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Optimal First-Line Use of Pembrolizumab in Metastatic Driver-Negative NSCLC: Monotherapy Versus Chemo-Immunotherapy (Evidence 2022–2025)

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Abstract

Pembrolizumab has redefined first-line treatment of metastatic non-small cell lung cancer (NSCLC) without targetable driver alterations, both as monotherapy in PD-L1-high disease and in combination with platinum-based chemotherapy across PD-L1 strata. Since 2021, the strategic focus has shifted from whether to use pembrolizumab to how best to deploy it. This review summarizes evidence from 2022–2025, including randomized trial updates, pembrolizumab-specific network meta-analyses, real-world cohorts, and guideline recommendations.

Across randomized and pooled analyses, pembrolizumab–chemotherapy improves objective response and progression-free survival compared with pembrolizumab monotherapy, particularly in PD-L1 tumor proportion score (TPS) 1–49% and <1% tumors. In PD-L1-high disease (TPS ≥50%), combination therapy achieves higher response rates and longer PFS but does not clearly improve overall survival compared with monotherapy after adjustment for cross-trial and real-world confounding. Real-world cohorts consistently show reduced early progression and early death with combination therapy, especially in patients with high tumor burden or aggressive disease, but only modest long-term survival benefit at the population level. Pembrolizumab monotherapy provides durable survival with lower acute toxicity, median overall survival of approximately 20–26 months, and a 5-year survival rate of ~20–30% in PD-L1-high cohorts, with good tolerability even in older patients. Clinical and biological modifiers, including tumor burden, disease aggressiveness, neutrophil-to-lymphocyte ratio, histology, age, and performance status, refine patient selection beyond PD-L1 alone. Current guidelines therefore view pembrolizumab monotherapy and pembrolizumab–chemotherapy as complementary options supporting individualized treatment selection.

Keywords

Metastatic non-small cell lung cancer, Pembrolizumab, First-line immunotherapy, Pembrolizumab monotherapy, Chemo-immunotherapy, PD-L1 expression, Real-world evidence

Introduction

Pembrolizumab, a humanized IgG4 monoclonal antibody against PD-1, has transformed the first-line treatment landscape for metastatic non-small cell lung cancer (NSCLC) without targetable driver alterations. Since the approval of pembrolizumab monotherapy for tumors with PD-L1 tumor proportion score (TPS) ≥50% and of pembrolizumab-chemotherapy combinations across PD-L1 strata, clinicians have faced a central strategic question: when is pembrolizumab monotherapy sufficient, and when should platinum-based chemotherapy be added up front?

Between 2022 and 2025, this question has been addressed by:

- Mature randomized trial updates, particularly 5-year analyses from KEYNOTE-189 and pooled PD-L1-negative datasets. [1,2]
- A pembrolizumab-specific network meta-analysis comparing monotherapy vs pembrolizumab-chemotherapy via chemotherapy nodes. [3]
- Large real-world series of pembrolizumab monotherapy in PD-L1-high disease. [4-7]
- Multiple comparative real-world cohorts directly contrasting pembrolizumab monotherapy vs pembrolizumab plus chemotherapy in PD-L1-high and PD-L1-positive populations. [8-17]

Concurrently, guideline bodies such as SITC and ASCO have integrated these emerging data into recommendations that emphasize PD-L1 TPS, disease burden, and patient fitness as primary determinants of strategy selection. [18,19]

This review synthesizes 2022-2025 evidence on pembrolizumab monotherapy versus pembrolizumab-chemotherapy as first-line treatment for metastatic NSCLC, focusing on PD-L1-stratified outcomes, toxicity, clinical modifiers of benefit, and evolving mechanistic understanding.

