#9019

A phase II study of AK112 (PD-1/VEGF Bispecific) in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC)

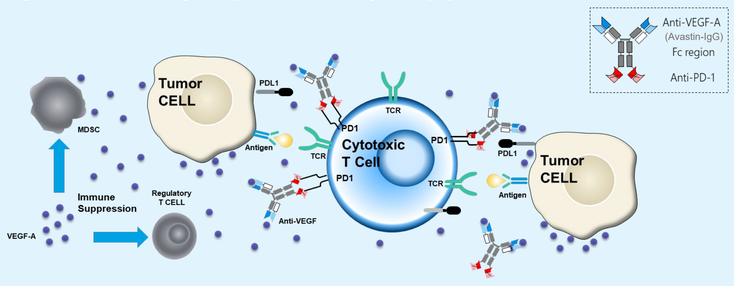
Yuanyuan Zhao[1], Wenfeng Fang[1], Yunpeng Yang[1], Jianhua Chen[2], Li Zhuang[3], Yingying Du[4], Qitao Yu[5], Wu Zhuang[6], Yanqiu Zhao[7], Ming Zhou[8], Weidong Zhang[9], Yu Zhang[10], Yixin Wan[11], Ziping Wang[12], Lin Wang[13], Yu Xia[14], Baiyong Li[14], Zhongmin Maxwell Wang[14] , Weifeng Song[14], Li Zhang[1]

[1]Sun Yat-Sen University Cancer Center, Zhongshan, P. R. China; [2]Hunan Cancer Hospital, Changsha, P. R. China; [3]Yunnan Cancer Hospital, Kunming, P. R. China; [4]The First Affiliated Hospital of Anhui Medical University, Hefei, P. R. China; [5]Cancer Hospital of Guangxi Medical University, Nanning, P. R. China; [6]Fujian Provincial Cancer Hospital, Fuzhou, P. R. China; [7]Henan Cancer Hospital, Zhengzhou, P. R. China; [8]Affillated Cancer Hospital and institute of Guangzhou Medical University, Guangzhou, P. R. China; [9]Hunan Provincial People's Hospital, Changsha, P. R. China; [10]Guizhou Provincial People's Hospital, Guiyang, P. R. China; [11]Lanzhou University Second Hospital, Lanzhou, P. R. China; [12]Beijing Cancer Hospital, Beijing, P. R. China; [13]Hainan Provincial People's Hospital, Haikou, P. R. China; [14]Akeso, Inc., Zhongshan, P. R. China

Background

- AK112 is a humanized IgG1 bispecific antibody targeting PD-1 and VEGF (***Figure 1***).
- An early study showed AK112 with tolerable safety and promising anti-tumor efficacy in patients (pts) with advanced NSCLC (***Refer to ASCO 2022 poster #9040***). According to this study, AK112 20mg/kg Q3W was chosen as a recommended phase II dose (RP2D).
- Therefore, AK112 plus chemotherapy, is expected to further improve anti-tumor efficacy with favorable safety in 1L NSCLC (compared to anti-PD-(L)1 and chemotherapy combination therapies), EGFR+ advanced NSCLC, and IO-R NSCLC.
- Here, we present the recent results from a phase II study of AK112 plus chemotherapy in pts with advanced NSCLC.

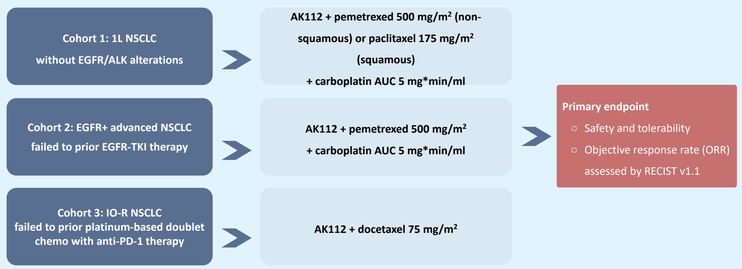
Figure 1. Schematic diagram of the mechanism of activity of AK112



Methods

- This was an open-label, multi-center phase II study evaluating the safety and efficacy of AK112 in combination with chemotherapy in pts with advanced NSCLC (NCT04736823).
- Enrolled pts were divided into 3 cohorts and treated with 10 or 20mg/kg AK112 plus chemotherapy once every 3 weeks (***Figure 2***).

Figure 2. Study design



Results

Patients

- 83 pts were enrolled from Feb 03, 2021 to Mar 20, 2022 to cohorts 1-3 and received at least one dose of AK112 plus chemotherapy. Baseline characteristics are shown in ***Table 1***.
- Of 25 pts with squamous NSCLC, 52.0% were central type of squamous cell carcinoma and 28.0% had a history of hemoptysis.
- As of Mar 20, 2022, median duration of follow-up (95% CI) was 9.2 months (range: 7.7 - 9.7) for Cohort 1, 7.0 months (range: 5.6 - 7.1) for Cohort 2, and 5.9 months (range: 4.4 - 6.9) for Cohort 3.

