Antitumor activity of STRO-002, a novel anti-folate receptor-α (FolRα) antibody drug conjugate (ADC), in patient-derived xenograft (PDX) models and preliminary Phase I dose escalation safety outcomes in patients with ovarian carcinoma (OC)

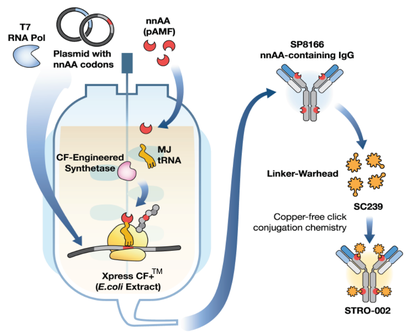
Denise Uyar[1] Russell J Schilder[2] R Wendel Naumann[3] Fadi S Braiteh[4] Erika Hamilton[5] Sami Diab[6] John Moroney[7] John Paul Diaz[8] Richard T Penson[9] Clifford DiLea[10] Jennifer Smith[11] Cristina Abrahams[11] Michael Palumbo[11] Venita DeAlmeida[11] Shannon Matheny[11] Arturo Molina[11]

1 Medical College of Wisconsin, Milwaukee, WI; 2 Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; 3 Levine Cancer Institute, Carolinas Medical Center, Charlotte, NC; 4 Comprehensive Cancer Centers of Nevada, Las Vegas, NV; 5 Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; 6 Rocky Mountain Cancer Center, Aurora, CO; 7 University of Chicago, Chicago, IL; 8 Miami Cancer Institute, Miami, FL 9 Massachusetts General Hospital, Boston, MA; 10 Aclairo Pharmaceutical Development Group, Vienna, VA; 11 Sutro Biopharma, South San Francisco, CA.

BACKGROUND

- Folate receptor alpha (FolRα) is a cell-surface glycoprotein that is overexpressed in OC and endometrial adenocarcinoma
- Sutro's cell-free synthesis platform enables rapid production and high-throughput selection for optimization of ADC candidates.
- STRO-002 is a novel FolRα-targeting ADC containing an anti-FolRα human IgG1 antibody (SP8166) conjugated to a cleavable dibenzocyclooctyne (DBCO)- 3-aminophenyl-hemiasterlin drug-linker, using site-directed conjugation technology to produce a well-defined ADC with the predominant species having a drug-antibody ratio (DAR) of 4.

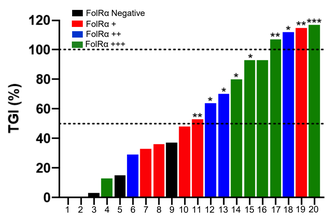
Generation of the FolRα-targeting lead antibody and a novel, specific and homogeneous ADC, STRO-002



Development of SP8166 and STRO-002 using Sutro's proprietary Xpress Cell-Free (XpressCF+TM) system. The non-natural amino acid (pAMF) was incorporated at two sites on the heavy chain of SP8166, with the sites selected based on conjugation efficiency, cell killing activity and in vivo activity in mice. SP8166 was conjugated at pAMF to the cleavable 3-aminophenyl hemiasterlin drug-linker SC239 to generate STRO-002.

STRO-002 EFFICACY IN ENDOMETRIAL PDX MODELS

A



B

FolRα expression	Significant % TGI
Negative	0/3
FolRα +	2/6
FolRα ++	3/5
FolRα +++	4/6

A. Bar graph shows mean TGI for 20 endometrial PDX models in response to STRO-002 treatment. Models are color coded based on FolRα expression levels. Lines indicate 50% and 100% TGI, while asterisks denote statistical significance. B. Table summarizes statistical analysis of TGI (using an unpaired t test) for PDX models grouped by expression level. A probability of less than 5% ($p < 0.05$) was considered as significant. * = $p < 0.5$, ** $p < 0.01$, *** $p < 0.001$

- STRO-002 was significantly efficacious in 53% (9/17) of the FolRα positive PDX models
- Significant tumor growth inhibition (TGI) ranged from 53% to > 100 %; one model (#16) exhibited 93% TGI but did not achieve statistical significance due to variability in the control group
- Correlation observed between STRO-002 response and FolRα expression levels.
  - High FolRα models showed highest tumor growth inhibition, some low and medium FolRα models exhibited good activity.

