Real-world Effectiveness and Safety of First-line Pembrolizumab Monotherapy for Patients With Advanced or Metastatic Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis

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INTRODUCTION

- Pembrolizumab was approved in the USA for its use as a first-line treatment for metastatic non-small cell lung cancer (NSCLC) patients with a high level of programmed death ligand-1 (PD-L1) expression. This approval was based on the results of the KEYNOTE-024 clinical trial.[1,2]
- This study undertakes a meta-analysis aiming to evaluate the effectiveness and safety of pembrolizumab monotherapy as first-line treatment for PD-L1 positive advanced or metastatic NSCLC.

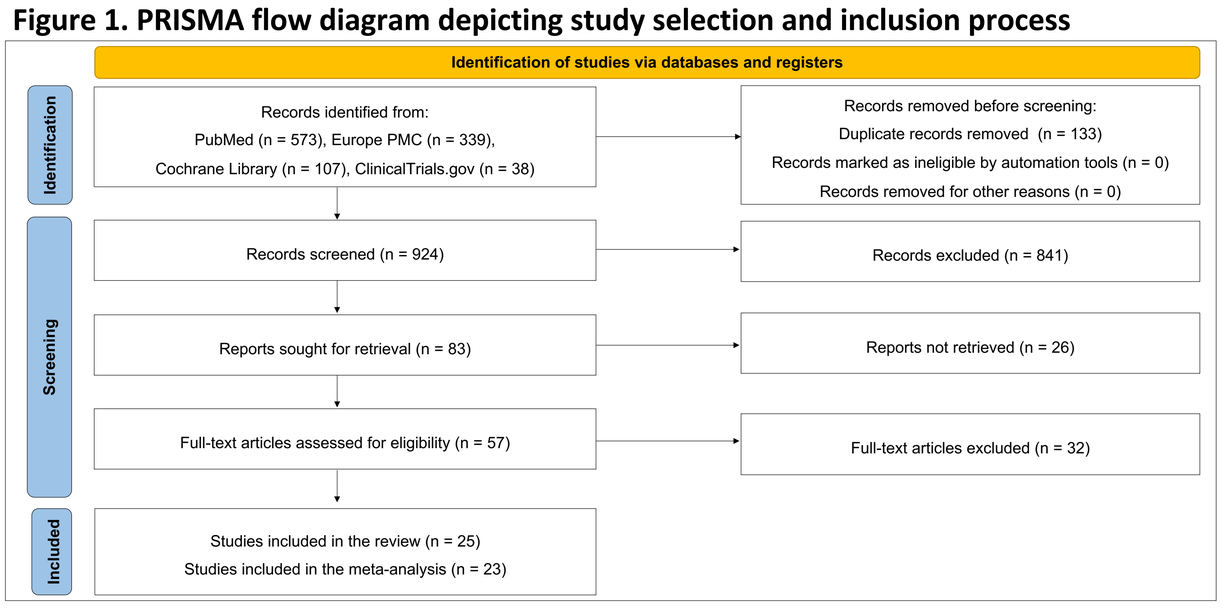
METHODS

- A comprehensive search was conducted across PubMed, Europe PMC, ClinicalTrials.gov, Google Scholar, and conference proceedings from ASCO, ESMO, and IASLC congress (2021-2023). Additionally, bibliographic search of relevant systematic reviews was performed.
- **Inclusion criteria:** Observational studies evaluating the effectiveness or safety of pembrolizumab monotherapy as a first-line treatment for PD-L1 positive advanced or metastatic NSCLC were included. Outcomes of interest included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), or safety parameters.
- **Exclusion criteria:** Studies assessing only geriatric patients, patients with a tumor proportion score of less than 1%, or studies not available freely.
- The National Institutes of Health (NIH) quality assessment tool for observational studies was used to assess the quality of included studies.
- A meta-analysis of proportions was performed in R software using a standard random-effects model. Cochran's Q-test and I^2 statistics were calculated to assess heterogeneity across studies.

