCT (unrelated donor)	Alive
11	1y	Refractory – induction failure	3 lines of therapy	N	4	4.3mg/kg q2wk monotherapy	SD	Patient progressed, transitioned to alternate therapy	Alive
12	3y	Relapse 3 months post SCT	5 lines of therapy including transplant	Y (allogeneic sibling donor)	4	4.3mg/kg q3wk; Dasatanib C1-4, DLI C3-4	CR after C2 (MRD negative)	On-treatment	Alive
13	6m	Refractory – induction failure	1 line of therapy;	N	2	4.3mg/kg q2wk monotherapy	PR after C2	On-treatment	Alive
14	21m (1Y)	Refractory – induction failure Initial diagnosis of sarcoma with large pelvic mass and multiple bone metastases	2 lines of therapy	N	2	4.3mg/kg q3wk monotherapy	PR (0.9% → 0.03% MRD by flow after C1)	Patient progressed with extramedullary disease, transitioned to alternate therapy	Alive
15	7Y	Late CNS relapse 6 years after SCT, then BM relapse	2 lines of systemic therapy 1 line of CNS-directed therapy cranial spinal XRT and IT MTX	Y	2	4.3mg/kg q3wk monotherapy (IT-MTX added prophylactically)	CR after C1 (MRD negative)	On-treatment	Alive
16	10m	Refractory – induction therapy	5 lines of therapy; No transplant	N	2	4.3mg/kg q3wk; MTX added C2	PR based on peripheral blood only (29% prior to C1 down to 4% post C1)	Progressive disease	Dead

-counting sequential induction therapies as separate lines of therapy
-considering induction therapy and then transplant as separate lines of therapy

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