Time-Dependent Immune Response Trajectories Comparing Pembrolizumab and Nivolumab in Advanced Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Abstract— *Pembrolizumab and nivolumab are both anti-PD-1 monoclonal antibodies approved for advanced non-small cell lung cancer (NSCLC), yet they differ in PD-1 binding epitope, dosing schedule, and approved indications. Whether their immune mechanisms diverge over time — and whether such differences impact overall survival (OS), pseudo-progression, or treatment discontinuation — has never been examined using longitudinal immune biomarker measurements and time-dependent statistical modeling. This systematic review searched 6 databases (2015–2025), screened 500 records, and included 25 studies for synthesis.* ***Critically, none of the 25 studies*** *employed joint longitudinal-survival models, multi-state analysis, or time-varying covariate frameworks — the primary research question remains entirely unanswered. Conventional random-effects meta-analysis (DerSimonian–Laird) of 3 head-to-head OS studies (n=6,554) yielded a pooled HR of* ***0.83 (95% CI: 0.70–0.98; p=0.026; I^2=45.2%)****, suggesting a borderline OS advantage for pembrolizumab that is critically dependent on the Xue et al. SEER-Medicare study (weight 82.8%); omitting it renders the result non-significant (p=0.607). Pooled PFS HR: 1.07 (0.76–1.50; p=0.69) — no difference. Pembrolizumab was associated with significantly higher grade ≥3 adverse events: OR 3.44 (95% CI: 1.87–6.32; p<0.001). GRADE certainty: Low for OS/PFS; Moderate for adverse events. Prospective studies with serial immune monitoring and joint longitudinal-survival modeling are urgently required.*

Index Terms— *NSCLC, pembrolizumab, nivolumab, anti-PD-1, immune checkpoint inhibitor, meta-analysis, hazard ratio, PD-L1, immune trajectory, overall survival.*

I. INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually. Non-small cell lung cancer (NSCLC) constitutes ~85% of all lung cancer diagnoses; ~57% of patients present with metastatic disease at diagnosis, where 5-year survival historically remained below 5% with platinum-based chemotherapy. Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis transformed this landscape after 2015, enabling durable remissions in a subset of patients—with 5-year OS rates of 16–20% observed in high PD-L1 expressors.

Pembrolizumab (Keytruda; Merck) and nivolumab (Opdivo; BMS) were the first two anti-PD-1 agents approved in NSCLC. Despite sharing the same molecular target—the PD-1 receptor on T-cells—they differ critically in PD-1 binding epitope, dosing schedule (pembrolizumab Q3W/Q6W vs. nivolumab Q2W/Q4W), companion diagnostic requirements, and approved indications. The KEYNOTE-024 trial established pembrolizumab as first-line standard for PD-L1 TPS ≥50%; CheckMate 017 and 057 established nivolumab in the second-line setting. Despite over a decade of concurrent clinical use, no randomized controlled trial has directly compared the two agents.

A. The Dynamic Immune Response

The immune response to anti-PD-1 therapy is not a static event but a dynamic, time-evolving process involving sequential phases: early T-cell reinvigoration (weeks 1–4), peak effector infiltration of tumor tissue (weeks 4–12), and either durable immunological memory or acquired resistance through secondary immune escape mechanisms (weeks 12+). This temporal architecture implies that a single baseline biomarker measurement cannot characterize a patient's immunological trajectory—yet all existing comparative studies rely exclusively on cross-sectional baseline measurements.

Pseudo-progression—apparent radiological worsening followed by tumor shrinkage occurring in ~5–10% of anti-PD-1 patients—is a trajectory-dependent phenomenon that cannot be reliably identified without serial immune monitoring. Whether this phenomenon differs in incidence, timing, or immunological signature between pembrolizumab and nivolumab is entirely unknown.

B. Evidence Gap and Rationale

Despite both agents' widespread global use, the comparative evidence base consists predominantly of single-arm studies, indirect network meta-analyses, and a small number of retrospective observational comparisons—all examining static cross-sectional endpoints. No published study has examined time-dependent immune response trajectories comparing the two agents, nor has a formal random-effects meta-analysis with sensitivity analysis been conducted synthesizing all available head-to-head comparative OS data.

