

Effectiveness of Immune Checkpoint Inhibitors + Chemotherapy vs Immune Checkpoint Inhibitor Monotherapy in Untreated Locally Advanced/Metastatic Non-Small Cell Lung Cancer: A Targeted Literature Review

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CONCLUSIONS

- Clinical outcomes generally favor ICI + CT over ICI monotherapy in untreated locally advanced/metastatic NSCLC patients with ≥50% PD-L1 expression, according to the identified RWE studies
- More research is needed to confirm patient subgroups benefitting from ICI + CT or ICI monotherapy
- For ICI + CT interventions, OS, PFS, and ORR estimates in RCTs were similar to those reported in RWE studies. However, outcomes for patients receiving ICI monotherapy were better in RCTs than in RWE studies; this discrepancy needs to be understood to enable clinicians to make informed treatment decisions
- It is important to note that while our study provides useful insights on specific research questions of the TLR, it has inherent limitations of the TLR study design, which are narrow scope, selection bias, and limited generalizability

INTRODUCTION

- Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases. With the 5-year survival rate of approximately 26.1%, NSCLC presents a significant health challenge¹
- Recently there was a shift in the NSCLC treatment landscape with the emergence of immune checkpoint inhibitors (ICIs), beginning with approval of pembrolizumab for first-line treatment in 2016²⁻⁴
- In Europe, ICIs are commonly recommended for untreated locally advanced/metastatic NSCLC with ≥50% programmed death-ligand 1 (PD-L1) expression, based on randomized controlled trials (RCTs).^{4,5} However, real-world evidence (RWE) suggests some patients benefit more from immuno-oncology (IO) plus chemotherapy (ICI + CT) compared to ICI alone^{2,6}
- The objectives of this review were to:
 - Identify and summarize relevant RWE literature on clinical outcomes in NSCLC patients with ≥50% PD-L1 expression, comparing ICI + CT versus ICI monotherapy
 - Identify patient subgroups who may benefit from ICI + CT or ICI monotherapy
 - Compare RWE outcomes with those from RCTs

METHODS

- A protocol-driven targeted literature review (TLR) was conducted in August 2024 to identify RWE studies on overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and adverse events (AEs)
- Searches in Embase and MEDLINE were conducted from inception to August 2024, and relevant abstracts were screened by a single reviewer (10% sample abstracts/full texts validated by a second reviewer). A manual search of abstracts from 2023 and 2024 was also conducted to identify any recent RWE studies unpublished as full-text manuscripts
 - Articles were selected according to their suitability to answer the research questions
 - Relevant RCTs (phase 2 and 3) were identified using a separate systematic literature review

Table 1. PICOS Criteria

Element	Criteria for Inclusion	Criteria for Exclusion ^a
Population	Adults with locally advanced/metastatic NSCLC (defined as IIIB/IV NSCLC), with ≥50% PD-L1 expression, receiving 1L treatment	Patients with resectable NSCLC (stage I to IIIA), locally advanced NSCLC indicated for chemoradiotherapy; patients with ECOG >1; patients with <i>EGFR</i> mutations or ALK gene translocations
Intervention	IO monotherapy regimens	Interventions that are not listed in the inclusion criteria
Comparator(s)	IO + chemotherapy regimens	Comparators that are not listed in the inclusion criteria
Outcomes	OS, PFS, ORR Overall grade 3+ TEAEs, overall SAEs, treatment discontinuations QoL	If outcomes are not of interest. Outcomes are not separable for population of interest, in cases of mixed populations where ≤80% patients are eligible for inclusion ^b
Study design	RWE, including prospective and retrospective studies; RCTs ^c	Single-arm clinical trials, systematic literature reviews, narrative literature reviews, case studies, letters to editor, and other study types not listed in the inclusion criteria
Geography	No limitations	NA
Date limit	2019 to present day ^d	Published before cut-off date ^d
Sample size	No limitation	NA
Language	English-only abstracts	Articles published in languages other than English

^aStudies which are not fully compliant with the PICOS criteria (eg, mixed outcomes data) were also considered for inclusion in the review, if they were close to being compliant, and are considered by the researcher to be highly relevant for answering one of the research questions. ^bThe threshold of ≥80% of participants meeting inclusion criteria was selected as it is commonly used in evidence reviews supporting clinical guidelines and is recommended in IQWiG methods.⁷ ^cThe electronic database searches did not identify RCTs. RCT data were included from another SLR. ^dThe time limit was selected due to the first regulatory approval of IO monotherapies occurring in 2015² and 2017² and assumed that relevant real-world evidence became available afterwards. The RCTs, which were sourced from the SLR previously conducted, had no time limit associated with them. **Abbreviations:** ALK, anaplastic lymphoma kinase; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IO, immuno-oncology; NA, not available; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial; RWE, real-world evidence; SAE, serious adverse event; SLR, systematic literature review; TEAE, treatment-emergent adverse event.

