

Preliminary Results from the First in Human Study of Activin A Inhibitor, STM 434, in Patients with Granulosa Cell Ovarian Cancer and Other Advanced Solid Tumors

David Michael Hyman¹, Drew W. Rasco², Jeffrey R. Infante³, Joyce F. Liu⁴, Esther Welkowsky⁵, Dung Luong Thai⁶, Christopher M. Haqq⁵

¹Memorial Sloan Kettering Cancer Center, New York, NY; ²South Texas Accelerated Research Therapeutics, San Antonio, TX; ³Sarah Cannon Research Institute, Nashville, TN; ⁴Dana-Farber Cancer Institute, Boston, MA; ⁵Atara Biotherapeutics, Westlake Village, CA; ⁶Atara Biotherapeutics, South San Francisco, CA

For more information, contact Chris Haqq: chaqq@atarabio.com

BACKGROUND

STM 434 is an ACVR2B soluble receptor ligand trap that inhibits Activin A, a protein in the TGF-beta superfamily implicated in tumor growth, angiogenesis and immune modulation.

Mutant FOXL2 drives Activin A signaling in granulosa cell tumors.

Elevated Activin expression promotes muscle wasting and contributes to cancer cachexia.

Activin A Plays a Role in Physiology and Pathophysiology

Physiology

- TGF-beta protein
- Enhances FSH biosynthesis and secretion and regulates menstrual cycle
- Paracrine factor in wound healing, cell proliferation and differentiation, immune response and angiogenesis

Pathophysiology

- Elevated in cancer and inflammation (Fig 1)
- Cancer cachexia
- Tumor progression through its effects on tumor microenvironment
- Mutations in Activin A and its regulators implicated in ovarian cancer in young women

STM 434/s Improves Survival and Increases Body Weight in Models of Granulosa and Clear Cell Ovarian Cancer