1. Guideline and conceptual framework since 2021

1.1 Contemporary guideline recommendations

The 2022 SITC clinical practice guideline on lung cancer immunotherapy and its living web updates recommend the following for metastatic NSCLC without EGFR/ALK/ROS1/BRAF driver alterations: [18]

- TPS ≥50%: first-line pembrolizumab monotherapy (or atezolizumab/cemiplimab) is recommended, with chemo-immunotherapy considered for high tumor burden or worrisome symptoms. [18]

- TPS 1-49%: pembrolizumab + platinum-based chemotherapy (KEYNOTE-189/407-type regimens) is preferred; monotherapy only when chemotherapy is not feasible. [18]
- TPS <1%: chemo-IO combinations are standard; monotherapy not recommended. [18]

The ASCO living guideline on systemic therapy for stage IV NSCLC without driver alterations (versions 2022.2 and 2023.3) echoes this framework: [19]

- For TPS ≥50%, clinicians may offer single-agent pembrolizumab (or atezolizumab/cemiplimab) or pembrolizumab-chemotherapy, individualizing choice based on burden, pace, and comorbidities. [19]
- For TPS 1-49% or <1%, chemo-IO is recommended, with monotherapy reserved for chemotherapy-ineligible patients. [19]

A 2024 narrative review in *Medicine* summarizes this paradigm: in PD-L1-high disease, monotherapy offers durable survival with less toxicity, but chemo-IO can reduce early progression and deepen responses; in lower PD-L1 strata, chemo-IO is generally required for adequate disease control. [20]

1.2 Mechanistic rationale

Recent reviews of long-term ICI outcomes in NSCLC emphasize that pembrolizumab monotherapy relies on a pre-existing inflamed tumor microenvironment (TME) with abundant CD8+ T cells, intact IFN-gamma signaling, and sustained antigen presentation. [20,21]

Chemotherapy added to pembrolizumab can:

- Promote immunogenic cell death and neoantigen release;
- Deplete immunosuppressive myeloid cells and Tregs;
- Increase PD-L1 expression and chemokine gradients, potentially converting "cold" or "immune-excluded" tumors into "hotter" phenotypes. [20,21]

This underpins a biologically rational division of labor: monotherapy for inherently inflamed PD-L1-high tumors vs chemo-IO for less inflamed or bulky/aggressive disease. [20,21]

2. Randomized evidence and comparative meta-analyses (2022-2025)

2.1 KEYNOTE-189: 5-year outcomes for pembrolizumab-chemotherapy

The 5-year update of KEYNOTE-189 (616 patients, nonsquamous, driver-negative) confirmed the durability of pembrolizumab + pemetrexed/platinum vs chemotherapy alone. [1]

- Intention-to-treat (all PD-L1 levels): OS HR 0.60 (95% CI 0.50-0.72); PFS HR 0.50 (0.42-0.60). [1]
- 5-year OS 19.4% vs 11.3%. [1]
- Benefit persisted across PD-L1 strata, including TPS <1%. [1]

These results reinforce chemo-IO as the preferred backbone in TPS <50%, but they do not directly compare to pembrolizumab monotherapy. [1]

2.2 Pembrolizumab in PD-L1-negative disease: 5-year pooled analysis

A 2024 pooled analysis combined individual patient data from KEYNOTE-189 and KEYNOTE-407 in previously untreated metastatic NSCLC with PD-L1 TPS <1%. [2]

- 442 patients (pembrolizumab + chemo n=255; chemo n=187); median follow-up 60.7 months. [2]
- OS: HR 0.64 (95% CI 0.51-0.79); 5-year OS 12.5% vs 9.3%. [2]
- PFS: HR 0.66 (95% CI 0.54-0.81). [2]
- Grade 3-5 treatment-related AEs in ~60% of both arms. [2]

This firmly establishes pembrolizumab-chemotherapy as a long-term standard in PD-L1-negative metastatic NSCLC. [2]

2.3 Pembrolizumab-specific network meta-analysis: monotherapy vs chemo-IO

Huang et al. (Front Immunol 2024) performed a pembrolizumab-focused systematic review and network meta-analysis including five first-line trials (n=2,878) with nodes for pembrolizumab monotherapy, pembrolizumab + chemotherapy, and chemotherapy alone. [3]

Key findings: [3]