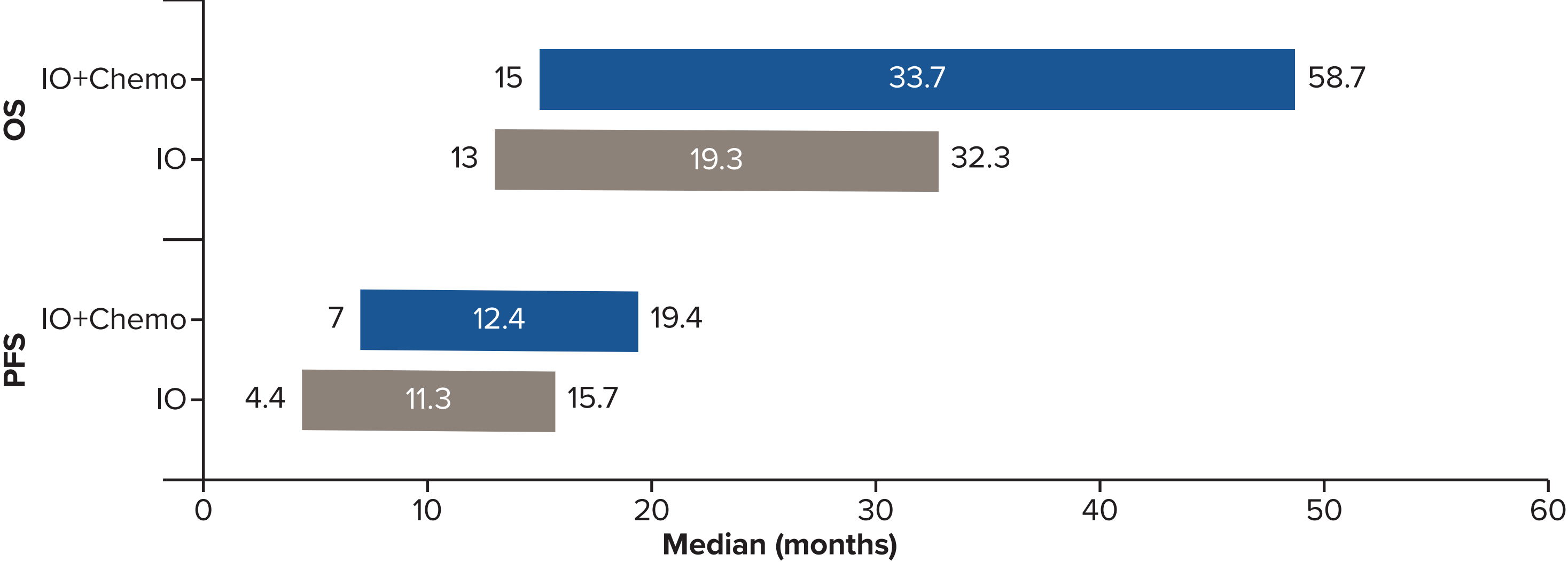
RESULTS

- After screening 193 abstracts, 17 RWE publications were included relating to 10 unique studies that reported relevant clinical, safety, and subgroup data. The studies not meeting the predetermined population, interventions and comparisons, outcomes, and study design (PICOS) criteria were excluded from the TLR

