Poster ID：80P

A phase Ib/II study of second-line cadonilimab, anlotinib and docetaxel in patients with checkpoint inhibitor (CPI) -experienced advanced non-small cell lung cancer

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BACKGROUND

- Patients confirmed stage IIIB/IIIC or IV NSCLC without specific gene mutations have limited treatment options after progressing through first-line immune checkpoint inhibitor therapy and chemotherapy[1].
- Cadonilimab (AK104) is a humanized immunoglobulin G1 bispecific antibody that simultaneously targets PD-1 and CTLA4 . The addition of CTLA4 target helps to enhance anti-tumor immunity and overcome immune resistance[2-3].
- Previous clinical studies have shown that the combination therapy of Cadonilimab (AK104) has the potential to overcome immune resistance and prolong patient survival[2].
- Considering the complex tumor microenvironment after immune resistance, we used Cadonilimab in combination with small molecule anti angiogenic drug anlotinib and standard treatment docetaxel, aiming to obtain improved efficacy, longer survival benefits. Here, we present preliminary safety and efficacy data in advanced NSCLC from this phase Ib/II study.

METHODS

- This is a single-arm, multi-center, phase Ib/II, dose exploration and expansion trial (NCT05816499).
- The study is divided into two parts. Three dosage levels of anlotinib (6/8/10 mg qd 2W/3W) will be administered to patients in dose exploration phase. The recommended dose of anlotinib is determined based on the safety of patients in dose exploration phase.
  All the patients were simultaneously received cadonilimab 10mg/kg Q3W and docetaxel 60 mg/m^2 Q3W.

Endpoints and Assessments:

- **Primary Endpoints：** RP2D of Anlotinib； 6-month progression-free survival (investigator, RECISTv1.1)
- **Secondary Endpoints：** ORR, PFS, DCR, DoR (investigator, RECISTv1.1) , OS, Quality of Life, Safety and tolerability.

Key eligibility criteria：

- ≥18 years old；
- Stage IIIB/C or IV NSCLC (American Joint Committee on Cancer [AJCC]);
- Without EGFR-sensitive mutation ,ALK, ROS1 gene rearrangement or fusion
- Patients must have progressed on at most a PD-1/L1 inhibitor and a platinum-based chemotherapy (combined or sequential, regardless of sequence), and at least two cycles of PD-1/L1 inhibitor (combined or non-combined chemotherapy) with clinical benefits (PFS ≥ 3 months)
- ECOG PS 0~1
- Life expectancy > 12 weeks

N=50~56

Phase Ib (dose exploration phase)

Cadonilimab 10mg/kg, Q3W, IV
Docetaxel 60mg/m^2 D1 Q3W

- Anlotinib 6mg qd 2W/3W (n=3~6)
- Anlotinib 8mg qd 2W/3W (n=3~6)
- Anlotinib 10mg qd 2W/3W (n=3~6)

Phase II (dose expansion phase)

- Cadonilimab
- 10mg/kg, Q3W, IV
  Docetaxel
- 60mg/m^2 D1 Q3W
  Anlotinib RP2D

N=44

Figure 1. Study Design

RESULT

Baseline Characteristics

- 50 patients were enrolled. A total of 9 patients were enrolled during the dose exploration period, 42 patients were enrolled during dose expansion phase. The baseline demographics and disease characteristics are reported in Table 1.
- The squamous (sq) and non-squamous (ns) NSCLC patients were 56% and 44%, IV stage patients almost were 70%.

Table 1. Patient Baseline Characteristics

	ALL（N=50）
Age (years)	
median (range)	65 (37-79)
<65	46.0% (23/50)
≥65	54% (27/50)
Gentle, n(%)	
male	88.0% (44/50)
female	12.0% (6/50)
ECOG PS, n(%)	
0	14.0% (7/50)
1	84.0% (42/50)
3	2.0% (1/50)
Smoking Status, n(%)	
Never	38.0% (19/50)
Current	4.0% (2/50)
Former	58.0% (29/50)
Clinical Stage, n(%)	
IIIB/IIIC	30.0% (15/50)
IV	70.0% (35/50)

	ALL（N=50）
Histological Type，n(%)	
Non-squamous	44.0% (22/50)
Squamous	56.0% (28/50)
PD-L1 TPS, n(%)	
< 1%	12.0% (6/50)
1-49%	32.0% (16/50)
≥50%	14.0% (7/50)
unknown	42.0% (21/50)
Brain Metastasis, n(%)	12.0% (6/50)
Liver Metastasis, n(%)	6.0% (3/50)
Bone Metastasis，n(%)	24.0% (12/50)
PFS of previous ICI treatment	
≤6 months	36.0%(18/50)
> 6 months	60.0%(30/50)
unknown	4.0%(2/50)

Efficacy

- At the Jan 08,2026(data cut-off), the overall median follow-up was 21.45 month，the 6-month PFS rate was 55.7% (95% CI: 37.3%-70.7%), and the median PFS was 7.0 months (95% CI: 4.5-8.0) (Figure 2).
- The median PFS was 7.5 months (95%CI: 5.7-9.7) in sq-NSCLC subgroup and 4.5 months (95%CI: 2.7-9.7) in nsq-NSCLC sungroup (Figure 3).
- the median PFS was 7.4 months and 4.1 months in patients with PD-L1 TPS ≥ 1% and PD-L1 TPS < 1% (Figure 4).
- The objective response rate (ORR) was 26.2%, and the disease control rate (DCR) was 95.2%. The duration of response (DoR) was 6.0 months (Figure 5, Table 2).
- Patients with circulating tumor DNA (ctDNA) clearance achieved a median PFS of 9.1 months, and ctDNA detection rate decreased from 1.5% to 0.5% after C1 (P < 0.05) (Figure 6).

