The efficacy and safety of KN046 combined with Axitinib for previously untreated and checkpoint inhibitor treated advanced non-small cell lung cancer: a single-arm, open-label, multicenter phase 2 clinical trial.

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BACKGROUND

- KN046 is a novel bispecific antibody that blocks both PD-1/PD-L1 and CTLA-4/CD80/CD86 pathways.
- Axitinib is a selective inhibitor of VEGFR, in combination with checkpoint inhibitors (CPIs) may sensitize tumors to CPIs.
- Preliminary data of KN046 combined with axitinib as 1L treatment for PD-L1 + advanced NSCLC have been reported (2023 ESMO 1449P)[1].

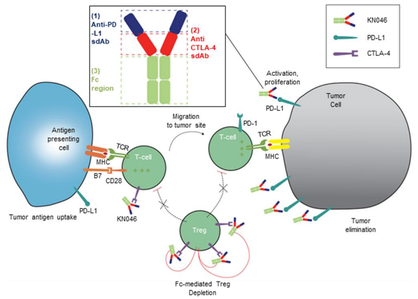
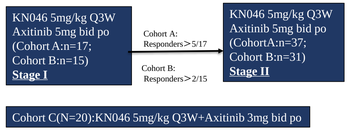


Figure 1 Structure of KN046

METHODS

- Study design is shown in Figure 2.
- Stage IIIB-IV non-small cell lung cancer (NSCLC) patients (pts) without driver mutations, will be enrolled in a phase 2 study in China, and receive KN046 (5 mg/kg, IV, Q3W) and Axitinib (5 mg or 3mg, PO, BID). The primary endpoint is ORR, the secondary endpoints include safety, DCR, DoR, PFS and OS. The study includes Cohort A (previously untreated and PD-L1 TPS ≥1%), Cohort B (progressed on CPIs) and Cohort C (previously untreated and PD-L1 TPS ≥50%). Here, we report the results of Cohort A and B.
- The study is still ongoing. The data cutoff date was Sep 1, 2024.
- This study is registered in ClinicalTrials.gov, number NCT05420220.

Key Inclusion Criteria:
- Stage IIIB-IV NSCLC
- PD-L1 TPS≥1%(Cohort A only); PD-L1 TPS≥50%(Cohort C only);
- (non-sq)No EGFR activating mutation and ALK rearrangement
- (sq)No known EGFR activating mutation and ALK rearrangement
- Baseline measurable disease
- ECOG 0-1



Primary endpoint: ORR
Secondary endpoints: DoR, DCR, CBR, TTR, PFS ,OS and Safety

Figure 2 Study Design

RESULTS

- As of Sep 1, 2024, 53 and 32 pts were treated in Cohort A and B, the median follow-up time was 14.6m and 11.2m, respectively.
- The median age was 62.0 y (min: 31, max: 73), 81.2% pts were male, 95.3% pts had ECOG PS=1, 85.9% pts had stage IV disease, 49.4% pts had squamous disease. By central lab testing, 67.1% and 24.7% pts had PD-L1 TPS ≥ 1% and ≥ 50%, respectively. Table 1.

Table 1 Baseline characteristics-safety set (SS)

	Cohort A (N=53)	Cohort B (N=32)	Total (N=85)
Age（years）, n (%)			
mean(SD)	61.9 (9.17)	59.3 (9.56)	60.9 (9.35)
median	63.0	60.5	62.0
min, max	35, 73	31, 72	31, 73
Gender			
Male	46(86.8)	23(71.9)	69(81.2)
Female	7(13.2)	9(28.1)	16(18.8)
ECOG, n (%)			
0	3(5.7)	1(3.1)	4(4.7)
1	50(94.3)	31(96.9)	81(95.3)
Pathological Type, n(%)			
Squamous	22(41.5)	20(62.5)	42(49.4)
Adenocarcinoma	29(54.7)	11(34.4)	40(47.1)
Other#	2(3.8)	1(3.1)	3(3.5)
Clinical Stage, n (%)			
IIIB	7(13.2)	2(6.3)	9(10.6)
IIIC	2(3.8)	1(3.1)	3(3.5)
IVA	23(43.4)	13(40.6)	37(43.5)
IVB	21(39.6)	16(50.0)	36(42.4)
PD-L1 Expression-Central Lab, n(%)			
<1%	6(11.3)	17(53.1)	23(27.1)
1-49%	29(54.7)	7(21.9)	36(42.4)
⩾ 50%	15(28.3)	6(18.8)	21(24.7)
other*	3(5.7)	2(6.2)	5 (5.9)

#The pathological type was unknown
*The quality control failed or no sample.