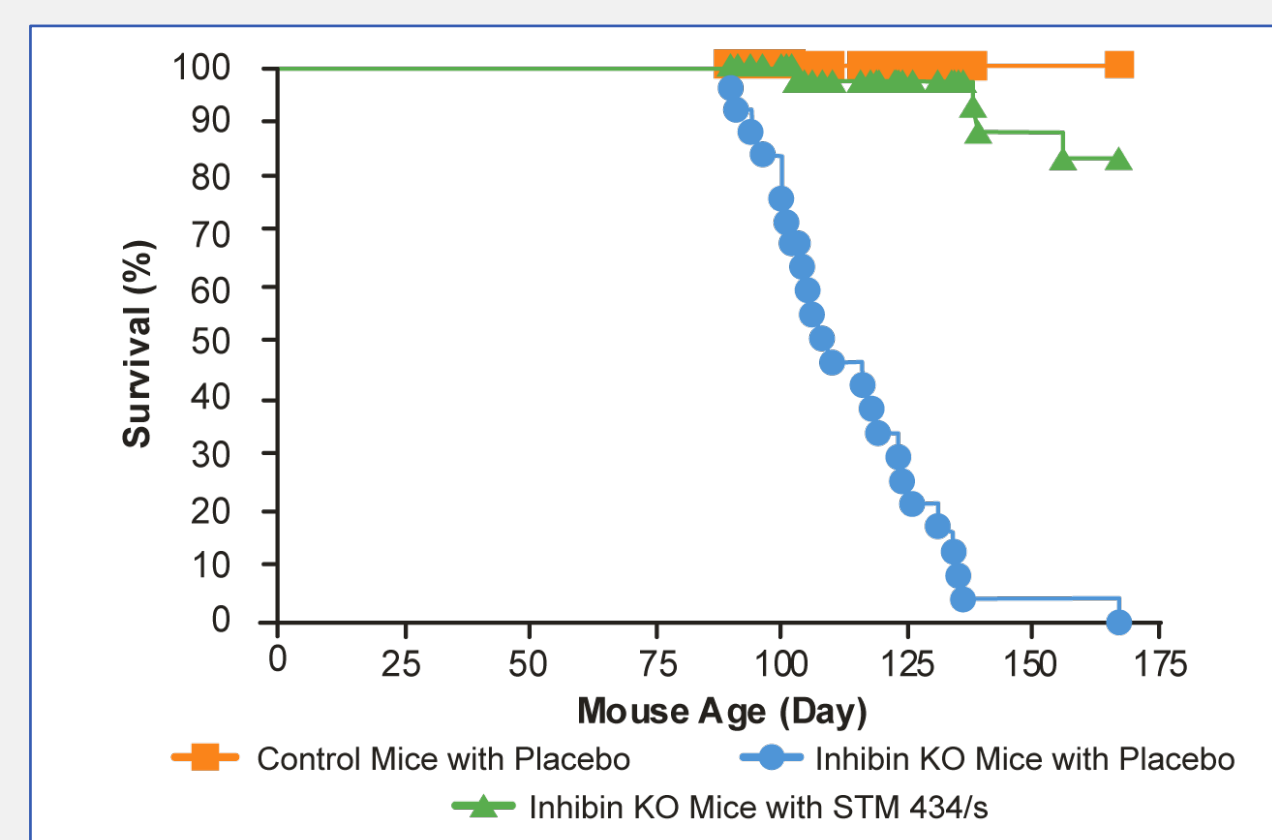
Preclinical Pharmacology

- Ligand trap for Activin A, myostatin and BMP9.
- Increased muscle and bone consistent with activin inhibition
- Mucosal bleeding consistent with BMP9 inhibition
- No effect on platelet number or function

Granulosa Model: Survival (Fig 2)

- Statically significant improvement in survival¹
- FOXL2 mutation present in 97% of granulosa cell tumors²
- STM 434/s is a closely related analogue of STM 434

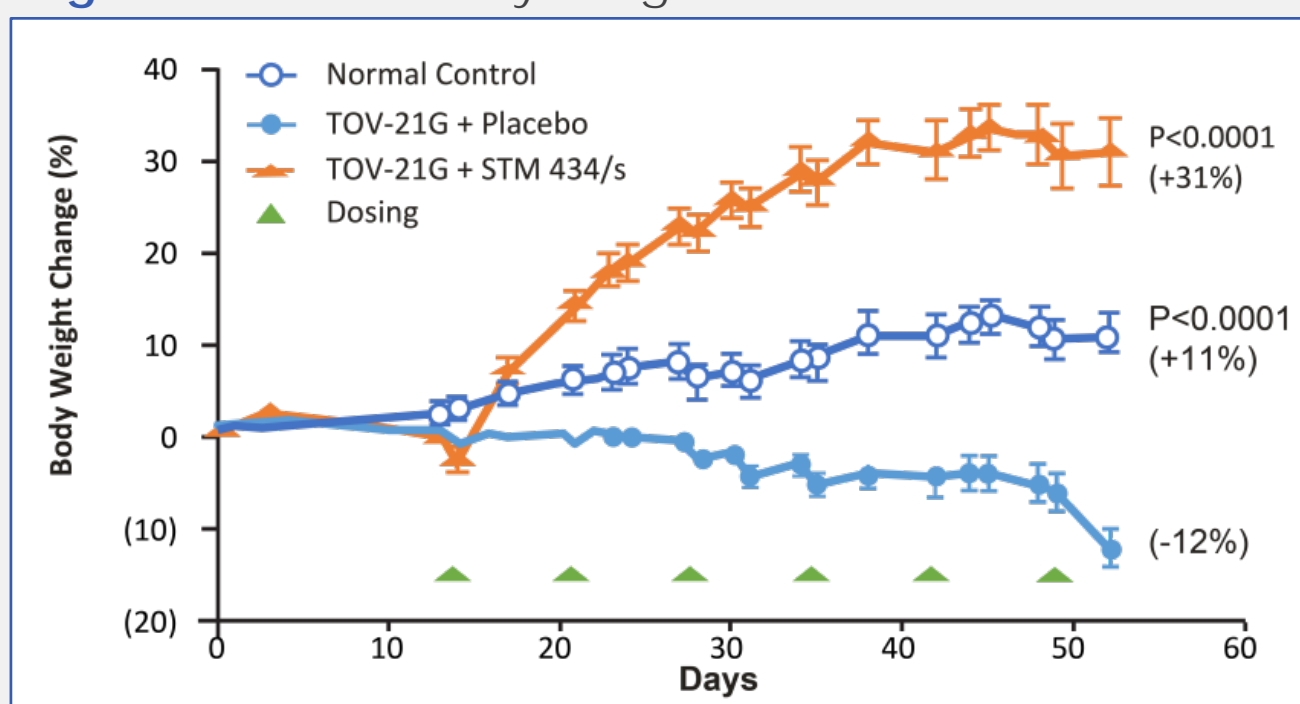
Fig 2. Granulosa Model: Survival.



