Preliminary results of a Phase 1 dose escalation study of the first-in-class anti-CD74 antibody drug conjugate (ADC), STRO-001, in patients with advanced B-cell malignancies

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INTRODUCTION

- CD74 is a transmembrane glycoprotein involved in MHC protein formation & transport
  - CD74 is expressed in ~ 90% of B-cell cancers including multiple myeloma (MM) and Non-Hodgkin Lymphoma (NHL)[1, 2]
  - Normal tissues have minimal CD74 expression
  - CD74 is rapidly internalized, making it an attractive target for antibody drug conjugates (ADCs)
- STRO-001 is a novel, specific and homogeneous anti-CD74 ADC, containing 2 non-cleavable maytansinoid linker warheads per molecule.
- STRO-001 demonstrated potent in vitro cytotoxicity in MM and NHL cell lines.
  - STRO-001 exhibited significant anti-tumor activity in MM (ARP-1 and MM.1S), NHL-diffuse large B-cell (DLBCL) (SU-DHL-6) and NHL mantle cell lymphoma (Jeko-1 and Mino) xenograft models in vivo.
  - Toxicology studies in cynomolgus monkeys did not produce any unexpected findings; treatment resulted in the intended pharmacodynamic effect, B-cell depletion. [3, 4]
- STRO-001-BCM1 (ClinicalTrials.gov NCT03424603) is first-in-human Phase 1, open-label dose escalation study with dose expansion to identify the maximum tolerated dose (MTD), the recommended phase 2 doses (RP2D) and to evaluate the safety, tolerability, and preliminary anti-tumor activity of STRO-001 in subjects with B-cell malignancies (MM and NHL)[4]

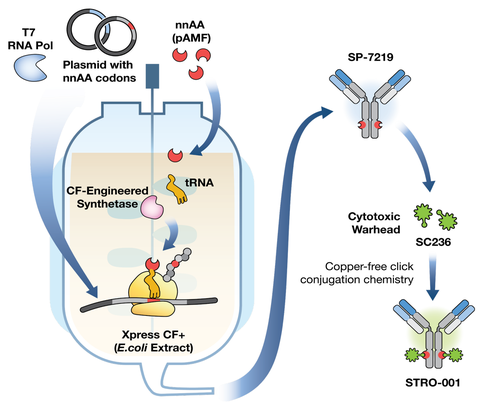


Figure 1. Generation of the CD74-targeting antibody and a novel, specific and homogeneous ADC, STRO-001

Development of SP7219 and STRO-001 using Sutro's proprietary Xpress Cell-Free (XpressCF+TM) system 6. The non-natural amino acid (nnAA) pAMF was incorporated at different sites on SP7219, with the optimal sites selected based on conjugation efficiency, cell killing activity and PK in mice. SP7219 was conjugated at pAMF to the noncleavable maytansinoid linker-warhead SC236 to generate STRO-001.

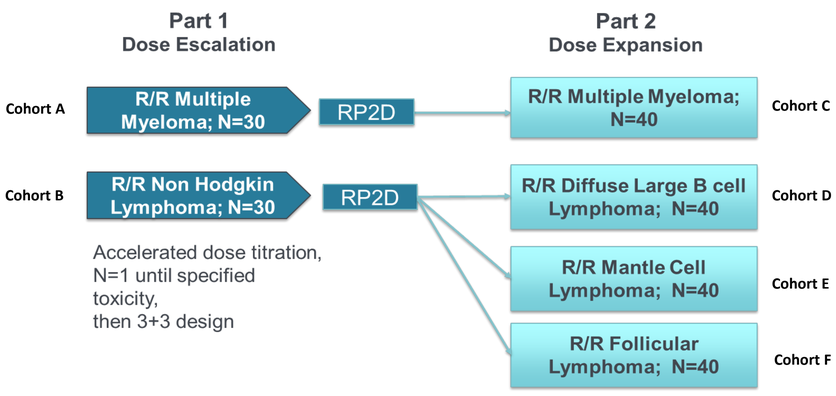
OBJECTIVES (ENDPOINTS)

- **Primary Objectives (Endpoints)**
  - –Dose escalation: Safety & tolerability of STRO-001 (adverse events); Define RP2D (dose limiting toxicities)
  - –Dose expansion: Anti-tumor activity of STRO-001 (overall response rate)
- **Secondary Objectives (Endpoints)**
  - –Dose escalation: Characterize pharmacokinetics (PK) and immunogenicity (anti-drug antibodies (ADA))
  - –Dose expansion: Toxicity, time to event endpoints, PK (AEs, duration of response, progression free survival, additional PK)
- **Exploratory Objectives**
  - –Dose escalation: Preliminary efficacy, PK correlation with efficacy, biomarkers
  - –Dose expansion: Further PK correlation with efficacy, biomarkers