- In safety analysis set (SS) of Cohort A, the ORR in PD-L1 TPS ≥1% and ≥50% pts were 56.8% (95% CI 41.034, 71.651) and 73.3% (95% CI 44.900, 92.213); confirmed ORR were 54.5% (95% CI 38.8, 69.6) and 66.7% (95% CI 38.4, 88.2). The DCR were 90.9% (95% CI 78.3,97.5) and 93.3%(95% CI 68.1, 99.8). The mDoR were 13.2 m (95% CI 6.6, NE) and NE (95% CI 4.1, NE).
- In SS of Cohort B, the ORR and confirmed ORR were both 9.4% (95% CI 2.0, 25.0) and the DCR was 81.3% (95% CI 63.6, 92.8).The mDoR was 7.4m (95% CI NE, NE). Table 2.

Table 2 Summary of Response –safety set

	Cohort A: PD-L1≥1 % (N=44)	Cohort A: PD-L1≥50 % (N=15)	Cohort B (N=32)
Best of Response(BOR), n (%)			
CR	0	0	0
uCR	0	0	0
PR	24 (54.5)	10 (66.7)	3 (9.4)
uPR	1(2.3)	1(6.7)	0
SD	15 (34.1)	3 (20.0)	23 (71.9)
PD	1 (2.3)	0	3 (9.4)
UNK	3 (6.8)	1 (6.7)	3 (9.4)
Confirmed ORR (cORR), n (%)	24 (54.5)	10 (66.7)	3 (9.4)
95% CI	(38.847, 69.609)	(38.380, 88.176)	(1.977, 25.023)
ORR (ORR), n	25 (56.8)	11 (73.3)	3(9.4)
95% CI	(41.034, 71.651)	(44.900, 92.213)	(1.977, 25.023)
Disease control rate (DCR), n (%)	40 (90.9)	14 (93.3)	26 (81.3)
95% CI	(78.331, 97.467)	(68.052, 99.831)	(63.561, 92.792)
Duration of Response(DoR),months			
Q1(95% CI)	6.571 (2.595, 13.175)	9.692 (4.074, NE)	7.392 (NE, NE)
Median(95% CI)	13.175 (6.571, NE)	NE (4.074, NE)	7.392 (NE, NE)
Q3(95% CI)	NE (13.175, NE)	NE (NE, NE)	7.392 (NE, NE)

- In safety analysis set (SS) of Cohort A , The mPFS in PD-L1 TPS ≥ 1% and ≥ 50% were 8.3 m (95% CI 6.8, 13.9) and 12.4 m (95% CI 4.9, NE);In safety analysis set (SS) of Cohort B, the mPFS was 5.6 m (95% CI 2.8, 7.0). Figure 3-5.