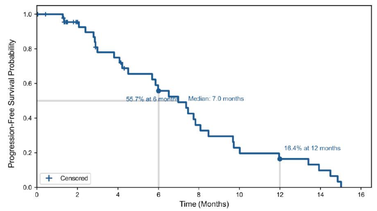

Figure 2. Kaplan-Meier Curve for Progression-Free Survival (PFS) Full Analysisd All Patients

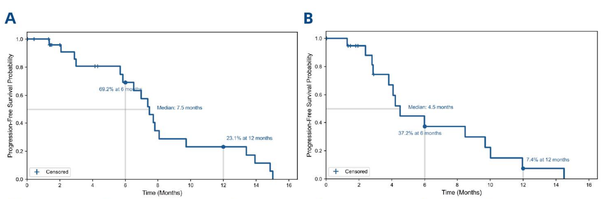

Figure 3. Kaplan-Meier Curve for Progression-Free Survival (PFS) Full Analysisd sq-NSCLC subgroup（A） and nsq-NSCLC subgroup（B）

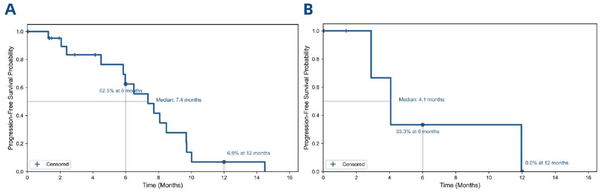

Figure 4. Kaplan-Meier Curve for Progression-Free Survival (PFS) Full Analysisd PD-L1 TPS ≥1%（A） and PD-L1 TPS <1%（B）

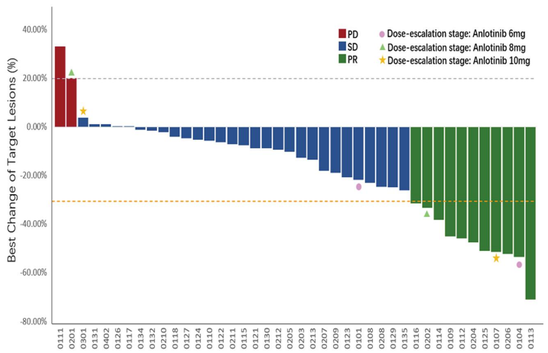

Figure 5. Waterfall plots for tumor activity

Table 2. ORR, DCR and Median DOR

	All patient (N=42)
Best overall response, n	
CR	0
PR	11
SD	29
PD	2
ORR, % (95% CI)	26.2 (13.9-42.0)
DCR , % (95% CI)	95.2 (83.8-99.4)
Median DoR ,mo (95% CI)	6.0 (2.2-12.0)

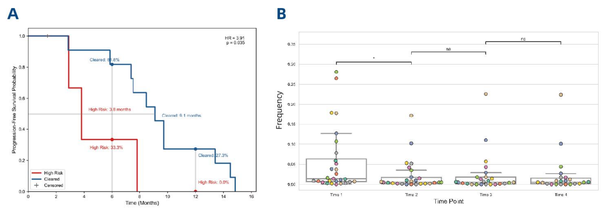

Figure 6. Baseline ctDNA Risk Status Is Associated With Progression-Free Survival（A） and ctDNA Mutation Frequency Across Treatment Time Points（B）

Safety

- No DLT occurred in any of the 3 dose groups during the dose exploration period.
- The safety of the combination of cadonilimab, anlotinib and docetaxel is tolerable and manageable, ≥3 grade TRAE was only 14.0%, cadonilimab-related TRAE leading to drug discontinuation was only occurred in 16.0% of anti-PD-1/L1 resistant patients, no drug-related death occurred.

Table 3. Safety Summary

n（%）	ALL N=50
At least one TEAE occurs	72.0% (36/50)
≥3 grade TEAE	18.0% (9/50)
TRAE	62.0% (31/50)
TRAE related to Cadonilimab	58.0% (29/50)
TRAE related to anlotinib	48.0% (24/50)
TRAE related to docetaxel	40.0% (20/50)
≥3 grade TRAE	**14.0% (7/50)**
≥3 grade TRAE related to Cadonilimab	13.0% (6/50)
≥3 grade TRAE related to anlotinib	10.9% (5/50)
≥3 grade TRAE related to docetaxel	4.3% (2/50)
SAE	**16.0% (8/50)**
TRSAE	16.0% (8/50)
TRAE leads to permanent discontinuation	20.0% (10/50)
TRAE leads to permanent discontinuation of Cadonilimab	**16.0% (8/50)**
TRAE leads to permanent discontinuation of anlotinib	6.0% (3/50)
TRAE leads to permanent discontinuation of docetaxel	2.0% (1/50)
TRAE that causes death	0

CONCLUSION

Cadonilimab in combination with anlotinib and docetaxel showed promising efficacy and well-tolerated in advanced NSCLC patients who had failed prior CPI, as a potential strategy to overcome resistant anti-PD-(L)1 therapy.

ACKOWNLEDGEMENTS

- We are grateful to the patients and their care givers, to investigators and all site staff who participated in the study.
- The presenter declares no conflicts of interest to disclose.

References: 1.Insa, A., et al.Crit Rev Oncol Hematol 2022;169;103538. 2.2021 ESMO Abstract# 1300P. 3. MAbs. 2023 Jan-Dec;15(1):2180794.