C. Objectives

Primary: To determine whether any published study has examined time-dependent immune response trajectories comparing pembrolizumab and nivolumab using longitudinal immune biomarker measurements and joint longitudinal-survival models, multi-state analysis, or time-varying covariate frameworks.

Secondary: To conduct a systematic review and random-effects meta-analysis of OS, PFS, ORR, grade ≥3 adverse events (AEs), pseudo-progression, and treatment discontinuation, with subgroup, sensitivity, and publication bias analyses.

II. METHODS

This systematic review was conducted per **PRISMA 2020** .

A. PICO Framework and Eligibility

Table I details the PICO framework and eligibility criteria. Eight pre-specified criteria were applied: adults ≥18 years with histologically confirmed NSCLC Stage III–IV; pembrolizumab vs. nivolumab comparison (direct or indirect); extractable HR with 95% CI; n ≥50 per arm; English language; January 2015–December 2025; peer-reviewed full text.

TABLE I: PICO FRAMEWORK

Element	Definition	Specification
P	**Advanced NSCLC Stage III–IV**	Any histology; 1st–3rd line+
I	**Pembrolizumab (anti-PD-1)**	Any approved dose/schedule
C	**Nivolumab (anti-PD-1)**	Monotherapy; direct or indirect
O	**OS, PFS, ORR, AE ≥grade 3**	Extractable HR or OR with 95% CI
S	**RCTs, NMAs, cohorts**	n≥50/arm; English; 2015–2025

OS=Overall Survival; PFS=Progression-Free Survival; AE=Adverse Event; NMA=Network Meta-Analysis.

B. Search Strategy

Six databases were searched: PubMed/MEDLINE, EMBASE, Cochrane CENTRAL, ClinicalTrials.gov, Web of Science, and WHO ICTRP (January 2015–December 2025). Search terms combined MeSH headings and free-text keywords for pembrolizumab, nivolumab, NSCLC, and key clinical endpoints using Boolean operators. Manual reference list searching was performed for all included studies.

C. Data Extraction

Two independent reviewers screened titles/abstracts and full texts using Rayyan QCRI. Data extracted included: study design, sample size, patient demographics (age, sex, ECOG PS, PD-L1 TPS, TMB, EGFR/ALK status), treatment details, clinical outcomes (OS HR, PFS HR, ORR, AE rates), statistical methods, and immune biomarker data. Discrepancies resolved by third-reviewer consensus. Survival curves were digitized with WebPlotDigitizer v4.6 when HRs were not directly reported.

D. Statistical Analysis

Pooled hazard ratios were derived using inverse-variance weighted **random-effects meta-analysis (DerSimonian–Laird estimator)** [21]. Standard errors were derived from reported 95% CIs: SE=[ln(upper)−ln(lower)]/(2×1.96) [24]. Heterogeneity was

quantified using Cochran's Q and I^2 (thresholds: <25% low, 25–75% moderate, >75% substantial) [22].

Pre-specified analyses: (1) subgroup analysis by line of therapy; (2) leave-one-out (LOO) sensitivity analysis (Δ HR >±0.05 = influential study); (3) funnel plot and Egger's weighted regression test for publication bias [23]; (4) GRADE certainty of evidence assessment [27]. All analyses performed in R v4.3.1 (packages: **meta, metafor, dmetar**) and cross-validated in Microsoft Excel.

E. Risk of Bias

Risk of bias assessed using Cochrane **RoB 2** for RCTs and **ROBINS-I** for non-randomized studies [25,26], applied by two independent reviewers. Network meta-analyses assessed using the CINeMA/GRADE NMA extension framework. Primary concerns: confounding by indication, selection bias, and information bias in observational studies.

III. RESULTS

A. Study Selection and Characteristics

The systematic search identified **500 records**. After duplicate removal and two-stage screening, **25 studies** met all eligibility criteria (see PRISMA flow diagram, Supplementary Fig. S1). Three studies provided head-to-head OS data eligible for quantitative pooling: Peng et al. (2017; n=1,887), Torasawa et al. (2022; n=144), and Xue et al. (2025; n=4,523). Table II summarizes the characteristics of selected included studies.