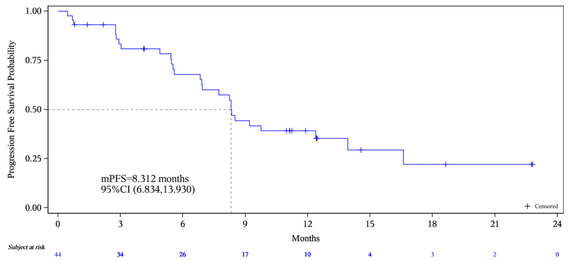


Figure 3 Kaplan-Meier estimates of PFS in PD-L1≥1% pts of cohort A-SS

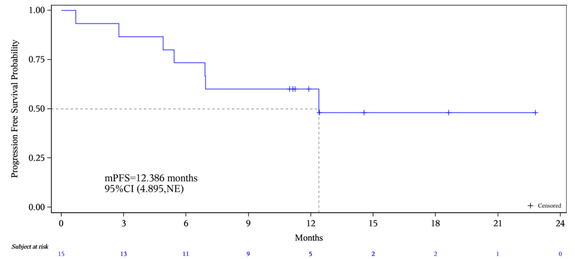


Figure 4 Kaplan-Meier estimates of PFS in PD-L1≥50% pts of cohort A-SS

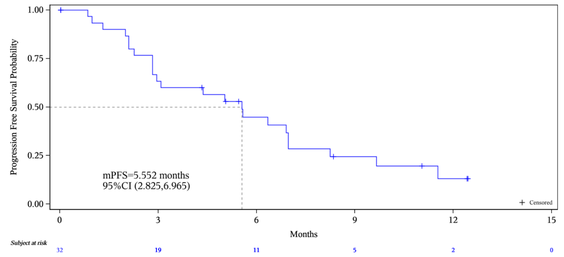


Figure 5 Kaplan-Meier estimates of PFS in cohort B-SS

- In safety analysis set (SS) of Cohort A , the OS was not reached yet. In SS of Cohort B, the OS was s 11.9m (95% CI 9.9, NE). Figure 6.

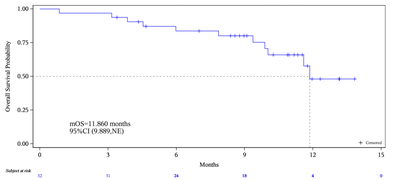


Figure 6 Kaplan-Meier estimates of OS in cohort B-SS

- 58.8% pts had grade ≥ 3 treatment-related adverse events (TRAEs). 24.7% pts had immune-related adverse events, 10.6% were grade ≥ 3. Table 3.
- The most common grade ≥ 3 TRAEs were ALT increased, AST increased and hypertension (10.6%), PPE and diarrhoea (7.1%). Table 4.

Table 3 Summary of Adverse Events-SS

	Cohort A (N=53)	Cohort B (N=32)	Total (N=85)
Treatment-Emergent Adverse Event (TEAE)	52(98.1)	32(100)	84(98.8)
CTCAE≥3	36(67.9)	21(65.6)	57(67.1)
Serious TEAE	33(62.3)	15(46.9)	48(56.5)
TEAE leading to death	6(11.3)	1(3.1)	7(8.2)
Treatment-Related Adverse Event (TRAE)	50(94.3)	32(100)	82(96.5)
CTCAE≥3 TRAE	31(58.5)	19(59.4)	50(58.8)
Serious TRAE	26(49.1)	13(40.6)	39(45.9)
TRAE leading to death	3(5.7)	0	3(3.5)
irAE	12(22.6)	9(28.1)	21(24.7)
CTCAE≥3	3(5.7)	6(18.8)	9(10.6)
IRR	24(45.3)	11(34.4)	35(41.2)
CTCAE≥3	0	0	0

Table 4 Incidence ≥2% of KN046 or Axitinib related CTCAE≥3 TRAE By PT-SS

PT term	Cohort A (N=53)	Cohort B (N=32)	Total (N=85)
Alanine aminotransferase increased	7(13.2)	2(6.3)	9(10.6)
Aspartate aminotransferase increased	7(13.2)	2(6.3)	9(10.6)
Hypertension	5(9.4)	4(12.5)	9(10.6)
Diarrhoea	4(7.5)	2(6.3)	6(7.1)
Palmar-plantar erythrodysaesthesia syndrome	6(11.3)	0	6(7.1)
Immune-mediated hepatitis	1(1.9)	2(6.3)	3(3.5)
Gastroenteritis	1(1.9)	1(3.1)	2(2.4)
Hyponatraemia	1(1.9)	1(3.1)	2(2.4)
Immune-mediated lung disease	1(1.9)	1(3.1)	2(2.4)
Platelet count decreased	1(1.9)	1(3.1)	2(2.4)
Rash	1(1.9)	1(3.1)	2(2.4)
Weight decreased	1(1.9)	1(3.1)	2(2.4)

CONCLUSIONS

- KN046-Axitinib combination showed encouraging efficacy and tolerability in advanced NSCLC pts. Further validation in a large-scale trial is warranted.

REFERENCES

1. 2023 ESMO 1449P

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The authors has declared no conflicts of interest