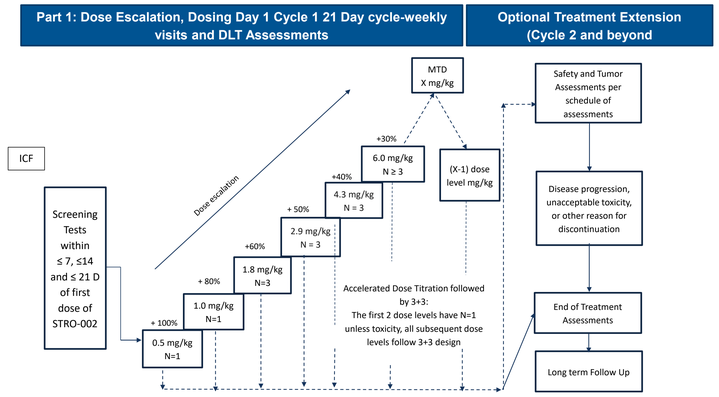
Methods: Tumor microarrays of human endometrial/uterine PDX models procured from South Texas Accelerated Research Therapeutics (START) were evaluated for presence and level of FolRα expression by IHC. 20 PDX models were selected for evaluation of STRO-002 activity based on tumor growth kinetics defined as ≤ 40 days to reach 100 mm^3 and different levels of FolRα expression including FolRα+++ (strong/high), FolRα ++ (moderate/medium), FolRα + (weak/low), or FolRα negative (no expression).
The in vivo STRO-002 efficacy screen was conducted at START. Animals (n=3 per group) were untreated (control group) or treated weekly with 10 mg/kg STRO-002. TGI measured how much STRO-002 treatment inhibited tumor growth relative to the control group on the day the controls reached the primary study endpoint (control group mean > 1,000 mm^3 or 45 days post treatment start).

STRO-002-GM1 OBJECTIVES

- **Primary Objectives (Endpoints)**
  - Dose escalation: Safety & tolerability of STRO-002 (adverse events); Define RP2D (dose limiting toxicities)
  - Dose expansion: Anti-tumor activity of STRO-002 (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

STRO-002-GM1 STUDY DESIGN

- First-in-human, Phase 1 study in OC including fallopian or primary peritoneal cancer
- Open-label, multicenter, dose escalation study with dose expansion to identify the maximum tolerated dose (MTD) and the recommended phase 2 doses (RP2D)
- Evaluate the safety, tolerability, and preliminary antitumor activity of STRO-002
  - **Part 1**-Dose Escalation- Single cohort for ovarian, fallopian tube or primary peritoneal cancer
  - **Part 2**: Dose Expansion- Separate cohorts for OC and epithelial endometrial cancer
- STRO-002 is given by intravenous (IV) infusion on Day 1 of 21-day cycles
- Accelerated dose titration for first 2 dose levels followed by 3+3 for all subsequent dose levels



ICF- informed consent form; D- day; DLT- dose limiting toxicity; N= number of patients treated

STRO-002-GM1 BASELINE CHARACTERISTICS AND RESULTS

- First patient was dosed in STRO-002- GM1 study in March 2019
- As of October 15, 2019, 13 patients have enrolled in STRO-002-GM1 study

Characteristic	Total N=13
Age, median (range), years	**61 (52-69)**
Median time from diagnosis in years (range)	**6.5 years (1.3- 17.1)**
ECOG performance status, median (range)	**0 (0-1)**
0, N (%)	**7 (54)**
1, N (%)	**6 (46)**
Race/Ethnicity, N (%)	
Black or African American	**2 (15)**
White	**11 (85)**
Disease Subtype, N (%)	
Ovarian	**10 (77)**
Fallopian tube	**2 (15)**
Peritoneal	**1 (8)**
Median lines of prior therapy (range)	**6 (2-8)**
Prior PARP inhibitor	**5 (38)**
Prior Bevacizumab	**10 (77)**
Prior checkpoint inhibitor	**3 (23)**

Treatment Emergent Adverse Events in >15% Subjects

Treatment Emergent Adverse Events (TEAE)	
TEAE >15%	Number of Subjects N=13 (%)
Nausea	**6 (46)**
Fatigue	**5 (39)**
Headache	**4 (31)**
Insomnia	**4 (31)**
Vomiting	**4 (31)**
Abdominal pain	**3 (23)**
Dizziness	**3 (23)**

The emerging STRO-002 safety profile includes mostly mild adverse events- 95% of all AEs reported as of Oct 15, 2019 are grade 1 or 2.

