Phase I study of A166 in patients with HER2-expressing locally advanced or metastatic solid tumors

Xi-Chun Hu[1], Jian Zhang[1], Rujiao Liu[1], Shuiping Gao[1], Yan Qing[2], Shuli Yi[2], Juanjuan Yuan[2], Hong Chen[2], Bin Fan[2], Haochuan Zheng[2], Jingyi Wang[2]
1 Fudan University Shanghai Cancer Center, Shanghai, China; 2 Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China

Background:

- A166 is an antibody-drug conjugate composed of a novel cytotoxic drug (Duo-5, anti-microtubule agent) site-specifically conjugated to an anti-HER2 antibody (transtuzumab) via a stable protease-cleavable valine citrulline linker.
- This is a phase I study of A166 in Chinese patients (pts) with locally advanced or metastatic solid tumors (CTR20181301).

Methods:

- A single arm, open-label, dose-escalation and dose-expansion phase I study evaluating A166 in patients with HER2-expressing locally advanced or metastatic solid tumors.
- The objectives were to determine the safety and tolerability, pharmacokinetics and antitumor activity of A166.

Figure 1. Phase 1 Study Design

Part 1 dose escalation

Enrolled 25 patients with HER2-expressing solid tumors
A166 dose cohorts: 0.1 mg/kg, n=1; 0.3 mg/kg, n=3; 0.6 mg/kg, n=3; 1.2 mg/kg, n=3; 2.4 mg/kg, n=3; 3.6 mg/kg, n=3; 4.8 mg/kg, n=6; 6.0 mg/kg, n=3;
4.8 and 6.0 mg/kg were the recommended part 2 doses

↓

Part 2 dose expansion

N=32, HER2-positive breast cancer
4.8 and 6.0 mg/kg
Primary End Point: ORR
Secondary End Points: Safety, DOR, PFS, OS, PK

Table 1. Characteristics of enrolled pts

Characteristic	Overall (N = 57)
Median age, years (range)	53 (26, 74)
Median Weight, kilogram (rang)	59(38.9, 80.2)
Female	50 (87.7%)
ECOG performance status	
1	57 (100%)
Cancer types	
Breast	50 (87.7%)
Gastric or gastrooesophageal junction	2 (3.5%)
Colon/rectal	5 (8.8%)
HER2	
Positive (3+ or 2+/ISH+)	51 (89.5%)
Low (1+ or 2+/ISH-)	6 (10.5%)
Median lines of prior therapy (Range)	
≥5	35 (61.4%)

Results:

1. Safety

- No DLTs were observed in all dose groups.
- 96.5% (55/57) pts experienced TRAEs, 31.6% (18/57) pts experienced grade 3 or higher TRAEs.
- Common TRAEs were corneal epitheliopathy (73.7%), vision blurred (59.6%), peripheral sensory neuropathy (26.3%), dry eye (21.1%), anemia (19.3%), hyponatremia (19.3%).

Conclusion:

- A166 had a manageable safety profile and high stability in the circulation with much lower acute hematological and gastrointestinal toxicities.
- A166 possessed promising antitumor activity with clinically meaningful responses in heavily pretreated subjects with HER2-positive breast cancer.

- 4 pts had SAEs, 2 of which were possibly related to A166.
- TRAEs led to 5.3% (3/57) dose reduction and 5.3% (3/57) treatment discontinuation.

2. PK characteristic

- The exposure of ADC in serum were dose dependent.
- Mean half-life 1.17-11.04 days.
- Serum free payload(Duo-5) was about 0.1% and 0.2% of total A166 (ADC) on a molar basis with the Cycle 1 C_{max} and AUC.