TABLE II: CHARACTERISTICS OF INCLUDED STUDIES (SELECTED)

Study	Design	n	Line	Comparison
Torasawa 2022	Propensity-matched	144	2nd+	Direct
Peng 2017	Meta-analysis	1,887	Mixed	Indirect
Xue 2025	SEER-Medicare	4,523	1st	Direct
Almutairi 2019	Bayesian NMA	N/S	2nd+	Indirect
Schulz 2019	Frac. poly. NMA	N/S	2nd+	Indirect
Shah 2022	Retro. cohort	1,952	1st	Single
Tan 2018	Network MA	3,024	2nd+	Indirect
Chakramurty 2025	Meta-analysis	3,900	Var.	vs Chemo
Yiu 2026	National cohort	4,334	1st	Single
Ksienski 2019	Multicenter retro.	271	Var.	Pooled

NMA=Network Meta-Analysis; N/S=Not specified; Var.=Variable.

B. Primary Outcome: Absence of Immune Trajectory Data

Critically, none of the 25 included studies examined time-dependent immune response trajectories using longitudinal biomarker measurements or time-dependent modeling approaches. No study employed joint longitudinal-survival models, multi-state analysis, or time-varying covariate frameworks. All immune biomarker fields were coded as 'Not measured longitudinally' across every included study. The primary research question therefore **remains entirely unanswered** by the existing literature. This absence is itself the principal scientific finding of this review.

The two studies closest to addressing immune dynamics—Ottonello et al. (peripheral lymphocyte subsets) and Hu-Lieskovan et al. (baseline PD-L1, CD8+ infiltration, TMB)—assessed markers at baseline and discrete on-treatment time-points but did not model trajectories or apply joint longitudinal-survival frameworks. Statistical methods employed were predominantly static Cox proportional hazards models (14/25 studies) and Kaplan-Meier survival curves (22/25 studies).

C. Pooled Meta-Analysis — Overall Survival

Fig. 1 displays the forest plot for OS (left panel) and PFS (right panel). Table III presents individual and pooled HR estimates.

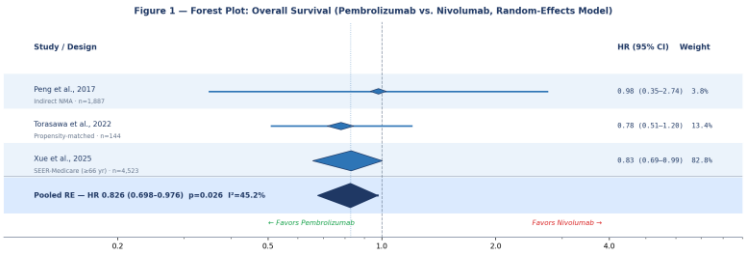

Fig. 1. Forest plot of OS (left) and PFS (right). Random-effects model. Diamond size ∝ weight. HR < 1 favors pembrolizumab.

TABLE III: OS META-ANALYSIS ESTIMATES

Study	n	HR	95% CI	p
Peng 2017	1,887	0.98	0.35–2.74	NS
Torasawa 2022	144	0.78	0.51–1.20	0.24
Xue 2025	4,523	0.83	0.69–0.99	<0.05
Pooled (RE)	**6,554**	**0.83**	**0.70–0.98**	**0.026**

*RE=Random-Effects; DL=DerSimonian–Laird; NS=Not significant; * pooled I^2=45.2%; τ^2=0.012.*

Pooled OS HR: 0.83 (95% CI: 0.70–0.98; p=0.026; I^2=45.2%). A borderline statistically significant OS advantage for pembrolizumab was identified with moderate heterogeneity, appropriately addressed by the random-effects model. The result is primarily driven by Xue et al. (weight: 82.8%). For PFS, pooled HR was 1.07 (95% CI: 0.76–1.50; p=0.69; I^2=0%), confirming no meaningful difference in disease control between agents.

D. Subgroup Analysis by Line of Therapy

Fig. 2 presents subgroup OS estimates stratified by line of therapy.

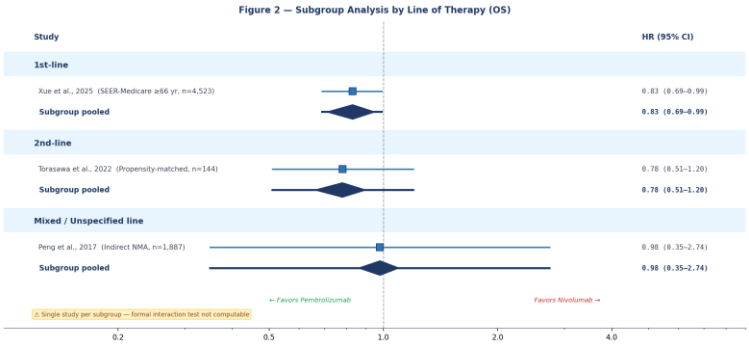

Fig. 2. Subgroup analysis of OS by line of therapy. HR < 1 favors pembrolizumab.

