

[EP11.36] Efficacy and safety of First-Line Immunotherapy Regimens in Advanced NSCLC with PD-L1-Positive: Systematic Review and Network Meta-Analysis



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1. Introduction

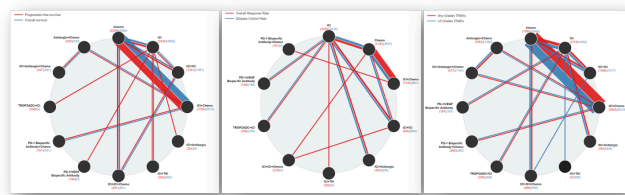
The therapeutic landscape for advanced NSCLC lacking actionable mutations has evolved rapidly. While ICI monotherapy or ICI+chemotherapy are standard first-line options for PD-L1 $\geq 1\%$, a substantial number of patients eventually experience progression.

Novel therapeutic classes—including PD-1/VEGF bispecific antibodies, TROP2-directed ADCs, and quadruplet therapies—have emerged. However, the lack of direct head-to-head trials creates a challenge for clinical decision-making. We conducted this NMA to quantitatively rank the efficacy and safety of 12 current and emerging regimens.

2. Methods

- Inclusion:** Phase III RCTs (until June 2026) of treatment-naïve, advanced NSCLC, PD-L1 $\geq 1\%$, EGFR/ALK-negative patients.
- Data Included:** 41 eligible RCTs comprising 22,491 patients and 12 distinct treatment regimens.
- Statistical Analysis:** Frequentist NMA using a graph-theoretical random-effects model (*netmeta*). Regimens were ranked using P-scores.

3.1 Network Geometry



▲ Figure 1: Network geometries for efficacy (PFS/OS/ORR/DCR) and safety outcomes.

12 distinct therapeutic regimens:

ICI monotherapy; Platinum-based doublet chemotherapy; ICI plus chemotherapy; Dual-ICI combination; Dual-ICI plus chemotherapy; ICI plus antiangiogenic agents; Antiangiogenic plus chemotherapy; Quadruplet therapy; ICI plus tyrosine kinase inhibitor (TKI); PD-1/VEGF bispecific antibody monotherapy; PD-1/VEGF bispecific antibody plus chemotherapy; TROP2-directed ADC plus ICI.

3.2 Efficacy Outcomes: Progression-Free & Overall Survival

OVERALL SURVIVAL (ROW VS. COLUMN)											
ICI+Antiangio+Chemo	1.52 [0.89, 2.56]	N/A	1.03 [0.72, 1.47]	N/A	0.73 [0.57, 0.94]	0.99 [0.67, 1.45]	N/A	0.95 [0.64, 1.39]	0.83 [0.57, 1.20]	0.71 [0.50, 1.02]	0.75 [0.48, 1.17]
PD-1/VEGF Bispecific Antibody+Chemo	0.96 [0.52, 1.75]	N/A	0.68 [0.46, 1.00]	N/A	0.48 [0.31, 0.76]	0.65 [0.43, 0.99]	N/A	0.63 [0.41, 0.95]	0.55 [0.37, 0.82]	0.47 [0.32, 0.70]	0.50 [0.31, 0.79]
TROP2ADC+ICI	0.89 [0.49, 1.52]	0.93 [0.49, 1.75]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ICI+Chemo	0.63 [0.42, 0.94]	0.66 [0.42, 1.04]	0.71 [0.45, 1.11]	N/A	0.71 [0.55, 0.91]	0.96 [0.82, 1.13]	N/A	0.92 [0.79, 1.07]	0.80 [0.71, 0.91]	0.69 [0.64, 0.75]	0.73 [0.56, 0.95]
PD-1/VEGF Bispecific Antibody	0.63 [0.34, 1.15]	0.66 [0.35, 1.24]	0.71 [0.40, 1.24]	0.99 [0.63, 1.55]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Antiangio+Chemo	0.59 [0.46, 0.75]	0.62 [0.36, 1.07]	0.67 [0.38, 1.15]	0.94 [0.68, 1.29]	0.94 [0.54, 1.64]	N/A	N/A	1.35 [1.01, 1.82]	1.30 [0.96, 1.75]	1.14 [0.85, 1.49]	0.98 [0.71, 1.47]
ICI+ICI+Chemo	0.47 [0.29, 0.75]	0.49 [0.29, 0.82]	0.53 [0.32, 0.86]	0.74 [0.56, 0.95]	0.75 [0.46, 1.22]	0.79 [0.53, 1.19]	N/A	0.96 [0.80, 1.15]	0.83 [0.71, 0.99]	0.72 [0.63, 0.83]	0.76 [0.57, 1.01]
ICI+Antiangio	0.48 [0.26, 0.82]	0.48 [0.26, 0.82]	0.51 [0.30, 0.89]	0.72 [0.47, 1.10]	0.73 [0.42, 1.26]	0.77 [0.46, 1.31]	0.97 [0.61, 1.55]	N/A	N/A	N/A	N/A
ICI+ICI	0.37 [0.24, 0.59]	0.39 [0.24, 0.64]	0.42 [0.26, 0.67]	0.59 [0.48, 0.73]	0.60 [0.37, 0.95]	0.63 [0.43, 0.93]	0.80 [0.61, 1.04]	0.82 [0.53, 1.27]	0.87 [0.75, 1.02]	0.75 [0.66, 0.86]	0.79 [0.60, 1.05]
ICI	0.32 [0.20, 0.50]	0.33 [0.20, 0.55]	0.36 [0.24, 0.54]	0.51 [0.41, 0.62]	0.51 [0.34, 0.76]	0.54 [0.37, 0.79]	0.68 [0.52, 0.90]	0.70 [0.48, 1.01]	0.86 [0.67, 1.09]	0.86 [0.79, 0.94]	0.91 [0.72, 1.15]
Chemo	0.32 [0.21, 0.48]	0.33 [0.21, 0.52]	0.36 [0.23, 0.55]	0.50 [0.45, 0.55]	0.50 [0.33, 0.78]	0.53 [0.38, 0.75]	0.67 [0.54, 0.84]	0.69 [0.46, 1.04]	0.84 [0.70, 1.02]	0.99 [0.83, 1.17]	1.05 [0.82, 1.35]
ICI+TKI	0.29 [0.16, 0.52]	0.30 [0.19, 0.56]	0.33 [0.19, 0.56]	0.46 [0.31, 0.69]	0.46 [0.27, 0.79]	0.49 [0.29, 0.83]	0.62 [0.39, 0.97]	0.64 [0.38, 1.06]	0.78 [0.51, 1.20]	0.91 [0.64, 1.30]	0.92 [0.62, 1.37]