ICI + CT vs ICI Monotherapy in RWE Studies

- OS outcomes were reported in eight studies,^{6,8-14} PFS outcomes in six studies,^{8,13} and ORR in three studies^{9,10,13}
- Overall, OS outcomes generally favored ICI + CT over ICI monotherapy (**Figure 1**)
 - Median OS was statistically significantly higher for ICI + CT compared with ICI monotherapy in one RWE study (33.7 months vs 17.2 months; hazard ratio [HR], 95% confidence interval [CI]: 0.63, 0.46-0.86; $P=0.045$)¹¹ and followed the same trend in three other studies^{9,10,12}
 - In four studies, the median OS was similar between ICI + CT and ICI monotherapy arms^{6,8,13,14}
- Similar to OS, PFS outcomes generally favored ICI + CT over ICI monotherapy, despite the limited amount of evidence (**Figure 1**)
 - Median PFS was statistically significantly higher for ICI + CT compared with ICI monotherapy in one study (13.1 months vs 7.1 months; HR, 95% CI: 0.65, 0.47-0.89)¹¹ and followed the same trend in three other studies^{9,10,12}
 - In two studies, the median PFS was similar between arms^{8,13}
- Across three studies, ICI + CT demonstrated a higher ORR, with rates ranging from 59.8%¹³ to 68.7%,¹¹ compared with 30.3%⁹ to 47.1%¹³ for ICI monotherapy^{9,11,13}
- AEs, including overall grade 3+ AEs and treatment discontinuation, were reported in two primary studies,^{11,15} whereas overall serious AEs were not reported in any of the studies
 - In one trial, patients in the ICI + CT arm reported a higher incidence of grade 3+ TEAEs (31.3% vs 26.8%) and a lower rate of treatment discontinuation (64.9% vs 82.9%) compared to patients in the ICI monotherapy arm¹¹

Figure 1. Real-World Evidence Key Findings for Overall Survival and Progression-Free Survival

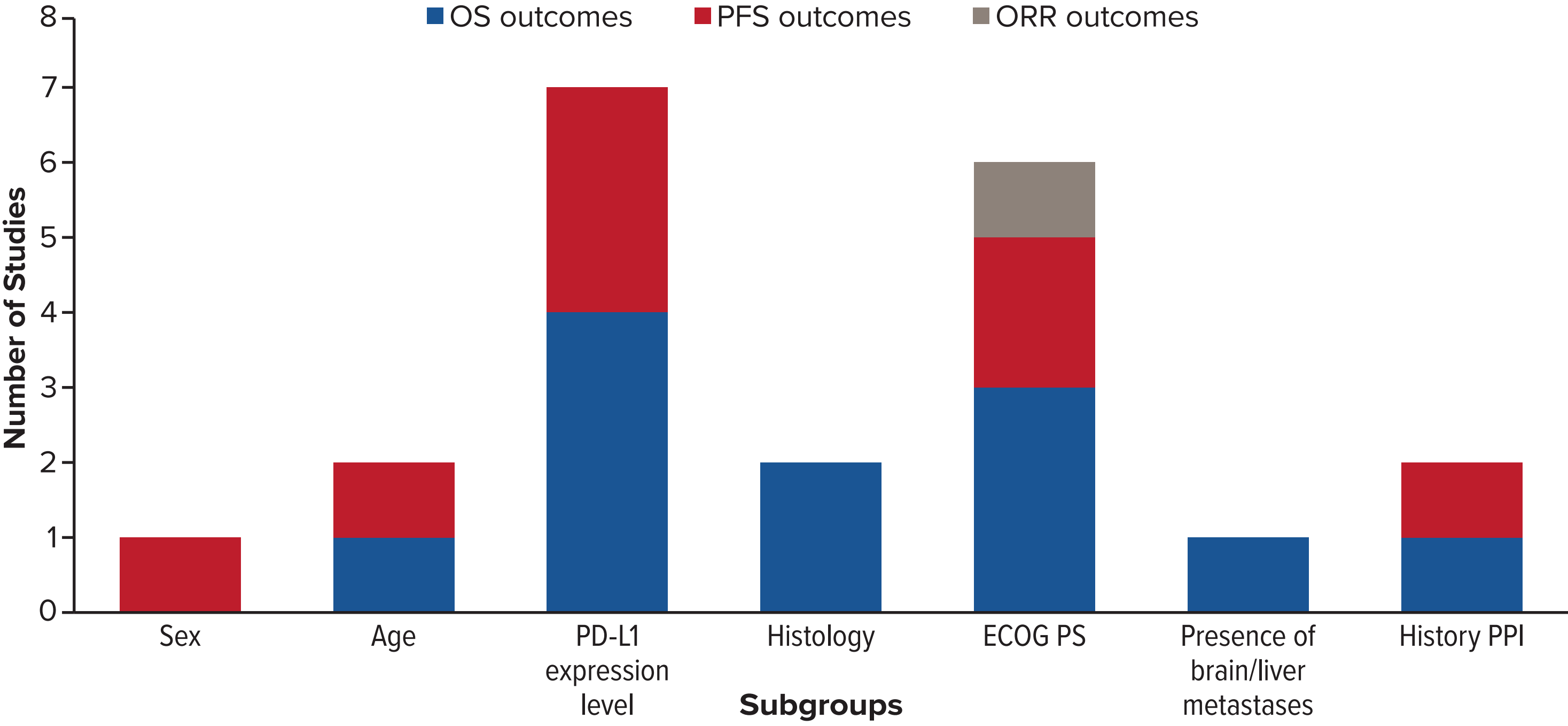


Abbreviations: Chemo, chemotherapy; IO, immuno-oncology; OS, overall survival; PFS, progression-free survival.