- **PD-L1 TPS ≥50%**:
    - PFS: 10.41 vs 7.41 months (pembro-chemo vs pembro-mono), HR 0.81 (95% CI 0.67-0.97). [3]
    - ORR: RR 1.74 (95% CI 1.25-2.43), favoring chemo-IO. [3]
    - OS: 22.54 vs 22.62 months, HR 0.89 (0.73-1.08) - no significant OS difference. [3]
- **PD-L1 TPS 1-49%**:
    - OS: HR 0.77 (0.62-0.95) for pembro-chemo vs pembro-mono. [3]
- **Safety**: similar rates of any-grade and grade ≥3 immune-related AEs, but significantly higher any-grade and grade ≥3 treatment-related AEs with chemo-IO. [3]

Thus, the NMA quantifies what many clinicians suspected: chemo-IO meaningfully improves early disease control but does not clearly prolong OS in PD-L1-high disease, whereas in PD-L1 1-49% it appears superior on both PFS and OS. [3]

2.4 Broader ICIs + chemotherapy network meta-analyses

A 2024 network meta-analysis of immune checkpoint inhibitor (ICI)-chemotherapy combinations in driver-negative advanced NSCLC compared multiple agents and regimens. [22]

- Pembrolizumab + chemotherapy ranked among the most effective first-line options, with particularly strong disease control and response rates. [22]

- Subgroup analysis suggested that PD-L1 ≥50%, male sex, smokers, and non-squamous histology derived the largest relative benefit from chemo-IO (monotherapy comparators varied). [22]

A complementary 2022 meta-analysis of PD-L1-negative, nonsquamous NSCLC confirmed that ICI-chemotherapy improves ORR, PFS (HR 0.63), and OS (HR 0.68) vs chemotherapy alone. [23]

These analyses reinforce that chemo-IO is the dominant strategy in PD-L1-low/negative disease, while direct comparison to monotherapy in PD-L1-high disease relies on real-world and indirect evidence. [3,22,23]

3. Real-world outcomes with pembrolizumab monotherapy (PD-L1 TPS >=50%)

3.1 Large multicenter cohorts

PEMBROREAL (Italy): Cafaro et al. reported 880 patients with metastatic NSCLC and PD-L1 ≥50% treated with first-line pembrolizumab monotherapy in 16 centers (median follow-up 35.1 months). [4]

- Median PFS 8.6 months (95% CI 7.6-10.0). [4]
- Median OS 25.5 months (21.8-31.6). [4]
- Only 6.3% discontinued for toxicity; 39.9% experienced any AE. [4]
- ECOG PS and PD-L1 level were significant prognostic factors. [4]

United States Flatiron cohort (5-year outcomes): Velcheti et al. examined 804 patients with advanced NSCLC, PD-L1 ≥50%, driver-negative, treated with frontline pembrolizumab monotherapy; median follow-up 60.5 months. [5]

- Median OS 19.2 months (95% CI 16.6-21.4). [5]
- 5-year OS 25.1% (95% CI 21.7-28.7). [5]
- 33% received subsequent systemic therapy; outcomes aligned closely with KEYNOTE-024 in a less-selected population. [5]

Serbian multicenter cohort (Biomedicines 2025): real-world frontline pembrolizumab monotherapy in PD-L1 ≥50% advanced NSCLC in a Central/Eastern European setting. [6]

Japanese national cohort including older patients: Yoh et al. conducted a 23-site study (441 patients, PD-L1 ≥50%) treated with first-line pembrolizumab monotherapy. [7]

- 31% were ≥75 years; for ≥75 years, median OS 23.5 months. [7]

Collectively, these series demonstrate that frontline pembrolizumab monotherapy yields PFS ~7-10 months, OS ~20-26 months, and a 5-year survival tail around 20-30% in routine practice, with manageable toxicity even in older populations. [4-7]

4. Real-world comparisons: pembrolizumab monotherapy vs pembrolizumab-chemotherapy in PD-L1-high disease

4.1 Japanese HOT/NJLCG program

4.1.1 Original Cancer Science cohort (2022)

Ikezawa et al. analyzed 300 consecutive patients with PD-L1 TPS ≥50%, driver-negative NSCLC treated with first-line pembrolizumab monotherapy (MONO, n=166) or pembrolizumab + platinum-based chemotherapy (COMB, n=134). [9]