Clear Cell: Body Weight (Fig 3)

- Anti-cachectic effect associated with increased body weight vs. both tumor and normal controls³

Fig 3. Clear Cell: Body Weight.



References

- 1 Zhou X, et al. *Cell*. 2010; 142(4):531-43.
- 2 Shah S. P., et al. *NEJM*. 2009; 360: 2719-29.
- 3 Lu J, Haqq C, Han HQ. Abstract 2541, *ASCO Annual Meeting*. 2013.
- 4 David L, et al. *Circulation Research*. 2008; 102: 914-922.

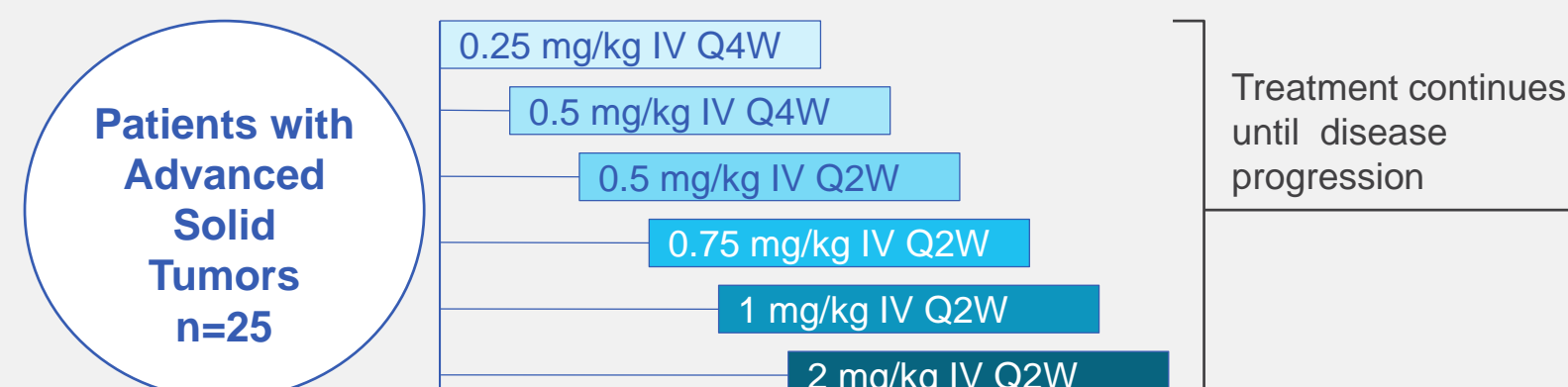
METHODS

Using a 3+3 dose escalation design, the safety and pharmacokinetics (PK) of STM 434 IV every 2-4 weeks was evaluated. All patients (pts) continued until disease progression or unacceptable toxicity. CT scans were performed every 8-12 weeks. (Fig 4)

Study Objectives

- To evaluate the safety, PK, pharmacodynamics (PD), and efficacy of STM 434 in patients with advanced solid tumors.
- To evaluate the effects of STM 434 on lean body mass by DEXA scan and muscle function by 6 minute walk distance.

Fig 4. STM 434 Monotherapy: Dose Escalation (3 + 3 Design)



RESULTS

- We report interim May 2016 data in 25 pts who received STM 434 at doses of 0.25, 0.5, 0.75, 1, and 2 mg/kg. (Table 1)

Table 1. STM-434-001: Patient Baseline Characteristics.

