Supplementary

Table S1 EGFR and RAS mutations in the combination therapy group

Patient number	Mutations
1	NRAS Q61K
2	KRAS G12C
3	NRAS Q61H
4	KRAS G12V
5	KRAS G12L
6	KRAS G12C, copy number amplification
7	EGFR 20ins
8	KRAS G12V
9	KRAS G12C
10	KRAS G12A
11	KRAS G12V
12	KRAS G13D
13	KRAS G12A
14	KRAS G12A
15	NRAS Q61L
16	KRAS G12C
17	KRAS G12V
18	KRAS 2G12S
19	EGFR 20ins
20	KRAS Q61H

EGFR, epidermal growth factor receptor; RAS, rat sarcoma; KRAS, Kirsten-RAS; NRAS, neuroblastoma-RAS.

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Table S2 Univariate analyses of the observation subgroup data related to progression-free survival

Characteristic	DCR (%)	Median PFS (months) (95% CI)	P value
Sex (male *vs.* female)	80.4 *vs.* 85.0	6.47 (4.73-8.20) *vs.* 6.00 (3.01-8.99)	0.920
Age (<65 years *vs.* ≥65 years)	76.3 *vs.* 87.9	5.50 (3.91-7.09) *vs.* 8.67 (2.63-14.71)	0.888
Smoke (No *vs.* Yes)	85.7 *vs.* 79.1	6.80 (0-13.73) *vs.* 6.00 (4.34-7.66)	0.561
Bone metastases (No *vs.* Yes)	86.7 *vs.* 73.1	8.67 (5.02-12.31) *vs.* 5.20 (3.89-6.51)	0.191
Brain metastases (No *vs.* Yes)	82.8 *vs.* 76.9	6.80 (3.52-10.08) *vs.* 3.67 (1.37-5.97)	0.259
PD-L1(-/unknown *vs.* +)	77.6 *vs.* 90.9	5.20 (3.40-7.01) *vs.* 8.67 (1.53-15.81)	0.337
Cavitation (No *vs.* Yes)	79.6 *vs.* 87.5	6.00 (4.09-7.91) *vs.* 8.67 (2.34-15.00)	0.683
RAS mutation (- *vs.* +)	77.4 *vs.* 94.4	5.50 (3.86-7.14) *vs.* 10.67 (not achieved)	0.082
Treatment line (2 *vs.* ≥ 3)	84.4 *vs.* 79.5	10.67 (3.95-17.38) *vs.* 5.13 (3.45-6.82)	0.077
Previously used PD-1 blockade therapy (No *vs.* Yes)	78.6 *vs.* 86.2	6.00 (4.79-7.21) *vs.* 6.80 (0-17.33)	0.456
Previously used antiangiogenic therapy (No *vs.* Yes)	86.5 *vs.* 76.5	10.67 (4.28-17.05) *vs.* 5.50 (4.06-6.94)	0.171

DCR, disease control rate; PFS, progression-free survival; 95%CI, 95% confidence interval; PD-L1, programmed cell death-ligand 1; RAS, rat sarcoma; PD-1, programmed cell death-1.

Table S3 Univariate analyses related to overall survival of the combination therapy group

Characteristic	Median OS (months) (95% CI)	P value
Sex (male *vs.* female)	14.60 (8.23-20.98) *vs.* 16.47 (6.44-26.50)	0.671
Age (<65 years *vs.* ≥65 years)	12.37 (4.92-19.81) *vs.* 25.67 (12.25-39.09)	0.105
Smoke (No *vs.* Yes)	16.47 (5.25-27.69) *vs.* 14.60 (4.42-24.78)	0.220
Bone metastases (No *vs.* Yes)	21.83 (12.61-31.06) *vs.* 12.00 (3.64-20.36)	0.052
Brain metastases (No *vs.* Yes)	16.47 (7.72-25.22) *vs.* 5.33 (3.42-7.25)	0.007
PD-L1(-/unknown *vs.* +)	14.60 (9.98-19.22) *vs.* 21.83 (8.07-35.60)	0.769
Cavitation (No *vs.* Yes)	16.47 (1.60–31.34) *vs.* 14.60 (6.16–23.05)	0.564
RAS mutation (- *vs.* +)	16.13 (10.12-22.15) *vs.* 14.60 (2.99-26.21)	0.412
Treatment line (2 *vs.* ≥ 3)	21.83 (12.17-31.49) *vs.* 12.37 (4.88-19.86)	0.077
Previously used PD-1 blockade therapy (No *vs.* Yes)	14.60 (5.69-23.51) *vs.* 25.67 (11.59-39.75)	0.378
Previously used antiangiogenic therapy (No *vs.* Yes)	16.47 (13.68-19.26) *vs.* 9.33 (2.97-15.70)	0.462

OS, overall survival; 95% CI, 95% confidence interval; PD-L1, programmed cell death-ligand 1; RAS, rat sarcoma; PD-1, programmed cell death-1.

