

# 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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## BACKGROUND

- CD74 is expressed in ~ 90% of B-cell cancers including multiple myeloma (MM) and Non-Hodgkin Lymphoma (NHL)<sup>1, 2</sup> - 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.<sup>3,4</sup> 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)<sup>4</sup> T7 RNA Pol Plasmid with nnAA codons Development of SP7219 and STRO-001 using SP-7219 Sutro's proprietary Xpress Cell-Free (XpressCF+<sup>™</sup>) system <sup>6</sup>. The non-natural amino acid (nnAA) pAMF was incorporated at Figure 1. Generation of the CD74 different sites on SP7219, with the optimal targeting antibody and a novel, specific sites selected based on conjugation efficiency, CF-Engineered Synthetase and homogeneous ADC, STRO-001 Cytotoxic 😽 🍾 Warhead cell killing activity and PK in mice. SP7219 was conjugated at pAMF to the noncleavable

• CD74 is a transmembrane glycoprotein involved in MHC protein formation & transport

# **OBJECTIVES (ENDPOINTS)**

Copper-free click

ugation chemistry

STRO-001

generate STRO-001.

#### Primary Objectives (Endpoints)

- Dose escalation: Safety & tolerability of STRO-001 (adverse events); Define RP2D (dose limiting toxicities)

Xpress CF+ (*E.coli* Extract)

- 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, addi
- **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<sup>5</sup> • 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).

maytansinoid linker-warhead SC236 to

tional PK)	

#### **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

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		3 (27)	3 (14)
Marginal zone lymphoma		1 (9)	1 (5)
Mantle cell lymphoma	NI / A	1 (9)	1 (5)
DLBCL	N/A	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 15<sup>th</sup> (unknown day).

#### **CURRENT STATUS, DOSE ESCALATION**

 DLT evaluable patients had to receive both doses of STRO-001 in Cycle 1 and complete Cycle 1 • Cut-off date used May 14<sup>th</sup>, 2019 for summary of initial safety in the STRO-001-BCM1 study

#### Table 2. Status of Dose Escalation, May 14, 2019

Dose Level, status	Cohort A (MM)	Cohort B (NHL)	Total patients treated	C	ose
<ol> <li>0.05 mg/kg Both Cohorts completed</li> </ol>	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET	Cohort A (MM)	Grad days
2) 0.075 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET	0.65 mg/kg	death as bu
<ol> <li>3) 0.15 mg/kg</li> <li>Both Cohorts completed</li> </ol>	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET		of sm to an dehv
4) 0.27 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET	Cohort B	Grad
5) 0.43 mg/kg Both Cohorts completed	N = 1, no DLTs	N = 1, no DLTs	N = 2, Dose level cleared by SET	(NHL) 0.91 mg/kg	of ST show thron
6) 0.65 mg/kg enrolling Cohort A, Cohort B completed	N=5, 1 DLT	N = 1, no DLTs	N = 6, still enrolling		femo persis x 10.0
7) 0.91 mg/kg, enrolling only Cohort B	N=0	N=5, 1 DLT	N = 5, still enrolling		(6.6x encas

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). 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 4. Treatment Emergent Adverse Events in** ≥15% Subjects

Treatment Emergent Adverse Events (TEAE)			
<b>TEAE ≥ 15%</b>	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)		

#### 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			

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

thromboembolic events and hyponatremia, which have been assessed by the investigator as 'possibly' related to STRO-001 treatment.

## RESULTS

### 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 pharmacokinetic 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.

#### **Figure 3. Duration on Study Treatment**



Neeks from First Dose 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).

## SUMMARY/CONCLUSIONS

- 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

- Anti-drug antibodies (ADA) have not been detected.

#### 1. Stein R, Mattes MJ, et al. Clin. Cancer Res. Sep 15 2007;13(18 Pt 2):5556s-5563s. 2. Zhao S, Molina A, et al. Journal of Pathology: Clin Research. Jan 2019, 5: 12-24. 3. Abrahams C, Li X, et al. Oncotarget, 2018 Vol 9. (No. 102), 37700-37714. Solis W, De Almeida V, et al. Proc AACR Annual Mtg,2018;78(13 Suppl):Abstract # 742.

**Table 3. Dose Limiting Toxicities** 

#### niting Toxicities Summary

• 5 thromboembolic event- Patient passed away suddenly 8 after first dose of study treatment. An autopsy reveale ad extensive bilateral pulmonary embolism as cause of ere were multiple risk factors for thromboembolism suc Iky plasmacytomas in the abdomen (9 x 6 x 2.5 cm), pelvis y 17 x 14 x 3.9 cm) and two focal areas of marked narrowing all and large intestine by plasmacytoma, prolonged car ride d from clinic, partial small bowel obstruction and possible

e 3 thromboembolic event- Nine days after the second dose RO-001, the patient reported feeling short of breath. A CT ed left upper lobe pulmonary emboli, acute venous nbosis involving bilateral external iliac veins, and commor ral veins. The CT scan also showed progressive extensive stent adenopathy in the abdomen (soft tissue mass 7.9 x 4.5 0 cm, lymph node- 15.3 x 8.6 cm, 13.0 x 7.9 cm), and pelvis 2.5 cm, 6.7x 6.2 cm, 6.4 x 4.3 cm, 3.0 x 1.7 cm), with sement 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 preexisting thromboembolism.







Complete response Partial response Still on study treatmen Disease progression

0.075 mg/kg 0.15 mg/kg 0.27 mg/kg 0.43 mg/kg 0.65 mg/kg 0.91 mg/kg

### 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 4. Complete Response in a 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/oxaliplati 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.

STRO-001 is the first ADC generated with novel cell-free protein synthesis technology and site-specific conjugation

Two thromboembolic DLTs have been observed in 2 patients with very bulky baseline disease (>15 cm).

• Enrollment is ongoing in the 3+3 escalation 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.

Preliminary anti-tumor activity (1 CR and 1 PR) has been observed in two patients with DLBCL.

### REFERENCES

5. Shah N, Krishnan A, et al. Proc AACR Annual Mtg, April 2019, Abs CT104. 6. Zimmerman ES, Heibeck TH et al. Bioconjug Chem Feb 2014 25(2): 351-61.