A Systematic Literature Review (SLR) of Real-World Evidence (RWE) on the First-Line Treatment of Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC) with Immunotherapy

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Background

- NSCLC accounts for 85% of diagnoses of lung cancer with most cases diagnosed at the metastatic stage, with advanced stages reportedly having considerably worse five-year survival in comparison to earlier stages of disease (8% vs 64%)[1–3]
- The cornerstone treatment for treatment-naive advanced NSCLC had been platinum doublet chemotherapy (PDC) until 2016, when new immunotherapy drugs began to be introduced, with promising results observed in randomised controlled trials (RCTs). However, results from RCTs are not easily generalisable and discrepancies in efficacy may occur between RCTs and clinical practice[4,5]
- The objective of this SLR was to conduct a review of RWE published since 2016 regarding the first-line treatment of advanced, metastatic, or recurrent NSCLC with existing immunotherapies in order to understand the treatment patterns, patient outcomes and potential data gaps[5]

Methods

- MEDLINE, Embase and the Cochrane Library searches were conducted in March 2023, supplemented by searches of congresses since 2019, clinical trial registries and the reference lists of relevant SLRs. Articles were screened for eligibility based on pre-specified PICOS criteria (**Table 1**)
- Due to the large volume of evidence identified and to ensure the most relevant evidence was included in the review, journal articles and conference proceedings published after 2019 and 2020, respectively, and studies with at least 50 participants were prioritised
- The SLR was performed in accordance with a pre-specified protocol and the methodological principles of conduct for SLRs as detailed in the University of York Centre for Reviews and Dissemination's (CRD) "Guidance for Undertaking Reviews in Health Care"

Table 1. PICOS Criteria

Domain	Inclusion	Exclusion
Population	Adult patients (≥18 years of age) with advanced, metastatic or recurrent NSCLC: patients with stage IIIB, IIIC or IV disease; studies with patients only specified as "stage III" were only eligible if patients with stage IV were also included within the study population	Patients without NSCLC; patients <18 years; patients with non-metastatic or earlier stages of disease (including locally advanced); studies where outcomes were not presented separately for the patients of interest; patient groups selected for a specific mutation, including but not limited to *EGFR*, *ALK* and *BRAF*
Intervention	Studies reporting on first-line immunotherapy treatments (as monotherapy, or as a combination treatment with PDC) including: nivolumab, nivolumab + ipilimumab, pembrolizumab, atezolizumab, durvalumab or cemiplimab	Studies not investigating a relevant intervention; durvalumab (when used as consolidative therapy)
Comparator	Any relevant intervention of interest; PDC: combination chemotherapy treatments, including but not limited to cisplatin, carboplatin, paclitaxel, nab-paclitaxel, gemcitabine, pemetrexed; BSC; none	Any other comparator, including single-agent chemotherapy
Outcomes	Clinical efficacy outcomes: survival (e.g., OS, PFS); ORR (including CR and PR); DoR; disease progression Safety outcomes: AEs (including TRAEs and serious AEs); deaths; discontinuation due to AEs/TRAEs	Studies not presenting relevant outcomes for the population of interest
Study design	The following observational studies: prospective cohort studies, retrospective cohort studies, database or registry studies, case-control studies	Any other study designs: RCTs or interventional non-RCTs; economic evaluations; cross-sectional studies; non-systematic or narrative reviews; case reports/case studies/case series
Publication type	Peer reviewed journal articles published in or since 2016; letters, if they reported primary research; congress abstracts published in or after 2019	Publications published prior to 2016; any other publication type, including studies not reporting any original research and non-peer-reviewed studies (e.g., narrative reviews, commentaries); SLR/NMAs unless they presented original research (n.b. included for hand-searching at title/abstract stage, but excluded at full-text stage); conference abstracts published prior to 2019
Other considerations	Human subjects; English language abstract/full text	Not in human subjects, no relevant data in English language

Abbreviations: AE, adverse event; **BSC**, best supportive care; **CR**, complete response; **DoR**, duration of response; **(N)MA**, (network) meta-analysis; **NSCLC**, non-small cell lung cancer; **ORR**, overall response rate; **OS**, overall survival; **PDC**, platinum doublet chemotherapy; **PFS**, progression-free survival; **PR**, partial response; **RCT**, randomised controlled trial; **SLR**, systematic literature review; **TRAE**, treatment-related AE.