- COMB patients were younger and more often ECOG 0-1. [9]
- Median PFS: 7.1 vs 13.1 months (MONO vs COMB). [9]
- ORR: 42.2% vs 67.9%. [9]
- Treatment discontinuation ~21-22% in both groups. [9]

4.1.2 Updated Cancer Medicine analysis (2024)

Updated follow-up on 298 patients (MONO n=164; COMB n=134; median follow-up 20.2 months). [10]

- Median OS: 17.2 months (MONO) vs 33.7 months (COMB) in unadjusted analysis. [10]
- After 1:1 propensity score matching (83 pairs), COMB no longer showed a statistically significant OS advantage; PFS remained longer and ORR higher, but adjusted OS converged. [10]
- Grade ≥3 AEs were more frequent with COMB; discontinuation rates were similar. [10]

Conclusion: COMB offers deeper and longer initial control but does not convincingly prolong OS after accounting for confounding, reinforcing the need for selective use. [10]

4.1.3 Elderly subgroup (JJCO 2024)

Subgroup analysis of patients ≥75 years within HOT/NJLCG (81 MONO, 19 COMB). [11]

- PFS: 7.8 vs 8.9 months (MONO vs COMB). [11]
- OS: 14.6 vs 20.3 months; differences not statistically significant. [11]

The authors concluded that MONO is generally appropriate for very elderly PD-L1-high patients, reserving COMB for carefully selected, fit individuals. [11]

4.1.4 Older (≥70 years) cohort with ECOG 0-1 (Front Immunol 2024)

Takei et al. focused on 199 older patients (≥70) with PD-L1 TPS ≥50% and ECOG 0-1 receiving MONO (n=131) or ICI+chemotherapy (COMBO, n=68). [8]

- No significant differences in PFS (10.9 vs 11.8 months) or OS (25.2 vs 42.2 months) after propensity matching. [8]
- In ECOG 0 and non-squamous histology subgroups, COMBO significantly improved PFS and OS. [8]

This suggests that among older but fit, non-squamous patients, chemo-IO may confer a real OS advantage, whereas broader older populations can reasonably receive monotherapy. [8]

4.2 Central European multicenter study (J Cancer 2025)

Svaton et al. assembled 793 stage IV NSCLC patients with PD-L1 ≥50% treated with pembrolizumab alone (P, n=706) or pembrolizumab + chemotherapy (P+CHT, n=87). [12]

- Unadjusted: P+CHT had higher response rate and OS. [12]
- After 2:1 propensity matching, RR remained higher with P+CHT, but OS and PFS differences disappeared. [12]
- Conclusion: P+CHT is useful when a rapid, secure tumor response is required (e.g., bulky symptomatic disease) but does not improve survival endpoints vs monotherapy after adjustment. [12]

4.3 Tumor aggressiveness and burden (Ther Adv Med Oncol 2025)

Lejeune et al. examined 164 PD-L1 ≥50%, ECOG 0-1 patients, stratifying by aggressiveness. [13]

- Using RMST: in the overall cohort, RMST for OS at 36 months was significantly shorter with chemo-IO than monotherapy after adjustment. [13]
- In ECOG 0 and low-burden patients, survival was worse with chemo-IO, likely reflecting toxicity without incremental benefit. [13]
- In aggressive disease subsets, RMST differences narrowed and were not significant. [13]

These data suggest that chemo-IO may harm low-burden, ECOG 0 PD-L1-high patients, while being neutral in high-burden/aggressive cases - cautioning against reflexive chemo-IO use solely due to high PD-L1. [13]

4.4 Histology-restricted and other comparative series

A 2024 real-world study in metastatic lung adenocarcinoma with PD-L1 ≥50% compared pembrolizumab monotherapy vs pembrolizumab-chemotherapy. [14]

