

Introduction

Direct head-to-head comparisons between currently approved immunotherapies (IO) — alone or combined with chemotherapy — for first-line metastatic NSCLC remain largely unavailable. Cross-trial comparison using reconstructed individual patient-level data (IPD) offers a rigorous methodology for indirect comparative evidence: demonstrating control-arm equivalence validates the population comparability needed before comparing experimental arms. We applied this framework across landmark trials of pembrolizumab, cemiplimab, and ipilimumab/nivolumab, comparing PFS and OS with subgroup analyses by histology (squamous vs. non-squamous) and PD-L1 expression (>50% vs. >1%).

Objectives

- Compare efficacy (PFS, OS) of pembrolizumab, cemiplimab, and ipilimumab/nivolumab — alone or with chemotherapy — in first-line metastatic NSCLC using reconstructed IPD.
- Validate cross-trial comparability by testing control-arm concordance before comparing experimental arms.
- Evaluate results across histology (squamous vs. non-squamous) and PD-L1 expression (≥50% vs. ≥1%) subgroups.

Direct head-to-head trial data comparing approved first-line immunotherapy regimens in metastatic NSCLC are largely unavailable — reconstructed IPD offers a rigorous alternative for indirect comparison.

Methods

1. Kaplan-Meier Reconstruction



Published KM curves and at-risk tables reconstructed into individual patient-level data (IPD) using the Guyot algorithm.

2. Trial Comparisons



IO + chemo: CheckMate-9LA vs. EMPOWER-Lung 3 vs. KEYNOTE-407 (squamous) vs. KEYNOTE-189 (non-squamous). IO alone: KEYNOTE-024 vs. EMPOWER-Lung 1 vs. CheckMate 227 (PD-L1 ≥50%); KEYNOTE-042 vs. CheckMate 227 (PD-L1 ≥1%).

3. Hazard Ratio Estimation



Cox proportional hazards models; between-group differences assessed by Fleming-Harrington weighted log-rank tests.

4. Control-Arm Validity Check



Control-arm concordance evaluated first, as an internal validity check, before interpreting experimental-arm comparisons.

5. Endpoints & Subgroups



OS and PFS compared overall and within histology (squamous/non-squamous) and PD-L1 (≥50%/≥1%) subgroups.

References

- Guyot P, Ades AE, Ouwers MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
- Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with NSCLC (CheckMate 9LA). Lancet Oncol. 2021;22(2):198-211.
- Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in NSCLC (EMPOWER-Lung 3). Nat Med. 2022;28(11):2374-2380.
- Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous NSCLC (KEYNOTE-407). N Engl J Med. 2018;379(21):2040-2051.
- Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-squamous NSCLC (KEYNOTE-189). N Engl J Med. 2018;378(22):2078-2092.
- Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive NSCLC (KEYNOTE-024). N Engl J Med. 2016;375(19):1823-1833.
- Sezer A, Kilickap S, Günnüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1). Lancet. 2021;397(10274):592-604.
- Hellmann MD, Paz-Ares L, Bernabé Caro R, et al. Nivolumab plus ipilimumab in advanced NSCLC (CheckMate 227). N Engl J Med. 2019;381(21):2020-2031.
- Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing NSCLC (KEYNOTE-042). Lancet. 2019;393(10183):1819-1830.
- Ismayilov R, Altundağ Ö. First-line immunotherapy-based regimens for metastatic non-small cell lung cancer: a network meta-analysis of landmark trials. Tuberk Toraks. 2025;73(4):299-308.

Results

Control-arm concordance

25/26

comparisons showed concordant control arms

Validates cross-trial comparability

Only significant PFS difference

HR 0.80

Pembro-chemo vs. ipi/nivo-chemo

Non-squamous NSCLC (p = 0.005)

Non-concordant control arms

1 of 26

comparison did not validate

CheckMate 227 vs. KEYNOTE-042 (PFS)