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Table S4 Relevant clinical outcomes reported in the literatures and our study

Study	Number of patients	PFS	OS
Yu L *et al.* (this study, advanced recurrent driver-negative LUAD, second-line and later)	anlotinib+PD-1 inhibitor (n=71) vs nivolumab (n=63)	median 6.00 months (95%CI 4.34-7.66) (ORR 7.0%, DCR 81.7%) vs 3.41 months (95%CI 2.16-4.67), P<0.001; patients with and without RAS mutations: median 10.67 months (95%CI not achieved) vs 5.50 months (95%CI 3.86-7.14), HR 0.444 (95%CI 0.172-1.143), P=0.082	median 16.13 months (95%CI 10.48-21.79) vs 11.88 months (95%CI 8.88-14.88), P=0.046; patients with and without RAS mutations: median 14.60 months (95%CI 2.99-26.21) vs 16.13 months (95%CI 10.12-22.15), HR 0.603 (95%CI 0.177-2.050), P= 0.412
LUME-Lung 1 (13) (stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy, second-line)	docetaxel+nintedanib (n=655, LUAD: n=322) vs docetaxel+placebo (n=659, LUAD: n=336)	median 3.4 months (95%CI 2.9-3.9) vs 2.7 months (95%CI 2.6-2.8), HR 0.79 (95%CI 0.68-0.92), P=0.0019	median 10.1 months (95%CI 8.8-11.2) vs 9.1 months (95%CI 8.4-10.4), HR 0.94 (95%CI 0.83-1.05), P=0.2720; LUAD: median 12.6 months (95%CI 10.6-15.1) vs 10.3 months (95%CI 8.6-12.2), HR 0.83 (95%CI 0.70-0.99), P=0.0359
REVEL (12) (stage IV NSCLC progressed during or after first-line platinum-based chemotherapy, second-line)	docetaxel+ramucirumab (n=628) vs docetaxel+placebo (n=625)	median 4.5 months (IQR 2.3-8.3) vs 3.0 months (IQR 1.4-6.9), HR 0.76 (95%CI 0.68-0.86), p<0.0001	median 10.5 months (IQR 5.1-21.2) vs 9.1 months (IQR 4.2-18.0), HR 0.86 (95%CI 0.75-0.98), P=0.023
VARGADO Cohort C (34) (locally advanced, metastatic, or locally recurrent LUAD following first line chemotherapy with ICIs, second-line)	docetaxel+nintedanib (n=137)	median 4.8 months (95%CI 3.7-6.6) (DCR 72.5%); patients with and without KRAS mutations: median 4.8 months (95%CI 2.2–not estimable) vs 6.4 months (95%CI 2.5–9.9), P=0.4784	immature
Brueckl WM *et al.* (35) (stage IV NSCLC following first-line chemotherapy plus ICI, second-line)	docetaxel+ramucirumab (n=77)	median 3.9 months (95%CI 3.1-4.6) (ORR 32.5%, DCR 62.4%); patients with and without KRAS mutations: median 2.8 months (95%CI 1.7-3.9) vs 4.5 months (95%CI 2.6-6.4), P=0.021	median 7.5 months (95%CI 5.1-10.0)
Brueckl WM *et al.* (45) (stage IV NSCLC following second-line ICI, third-line)	docetaxel+ramucirumab (n=67)	median 6.8 months (95%CI 4.6-9.0) (ORR 36%, DCR 69%)	median 11.0 months (95%CI 7.1-14.9)
Lung-MAP S1800A (30) (advanced NSCLC previously treated with ICI and platinum-based chemotherapy)	ramucirumab+pembrolizumab (n=69) vs standard of care (docetaxel/ramucirumab,docetaxel,gemcitabine, and pemetrexed) (n=67)	median 4.5 months (80%CI 4.2-6.1) vs 5.2 months (80%CI 4.2-5.7), HR 0.86 (80%CI 0.66-1.14), P=0.25 (one-sided, standard log-rank test), P=0.14 (one-sided, weighted log-rank test)	median 14.5 months (80%CI 13.9-16.1) vs 11.6 months (80%CI 9.9-13.0), HR 0.69 (80%CI 0.51-0.92), P=0.05 (one-sided, standard log-rank test), P=0.15 (one-sided, weighted log-rank test)

References

45. Brueckl WM, Reck M, Rittmeyer A, et al. Efficacy of Docetaxel Plus Ramucirumab as Palliative Third-Line Therapy Following Second-Line Immune-Checkpoint-Inhibitor Treatment in Patients With Non-Small-Cell Lung Cancer Stage IV. Clin Med Insights Oncol 2020; 14:1179554920951358.

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