Results (continued)

Table 1. Baseline Characteristics

Characteristics	Cohort 1 (N = 44)	Cohort 2 (N = 19)	Cohort 3 (N = 20)	Overall (N = 83)
Age, median (range), years	57.6 (44.3, 73.0)	60.2 (34.7 - 64.9)	60.0 (31.6 - 73.4)	58.03 (31.6 - 73.4)
Male, n(%)	28 (63.6)	6 (31.6)	16 (80.0)	50 (60.2)
ECOG performance status, n(%)				
1	42 (95.5)	14 (73.7)	19 (95.0)	75 (90.4)
Smoking status, n(%)				
Former or Current	24 (54.5)	4 (21.1)	15 (75.0)	43 (51.8)
Never	20 (45.5)	15 (78.9)	5 (25.0)	40 (48.2)
PD-L1 TPS, n(%)				
<1%	20 (45.5)	10 (52.6)	6 (30.0)	36 (43.4)
1-49%	16 (36.4)	6 (31.6)	8 (40.0)	30 (36.1)
≥50%	6 (13.6)	3 (15.8)	4 (20.0)	13 (15.7)
NE	2 (4.5)	0 (0.0)	2 (10.0)	4 (4.8)
Clinical Stage at Study Entry, n(%)				
IIIB/IIIC	4 (9.1)	0 (0.0)	3 (15.0)	7 (8.4)
IV	40 (90.9)	19 (100.0)	17 (85.0)	76 (91.6)
Histology, n(%)				
Squamous	18 (40.9)	0 (0.0)	7 (35.0)	25 (30.1)
Non-squamous	26 (59.1)	19 (100.0)	13 (65.0)	58 (69.9)
Brain metastasis, n(%)	8 (18.2)	7 (36.8)	1 (5.0)	16 (19.3)

Safety

- Treatment related adverse events (TRAEs) are summarized in ***Table 2***.
- TRAEs leading to permanent discontinuation of AK112 occurred in 3.6% (3 pts).
- Most common TRAEs (≥10% of patients) included alanine/aspartate aminotransferase increased, anemia, amylase increased, white blood cell count decreased, neutrophil count decreased, epistaxis, and platelet count decreased.
- There was no significant difference in the incidences of TRAEs between the squamous and the non-squamous group.

Table 2. Overview of TRAE[a]

Categories, n(%)	Overall (N = 83)	Squamous (N = 25)	Non-squamous (N = 58)
Any TRAE	71 (85.5)	20 (80.0)	51 (87.9)
Grade[b] 3-5 TRAE	20 (24.1)	8 (32.0)	12 (20.7)
Treatment Related SAE	15 (18.1)	7 (28.0)	8 (13.8)
TRAE leading to AK112 discontinuation	3 (3.6)	0 (0.0)	3 (5.2)
TRAE leading to death	1 (1.2)	0 (0.0)	1 (1.7)
Most common TRAEs (≥10% of patients)			
Alanine aminotransferase increased	17 (20.5)	5 (20.0)	12 (20.7)
Aspartate aminotransferase increased	15 (18.1)	3 (12.0)	12 (20.7)
Anemia	13 (15.7)	2 (8.0)	11 (19.0)
Amylase increased	12 (14.5)	2 (8.0)	10 (17.2)
White blood cell count decreased	12 (14.5)	4 (16.0)	8 (13.8)
Neutrophil count decreased	10 (12.0)	4 (16.0)	6 (10.3)
Epistaxis	10 (12.0)	4 (16.0)	6 (10.3)
Platelet count decreased	9 (10.8)	3 (12.0)	6 (10.3)
Haemorrhage related AESI			
Epistaxis	10 (12.0)	4 (16.0)	6 (10.3)
Hemoptysis	5 (6.0)	4 (16.0)	1 (1.7)
Haematuria	1 (1.2)	1 (4.0)	0 (0.0)
Haematochezia	1 (1.2)	1 (4.0)	0 (0.0)
Gingival bleeding	1 (1.2)	0 (0.0)	1 (1.7)
Anal haemorrhage	1 (1.2)	0 (0.0)	1 (1.7)
Conjunctival haemorrhage	1 (1.2)	0 (0.0)	1 (1.7)

[a] Treatment related indicates AK112 or AK112+chemo related; [b] Maximum reported CTCAE grade;
SAE, serious adverse event; AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse events.