	STM 434 Monotherapy, n=25
Gender, Female	20 (80%)
Age, median, years [range]	62.0 [41, 79]
ECOG PS	68% PS 0; 32% PS 1
Number of prior chemotherapy regimens, median [range]	3 [0, 9]
Body weight (kg), mean [range]	78.7 [45.9, 154.4]
6 minute walk distance (6MWD), mean [range]	336.2 [161, 660]
Tumor Type	
Ovarian - Granulosa cell	10 (40%)
Ovarian - serous/adenocarcinoma	3 (12%)
Ovarian - clear cell	2 (8%)
Colorectal	2 (8%)
Squamous cell	2 (8%)
Other*	6 (24%)

*One each of: Chondrosarcoma, Kidney, Leiomyosarcoma, Pancreatic, Thymic, Urachal

Table 2. Treatment Emergent Adverse Events (TEAEs) in ≥ 10% of subjects.

Patient, n (%)	0.25 mg/kg Q4W n=4	0.5 mg/kg Q4W n=6	0.5 mg/kg Q2W n=4	0.75 mg/kg Q2W n=3	1 mg/kg Q2W n=4	2 mg/kg Q2W n=4	All n=25
Any AE	3 (75)	6 (100)	3 (75)	3 (100)	4 (100)	2 (50)	21 (84)
Fatigue	0 (0)	4 (67)	1 (25)	2 (67)	2 (50)	0 (0)	13 (52)
Epistaxis	0 (0)	0 (0)	0 (0)	2 (67)	4 (100)	1 (25)	7 (28)
Abdominal Pain	2 (50)	1 (17)	1 (25)	1 (33)	0 (0)	1 (25)	6 (24)
Headache	0 (0)	1 (17)	0 (0)	0 (0)	4 (100)	0 (0)	5 (20)
Diarrhea	1 (25)	2 (33)	0 (0)	0 (0)	1 (25)	1 (25)	5 (20)
Edema peripheral	0 (0)	3 (50)	0 (0)	1 (33)	0 (0)	1 (25)	5 (20)
Gingival Bleeding	0 (0)	2 (33)	0 (0)	0 (0)	2 (50)	0 (0)	4 (16)
Rash maculo-popular	0 (0)	2 (33)	1 (25)	0 (0)	1 (25)	0 (0)	4 (16)
Gastroesophageal Reflux	0 (0)	0 (0)	2 (50)	0 (0)	1 (25)	0 (0)	3 (12)