Results

Included studies

- Of 4,855 records retrieved, 131 publications reporting on 105 unique studies were included in the SLR after evidence prioritisation (**Figure 1**)
- Baseline characteristics were representative of the real-world NSCLC population, with the median patient age ranging from 61 to 80 years, with most studies including more male patients than female. Nineteen studies included >50% of patients with ECOG performance status (PS) 1 (able to carry out work) followed by 5 and 3 studies for PS 2 (capable of self-care but unable to carry out work) and 0 (fully active), respectively
- The most reported outcome was overall survival (OS) (n=91 studies), followed by progression-free survival (PFS) (n=76) and overall response rate (ORR) (n=51)
  - Included studies investigated pembrolizumab as monotherapy (n=86) or in combination with PDC (n=29), with limited studies investigating atezolizumab plus PDC (n=2). No RWE data were identified for first-line nivolumab based regimens
  - As pembrolizumab monotherapy received regulatory approval in the United States (US) for first-line treatment of patients with metastatic NSCLC in 2016, earlier than the regulatory approvals for first-line pembrolizumab + PDC (2018), atezolizumab + PDC (2019), nivolumab plus ipilimumab-based combinations (2020), it is not unexpected that more RWE is available for pembrolizumab monotherapy than the other interventions discussed in this SLR

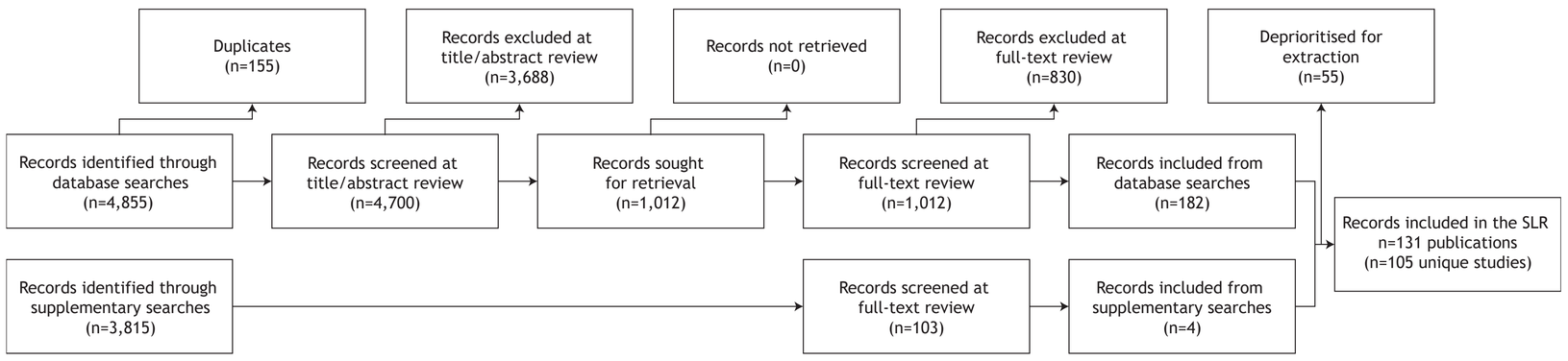
RWE versus clinical trial evidence

A side-by-side view of the median OS and PFS reported in the main clinical trials and RWE studies identified in the SLR is provided in **Table 2**, with differences in the key efficacy outcomes observed

Conclusion

- Although a substantial amount of RWE was identified regarding the first-line use of pembrolizumab for patients with advanced or metastatic NSCLC, future RWE data with longer-term follow-up are warranted to capture the evolving evidence for more recently approved immunotherapies
- The observation of poorer survival outcomes relative to RCTs further emphasises the need for RWE studies to assess immunotherapy effectiveness outside of controlled environments

Figure 1. PRISMA Flow Diagram

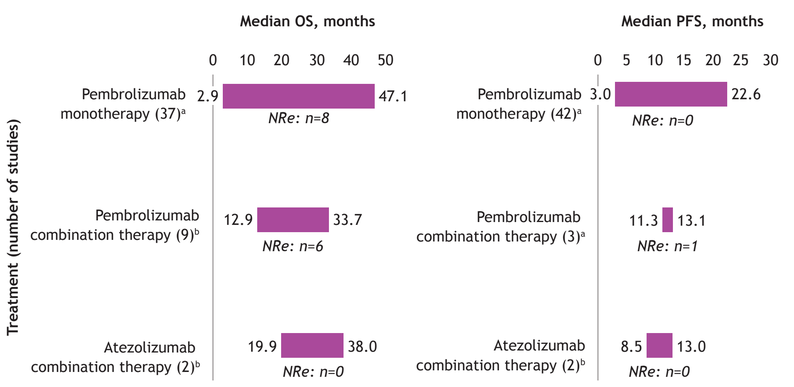


Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SLR**, systematic literature review.