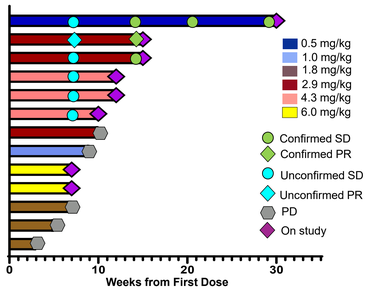
Grade 3 Treatment Emergent Adverse Events

Grade 3 TEAE	
Adverse Event (Grade)	Number of Subjects N=13 (%)
Small intestine obstruction	**2 (15)**
Neutropenia	**2 (15)**
Dehydration	**1 (8)**
Hypokalemia	**1 (8)**
Hyponatremia	**1 (8)**
Hematuria	**1 (8)**

Neutropenia events (dose level 4.3 mg/kg and 6.0 mg/kg) were noted to be likely or highly likely related to STRO-002 treatment. All other grade 3 events we listed as 'not related' or 'doubtful' regarding relationship to study drug and occurred in patients at time of disease progression. As of October 15, 2019, no grade 4 or grade 5 events have been reported.

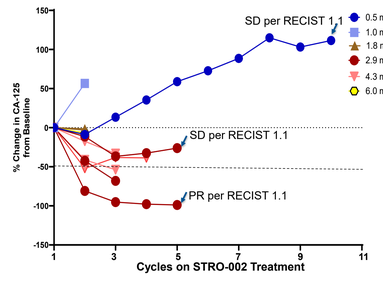
RESULTS

Duration on Study Treatment



Duration of study was calculated from first dose of STRO-002 until disease progression as of Oct 15, 2019. All discontinuations were due to disease progression. Partial response (PR) and stable disease (SD) are measured by investigator using RECIST 1.1 criteria. Progressive disease (PD) was either by RECIST 1.1 criteria or clinical progression.

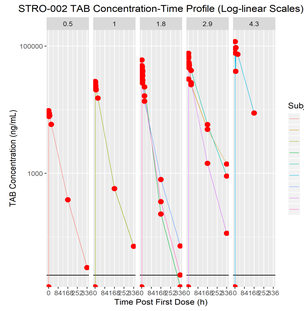
Percent Change in CA-125 from Baseline



Percent change from baseline of CA-125 levels; One patient with confirmed CA-125 response also has a confirmed PR per RECIST 1.1.

Preliminary Pharmacokinetic Summary

STRO-002 TAB Concentration-Time Profile (Log-linear Scales)



Dose mg/kg	ID	Cmax ng/mL	tmax h	clast ng/mL	tlast h	AUC0-tlast h·ng/mL
0.5	1037001	9680	1.083	32.8	336	661101
1.0	1127001	27900	1.083	70.8	336	1653731
1.8	1127002	49200	1.083	228.0	168	2499424
1.8	1157001	38200	1.083	71.8	336	1704969
1.8	1177001	60700	2.000	25.1	336	1937031
2.9	1037002	69000	1.083	1400.0	336	3647336
2.9	1137001	64700	2.000	901.0	336	5108849
2.9	1157002	77100	1.083	114.0	336	3190167
4.3	1137002	118000	1.083	8870.0	168	7928009

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-002. Preliminary PK profile reveals an estimated half-life for total antibody of 22-76 hours while exposure increased with dose in an apparent linear manner.

SUMMARY/CONCLUSIONS

- STRO-002 is the first ADC generated with novel cell-free protein synthesis technology and site-specific conjugation to be tested in solid tumors
- STRO-002 has been well tolerated; most AEs are grade 1 and no DLTs have been observed
  - 80% of AEs reported are grade 1; 15% grade 2 and 5% grade 3
  - No grade 4 or 5 events have been reported
  - No prophylactic corticosteroid eye drops are being utilized
  - No infusion reactions have been observed
- Enrollment is ongoing at 6.0 mg/kg dose level; MTD has not been reached
  - 13 patients have been treated and dose levels 0.5, 1.0, 1.8, 2.9 and 4.3 mg/kg have been cleared
- Preliminary PK profile reveals an estimated half-life for total antibody of 22-76 hours while exposure increased with dose in an apparent linear manner.
- Preliminary evidence of anti-tumor activity has been observed in this heavily pre-treated patient population:
  - One confirmed PR by RECIST 1.1 (Cycle 5) with a confirmed CA-125 response
  - Two ongoing patients have confirmed stable disease per RECIST 1.1, one up to Cycle 5, one up to Cycle 10
  - Three ongoing patients at 4.3 mg/kg have stable disease per RECIST 1.1 at Cycle 3 (unconfirmed)
- STRO-002 demonstrates potent anti-tumor activity in PDX models of endometrial cancer supporting further clinical development in this indication

SUTRO BIOPHARMA