RESULTS

- Twenty-five studies with 7,855 patients were included in the review (**Figure 1**).[3-27]
- Characteristics of the studies included in the review are presented in **Table 1.**
- All studies were either of fair or good quality according to NIH quality assessment tool.
- Visual inspection of funnel plots revealed no to minimal levels of publication bias.

Figure 1. PRISMA flow diagram depicting study selection and inclusion process



PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

Table 1. Characteristics of the included studies

Study Name (Country)	Study Design	Sample Size	Follow-up, Median (range/ 95% CI/ IQR)	Tumor PD-L1 expression	NIH Quality of Evidence
Bérard, 2023 (Canada)[4]	Retrospective cohort	279	7.53 (0.03 to 26.84) months	≥50%: 276 (98.9), <50%: 2 (0.7), Unknown: 1 (0.4)	Fair
Decroisette, 2023 (France)[10]	Retrospective cohort	845	45 (44.1, 45.9) months	>75%: 413 (48.9)	Good
Faoro, 2023 (Italy)[12]	Retrospective cohort	98	13 months	<75%: 46 (46.9), ≥75%: 52 (53.1)	Good
Pons-Tostivint, 2023 (France)[19]	Retrospective cohort	243	11.5 (10.4-13.3) months	90-100%: 59 (41.8), 50-89%: 82 (58.2)	Good
***Rittberg, 2023** (Canada)[20]	Retrospective cohort	718	16 months	≥50%: 718 (100)	Good
***Tamayo-Bermejo, 2023** (Spain)[21]	Retrospective cohort	62	3 (1 to 38) months	≥50%: 31 (93.94), 1-19%: 2 (6.06)	Good
Goto, 2022 (Japan)[14]	Retrospective cohort	441	13.5 (<0.1 to 26.9) months	≥50%: 441 (100)	Good
Ikezawa, 2022 (Japan)[15]	Retrospective cohort	300	10.6 (0.1 to 20.6) months	50-89%: 101 (60.8), ≥90%: 60 (36.1), ≥50% (details are unknown): 5 (3.1)	Good
Matsumoto, 2022 (Japan)[18]	Retrospective cohort	96	379 (58 to 1169) days	1-49%: 1 (2.1), ≥50%: 46 (97.9)	Good
Tibaldi, 2022 (Italy)[24]	Retrospective cohort	205	15.2 months	≥50%: 205 (100)	Good
Velcheti, 2022 (USA)[26]	Retrospective cohort	EHR cohort, n = 566; Spotlight cohort, n = 228	EHR cohort: 35.1 (12.0-52.7) months, Spotlight cohort: 38.4 (33.1-44.9) months	EHR cohort, ≥50%: 566 (100), Spotlight cohort, ≥50%: 228 (100)	Good
Cavaille, 2021 (France)[5]	Retrospective cohort	41	7.60 months	50-70%: 14 (34.1), 71-89%: 10 (24.4), 90-100%: 17 (41.5)	Good
Chen, 2021 (China)[6]	Retrospective cohort	206	17.13 months	≥50%: 91 (100)	Good
Cramer-van der Welle, 2021 (The Netherlands)[9]	Retrospective cohort	83	NR	≥50%: 83 (100)	Fair
Dudnik, 2021 (Israel)[11]	Retrospective cohort	256	22.3 [14.5 to 28.9] months	≥90%: 32 (16), <90%: 68 (33), ≥50% (details are unknown): 103 (51)	Fair
Geiger-Gritsch, 2021 (Austria)[13]	Retrospective cohort	89	16.9 (0.2 to 28.2) months	1-49%: 1 (2.4), ≥50%: 41 (97.6)	Good
Ivanovic, 2021 (Slovenia)[17]	Prospective cohort	26	19.9 months	≥50%: 26 (100)	Good
Isono, 2021 (Japan)[16]	Retrospective cohort	71	12 (0.4 to 40.3) months	≥50%: 37 (97.4), 1-49%: 1 (2.6)	Good
Velcheti, 2021 (USA)[25]	Retrospective cohort	EHR cohort, n = 423; Spotlight cohort, n = 188	EHR cohort: 18.4 (6.2-28.7) months, Spotlight cohort: 15.5 (10.0-22.1) months	EHR cohort: ≥90%: 423 (100), Spotlight cohort: ≥90%: 188 (100)	Good
Yamaguchi, 2021 (Japan)[27]	Retrospective cohort	72	NR	50-75%: 31 (NR), >75%: 41 (NR)	Fair
Amrane, 2020 (France)[3]	Retrospective cohort	108	8.2 (0.9 to 20.9) months	≥50%: 108 (100)	Fair
Cortellini, 2020a (Italy)[7]	Retrospective cohort	877	14.8 months	≥50%: 877 (100)	Fair
Cortellini, 2020b (Germany)[8]	Retrospective cohort	1026	14.6 (13.5, 15.6) months	≥50%: 1026 (100)	Fair
Tambo, 2020 (Japan)[22]	Retrospective cohort	95	8.8 months	≥50%: 95 (100)	Good
Tamiya, 2019 (Japan)[23]	Retrospective cohort	213	11.0 months	50-74%: 97(45.5), 75-89%: 47 (22.1), 90-100%: 69 (32.4)	Good