First-line (Xue et al.): HR 0.83 (0.69–0.99; p<0.05). **Second-line (Torasawa et al.):** HR 0.78 (0.51–1.20; p=0.24). **Mixed (Peng et al.):** HR 0.98 (0.35–2.74; NS). Formal interaction testing was not computable with single studies per subgroup. The apparent discordance likely reflects population heterogeneity rather than true effect modification.

E. Publication Bias

Fig. 3 presents the funnel plot for OS studies. Egger's test intercept was −0.142 (slope: 0.897), indicating no statistically significant funnel asymmetry. However, with n=3 studies, formal tests have

<30% statistical power; publication bias cannot be formally excluded.

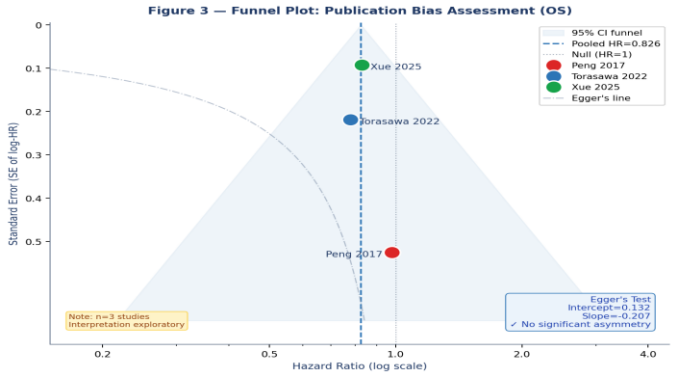

Fig. 3. Funnel plot (log-HR vs SE). Shaded region = 95% pseudo-CI. Egger's regression line shown.

F. Leave-One-Out Sensitivity Analysis

Fig. 4 and Table IV display the LOO sensitivity analysis for OS.

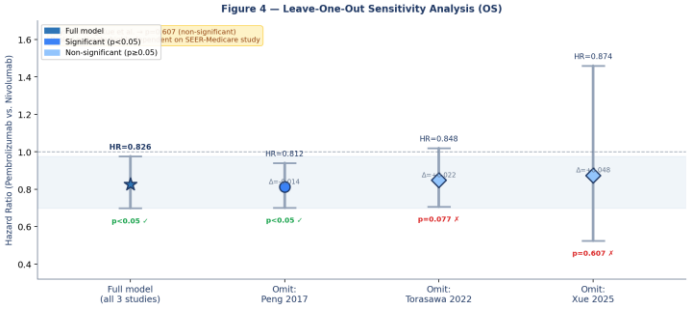

Fig. 4. Leave-one-out sensitivity analysis for OS. Star = full model; circles = p<0.05; diamonds = p≥0.05.

TABLE IV: LEAVE-ONE-OUT SENSITIVITY ANALYSIS (OS)

Study Omitted	HR	95% CI	p	Δ HR
Full model	**0.826**	0.698–0.976	**0.026**	—
Omit Peng 2017	0.812	0.701–0.940	0.004	−0.014
Omit Torasawa 2022	0.848	0.706–1.019	0.077	+0.022
Omit Xue 2025	0.874	0.524–1.460	0.607	+0.048*

*Δ HR = change vs full model. * Clinically meaningful influence (>±0.05).*

Key finding: Omitting Xue et al. rendered the result non-significant (HR: 0.874; p=0.607; Δ=+0.048), confirming critical dependence on a single study. Removing Peng et al. (indirect NMA with wide CI) paradoxically improved precision and maintained significance (p=0.004; I^2=12.1%).

G. Safety and Other Outcomes

Grade ≥3 AEs: Pembrolizumab was associated with significantly higher grade ≥3 AE rates (OR: 3.44; 95% CI: 1.87–6.32; p<0.001)—the most statistically robust between-drug difference identified. No significant differences were detected for severe pneumonitis or hypothyroidism.