METHODS

STRO-001-BCM1 STUDY DESIGN

- Part 1: Dose Escalation- Separate cohorts for MM and NHL
- Part 2: Dose Expansion- Separate cohorts for MM, DLBCL, MCL, FL
- STRO-001 is given by intravenous (IV) infusion on Day 1 and Day 15 of 28 day Cycles
- Accelerated dose titration followed by 3+3 design in Part 1
- Key Eligibility requirements include relapsed or relapsed/refractory disease, adequate organ function[5]
- Key Assessments include chemistry and hematology labs, PK and tumor assessments



Dose escalation will be complete when the MTD is determined and the recommended dose for Part 2 (dose expansion) is identified based on the safety, tolerability and exposure of STRO-001. After determination of the RP2D, subjects with MM or NHL will be enrolled into indication specific dose expansion cohorts (Part 2).

RESULTS

Table 1. Status of Dose Escalation, May 14, 2019

Dose Level, status	Cohort A (MM)	Cohort B (NHL)	Total patients treated
1) 0.05 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET
2) 0.075 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET
3) 0.15 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET
4) 0.27 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET
5) 0.43 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET
6) 0.65 mg/kg enrolling Cohort A, Cohort B completed	N=5, 1 DLT	N = 1, no DLTs	N = 6, still enrolling
7) 0.91 mg/kg, enrolling only Cohort B	N=0	N=5, 1 DLT	N = 5, still enrolling

As of May 14, 2019, enrolling dose level 6 for Cohort A (0.65 mg/kg), and dose level 7 for Cohort B (0.91 mg/kg). DLT evaluable patients had to receive both doses of STRO-001 in Cycle 1 and complete Cycle 1. One patient in Cohort A, dose level 6 was ineligible for DLT evaluation due to disease progression and discontinuation prior 2nd dose. SET- Safety evaluation team.

Table 2. Dose Limiting Toxicities

Dose Limiting Toxicities Summary	
Cohort A (MM) 0.65 mg/kg	**Grade 5 thromboembolic event-** Patient passed away suddenly 8 days after first dose of study treatment. An autopsy revealed patient had extensive bilateral pulmonary embolism as cause of death. There were multiple risk factors for thromboembolism such as bulky plasmacytomas in the abdomen (9 x 6 x 2.5 cm), pelvis (ovary 17 x 14 x 3.9 cm) and two focal areas of marked narrowing of small and large intestine by plasmacytoma, prolonged car ride to and from clinic, partial small bowel obstruction and possible dehydration.
Cohort B (NHL) 0.91 mg/kg	**Grade 3 thromboembolic event-** Nine days after the second dose of STRO-001, the patient reported feeling short of breath. A CT showed left upper lobe pulmonary emboli, acute venous thrombosis involving bilateral external iliac veins, and common femoral veins. The CT scan also showed progressive extensive persistent adenopathy in the abdomen (soft tissue mass 7.9 x 4.5 x 10.0 cm, lymph node- 15.3 x 8.6 cm, 13.0 x 7.9 cm), and pelvis (6.6x 2.5 cm, 6.7x 6.2 cm, 6.4 x 4.3 cm, 3.0 x 1.7 cm), with encasement of the inferior vena cava and abdominal aorta.

The 2 DLTs observed in STRO-001-BCM1 study are described in the above table. After these events, the protocol was amended to screen for pre-existing thromboembolism.

RESULTS (CONTINUED)

BASELINE CHARACTERISTICS

- First patient was dosed with STRO-001-BCM1 in April 2018
- As of May 14, 2019, 21 patients have enrolled in STRO-001-BCM1 study
  10 patients in Cohort A- Multiple myeloma, 11 patients in Cohort B- NHL