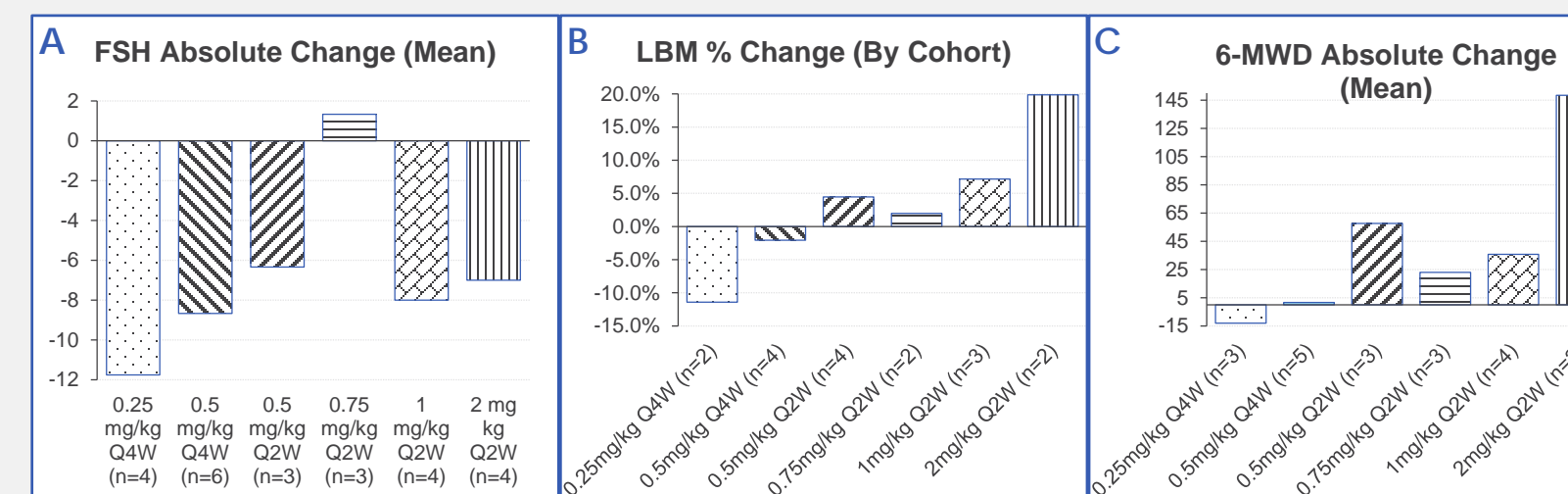
RESULTS

- The most common TEAEs were fatigue (n = 13), epistaxis (n = 7), and abdominal pain (n = 6); Adverse Events (AEs) were generally Grade 1-2. (Table 2)
- AEs of interest are an expected consequence of STM 434 inhibition of bone morphogenetic protein 9, a vascular quiescence protein at the mucosa.⁴
- The mean T1/2 was 5-7 days, and PK was linear between 0.25 mg/kg and 1 mg/kg.
- STM 434 administration resulted in the expected endocrine PD response to Activin A inhibition with reciprocal decreases in follicle stimulating hormone (FSH) in a majority of patients. (Fig 5A)
- Increasing doses of STM 434 were associated with modulation of cachexia as assessed by changes in LBM (p=0.005, based on a linear contrast by cohort) and 6-MWD. (Fig 5B-C)
- Stable disease (SD) up to 12 months (thymic; n=1) and up to 6.1 months (granulosa; n=4) in duration has been observed in 5/25 (20%). The SD rate in granulosa tumors was 4/10 (40%). (Fig 6)

Table 3. Adverse Events of Interest.

Patient, n (%)	0.25 mg/kg Q4W n=4	0.5 mg/kg Q4W n=6	0.5 mg/kg Q2W n=4	0.75 mg/kg Q2W n=3	1 mg/kg Q2W n=4	2 mg/kg Q2W n=4	All n=25
Epistaxis	0 (0)	0 (0)	0 (0)	2 (67)	4 (100)	1 (25)	7 (28)
Edema peripheral	0 (0)	3 (50)	0 (0)	1 (33)	0 (0)	1 (25)	5 (20)
Gingival Bleeding	0 (0)	2 (33)	0 (0)	0 (0)	2 (50)	0 (0)	4 (16)
Rash maculo-papular	0 (0)	2 (33)	1 (25)	0 (0)	1 (25)	0 (0)	4 (16)

Fig 5. Effects on FSH, Change in Lean Body Mass, and 6-MWD.



LBM (body weight minus body fat mass) was assessed by DEXA scan. Percent change in LBM represents the last available time point relative to pre-dose baseline. The 6-MWD measuring distance covered by a subject in 6 minutes over a flat surface was performed in accordance with guidelines from the American Thoracic Society. Absolute change represents the last available time point relative to pre-dose baseline.

Fig 6. Best Overall Response and Time on Trial (Granulosa).