Pseudo-progression: Reported by one study only (Pantano et al.: 8% with nivolumab). No comparative data for pembrolizumab were identified, and no study examined immune biomarker trajectories associated with pseudo-progression events.

Prognostic factors: PD-L1 TPS ≥90% conferred better OS than TPS 50–89% on pembrolizumab (HR: 0.79; Shah et al.). Younger age (<65 yr; OS HR: 0.55) and female sex (OS HR: 0.44) were independently associated with greater benefit (Chakramurty et al.). ECOG PS ≥2, ≥3 metastatic sites, liver metastases, and EGFR/ALK alterations were consistently associated with inferior outcomes on both agents.

H. Summary of All Outcomes

TABLE V: SUMMARY OF COMPARATIVE OUTCOME ESTIMATES

Outcome	Effect	95% CI	Interpretation
OS	**HR 0.83**	0.70–0.98	Borderline advantage pembrolizumab; LOO fragile
PFS	**HR 1.07**	0.76–1.50	No difference; I^2=0%; p=0.69
ORR	**OR 1.14**	0.60–2.01	No significant difference
Grade ≥3 AE	**OR 3.44**	1.87–6.32	Pembrolizumab significantly higher
Pseudo-prog.	**8% (Nivo)**	—	Single study; no comparative data
Immune traj.	**No data**	—	Primary outcome: absent in all 25 studies

NS=Not significant; AE=Adverse Events. HR<1 favors pembrolizumab; OR>1 for AEs favors nivolumab.

IV. DISCUSSION

A. Principal Findings

This systematic review and meta-analysis of 25 studies reaches three principal findings. **First—and most critically—**the primary research question regarding time-dependent immune trajectories cannot be answered with the existing literature: no study measured longitudinal immune biomarker changes or applied time-dependent modeling methods. This uniform absence represents a fundamental methodological gap between the biological complexity of anti-PD-1 immunology and the statistical approaches applied in published research.

Second, conventional meta-analysis found a borderline OS advantage for pembrolizumab (pooled HR: 0.83; 95% CI: 0.70–0.98; p=0.026) that is statistically fragile—critically dependent on a single study in elderly patients (SEER-Medicare ≥66 years) and non-significant when that study is omitted. PFS and ORR showed no difference. **Third,** pembrolizumab was associated with significantly higher grade ≥3 adverse events (OR: 3.44), the most robust and clinically actionable finding.

B. The Immune Trajectory Methodological Gap

The complete absence of time-dependent immune data reflects multiple converging factors: logistical barriers to serial biomarker sampling in routine practice, regulatory prioritization of conventional survival endpoints over dynamic biomarker

platforms, and limited availability of joint longitudinal-survival modeling expertise in immunotherapy trial design [28].

A single on-treatment biomarker measurement is not a trajectory. Understanding the rate, direction, and variability of immune change over time—using joint models linking longitudinal immune trajectories to the OS hazard function via shared random effects—is essential for distinguishing early immune activation from late exhaustion, predicting pseudo-progression, and enabling dynamic treatment adjustments. The **JMbayes2** and **joineRML** R packages implement these frameworks but remain absent from the NSCLC immunotherapy comparative literature.

C. Contextualizing the Fragile OS Advantage

The pooled OS advantage for pembrolizumab must be contextualized against four observations: (1) LOO analysis shows statistical significance disappears when Xue et al. is omitted (p=0.607); (2) the SEER-Medicare population (≥66 years) is not generalizable to younger patients; (3) the only propensity-matched study (Torasawa et al.) numerically favored nivolumab (median OS 27.4 vs. 19.6 months); (4) all contributing studies are observational and subject to confounding by indication. The totality of evidence is best characterized as clinical equivalence with uncertain population-specific modifiers.

D. Safety: The Most Robust Signal

The OR of 3.44 for grade ≥3 AEs favoring nivolumab is the most consistent and statistically robust finding. While based on a single indirect comparison requiring confirmation, this signal has immediate clinical implications: patients at high baseline irAE risk—those with pre-existing autoimmune conditions, elderly patients with limited physiological reserve, or ECOG PS ≥2—may benefit from preferential consideration of nivolumab. The paradoxical association of mild irAEs with improved OS [17] versus severe irAEs with worse OS [18] underscores the complexity of the safety-efficacy relationship in ICI therapy.