Survival and response outcomes

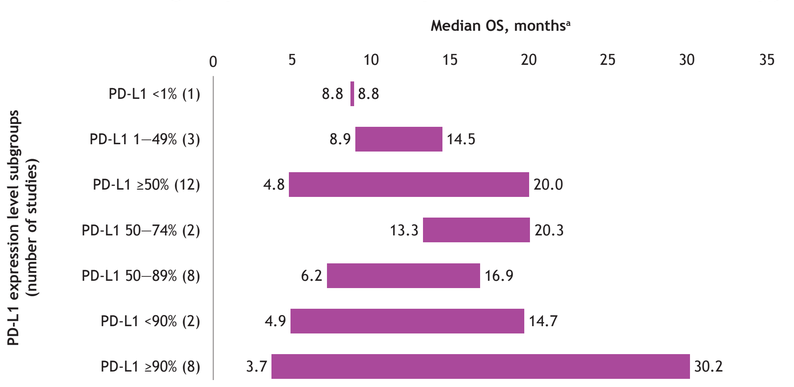
- Median OS ranged from 2.9 to 47.1 months, whereas median PFS ranged from 3.0 to 22.6 months across all identified studies and treatments (**Figure 2**)
- Median OS and PFS for patients with tumor programmed cell death ligand 1 (PD-L1) ≥50% ranged from 4.8 to 20.0 months and 3.2 to 9.2 months, respectively across studies reporting results for more than one PD-L1 expression subgroup. Improved OS and PFS with increased PD-L1 expression levels for pembrolizumab monotherapy were seen (**Figure 3** and **Figure 4**)
  - Median OS was significantly higher in the PD-L1 ≥90% subgroup compared with the PD-L1 50–89% subgroup in three studies (p<0.01)
  - Three studies reported statistically significant hazard ratios (HR) favouring the PD-L1 ≥90% subgroup compared with the PD-L1 50–90% subgroup for PFS (p<0.05), with two reporting a non-significant favourable HR for the PD-L1 50–90% subgroup (p>0.05)
- Median OS (n=7, any PD-L1 level) and PFS (n=3, PD-L1 ≥50%) were higher for patients treated with pembrolizumab combination therapy compared with pembrolizumab monotherapy
  - No clear relationship between treatment efficacy and tumour histology (n=12 studies) was observed
- ORR ranged from 37.6% to 67.9% across after treatments in patients with PD-L1 ≥50% (**Figure 5**). Pembrolizumab combination therapy was found to result in a higher ORR compared with pembrolizumab monotherapy in three studies

Figure 2. Range of reported median OS and PFS in patients with NSCLC



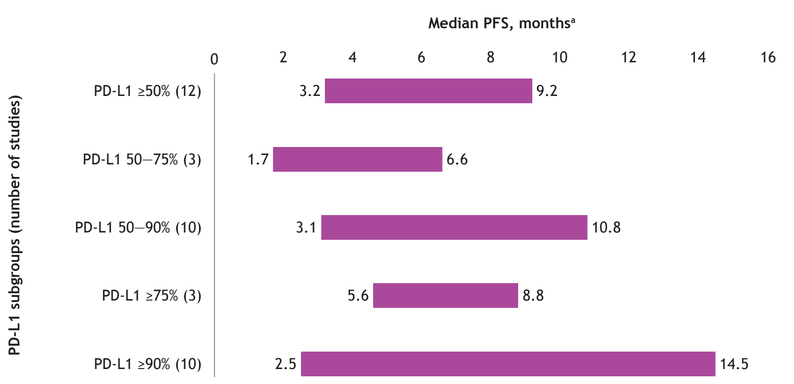
[a]Range for patients with PD-L1 >50%; [b] Range for all patients (any PD-L1 level). Does not include studies where data were stratified by subgroups with no overall results reported. **Abbreviations: NRe**, not reached; **NSCLC,** non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **PD-L1**, programmed cell death ligand 1.