- Median OS: 14.2 vs 22.6 months; adjusted HR for death 0.74 (95% CI 0.54-1.00). [14]
- Risk of early death (<3-6 months) was lower with combination (adjusted HR 0.41; 95% CI 0.23-0.76). [14]

Tsai et al. (Pharmaceuticals 2022) reported combination therapy improved PFS but not OS, with greater PFS benefit in patients with low neutrophil-to-lymphocyte ratio (NLR). [15]

Taken together, real-world comparative data in PD-L1 ≥50% can be summarized as:

- Chemo-IO consistently yields higher ORR and often longer PFS. [8-15,17]
- OS differences are small or disappear after rigorous adjustment, with some evidence of harm in low-burden, ECOG 0 subsets. [10,12-14,16,17]

- Chemo-IO reduces early progression/death risk, important for bulky or symptomatic disease. [12-14,17]

5. Evidence in PD-L1 TPS 1-49% and PD-L1 <1%

Direct head-to-head monotherapy vs chemo-IO comparisons are limited in PD-L1-low disease because guidelines and practice favor chemo-IO. [18,19]

5.1 PD-L1 TPS 1-49%

From the pembrolizumab-specific NMA, chemo-IO improved OS vs pembrolizumab monotherapy in TPS 1-49% (HR 0.77). [3]

The 2024 *Medicine* review synthesizes trial and real-world data to conclude that first-line pembrolizumab monotherapy in PD-L1 1-49% has modest efficacy and higher early progression than chemo-IO, whereas KEYNOTE-189/407-type regimens achieve more robust disease control. [20]

ASCO and SITC therefore recommend chemo-IO as default in TPS 1-49%, with monotherapy only for chemotherapy-ineligible patients. [18,19]

5.2 PD-L1 TPS <1%

Beyond the 5-year pooled KEYNOTE-189/407 analysis, a patient-level pooling of East Asian participants with TPS <1% showed pembrolizumab-chemotherapy improved OS and PFS vs chemotherapy alone. [24]

A Chinese multicenter real-world cohort emphasized PD-L1-negative populations and reported improved PFS (and borderline OS benefit) with pembrolizumab-chemotherapy vs platinum doublet ± bevacizumab. [25]

These data, together with meta-analyses, underpin the consensus that pembrolizumab monotherapy should not be used first line in PD-L1-negative NSCLC and that pembrolizumab-chemotherapy is standard of care. [2,23-25]

6. Broader comparative cohorts including PD-L1 ≥1%

A 2025 propensity-matched cohort by Wang et al. analyzed 392 PD-L1 TPS ≥1% patients treated with pembrolizumab monotherapy vs pembrolizumab + chemotherapy. [17]

After matching:

- OS: 31.8 vs 20.7 months; HR 0.67 (95% CI 0.46-0.96). [17]
- PFS: 12.5 vs 7.0 months; HR 0.59 (95% CI 0.43-0.81). [17]
- Greater relative benefit in patients <75 years, ECOG 0-1, TPS 1-49%, and non-squamous histology. [17]
- Grade ≥3 trAEs were more frequent with combination. [17]

This suggests that in unselected PD-L1-positive populations, chemo-IO may confer a durable survival advantage, likely driven predominantly by TPS 1-49%. [3,17]

7. Toxicity profiles: monotherapy vs chemo-immunotherapy

7.1 Monotherapy

Across real-world monotherapy cohorts, grade ≥3 treatment-related AE rates are typically 20-30%, with discontinuation for toxicity in ~5-10%. [4-7]

Common immune-related AEs include thyroid dysfunction, rash, hepatitis, colitis, and pneumonitis; most are manageable with standard algorithms, and fatal events are rare. [4-7]

Long-term toxicity beyond 2 years appears limited, especially once pembrolizumab is stopped. [20,21]

7.2 Pembrolizumab-chemotherapy

Randomized data and pooled analyses show very high overall AE rates and grade ≥3 AEs dominated by chemotherapy toxicities. [1,2]