Grade ≥3 irAEs

33–47%

with dual checkpoint blockade (CheckMate)

vs. 8–18% with PD-1 monotherapy

Figure 2. Forest Plot of Hazard Ratios Across All Cross-Trial Comparisons

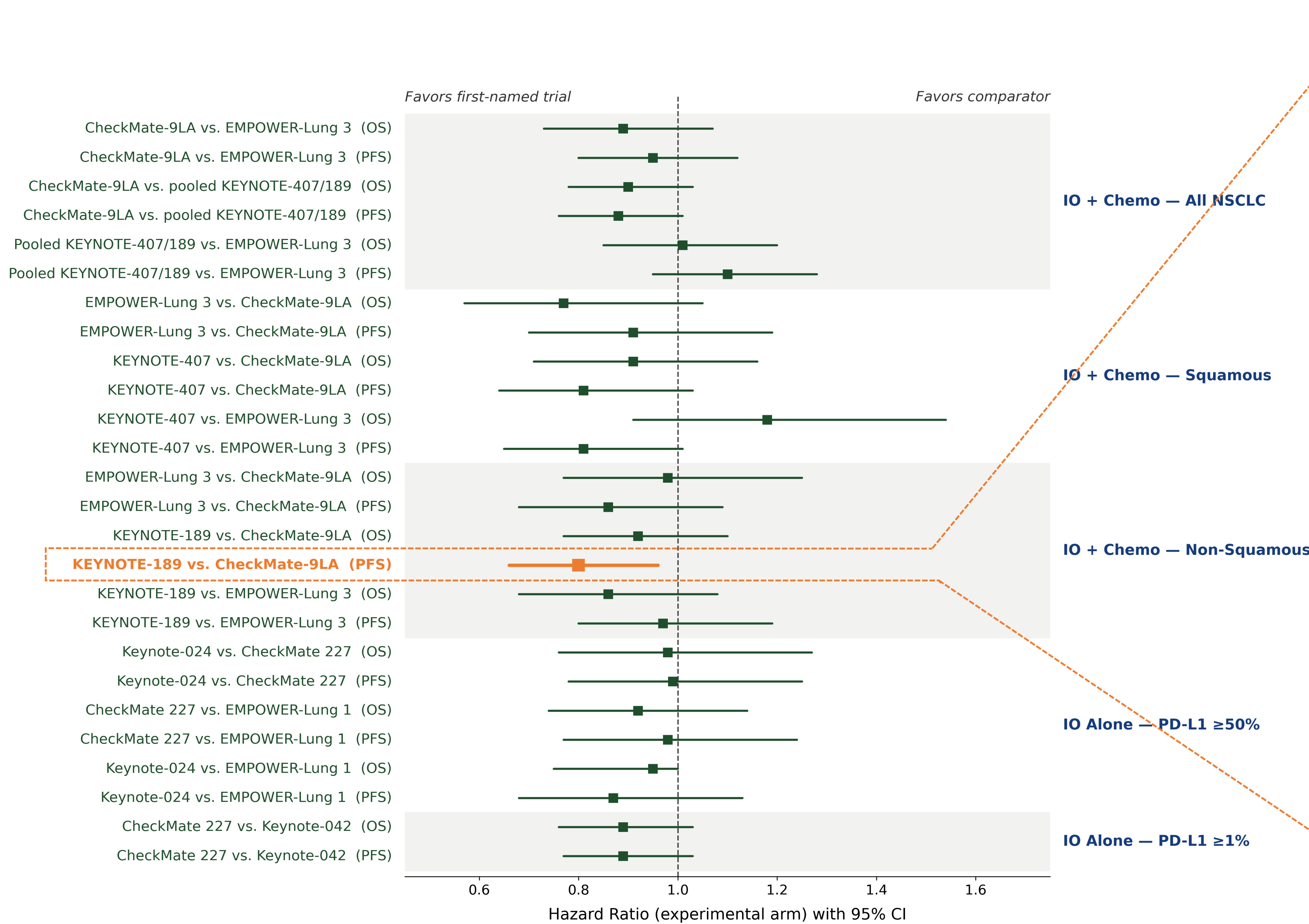


Figure 2. Forest plot of experimental-arm hazard ratios (95% CI) across all 26 cross-trial comparisons, grouped by regimen category. Dashed line = HR 1.0 (no difference).