▲ Figure 2: League table comparing PFS and OS across all regimens.

Progression-Free Survival (PFS):

(compare to ICI monotherapy).

- The quadruplet (ICI+Antiangio+Chemo) yielded the greatest risk reduction (HR 0.32).
- Crucially, non-chemotherapy or targeted combinations like PD-1/VEGF bispecific + Chemo (HR 0.33) and TROP2 ADC + ICI (HR 0.36) demonstrated comparable and highly significant benefits.
- PD-1/VEGF bispecific monotherapy provided a statistically equivalent PFS benefit (HR 0.51) to standard chemo-immunotherapy doublets.

Overall Survival (OS):

(compare to ICI monotherapy).

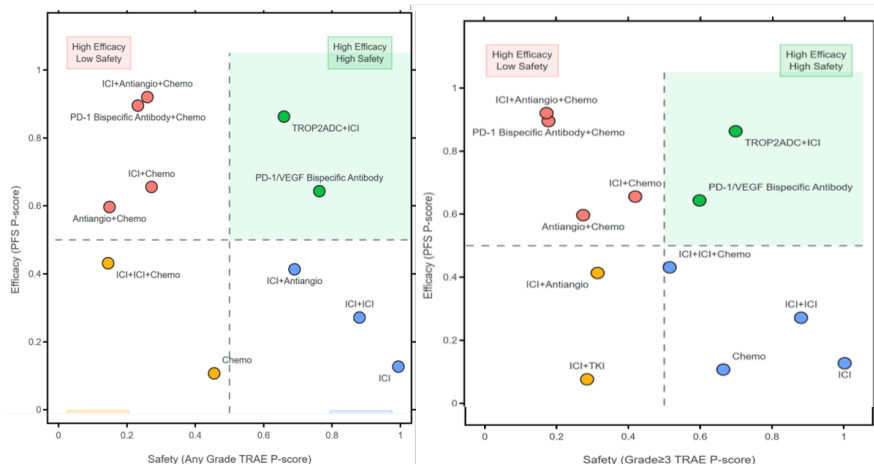
- PD-1/VEGF bispecific + chemo demonstrated the highest efficacy (HR 0.55).
- Standard ICI+chemo (HR 0.80) and dual ICI+chemo (HR 0.83) conferred significant survival benefits.
- Caution:** The quadruplet regimen failed to show a statistically significant OS advantage. (*Note: OS data for novel agents are not yet mature*).