**Not included in meta-analysis. CI: Confidence interval; EHR: Electronic health record; IQR: Inter quartile range; NIH: National Institutes of Health ; PD-L1: Programmed death-1 ligand 1.*

Effectiveness

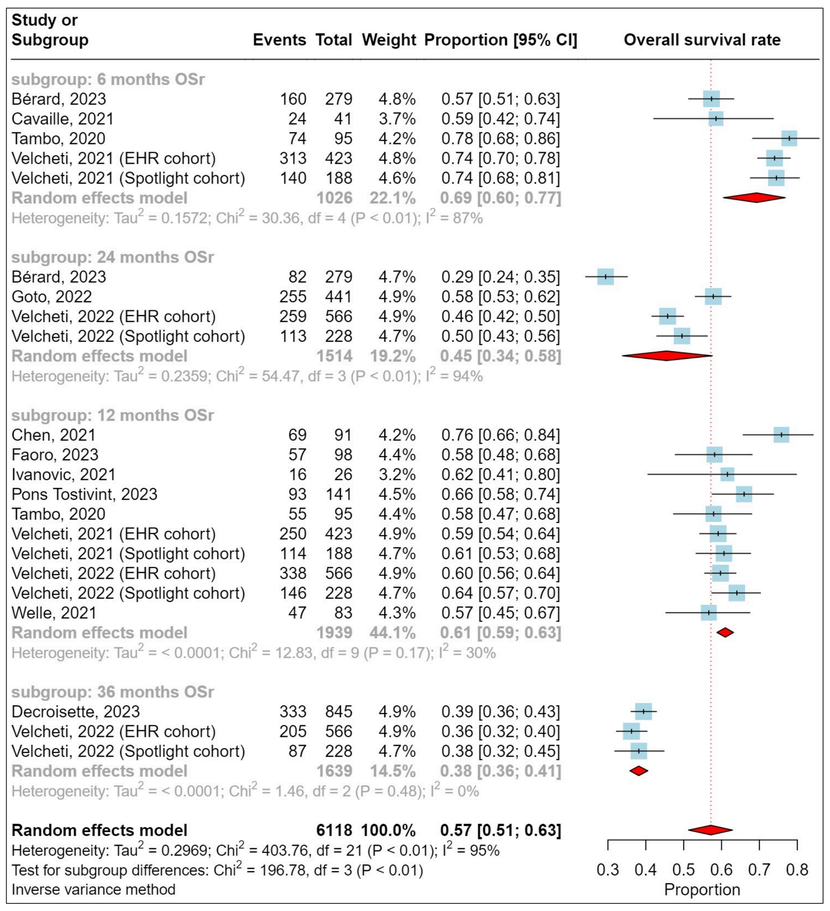
- Pembrolizumab monotherapy as a first-line treatment demonstrates notable effectiveness in improving OS and PFS in PD-L1 positive advanced or metastatic NSCLC patients (**Table 2**).
- The pooled survival rates at 6, 12, and 36 months were as follows:
  - **OS:** 69%, 45%, and 38%, respectively
  - **PFS:** 60%, 33%, and 20%, respectively.
- Additionally, the pooled ORR was found to be 46%.