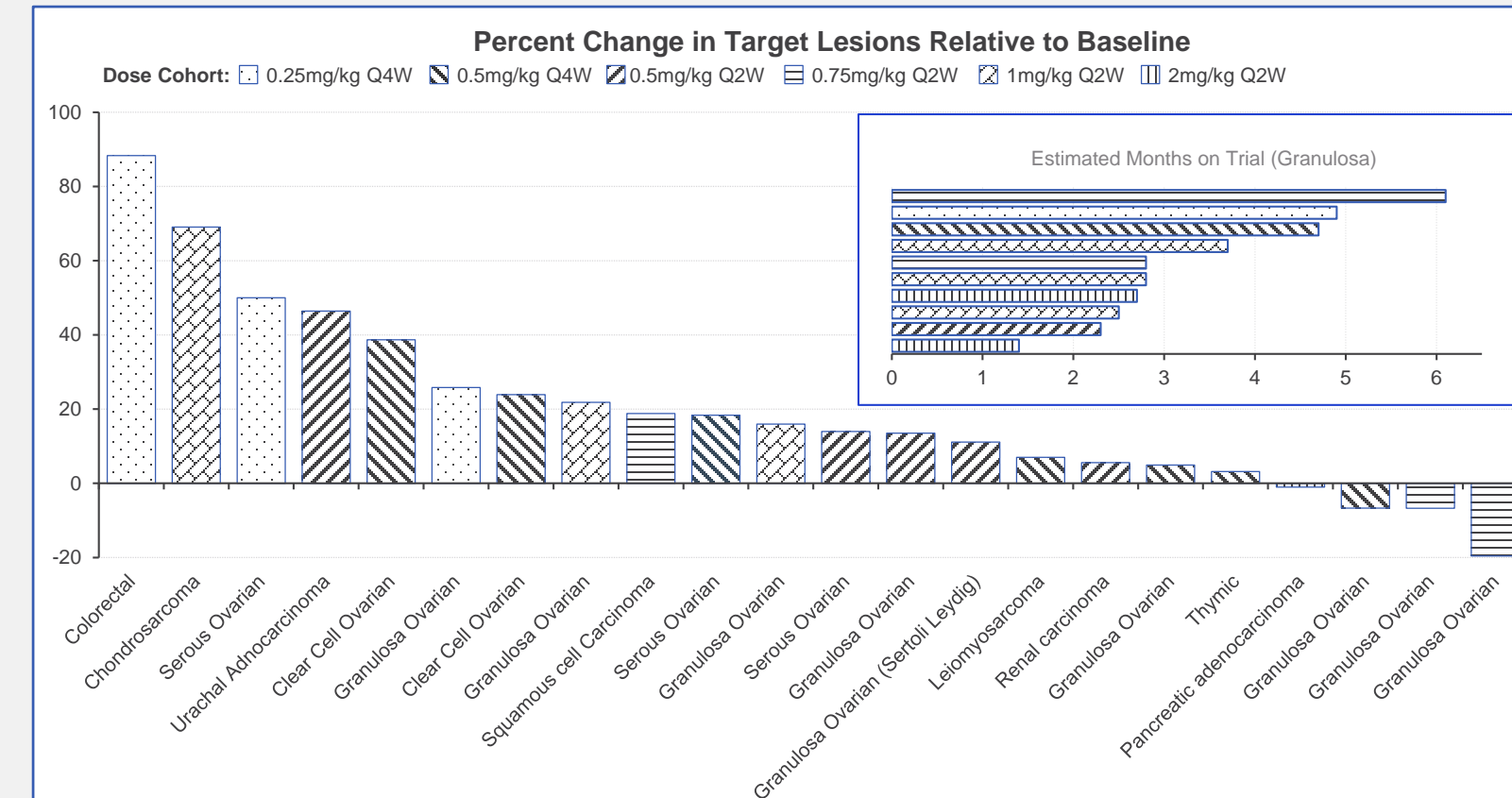


Table 4. Grade ≥ 3 Treatment Emergent Adverse Events in ≥ 2 subjects.

Patient, n (%)	0.25 mg/kg Q4W n=4	0.5 mg/kg Q4W n=6	0.5 mg/kg Q2W n=4	0.75 mg/kg Q2W n=3	1 mg/kg Q2W n=4	2 mg/kg Q2W n=4	All n=25
Abdominal Pain	1 (25)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	2 (8)
Hypokalemia	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (25)	2 (8)
Hyponatremia	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (25)	2 (8)