Table 3. Demographics of STRO-001-BCM1 study

Characteristic	Cohort A (MM) N =10	Cohort B (NHL) N=11	Total N=21
Age, median (range), years	**64.5 (42-80)**	**64 (21-82)**	**64 (21-82)**
Median time from diagnosis in years (range)	**6.4 (1.3-13.6)**	**3.2 (1.0-29.8)**	**4.0 (1.0-29.8)**
ECOG performance status, median (range)	**1 (0-2)**	**1 (0-2)**	**1 (0-2)**
0, N (%)	**4 (40)**	**3 (27)**	**7 (33)**
1, N (%)	**5 (50)**	**7 (64)**	**12 (57)**
2, N (%)	**1 (10)**	**1 (9)**	**2 (10)**
Race/Ethnicity, N (%)			
Black or African American	**1 (10)**	**0**	**1 (5)**
Hispanic/Latino	**1 (10)**	**2 (18)**	**3 (14)**
White	**8 (80)**	**9 (82)**	**17 (81)**
Disease Subtype, N (%)			
Multiple myeloma	**10 (100)**	**N/A**	**10 (48)**
Follicular lymphoma	**N/A**	**3 (27)**	**3 (14)**
Marginal zone lymphoma		**1 (9)**	**1 (5)**
Mantle cell lymphoma		**1 (9)**	**1 (5)**
DLBCL		**4 (36)**	**4 (19)**
Burkitt's lymphoma		**1 (9)**	**1 (5)**
DLBCL/FL		**1 (9)**	**1 (5)**
Median lines of prior therapy, N (range)	**6 (3-11)**	**4 (2-12)**	**6 (2-12)**
Prior autologous stem cell transplant, N (%)	**6 (60)**	**2 (18)**	**8 (38)**
Prior related donor allogeneic stem cell transplant, N (%)	**1 (10)**	**0**	**1 (5)**
Prior unrelated donor allogeneic stem cell transplant, N(%)	**0**	**1 (9)**	**1 (5)**
Prior CAR-T therapy, N (%)	**1 (10)**	**1 (9)**	**2 (10)**

For time from diagnosis calculations, unknown dates were imputed as June (unknown month) and the 15th (unknown day).

Table 4. Treatment Emergent Adverse Events in ≥15% Subjects

Treatment Emergent Adverse Events (TEAE)	
TEAE ≥ 15%	**Number of Subjects N=21 (%)**
Fatigue	**6 (29)**
Chills	**6 (29)**
Nausea	**5 (24)**
Fever	**5 (24)**
Cough	**4 (19)**
Infusion related reaction	**4 (19)**

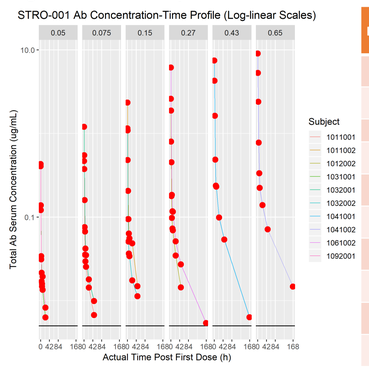
The emerging STRO-001 safety profile includes mostly mild adverse events- 91% of all AEs are grade 1 or 2. Observance of infusion reactions prompted a premedication requirement in a protocol amendment.

Table 5. Grade 3 and Higher Treatment Emergent Adverse Events

Grade ≥ 3 TEAE	
Adverse Event (Grade)	**Number of Subjects N=21 (%)**
Thromboembolic event (3,5)	**2 (10)**
Fall (3)	**1 (5)**
Hyponatremia (3)	**1 (5)**
Lung infection (3)	**1 (5)**
Pleural effusion (3)	**1 (5)**
Pneumothrorax (3)	**1 (5)**
Urinary tract infection (3)	**1 (5)**

All grade ≥ 3 events were assessed as not related to study drug with the exceptions of the thromboembolic events and hyponatremia, which have been assessed by the investigator as 'possibly' related to STRO-001 treatment.

Figure 2. Preliminary Pharmacokinetic Summary (total antibody)



Dose (mg/kg)	ID	cmax ug/mL	tmax h	tlast h	AUC0-tlast h·ug/mL
0.05	1031001	0.432	1.083	24	0.93
0.05	1092001	0.406	1.083	24	0.92
0.075	1011001	0.469	1.083	48	1.85
0.075	1032001	1.200	1.083	48	3.28
0.15	1011002	2.350	1.083	48	6.21
0.15	1032002	1.150	1.083	48	2.96
0.27	1012002	2.600	1.083	48	5.85
0.27	1061002	6.170	1.083	168	14.60
0.43	1041001	7.490	1.083	168	26.44
0.65	1041002	9.080	1.083	168	34.29

