Abstract #3016: First-in-human dose escalation and expansion study of SYSA1801, an antibody-drug conjugate targeting Claudin 18.2 in patients with resistant/refractory solid tumors

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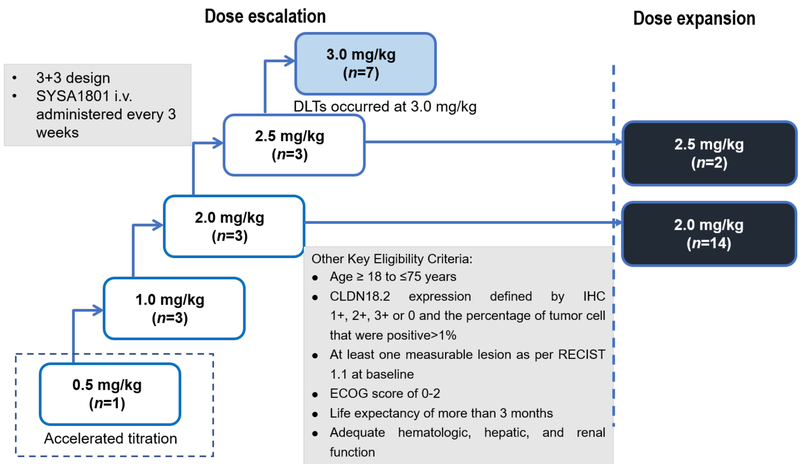
Background

- SYSA1801 is a monomethyl auristatin E (MMAE) antibody-drug conjugate (ADC) targeting claudin 18.2 (CLDN18.2), a tight junction protein broadly expressed in gastric, pancreatic, and other solid tumors.
- CLDN18.2 has a highly selective cell surface expression profile that is limited to normal gastric mucosa, making it a promising ADC therapeutic target.
- SYSA1801 has shown significant in vitro and in vivo anti-tumor activity in multiple cell lines and xenografts expressing CLDN18.2.

Methods

- In this open-label, multi-center, phase I study, patients with histologically confirmed resistant/refractory solid tumors that express CLDN18.2 who progressed on or were intolerant to standard treatment, or had no standard treatment were recruited.



Outcomes

- The primary endpoint was safety, adverse events were graded according to CTCAE 5.0.
- The secondary endpoints were pharmacokinetics profiles and efficacy as per RECIST 1.1.

Results

- Data cut-off date: November 5, 2022.
- 33 eligible patients were enrolled to receive up to SYSA1801 3.0 mg/kg.
- The demographics and baseline characteristics were summarized in Table 1.

Table 1. Demographics and baseline characteristics of enrolled patients

Characteristics	0.5 mg/kg (n=1)	1.0 mg/kg (n=3)	2.0 mg/kg (n=17)	2.5 mg/kg (n=5)	3.0 mg/kg (n=7)	Total (n=33)
Age, years						
Median (range)	48.0 (48, 48)	62.0 (47, 69)	61.0 (29, 71)	49.0 (42, 64)	47.0 (22, 67)	59.0 (22, 71)
Male, n (%)	1 (100.0)	1 (33.3)	12 (70.6)	2 (40.0)	4 (57.1)	20 (60.6)
Disease type, n (%)						
Gastric cancer	1 (100.0)	2 (66.7)	13 (76.5)	5 (100.0)	5 (71.4)	26 (78.8)
Pancreatic cancer	0 (0.0)	1 (33.3)	4 (23.5)	0 (0.0)	2 (28.6)	7 (21.2)
ECOG score						
0	0 (0.0)	0 (0.0)	5 (29.4)	0 (0.0)	0 (0.0)	5 (15.2)
1	1 (100.0)	3 (100.0)	12 (70.6)	5 (100.0)	7 (100.0)	28 (84.8)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of prior lines, n (%)						
1-2 line	1 (100.0)	3 (100.0)	12 (70.6)	3 (60.0)	3 (42.9)	22 (66.7)
≥ 3 lines	0 (0.0)	0 (0.0)	5 (29.4)	2 (40.0)	4 (57.1)	11 (33.3)
Metastasis						
Yes	1 (100.0)	3 (100.0)	17 (100.0)	5 (100.0)	7 (100.0)	33 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Numbers of metastatic organs, n (%)						
≤2	0 (0.0)	3 (100.0)	13 (76.5)	3 (60.0)	5 (71.4)	24 (72.7)
≥3	1 (100.0)	0 (0.0)	4 (23.5)	2 (40.0)	2 (28.6)	9 (27.3)

Safety

- Two DLTs (grade-3 nausea and vomiting) occurred at the 3.0 mg/kg dose.
- Treatment-related adverse events (TRAEs) of any grade occurred in 25 patients (75.8%), in which 8 (24.2%) were ≥ grade 3. No treatment related death was reported.
- The most common TRAEs were summarized in Table 2.

