A phase Ib/II study of AK112, a PD-1/VEGF bispecific antibody, as first or second-line therapy for advanced non-small cell lung cancer (NSCLC)

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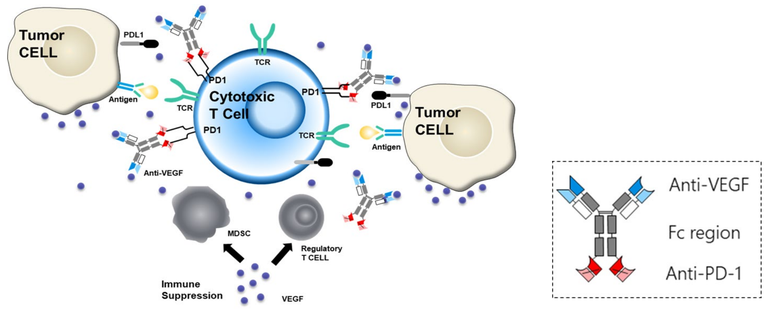
BACKGROUND

- AK112 is a humanized IgG1 bispecific antibody targeting PD-1 and VEGF (Figure 1).
- Besides the well-known antiangiogenic effects, anti-VEGF agents also modulate the tumor immune micro-environment. The efficacy of PD-1 inhibitors may be enhanced by anti-VEGF agents.
- Pembrolizumab monotherapy has been approved by FDA as a first-line treatment for PD-L1 positive advanced NSCLC[1, 2]. Its ORRs ranged from 27% to 45%, depending on PD-L1 expression and other factors.
- Given the efficacy and manageable safety presented by both PD-1 and VEGF inhibitors, along with their synergistic effects, it is postulated that the dual-blockade of PD-1 and VEGF by bispecific antibody will further provide anti-tumor effects for advanced NSCLC.
- Here, we present preliminary safety and efficacy data in advanced NSCLC from a phase Ib/II study of AK112.

Figure 1. Schematic diagram of the mechanism of activity of AK112



METHODS

- This multi-center, Phase Ib/II, open label study enrolling pts with IIIB/C or IV NSCLC (NCT04900363) is summarized in Figure 2.
- The study consists of a dose-selection part (Phase Ib) and a randomized controlled part (Phase II). Here, we only introduce the dose-selection part.

Figure 2. Study design (Ib)

Key eligibility criteria

- 18-75 years old
- ECOG PS 0 or 1
- Life expectancy ≥ 3 months
- Histologically/cytologically-confirmed diagnosis of advanced NSCLC (stage IIIB/C that were unsuitable for radical therapy or IV)
- Treatment-naïve or with disease progression after platinum-containing chemotherapy
- No sensitizing EGFR mutations or ALK translocation
- At least one measurable lesion as defined by RECIST v1.1
- Adequate organ function

AK112 IV
10 mg/kg Q3W,
20 mg/kg Q2W,
20 mg/kg Q3W,
or 30 mg/kg Q3W

End of treatment
whichever occurs first:
- Disease progression as determined by the investigator according to RECIST v1.1
- Intolerable toxicity
- A maximum of 24 months

Primary endpoints
- Safety (graded according to NCI-CTCAE v5.0)
- ORR (investigator assessed) per RECIST v1.1

Secondary endpoints
- DoR, DCR, TTR and PFS per RECIST v1.1, and OS
- Pharmacokinetics
- ADA assessment
- Correlation between PD-L1 level and efficacy

RESULTS

Baseline Characteristics

- As of 4 March, 2022, 96 pts were enrolled, in which 66 (68.8%) were PD-L1 positive (TPS ≥1%) and 81 (84.4%) were treatment-naïve. Baseline characteristics are shown in Table 1.

Table 1. Baseline Characteristics

Characteristics	Total (N=96)	10 mg/kg Q3W (N=30)	20 mg/kg Q2W (N=29)	20 mg/kg Q3W (N=29)	30 mg/kg Q3W (N=8)
Age, years					
Median (range)	65.5 (48-75)	64.0 (48-74)	68.0 (51-74)	65.0 (53-75)	63.5 (51-70)
Sex, n (%)					
Male	82 (85.4)	23 (76.7)	26 (89.7)	25 (86.2)	8 (100.0)
ECOG PS, %					
0/1	9.4/90.6	10.0/90.0	13.8/86.2	3.4/96.6	2.5/87.5
Histology, %					
Non-squamous/ Squamous	50.0/ 50.0	53.3/ 46.7	48.3/ 51.7	48.3/ 51.7	50.0/ 50.0
PD-L1 expression, n (%)					
TPS ≥1	66 (68.8)	21 (70.0)	22 (75.9)	19 (65.5)	4 (50.0)
Treatment condition, n (%)					
Treatment-naïve	81 (84.4)	26 (86.7)	25 (86.2)	22 (75.9)	8 (100.0)

Safety

- Grade 3/4 and most frequent TRAEs are presented in Table 2.
- All grade TRAEs occurred in 85 (88.5%) of pts.
- No TRAE led to permanent treatment discontinuation.
- No significant difference in the incidences of TRAEs were observed between non-squamous and squamous pts.