Real-world chemo-IO cohorts report higher serious AE burden vs monotherapy, with discontinuation due to toxicity varying by age/comorbidity. [8-15,17,25]

Taken together: monotherapy carries lower acute toxicity and cleaner attribution of irAEs, whereas chemo-IO has higher trAE burden but can be justified in fit patients when rapid disease control is needed. [8-15,17]

8. Economic considerations

A 2022 cost-effectiveness analysis compared pembrolizumab monotherapy vs pembrolizumab + chemotherapy in PD-L1 ≥50% NSCLC. [26]

- In nonsquamous NSCLC, P+chemo gained 1.08 QALYs at an incremental cost yielding an ICER above typical U.S. willingness-to-pay thresholds. [26]
- In squamous NSCLC, incremental QALY gain was modest with a much lower ICER. [26]

This suggests routine use of chemo-IO over monotherapy in PD-L1-high nonsquamous disease is economically difficult to justify given modest OS differences, while cost-effectiveness may be more favorable in squamous histology. [26]

9. Mechanistic and biomarker insights informing strategy choice

9.1 Clinical surrogates of tumor biology

Baseline tumor burden and aggressiveness modify benefit. [13,14,17]

Systemic inflammation markers also matter; low NLR may predict larger PFS gains from combination therapy in high PD-L1 patients. [15]

9.2 Age, performance status, and histology

Older-patient studies suggest a niche where chemo-IO may confer OS benefit (older but fit, ECOG 0-1, non-squamous), while very elderly or PS ≥2 may not benefit and may be harmed by toxicity. [7,8,11]

9.3 Broader immunobiologic context

Durable benefit is more likely when tumors have high clonal neoantigen load, intact antigen presentation, and an inflamed TME; STK11/KEAP1-mutant "cold" phenotypes show attenuated benefit and may require combination approaches. [20,21]

10. Integrated clinical perspective (2022-2025)

10.1 PD-L1 TPS ≥50%

Efficacy: Chemo-IO yields higher ORR/longer PFS and reduces early progression/early death. [3,8-15,17]

OS: Often similar after adjustment; occasional subgroup signals favor combination (younger, ECOG 0, non-squamous, high-risk). [8,10,12,14,17]

Toxicity and economics: Higher toxicity and higher costs with chemo-IO; incremental gains may be modest in nonsquamous disease. [1,4-7,13,26]

Clinical stratification (synthesizing 2022-2025 data):

Favors pembrolizumab-chemotherapy up front when: high tumor burden/rapid kinetics; age <75 and ECOG 0-1; aggressive disease; low NLR. [8,12-15,17]

Favors pembrolizumab monotherapy when: low burden/indolent course, ECOG 0-1 (especially low-burden), very elderly (≥75) or PS ≥2, or strong QoL preference. [7,11,13]

Sequential strategies (monotherapy then chemotherapy at progression) can yield similar strategy-level outcomes for many PD-L1-high patients if they remain fit enough for second-line treatment. [5,6,10,21]

10.2 PD-L1 TPS 1-49%

Chemo-IO is superior to pembrolizumab monotherapy for PFS and OS; monotherapy reserved for chemo-ineligible patients. [3,18-20,17]

10.3 PD-L1 TPS <1%

Pembrolizumab-chemotherapy improves OS/PFS vs chemotherapy alone; pembrolizumab monotherapy should not be used first line. [2,23-25]

11. Future directions

The 2022-2025 literature indicates that simple PD-L1 cutoffs are insufficient for full individualization. Priorities include integrated clinical-molecular prediction models, emulated

target trials or prospective comparisons in PD-L1 ≥50% with biomarker-driven stratification, de-escalation studies, and novel combination partners. [3,20,21]

Until such data mature, the most evidence-based approach is to treat pembrolizumab monotherapy and pembrolizumab-chemotherapy as complementary tools: monotherapy as default for PD-L1 high/low burden/frail patients, and chemo-IO as default for PD-L1 low/negative and selectively for PD-L1 high with aggressive disease and sufficient reserve. [1,2,3, 18-20]

Disclosure

Author's contribution

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