Figure 3. Median OS across different PD-L1 expression subgroups treated with pembrolizumab monotherapy



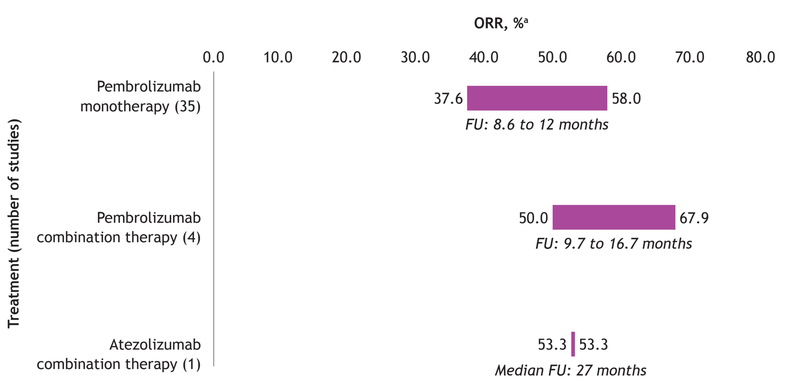
[a]To note that not all studies reported data for each of the PD-L1 subgroups listed in the figure.
Abbreviations: OS, overall survival; **PD-L1**, programmed cell death ligand 1.

Figure 4. Median PFS across different PD-L1 expression subgroups treated with pembrolizumab monotherapy



[a]To note that not all studies reported data for each of the PD-L1 subgroups listed in the figure.
Abbreviations: PFS, progression-free survival; **PD-L1**, programmed cell death ligand 1.

Figure 5. Range of reported ORR in patients with NSCLC with PD-L1 ≥50%



[a]Range reported exclusive to PD-L1 ≥50% subgroup and does not include studies where this group was split into further subgroups, with no overall results reported. **Abbreviations: FU**, follow-up; **NSCLC,** non-small cell lung cancer; **ORR**, overall response rate; **PD-L1**, programmed cell death ligand 1.

Safety outcomes

- Safety outcomes were reported in 40 studies, with 29 studies reporting outcomes for pembrolizumab monotherapy, 14 for pembrolizumab combination therapy, and only two for atezolizumab combination therapy
  - The proportion of patients experiencing adverse events (AEs) and immune-related adverse events (irAEs) was found to be mostly consistent across treatments and identified studies

Table 2. A side-by-side view of the median OS and PFS reported in RWE identified in the SLR versus published clinical trials

Treatment	PD-L1 status	Median PFS (months)	Median OS (months)
PEMBROLIZUMAB MONOTHERAPY	All ≥50%	KEYNOTE-024 trial[6]: 7.7 Kehl 2022[7]: NR	KEYNOTE-024 trial[6]: 26.3 Kehl 2022[7]: 11.4
PEMBROLIZUMAB COMBINATION THERAPY*	≤1%	KEYNOTE-189 trial[8]: 6.2 Alessi 2022[9]: 5.2 Liu 2022[10]: 5.0 Velcheti 2020[11]: 3.7 Velcheti 2021[12]: 5.0	KEYNOTE-189 trial[8]: 17.2 Alessi 2022[9]: 13.1 Liu 2022[10]: 13.2 Velcheti 2020[11]: 8.9 Velcheti 2021[12]: 13.2
	1–49%	KEYNOTE-189 trial[8]: 9.4 Alessi 2022[9]: 6.1 Liu 2022[10]: 5.7 Velcheti 2020[11]: 9.7 Velcheti 2021[12]: 5.9	KEYNOTE-189 trial[8]: 21.8 Alessi 2022[9]: 14.6 Liu 2022[10]: 16.9 Velcheti 2020[11]: 18.0 Velcheti 2021[12]: 16.3
	≥50%	KEYNOTE-189 trial[8]: 11.3 Liu 2022[10]: 9.3 Velchetti 2020[11]: 10.9 Velcheti 2021[12]: 8.8	KEYNOTE-189 trial[8]: 27.7 Liu 2022[10]: 20.6 Velchetti 2020[11]: 20.6 Velcheti 2021[12]: 20.6

To note that exact eligibility criteria would differ between that used in the clinical trials and the included studies in the RWE SLR and direct comparisons are not warranted. *These studies only included patients with NS NSCLC. **Key:** Blue: Clinical trial data; Pink: RWE. **Abbreviations: OS,** overall survival; **PFS,** progression-free survival; **PD-L1,** programmed cell death ligand 1; **NS,** non-squamous; **NR,** not reported.

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Acknowledgements

All authors contributed to and approved the presentation. This study was funded by Bristol Myers Squibb, Uxbridge, London, UK. Editorial and design support were provided by Costello Medical and funded by Bristol Myers Squibb.