Control Arm PFS

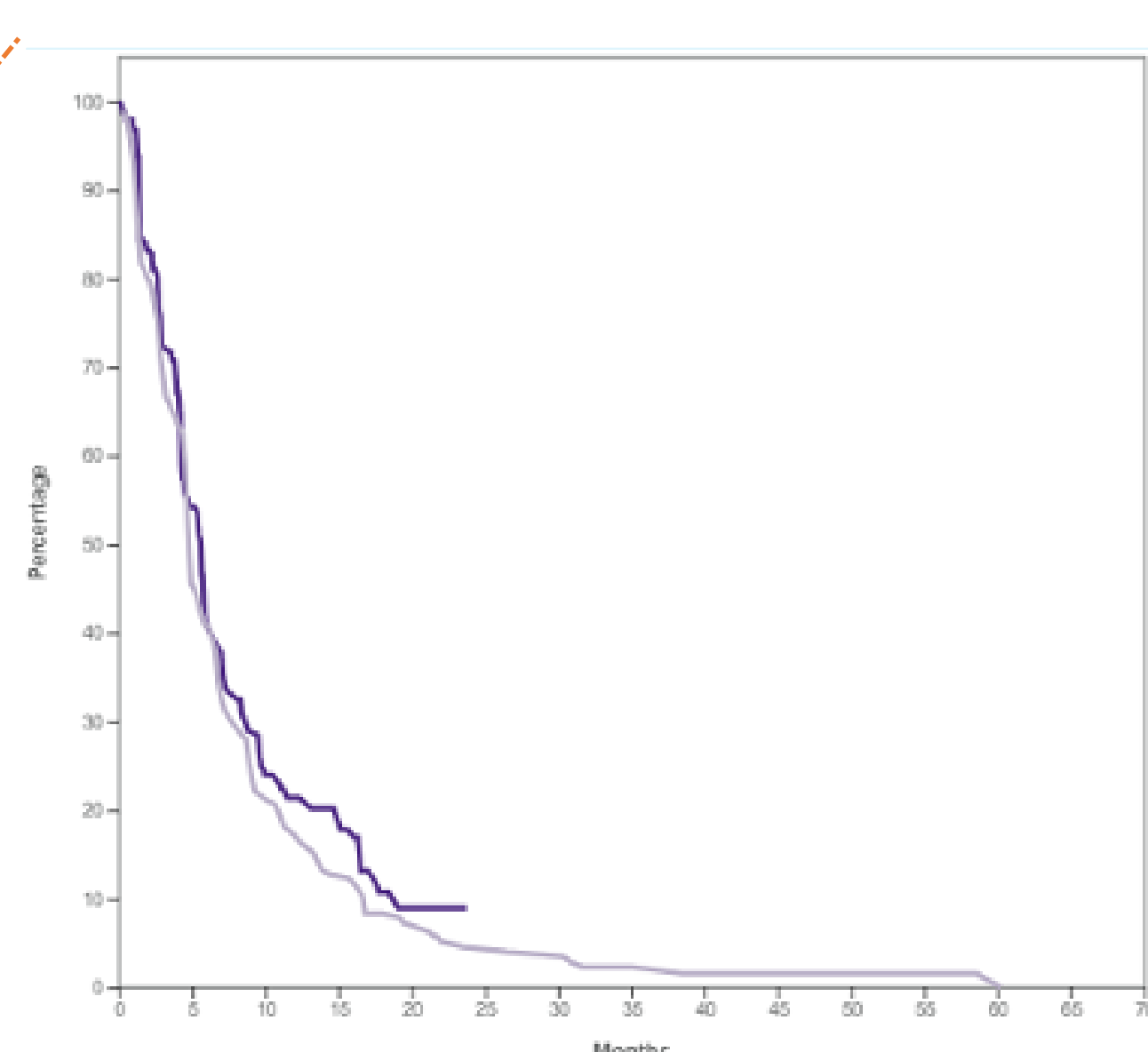


Figure 3. KM progression-free survival, control arms (KEYNOTE-189 vs. CheckMate-9LA).