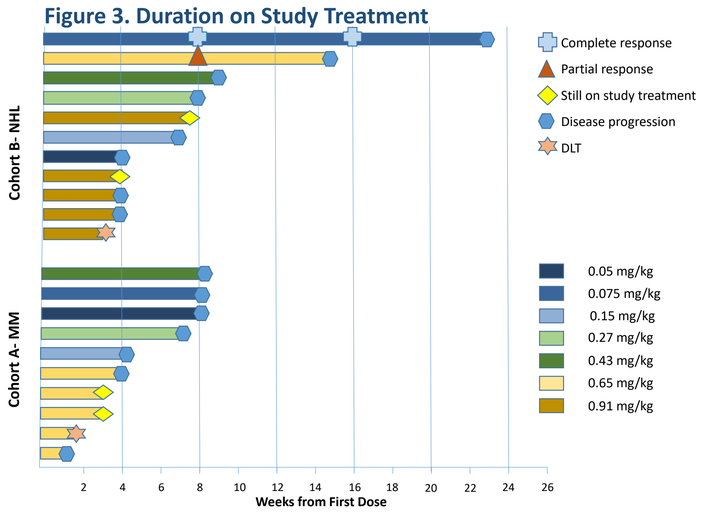
Log-linear plot of total anti-body serum concentrations vs time by dose (mg/kg) group and ID with a table of PK parameters after the first intravenous dose of STRO-001. Preliminary PK profile in 3 patients reveals an estimated half-life for total antibody of 37-47 hours.

Table 6. Testing for Anti-drug Antibodies (ADA)

Dose Level	Cohort A (MM)	Cohort B (NHL)	ADA present?
0.05 mg/kg	4 samples	2 samples	No
0.075 mg/kg	4 samples	7 samples	No
0.15 mg/kg	3 samples	3 samples	No
0.27 mg/kg	2 samples	3 samples	No
0.43 mg/kg	3 samples	-	No
0.65 mg/kg	1 sample	-	No

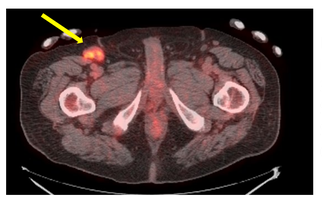
32 available samples were sent for ADA testing. None of the samples had detectable ADA to STRO-001. Samples are taken at screening, the beginning of each cycle starting with Cycle 2, and the End of Treatment visit.

Figure 3. Duration on Study Treatment

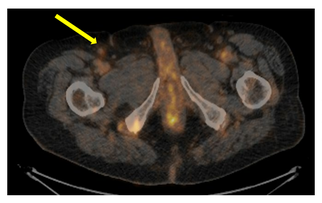


Preliminary anti-tumor activity (CR and PR) has been observed in two patients with DLBCL. Duration of study was calculated from first dose of STRO-001 until disease progression or patient experienced a DLT as of May 14, 2019. All discontinuations were due to disease progression except for 2 patients with DLTs (See Table 3).

Figure 4. Complete Response in Patient with DLBCL



Baseline Scan: Right inguinal lymph node, 34.2 x 15.6 mm, SUV 5.52
Spleen 94 mm
Overall Deauville : 4



Cycle 3 Day 1 Scan: Right inguinal lymph node, 25.3 x 12.7 mm, SUV 2.65
Spleen 72 mm
Overall Deauville : 2
Complete response

Patient 103-2001 is an 82 year old man diagnosed with Stage III DLBCL in 2015. Prior to study entry, he received CHOP-R, Rituxan/lenalidomide, bendamustine/Rituxan, and obinituzumab/gemcitabine/oxaliplatin. He received 12 doses of STRO-001, and had a complete response at Cycle 3 and Cycle 5 scans. The patient had progressive disease at Cycle 7. Arrow indicates target lesion.

CONCLUSIONS

- STRO-001 is the first ADC generated with novel cell-free protein synthesis technology and site-specific conjugation to be tested in the clinic.
- STRO-001 has been well tolerated, most AEs are grade 1 or 2.
  Mild infusion reactions have been observed, requiring standard of care pre-medications.
  No ocular toxicity signals have been observed
  Two thromboembolic DLTs have been observed in 2 patients with very bulky baseline disease (>15 cm).
- Enrollment is ongoing at 0.65 mg/kg in MM cohort and 0.91 mg/kg in NHL cohort.
- Preliminary PK profile in 3 patients reveals an estimated half-life for total antibody of 37-47 hours.
- Anti-drug antibodies (ADA) have not been detected.
- Preliminary anti-tumor activity (1 CR and 1 PR) has been observed in two patients with DLBCL.

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