Subgroups That Benefit From ICI + CT or ICI Monotherapy

- In RWE reporting subgroup data, patients generally benefitted from ICI + CT regimens, regardless of age or PD-L1 expression levels
- Some subgroups showed a trend favoring ICI + CT, including women, PD-L1 ≥50%, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, and history of proton pump inhibitor use
- Conversely, some subgroups showed a trend towards a benefit in favor of ICI monotherapy, including men and patients with liver or brain metastases
- Results based on histology were inconclusive; a summary of available data for the subgroups is presented in **Figure 2**

Figure 2. Summary of Available Data for Subgroups (Real-World Evidence)



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor.

ICI Monotherapy: RWE vs RCT

- OS, PFS, and ORR outcomes were reported in three RCTs: KEYNOTE-024,^{16,17} KEYNOTE-598,¹⁸ and KEYNOTE-042.¹⁹⁻²¹ Among RWE studies, eight, six, and three RWE studies reported OS, PFS, and ORR, respectively. Safety events were reported in two RWE studies
- OS rates were higher in RCTs:
 - RCTs 24-month OS (n=2): 45%¹⁹ and 71%¹⁷; RWE (n=2): 41.9%¹¹ to 43.5%²²
 - Median OS commonly not reached in RCTs
- PFS was higher in RCTs:
 - RCTs 12-month PFS (n=2): 42.1%¹⁸ and 52%¹⁷; RWE (n=1): 50%¹³
 - RCTs median PFS (n=3): 6.5¹⁹ to 14.6¹⁷ months; RWE (n=6): 4.37¹² to 11.3 months¹³
- ORR was higher in RCTs (RCTs [n=3]: 39.1% to 67%; RWE [n=3]: 30.3%⁹ to 47.1%)¹³
- Grade 3+ AEs were generally higher in RCTs (RCTs [n=3]: 19.7% to 50.2%; RWE [n=2]: 23.7%¹⁵ and 26.8%)¹¹

ICI + CT: RWE vs RCT

- OS, PFS, and ORR outcomes were reported in two RCTs for the subgroup of patients with PD-L1 ≥50%: KEYNOTE-407^{9,23,24} and KEYNOTE-189²⁵ (vs eight, six, and three RWE studies, respectively). None of the RCTs reported safety events specifically for the patient subgroup with PD-L1 ≥50%
- OS was similar between RCT and RWE studies despite limited availability of data:
 - RCTs 12-month OS (n=2): 63.4%²³ and 73.3%²⁵; RWE (n=2): 57%⁶ and 70.2%¹³; RCTs 24-month OS (n=1): 52.2%²⁵; RWE (n=1): 57.3%¹¹; OS rates in a subgroup of China were lower (RCT: 48.7% at 12 months, 37.6% at 24 months)^{9,24}
 - Median OS was not reached in one RCT²³ and reached at 27.7 months²⁵ in another. In the RWE studies, median OS ranged from 15 months¹⁴ to 33.7 months¹¹ across six studies. Median OS was not reached in two RWE studies^{9,13}
- Median PFS was similar between RCT and RWE studies:
 - RCTs 12-month PFS (n=2): 48.8%²⁵ and 15.3%^{9,24} (China); RWE: not reported
 - RCTs median PFS (n=2): 8 months²³ and 11.1 months²⁵ (4.2 months^{9,24} in a subgroup of patients from China); RWE (n=6): 7 months¹⁰ to 13.1 months¹¹
- ORR was similar between RCT and RWE (RCTs [n=2]): 62.1%²⁵ and 30.1%⁹ (China); RWE (n=3): 59.8%¹³ to 68.7%¹¹
- A key limitation of comparing RWE and RCT studies was population heterogeneity—patients in RCTs were generally younger, had lower ECOG PS, and fewer brain metastases than those in RWE populations

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DISCLOSURES

EP, SM, and MAT are employees of BeOne Medicines. **MF and CWM** are employed by PPD Evidera Health Economics & Market Access, Thermo Fisher Scientific.

ACKNOWLEDGMENTS

Evidera, a business unit of PPD, part of Thermo Fisher Scientific, Ltd received support from BeOne Medicines to conduct this study. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Ethan Maughan, MSc, and Pip White, PhD, from Source Health Economics and supported by BeOne Medicines.