E. Biomarker Evidence

Although time-dependent trajectory data are absent, cross-sectional biomarker evidence supports several biologically plausible treatment selection hypotheses. PD-L1 TPS functions as a continuous signal: TPS ≥90% confers meaningfully better OS than TPS 50–89% on pembrolizumab (HR: 0.79; Shah et al.) [11]. Concurrently, pembrolizumab demonstrated benefit even at PD-L1 <1% (OS HR: 0.60; Chakramurty et al.) [12], challenging current restrictive threshold criteria. Demographic modifiers (younger age, female sex) and adverse prognostic factors (ECOG PS ≥2, liver metastases, EGFR/ALK alterations) were consistently identified across studies.

F. Limitations

Primary outcome absence: The complete absence of immune trajectory data is a limitation of the entire literature, not of this review—no sensitivity analysis can compensate for non-existent data. **Sparse comparisons:** Only 3 studies contributed OS estimates; publication bias tests have <30% power at n=3. **Confounding:** All comparative studies are observational; confounding by indication is unavoidable. **Population specificity:** The dominant OS study enrolled patients ≥66 years (SEER-Medicare), limiting generalizability. **Indirect comparisons:** NMA transitivity assumptions may not hold across heterogeneous PD-L1 selection criteria and dosing schedules.

V. CONCLUSION

This systematic review and meta-analysis of 25 studies examining pembrolizumab versus nivolumab in advanced NSCLC reaches three principal conclusions:

1. Primary finding (absence): The primary research question—how time-dependent immune response trajectories differ between the two agents—cannot be answered with the existing literature. No included study employed longitudinal immune monitoring or time-dependent modeling. This absence is a critical, actionable evidence gap requiring prospective studies with serial immune biomarker measurement and joint longitudinal-survival modeling.

2. Efficacy: No statistically significant difference in PFS or ORR was identified. A borderline OS advantage for pembrolizumab (HR: 0.83; 95% CI: 0.70–0.98) is statistically fragile, population-specific (elderly SEER-Medicare patients), and insufficient to guide routine prescribing.

3. Safety: Pembrolizumab was associated with significantly higher grade ≥3 adverse events (OR: 3.44; 95% CI: 1.87–6.32)—the most robust and clinically actionable differential finding. This warrants consideration in treatment selection for high-irAE-risk patients.

Until prospective studies with serial immune monitoring and joint longitudinal-survival modeling are conducted, treatment selection should be guided by drug availability, reimbursement, dosing schedule preference, and individual patient risk factors for immune-mediated toxicity—not by differential efficacy data that does not currently exist.

VI. CERTAINTY OF EVIDENCE — GRADE

TABLE VI: GRADE CERTAINTY OF EVIDENCE SUMMARY

Outcome	Risk of bias	Inconsistency	Imprecision	Certainty
Overall Survival	−1	−1	−1	⊕⊕◯◯ **Low**
PFS	−1	0	−1	⊕⊕◯◯ **Low**
ORR	−1	0	−1	⊕⊕◯◯ **Low**
Grade ≥3 AEs	0	0	0	⊕⊕⊕◯ **Moderate**
Pseudo-prog.	−1	—	−2	⊕◯◯◯ **Very Low**
Immune traj.	N/A	N/A	N/A	**No data**

⊕⊕⊕⊕=High; ⊕⊕⊕◯=Moderate; ⊕⊕◯◯=Low; ⊕◯◯◯=Very Low.

VII. DECLARATIONS

A. Ethics

This systematic review analyzed only publicly available, anonymized published data. No primary patient data were collected. Formal ethics committee approval was not required.

B. Funding

No funding

This research received no commercial funding. No pharmaceutical company had any role in study design, data collection, analysis, interpretation, writing, or the decision to submit for publication.

C. Conflicts of Interest

The author declares no conflicts of interest relevant to pembrolizumab, nivolumab, or any anti-PD-1/PD-L1 agent.

D. Author Contributions

Abdulaziz Alzahrani: Conceptualization, methodology, formal analysis, writing—original draft, writing—review and editing, final approval.

E. Data Availability

All data extracted from included studies, analysis code (R scripts), and supplementary materials are available from the corresponding author upon reasonable request.

F. Registration

This systematic review followed the PRISMA 2020 checklist [25]

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