Table 2. Safety Summary

Categories, n (%)	AK112 (N=96)
Grade 3/4 TRAEs	13 (13.5)
Pneumonia	3 (3.1)
Hypertension	1 (1.0)
Proteinuria	1 (1.0)
Diarrhoea	1 (1.0)
Pyrexia	1 (1.0)
Urticaria chronic	1 (1.0)
Rhabdomyolysis	1 (1.0)
Hepatic failure	1 (1.0)
Lacunar infarction	1 (1.0)
Cognitive disorder	1 (1.0)
Tracheo-oesophageal fistula	1 (1.0)
Most frequent TRAEs (incidence ≥10%)	
Proteinuria	19 (19.8)
Hypertension	15 (15.6)
Blood urea increased	15 (15.6)
Blood cholesterol increased	14 (14.6)
Hyperglycaemia	14 (14.6)
Lipase increased	13 (13.5)
Apolipoprotein E increased	13 (13.5)
Alanine aminotransferase increased	12 (12.5)
C-reactive protein increased	11 (11.5)
Aspartate aminotransferase increased	11 (11.5)
Amylase increased	10 (10.4)

Efficacy

- 90 pts had at least one post-baseline tumor evaluation, of which one was evaluated as NE. ORR (unconfirmed, similarly hereinafter)/DCR each were 21.4%/92.9% at dose of 10 mg/kg Q3W, 50.0%/92.3% at dose of 20 mg/kg Q2W, 37.9%/89.7% at dose of 20 mg/kg Q3W, and 50.0%/83.3% at dose of 30 mg/kg Q3W.
- Of 54 treatment-naïve pts with PD-L1 positive, ORR was 50.0% and DCR was 96.3% (Figure 3 and Figure 4). ORR/DCR were 31.6%/94.7% at dose of 10 mg/kg Q3W, 62.5%/100.0% at dose of 20 mg/kg Q2W, 53.3%/93.3% at dose of 20 mg/kg Q3W, and 75.0%/100.0% at dose of 30 mg/kg Q3W, respectively.
- Of 50 treatment-naïve pts receiving AK112 > 10mg/kg Q3W, ORR was 46.0% and DCR was 88.0% (Table 3). Pts with TPS 1-49% had an ORR and DCR of 50.0% and 95.5%, while pts with TPS ≥50% had a significantly higher ORR (76.9%) and DCR (100.0%). Pts with TPS <1% also showed an ORR of 13.3% and a DCR of 66.7%.

Figure 3.
Best percentage change in tumor size from baseline
Treatment-naïve pts with PD-L1 positive (N=54)

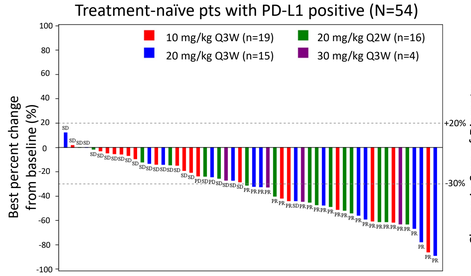


Figure 4.
Spider Plot of Percentage Change from Baseline
Treatment-naïve pts with PD-L1 positive (N=54)

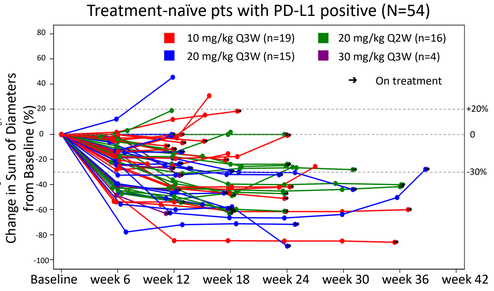


Table 3. Response rate of treatment-naïve pts (AK112 > 10mg/kg Q3W)

PD-L1 TPS	≥ 1% (N=35)	1-49% (N=22)	≥ 50% (N=13)	< 1% (N=15)	Total (N=50)
ORR, %	60.0	50.0	76.9	13.3	46.0
DCR, %	97.1	95.5	100.0	66.7	88.0
CR, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR, n (%)	21 (60.0)	11 (50.0)	10 (76.9)	2 (13.3)	23 (46.0)
SD, n (%)	13 (37.1)	10 (45.5)	3 (23.1)	8 (53.3)	21 (42.0)
PD, n (%)	1 (2.9)	1 (4.5)	0 (0.0)	5 (33.3)	6 (12.0)
NE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CONCLUSIONS

- **AK112 was well-tolerated and presented remarkable anti-tumor efficacy in advanced NSCLC at doses of 20 mg/kg Q2W, 20 mg/kg Q3W, and 30mg/kg Q3W, achieving 60.0% ORR in treatment-naïve pts with PD-L1 positive, which is two times higher than the historical research data of SOC.**
- **Further phase III studies are planned to validate the findings of this study.**

References

1. Martin Reck, et al. N Engl J Med. 2016 Nov 10. 2. Tony S K Mok, et al. Lancet. 2019 May 4.

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