Figure 2. ADC Concentrations versus Time (Semi-logarithmic Scale) (Cycle 1~5), Q3W

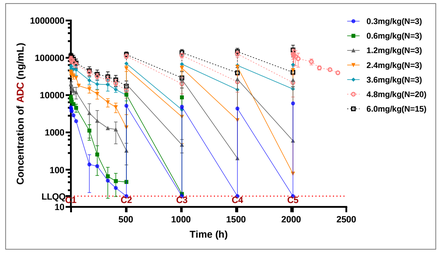
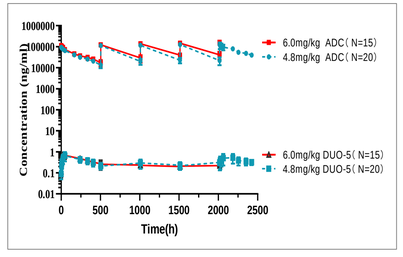


Figure 3. Concentrations versus Time (Semi-logarithmic Scale) (Cycle 1~5), Q3W



3. The safety advantage of A166

- Interstitial lung disease or pneumonitis, not reported in any dose groups.
- Lower incidence rate and grade in acute hematological and gastrointestinal toxicities .

Table 2. Comparison of toxicity between A166 and other ADC drugs in breast cancer

TRAEs		T-DM1 (3.6 d1, Q3W)	DS-8201 (5.4 d1, Q3W)	IMMU-132 (10 d1 d8, 21d/cycle)	A166 (4.8、6.0 d1, Q3W)	P value*
No pts		490	184	108	41	-
Plalet decrease	total	150(30.6)	39(21.2)	<10%	2(4.9)	<0.001
	Grade ≥ 3	70(14.3)	8(4.3)	3(2.8)	0	<0.001
Neutropenia	total	37(7.6)	64(34.8)	69 (63.9)	2(4.9)	<0.001
	Grade ≥ 3	11(2.2)	38(20.7)	45 (41.7)	0	<0.001
Leucopenia	total	<1%	39(21.2)	23 (21.3)	1(2.4)	<0.001
	Grade ≥ 3	<1%	12(6.5)	12 (11.1)	0	<0.001
Anemia	total	68(13.9)	55(29.9)	54 (50.0)	8(19.5)	<0.001
	Grade ≥ 3	19(3.9)	16(8.7)	12 (11.1)	1(2.4)	0.007
Nausea	total	202(41.2)	143(77.7)	72(67.0)	6(14.6)	<0.001
	Grade ≥ 3	4(0.8)	14(7.6)	7(6.0)	0	<0.001
Vomiting	total	102(20.8)	84(45.7)	53(49.0)	4(9.8)	<0.001
	Grade ≥ 3	5(1.0)	8(4.3)	7(6.0)	0	0.002
Diarrhea	total	124(25.3)	54(29.3)	67 (62.0)	3(7.3)	<0.001
	Grade ≥ 3	9(1.8)	5(2.7)	9 (8.0)	0	0.007
Lung toxicity	total	0	25(13.6)	0	0	<0.001
	Grade ≥ 3	0	5(2.7)	0	0	0.004

*$p < 0.05$ statistically significant

4. Effects

- A166: 59.1%, 71.4% best ORR and 86.4%, 85.7% best DCR in 4.8 and 6.0 mg/kg cohort.
- A166 showed rapid, deep response in the two cohorts, and one patient has been in the group more than 19 months.

Figure 4. Waterfall plot

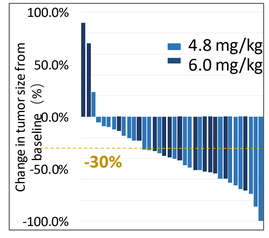


Figure 5. Spider plot

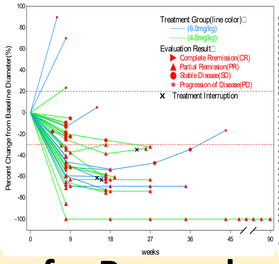
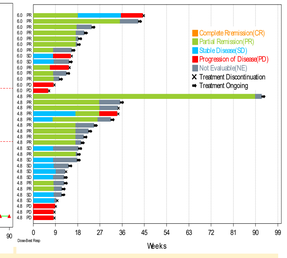


Figure 6. Swimmer plot



Future Directions for Research:

- A pivotal phase II study of A166 in heavily pretreated subjects with HER2-positive breast cancer is under planning.
- A series of exploratory studies of A166 in other cancer types are in progress.