- Haemorrhage related AESI included epistaxis, hemoptysis, haematuria, haematochezia, gingival bleeding, anal haemorrhage and conjunctival haemorrhage.
- Risk of haemorrhage correlated to anti-VEGF antibody declined significantly, even in pts with squamous NSCLC.

Efficacy

- In Cohort 1, of 43 evaluable pts, ORR and DCR were 77.8% (including 3 unconfirmed PR) and 100.0% for squamous NSCLC, 52.0% (including 1 unconfirmed PR) and 100.0% for non-squamous NSCLC, respectively (***Table 3, Figure 3-A and B***).
- In Cohort 2, of 19 evaluable pts, ORR and DCR were 68.4% and 94.7% (***Table 3, Figure 3-C***).
- In Cohort 3, of 20 evaluable pts, ORR and DCR were 40.0% and 80.0% (***Table 3, Figure 3-D***).

Table 3. Summary of Efficacy Outcomes

Response	Cohort 1		Cohort 2	Cohort 3
	Squamous (N = 18)	Non-squamous (N = 25)	(N = 19)	(N = 20)
ORR, % (95% CI)	77.8 (52.4 - 93.6)	52.0 (31.3 - 72.2)	68.4 (43.4 - 87.4)	40.0 (19.1 - 63.9)
DCR, % (95% CI)	100.0 (81.5 - 100.0)	100.0 (86.3 - 100.0)	94.7 (74.0 - 99.9)	80.0 (56.3 - 94.3)

Figure 3. Waterfall plots and Spider plots

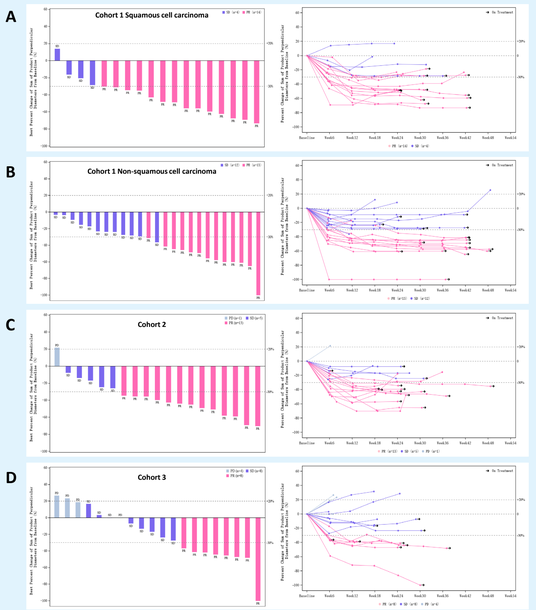
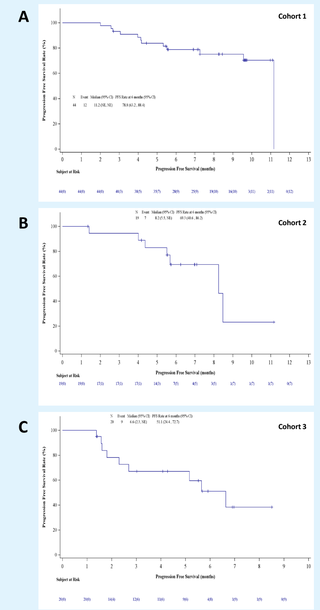


Figure 4. Kaplan-Meier Curves of PFS



- In Cohort 1, median PFS was not reached and 6-month PFS rate was 78.8% (95% CI: 63.2, 88.4) (***Figure 4-A***).
- In Cohort 2, median PFS was 8.2 months (95% CI: 5.5, NE) and 6-month PFS rate was 69.3% (95% CI: 40.6, 86.2) (***Figure 4-B***).
- In Cohort 3, median PFS was 6.6 months (95% CI: 2.3, NE) and 6-month PFS rate was 51.1% (95% CI: 24.4, 72.7) (***Figure 4-C***).

Conclusions

- AK112 in combination with chemotherapy demonstrated favorable safety characteristics and was well-tolerated, especially in pts with squamous NSCLC.
- In every cohort, AK112 plus chemotherapy demonstrated potentially superior anti-tumor activities.
- Therefore, a phase III study of AK112 plus chemotherapy versus chemotherapy in EGFR+ advanced non-squamous NSCLC failed to prior EGFR-TKI therapy (NCT05184712) is currently underway, and other phase III studies of AK112 plus chemotherapy in advanced NSCLC will be initiated soon.

Acknowledgements

On behalf of the study team, the authors thank the patients and their families and caregivers for participating in this study, as well as all investigators, coordinators and research staff. This study was sponsored by Akeso Biopharma. Medical writing and editorial assistance were provided by Wenting Li and Pengzhong Wang.

Please contact the author at zhaoyy@sysucc.org.cn for questions or comments.