Table 2. Summary of results from single-arm meta-analysis on pembrolizumab

Outcomes	Proportion (95% CI)	Heterogeneity: I^2
Overall survival rate (OSr) – 6 months[4-5,22,25]	0.69 [0.60, 0.77]	87%
Overall survival rate (OSr) – 12 months[6,9,12,17,19,22,25-26]	0.61 [0.59, 0.63]	30%
Overall survival rate (OSr) – 24 months[4,14,26]	0.45 [0.34, 0.58]	94%
Overall survival rate (OSr) – 36 months[10,26]	0.38 [0.36, 0.41]	0%
Progression-free survival rate (PFSr) – 6 months[3-4,22,25]	0.60 [0.50, 0.69]	84%
Progression-free survival rate (PFSr) – 12 months[4,14,26]	0.41 [0.36, 0.47]	64%
Progression-free survival rate (PFSr) – 24 months[14,19,22,25-26]	0.33 [0.25, 0.43]	86%
Progression-free survival rate (PFSr) – 36 months[10,26]	0.20 [0.11, 0.33]	92%
Objective response rate (ORR)[3,7-8,13,15-19,22-23,26-27]	0.46 [0.43, 0.49]	42%
Complete response (CR)[3,5,15-16,18-19,22,25-26]	0.05 [0.04, 0.07]	1%
Partial response (PR)[3,5,15-19,22,25-27]	0.42 [0.37, 0.47]	66%
Stable disease (SD)[3,5,15-19,22,25-27]	0.20 [0.16, 0.24]	57%
Progressive disease (PD)[3,15-16,18-19,22-23,26-27]	0.25 [0.23, 0.28]	0%

CI: Confidence interval.

Figure 2. Forest plot for overall survival rate of pembrolizumab



CI: Confidence interval; EHR: Electronic health record; OSr: Overall survival rate.

Safety

- The evidence revealed incidence of all-grade treatment-related adverse events (TRAEs), immune-related adverse events (IRAEs), and pneumonitis to be 37%, 54%, and 22%, respectively (**Table 3**).
- The respective grade ≥3 incidence rates were 12%, 7%, and 5%.
- Rate of pembrolizumab discontinuation due to AEs was 15%.

Table 3. Safety analysis of pembrolizumab

Outcomes	Proportion (95% CI)	Heterogeneity: I^2
All grade Pneumonitis[16,18,27]	0.22 [0.16, 0.29]	0%
All grade IRAEs[7,22,27]	0.37 [0.34, 0.40]	32%
All grade TRAEs[3,18,24]	0.54 [0.45, 0.62]	54%
Grade 3+ Pneumonitis[15-16,18,23-24,27]	0.05 [0.04, 0.08]	34%
Grade 3+ IRAEs[4-5,7,16,22]	0.12 [0.09, 0.16]	48%
Grade 3+ TRAEs[3,11,18]	0.07 [0.05, 0.10]	0%
Discontinuation due to AEs[4-5,7,14-16,18-19,25-26]	0.15 [0.13, 0.18]	71%

AEs: Adverse events; CI: Confidence interval; IRAEs: Immune-related AEs; TRAEs: Treatment-related AEs.

CONCLUSIONS

Real-world evidence for the effectiveness and safety of pembrolizumab is consistent with the findings of KEYNOTE-024 and KEYNOTE-042 trials. The congruence of results lends support to pembrolizumab monotherapy use as first-line treatment for improving outcomes of advanced or metastatic NSCLC.

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