Table 2. Treatment-related adverse events (occurring in >20% of patients)

	0.5 mg/kg (n=1)	1.0 mg/kg (n=3)	2.0 mg/kg (n=17)	2.5 mg/kg (n=5)	3.0 mg/kg (n=7)	Total (n=33)
Nausea	0 (0.0)	1 (33.3)	7 (41.2)	0 (0.0)	6 (85.7)	14 (42.4)
≥ grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)	3 (9.1)
Vomiting	0 (0.0)	2 (66.7)	5 (29.4)	0 (0.0)	5 (71.4)	12 (36.4)
≥ grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	2 (6.1)
Dry eye syndrome	1 (100.0)	2 (66.7)	3 (17.6)	0 (0.0)	1 (14.3)	7 (21.2)
≥ grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	0 (0.0)	2 (66.7)	3 (17.6)	0 (0.0)	2 (28.6)	7 (21.2)
≥ grade 3	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (3.0)

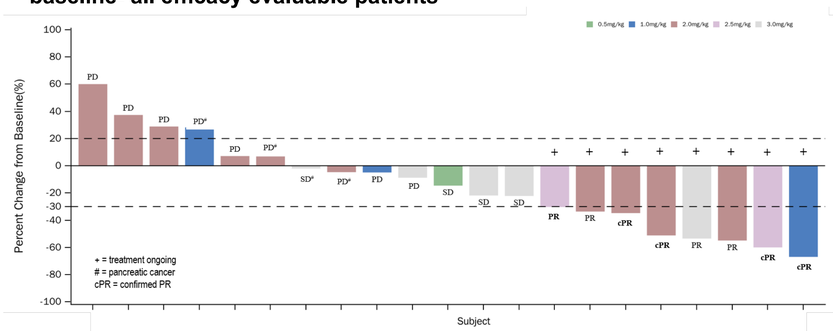
Efficacy

- 21 patients were evaluable for response, while 12 patients did not have their first tumor assessment due to adverse events (n=4), not reached assessment date (n=4), unknown death (n=2; not related to study drug) and withdrawal (n=2).
- Efficacy outcomes were summarized in Table 3 and Figure 1.

Table 3. Tumor response by dose levels

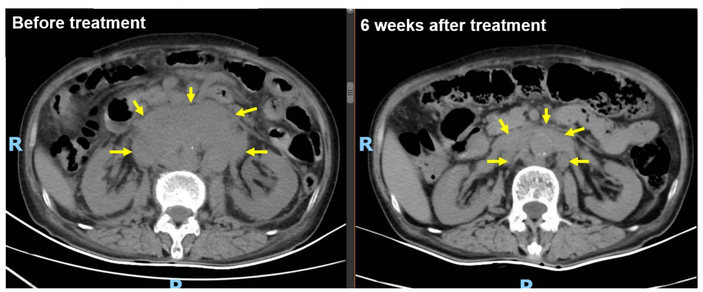
	0.5 mg/kg (n=1)	1.0 mg/kg (n=3)	2.0 mg/kg (n=10)	2.5 mg/kg (n=2)	3.0 mg/kg (n=5)	Total (n=21)
ORR, n (%)	0 (0.0)	1 (33.3)	4 (40.0)	2 (100.0)	1 (20.0)	8 (38.1)
95%CI	0.0, 97.5	0.8, 90.6	12.2, 73.8	15.8, 100.0	0.5, 71.6	18.1, 61.6
DCR, n (%)	1 (100.0)	1 (33.3)	4 (40.0)	2 (100.0)	4 (80.0)	12 (57.1)
95%CI	2.5, 100.0	0.8, 90.6	12.2, 73.8	15.8, 100.0	28.4, 99.5	34.0, 78.2

Figure 1. Waterfall plot of best percentage change of target lesions from baseline- all efficacy evaluable patients



- Among 17 evaluable patients with gastric cancer, ORR and DCR were 47.1% (95% CI: 23.0-72.2%, 8 PRs) and 64.7% (95% CI: 38.3-85.8%, 3 SDs).
- One patient with gastric cancer receiving SYSA1801 at 1.0 mg/kg IV Q3W tolerated treatment for 44 weeks with durable confirmed partial response ongoing at the time of analysis.
- Another patient with gastric cancer who failed previous anti-CLDN18.2 treatment achieved partial response on SYSA1801 2.0 mg/kg IV Q3W

Figure 2. Activity of SYSA1801 in gastric cancer



- 64y, female
- CLDN 18.2 IHC 3+35%, 2+15%, 1+10%
- Previously treated with 3 lines of therapy
- Received SYSA1801 at 2.0 mg/kg

Conclusion

- SYSA1801 exhibited promising early signs of efficacy with a well-tolerated safety profiles in patients with CLDN18.2-expressing resistant/refractory solid tumors, especially gastric cancer.
- Dose expansion study is ongoing with cohort expansion study to start when the optimized dose is determined in China; studies outside of Greater China including in the United States are being planned by Elevation Oncology.

Acknowledgment

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