3.3 Safety and Toxicity Profiles

≥3 GRADES TRAES (ROW VS. COLUMN)											
ICI	0.68 [0.58, 0.80]	0.56 [0.40, 0.79]	0.52 [0.44, 0.59]	0.53 [0.33, 0.84]	0.48 [0.39, 0.59]	0.46 [0.40, 0.53]	0.43 [0.32, 0.57]	0.42 [0.30, 0.58]	0.42 [0.32, 0.54]	0.39 [0.28, 0.53]	0.40 [0.31, 0.51]
ICI+ICI	0.96 [0.82, 1.00]	0.83 [0.57, 1.21]	0.76 [0.66, 0.88]	0.78 [0.48, 1.27]	0.71 [0.59, 0.86]	0.67 [0.57, 0.79]	0.63 [0.45, 0.88]	0.62 [0.47, 0.88]	0.62 [0.47, 0.88]	0.57 [0.43, 0.79]	0.58 [0.45, 0.74]
TROP2ADC+ICI	0.87 [0.81, 0.94]	0.91 [0.83, 1.00]	0.92 [0.64, 1.32]	0.94 [0.53, 1.66]	0.85 [0.57, 1.27]	0.81 [0.56, 1.17]	0.76 [0.49, 1.18]	0.74 [0.46, 1.18]	0.74 [0.48, 1.13]	0.69 [0.43, 1.09]	0.70 [0.46, 1.07]
Chemo	0.80 [0.77, 0.83]	0.83 [0.80, 0.87]	0.92 [0.84, 1.00]	1.02 [0.68, 1.64]	0.93 [0.76, 1.11]	0.88 [0.83, 0.94]	0.82 [0.60, 1.13]	0.80 [0.57, 1.14]	0.81 [0.64, 1.01]	0.75 [0.56, 1.00]	0.76 [0.61, 0.95]
PD-1 Bispecific Antibody	0.91 [0.83, 1.01]	0.95 [0.85, 1.06]	1.04 [0.92, 1.19]	1.14 [1.02, 1.27]	0.91 [0.55, 1.51]	0.86 [0.55, 1.51]	0.81 [0.47, 1.39]	0.79 [0.45, 1.39]	0.79 [0.47, 1.34]	0.73 [0.42, 1.28]	0.75 [0.44, 1.26]
ICI+ICI+Chemo	0.77 [0.72, 0.82]	0.80 [0.74, 0.86]	0.88 [0.79, 0.97]	0.96 [0.91, 1.01]	0.84 [0.75, 0.95]	0.95 [0.79, 1.14]	0.89 [0.62, 1.26]	0.87 [0.58, 1.27]	0.87 [0.65, 1.13]	0.81 [0.58, 1.13]	0.82 [0.62, 1.09]
ICI+Chemo	0.78 [0.75, 0.81]	0.82 [0.78, 0.86]	0.90 [0.82, 0.98]	0.98 [0.96, 0.99]	1.02 [0.96, 1.09]	0.91 [0.68, 1.29]	0.94 [0.64, 1.30]	0.91 [0.74, 1.13]	0.85 [0.64, 1.13]	0.87 [0.64, 1.13]	0.87 [0.70, 1.07]
ICI+Antiangio	0.88 [0.82, 0.95]	0.92 [0.85, 1.00]	1.01 [0.91, 1.12]	1.10 [1.02, 1.19]	0.97 [0.86, 1.10]	1.15 [1.05, 1.27]	1.12 [1.04, 1.22]	0.98 [0.66, 1.44]	0.98 [0.66, 1.44]	0.91 [0.59, 1.47]	0.92 [0.66, 1.43]
ICI+TKI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.00 [0.66, 1.52]	0.93 [0.59, 1.47]	0.95 [0.62, 1.43]	0.95 [0.62, 1.43]
Antiangio+Chemo	0.77 [0.72, 0.82]	0.80 [0.75, 0.84]	0.88 [0.80, 0.98]	0.96 [0.91, 1.01]	0.84 [0.75, 0.95]	1.00 [0.93, 1.08]	0.96 [0.83, 1.03]	0.87 [0.79, 0.96]	N/A	0.93 [0.85, 1.02]	0.95 [0.85, 1.12]
PD-1 Bispecific Antibody+Chemo	0.78 [0.72, 0.84]	0.81 [0.75, 0.88]	0.89 [0.80, 0.99]	0.97 [0.91, 1.04]	0.85 [0.75, 0.96]	1.01 [0.93, 1.10]	0.99 [0.89, 1.06]	0.88 [0.79, 0.97]	N/A	1.01 [0.93, 1.10]	1.02 [0.72, 1.45]
ICI+Antiangio+Chemo	0.78 [0.73, 0.83]	0.81 [0.76, 0.87]	0.89 [0.81, 0.99]	0.98 [0.93, 1.03]	0.86 [0.76, 0.96]	1.02 [0.95, 1.05]	1.00 [0.95, 1.05]	0.88 [0.80, 0.97]	N/A	1.01 [0.97, 1.05]	1.00 [0.93, 1.09]

Grade ≥ 3 TRAES: ICI monotherapy and dual-ICI were best tolerated. TROP2 ADC+ICI maintained a relatively favorable safety profile. The quadruplet regimen ranked as the least safe intervention.

3.4 Efficacy vs. Safety: Cluster Analysis



▲ Figure 4: Cluster analysis based on PFS and Safety P-scores.

- Optimal (Upper-Right):** TROP2 ADC + ICI, PD-1/VEGF bispecific monotherapy (robust efficacy + superior safety).
- High Efficacy/Toxicity (Upper-Left):** The quadruplet regimen, PD-1/VEGF+Chemo and standard ICI+Chemo.

4. Conclusions

- TROP2 ADC + ICI, PD-1/VEGF bispecific monotherapy offers a compelling chemo-free alternative, providing PFS benefits equivalent to chemo-immunotherapy but with a superior safety profile.

5. Disclosures

Conflicts of Interest: The authors declare no potential conflicts of interest regarding the publication of this abstract.

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