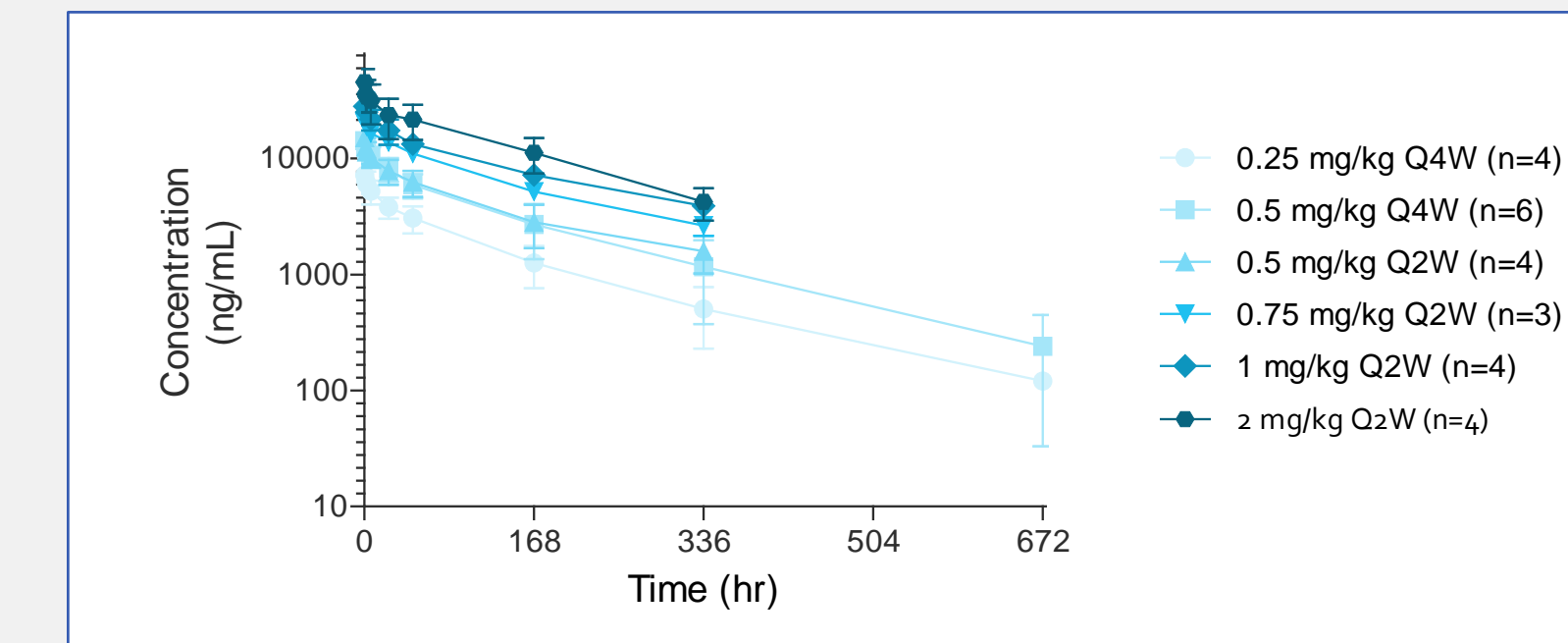
All events were Grade 3 in severity. One DLT of Grade 3 self-limited peritoneal bleeding was observed at 0.5 mg/kg Q4W in a patient with clear cell ovarian cancer and peritoneal metastases.

Table 5. Pharmacokinetics of STM 434.

	Dose Level				
	0.25 mg/kg	0.5 mg/kg	0.75 mg/kg	1 mg/kg	2 mg/kg
C _{max} , µg/mL*	7.31	14.9	20.5	30.5	45.4
AUC _{0-∞} , day-µg/mL*	28.2	60.4	114	161	218
T _{max} , hr†	0.5	0.5	1.2	0.5	0.5
t _{1/2} , day‡	5.04	5.04	5.83	6.96	5.13

*Mean (% coefficient of variation [CV]); †Median (quantile [Q1, Q3]). AUC_∞, area under curve from time 0 to infinity; AUC_{0-∞}, AUC from time 0 to last measurable concentration time point; C_{max}, maximal concentration; t_{1/2}, terminal half-life; T_{max}, time to C_{max}.

Fig 7. Pharmacokinetics of STM 434.



CONCLUSIONS

- Single agent STM 434 showed an acceptable safety profile in patients with advanced solid tumors and early evidence of clinical activity in granulosa ovarian cancer.
- STM 434 exhibits linear PK that support an every other week dosing.
- Increasing doses of STM 434 were associated with decreased FSH suggestive of PD target coverage.
- Increasing doses of STM 434 resulted in modulation of cancer cachexia as assessed by increased LBM and 6-MWD.
- The maximum tolerated dose has not been determined and dose escalation is ongoing to determine the recommended phase 2 dose in granulosa ovarian cancer and other solid tumors.