#3021 First-in-human, Phase I Study of AK109, an Anti-VEGFR2 Antibody in Patients with Advanced or Metastatic Solid Tumors

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Background

- Multiple clinical and pre-clinical data of anti-VEGFR2 antibodies demonstrated their anti-tumor effect [1-3].
- AK109 is a fully-humanized monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2) to inhibit angiogenesis, edothelial cell migration and proliferation of tumor cells.

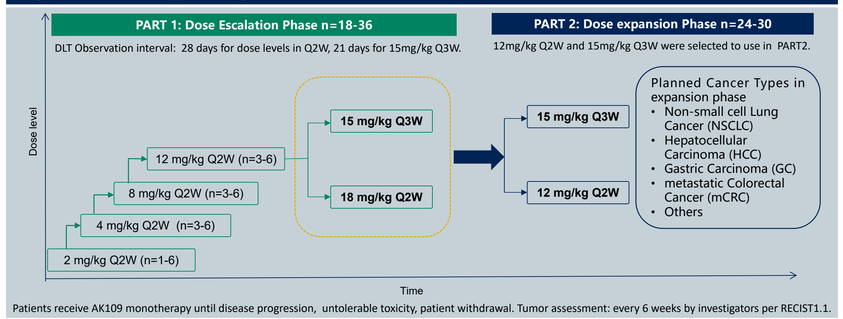
Objective

- Primary objective: To assess safety/tolerability and to determine MTD and RP2D.
- Secondary objective: PK, PD, immunogenicity and antitumor activities.

Methods

- This is a phase I, first-in-human, multi-center, dose escalation (PART 1) and expansion (PART 2) study of AK109 (Fig 1).
- Patients with advanced solid tumor that is refractory/ relapsed/intolerant to standard therapies were enrolled.
- "3+3 design" after initial dose 2mg/kg q2w was used to explore 6 dose levels of AK109 in eligible patients in PART 1, 2 dose levels(1 level for q2w and 1 level for q3w) were selected in PART 2 to expand in eligible patient with certain cancer types.

Figure 1. Study design



Patients receive AK109 monotherapy until disease progression, untolerable toxicity, patient withdrawal. Tumor assessment: every 6 weeks by investigators per RECIST1.1.

Results

- 40 Chinese patients (Table 1) were enrolled. No DLT were observed, 12 mg/kg Q2W and 15 mg/kg q3w were selected to expand in PART 2.
- Data cut-off date was December 30th, 2021, with a median follow-up of 6.0 months.
- Details of safety was shown in Table 2, the most common TRAEs were proteinuria (22/40, 55%), hypertension (13/40, 32.5%) and AST increased (11/40, 27.5%).
- Preliminary PK analyses showed systemic exposure in C_{max} and AUC_{last} increased proportionally at doses of 8 mg/kg and above, with a mean half-life of 8.5 to 10 days.
- ORR was 10.0% (4/40), DCR was 62.5% (25/40). Tumor regression were observed in 47.5% (19/40) patients (Fig 2).
- Mean cycles of AK109 administration was 6.9. 8 patients had received over 10 cycles, and 7 patients were still on study treatment.
- Median PFS of FAS population, NSCLC and GC were 4.2 months (95%CI: 2.0, 5.6), 5.6 months (95%CI: 1.3, NE) and 5.5 months (95%CI:1.4, NE), respectively (Fig 3).

Conclusions: AK109 is tolerable and has promising anti-tumor activity. Phase II studies of AK109 combined with PD-1/CTLA-4 bispecific antibodies are ongoing (NCT05142423, NCT04982776).

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There were no conflict of interests.

Table 1. Patient characteristics

	Total (N = 40)	2 mg/kg Q2W (N = 1)	4 mg/kg Q2W (N = 3)	8 mg/kg Q2W (N = 3)	12 mg/kg Q2W (N = 10)	18 mg/kg Q2W (N = 3)	15 mg/kg Q3W (N = 20)
Age(Median)	59.5	57.0	58.0	70.0	59.5	62.0	59.5
Sex							
Male	29 (72.5%)	1 (100%)	3 (100%)	1 (33.3%)	7 (70.0%)	2 (66.7%)	15 (75.0%)
Female	11 (27.5%)	0	0	2 (66.7%)	3 (30.0%)	1 (33.3%)	5 (25.0%)
Cancer Type							
GC	9 (22.5%)	0	1 (33.3%)	1 (33.3%)	1 (10.0%)	0	6 (30.0%)
NSCLC	8 (20.0%)	0	1 (33.3%)	0	3 (30.0%)	2 (66.7%)	2 (10.0%)
HCC	8 (20.0%)	0	0	0	3 (30.0%)	0	5 (25.0%)
CRC	5 (12.5%)	1 (100%)	0	0	2 (20.0%)	0	2 (10.0%)
Others*	10(25.0%)	0	1 (2.5%)	2 (5.0%)	1 (2.5%)	1(2.5%)	5 (12.5%)
Staging							
III	3 (7.5%)	0	0	0	0	0	3 (15.0%)
IV	37 (92.5%)	1 (100%)	3 (100%)	3 (100%)	10 (100%)	3 (100%)	17 (85.0%)
ECOG PS							
0	10 (25.0%)	1 (100%)	0	1 (33.3%)	4 (40.0%)	2 (66.7%)	2 (10.0%)
1	30 (75.0%)	0	3 (100%)	2 (66.7%)	6 (60.0%)	1 (33.3%)	18 (90.0%)

*Other tumor type included pancreatic carcinoma (n=2), oesophagus carcinoma (n=1), endometrial cancer (n=1), small cell lung cancer (n=1), urothelium carcinoma (n=1), thyroid cancer (n=1), Gastroesophageal junction tumor (n=1), cholangiocarcinoma (n=1).

Table 2. Safety

AEs	Total (n=40)	2mg/kg Q2W(N=1)	4mg/kg Q2W(N=3)	8mg/kg Q2W(N=3)	12 mg/kg Q2W(N=10)	18 mg/kg Q2W(N=3)	15 mg/kg Q3W(N=20)
TEAEs	39 (97.5%)	1 (100%)	3 (100%)	3 (100%)	9 (90%)	3 (100%)	20 (100%)
TRAEs	38 (95%)	1 (100%)	3 (100%)	2 (66.7%)	9 (90%)	3 (100%)	20 (100%)
≥G3 TRAEs	10 (25%)	0	1 (33.3%)	1 (33.3%)	4 (40%)	1 (33.3%)	3 (15%)
TRSAEs	2(5%)	0	0	0	0	0	2 (10%)
≥G3 TRSAEs	0	0	0	0	0	0	0
TRAEs leading to discontinuation	2(5%)	0	0	0	1 (10%)	0	1 (5%)

Figure 2. Tumor Respnse - Waterfall Plot

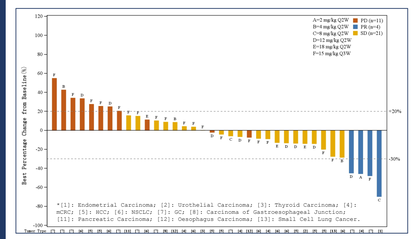
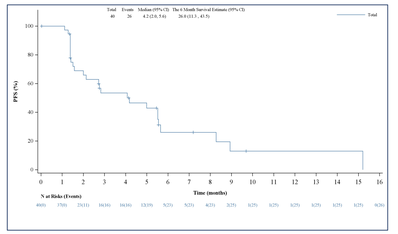


Figure 3. mPFS of FAS population



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