Intervention Arm PFS

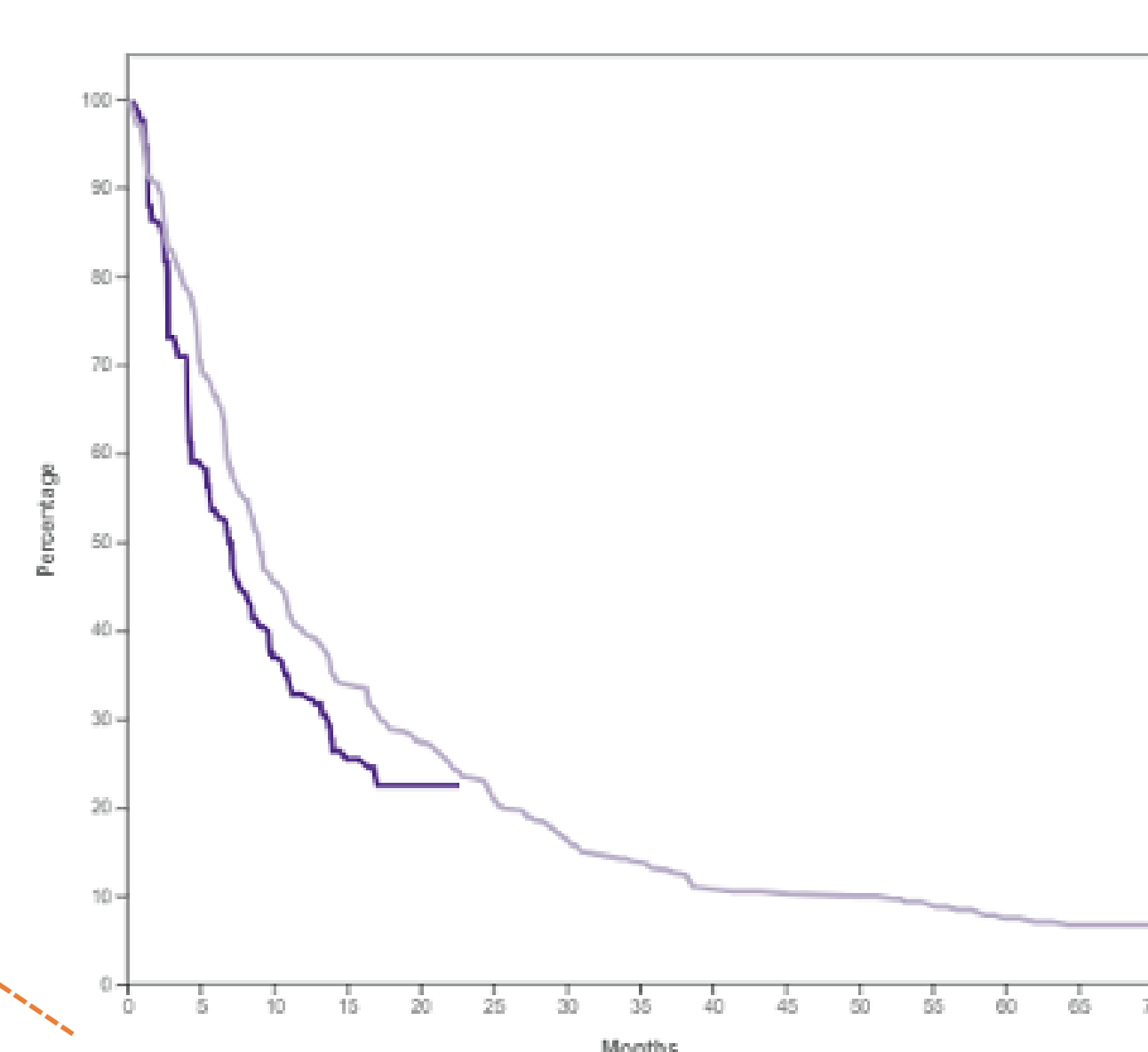


Figure 4. KM progression-free survival, intervention arms (KEYNOTE-189 vs. CheckMate-9LA).

Conclusions and Clinical Implications



1. Broad efficacy equivalence across regimens.

This cross-trial IPD comparison demonstrates broad equivalence in OS and PFS across pembrolizumab, cemiplimab, and ipilimumab/nivolumab — alone or with chemotherapy — in first-line metastatic NSCLC.



2. One meaningful PFS difference, not reflected in OS.

Pembrolizumab-chemotherapy showed superior PFS over ipilimumab/nivolumab-chemotherapy in non-squamous NSCLC (HR 0.80; p=0.005), but this advantage did not translate into an OS difference.



3. Decisions may hinge on toxicity, not efficacy.

With efficacy largely equivalent, treatment selection may reasonably shift toward weighing adverse-event profiles: grade ≥3 irAEs were 8–18% with PD-1 monotherapy vs. 33–47% with dual checkpoint blockade.



4. Consistent with external network meta-analysis.

Ismayilov & Altundağ (2025 NMA, 5 trials) found pembrolizumab-chemo significantly OS-superior to nivolumab-ipilimumab-chemo in non-squamous NSCLC (HR 0.76, 95% CI 0.58–0.99) — the same pairing and direction as our PFS finding, reached independently via aggregate-data network methods rather than our IPD approach.



5. Open questions remain.

PD-L1-negative disease and STK11/KEAP1 mutation subgroups were beyond the scope of this analysis due to methodology and available trial data.

Clinical Takeaways

- Reconstructed IPD enables robust cross-trial comparison when head-to-head data are unavailable.
- Control-arm concordance should be verified before interpreting experimental-arm comparisons in any cross-trial framework.
- With efficacy largely equivalent, first-line IO regimen selection may reasonably weigh toxicity and administration burden.
- Prospective, biomarker-defined validation (PD-L1-negative disease, STK11/KEAP1 status) is needed to extend these findings.