Trial-Ineligible Patients Receiving Immune Checkpoint Inhibitors for Advanced NSCLC: A Systematic Review of Real-World Evidence

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Introduction

- Pivotal immune checkpoint inhibitor (ICI) trials in advanced non-small cell lung cancer (NSCLC) used restrictive eligibility criteria.
- Trial-ineligible patients are nonetheless treated routinely, while treatment and coverage decisions rely on trial evidence.
- To our knowledge, how consistently real-world ICI studies have reported trial-ineligible patients and their outcomes has not been systematically summarized.

Objectives

- To assess how consistently prespecified trial-eligibility–related domains are reported in real-world ICI studies.
- To summarize reported overall survival (OS) differences by trial eligibility and individual eligibility-related characteristics.

Methods

Data Sources

- MEDLINE (via PubMed), Embase, and Web of Science
- Studies published from 2014 to 12 June 2026 (date of last search)

Eligibility

- Full-text, peer-reviewed real-world studies of ICI in advanced/metastatic NSCLC reporting trial eligibility or outcomes by a prespecified eligibility-related characteristic.
- Studies reporting access or utilization outcomes only, preprints, and conference abstracts were excluded.

Study Selection

- Titles and abstracts were screened hierarchically in three sequential stages (primary clinical studies, real-world study design, and ICI use in advanced NSCLC), followed by full-text assessment against the eligibility criteria (Figure 1).

Prespecified Trial-Eligibility–Related Domains

ECOG PS ≥2 · Brain metastases · Autoimmune disease · Corticosteroid use · Organ dysfunction

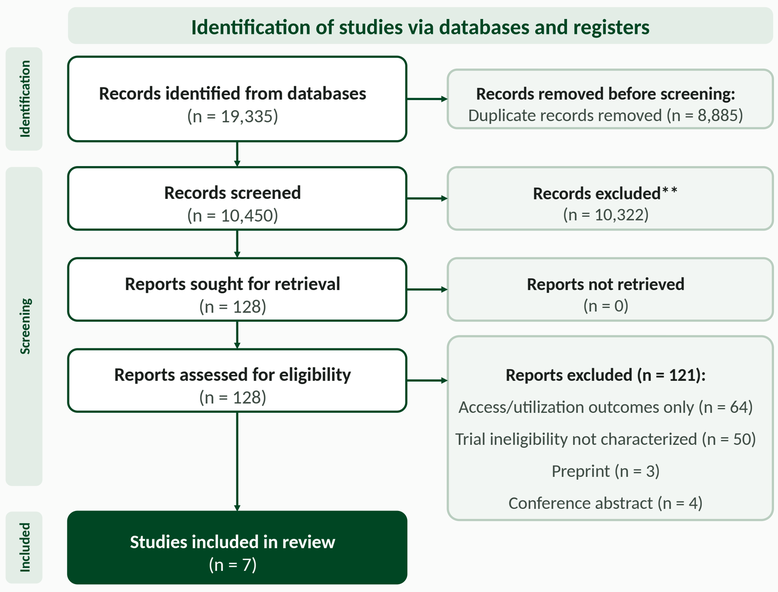
Outcomes

- **Primary:** number of studies reporting each prespecified domain, either as prevalence or as an explicit criterion in a composite eligibility classification.
- **Secondary:** domain-specific and composite eligibility–based OS comparisons.

Synthesis

- Findings were synthesized narratively because of heterogeneity in populations, definitions, and outcomes.

Figure 1. PRISMA 2020 flow diagram



**Excluded at hierarchical title/abstract screening.

Results

- Of 19,335 records identified and 10,450 screened, seven studies met inclusion criteria: first-line (n=2), later-line (n=1), and mixed/all-line (n=4)[a] (Table 1).

Table 1. Characteristics of included studies

Study	Country / data source / design	ICI line	ICI	N	Main comparison
Griesinger 2024	Germany; CRISP prospective registry	First-line	Pembrolizumab	746	Trial eligibility
Rittberg 2023	Canada; BC Cancer retrospective cohort	First-line	Pembrolizumab	718	ECOG PS
Abbas 2022	Australia; single-centre retrospective cohort	Later-line	Nivolumab	66	ECOG PS
Tang 2022	Australia; EnRICH prospective cohort	Mixed[a]	ICI ± chemotherapy	454 (216 ICI)	Trial eligibility
Hu 2024	USA; single-centre retrospective cohort	Mixed	PD-(L)1 ± CTLA-4 ± chemo	125[b]	Clinical characteristics
Jemielita 2021	USA; Flatiron retrospective EHR cohort	Mixed	Pembrolizumab	3,877	ECOG PS + organ function
Morinaga 2023	Japan; multicentre retrospective cohort	Mixed	Nivolumab / pembrolizumab	676	Age; ECOG PS

Table 2. Patient characteristics: prevalence and survival reporting

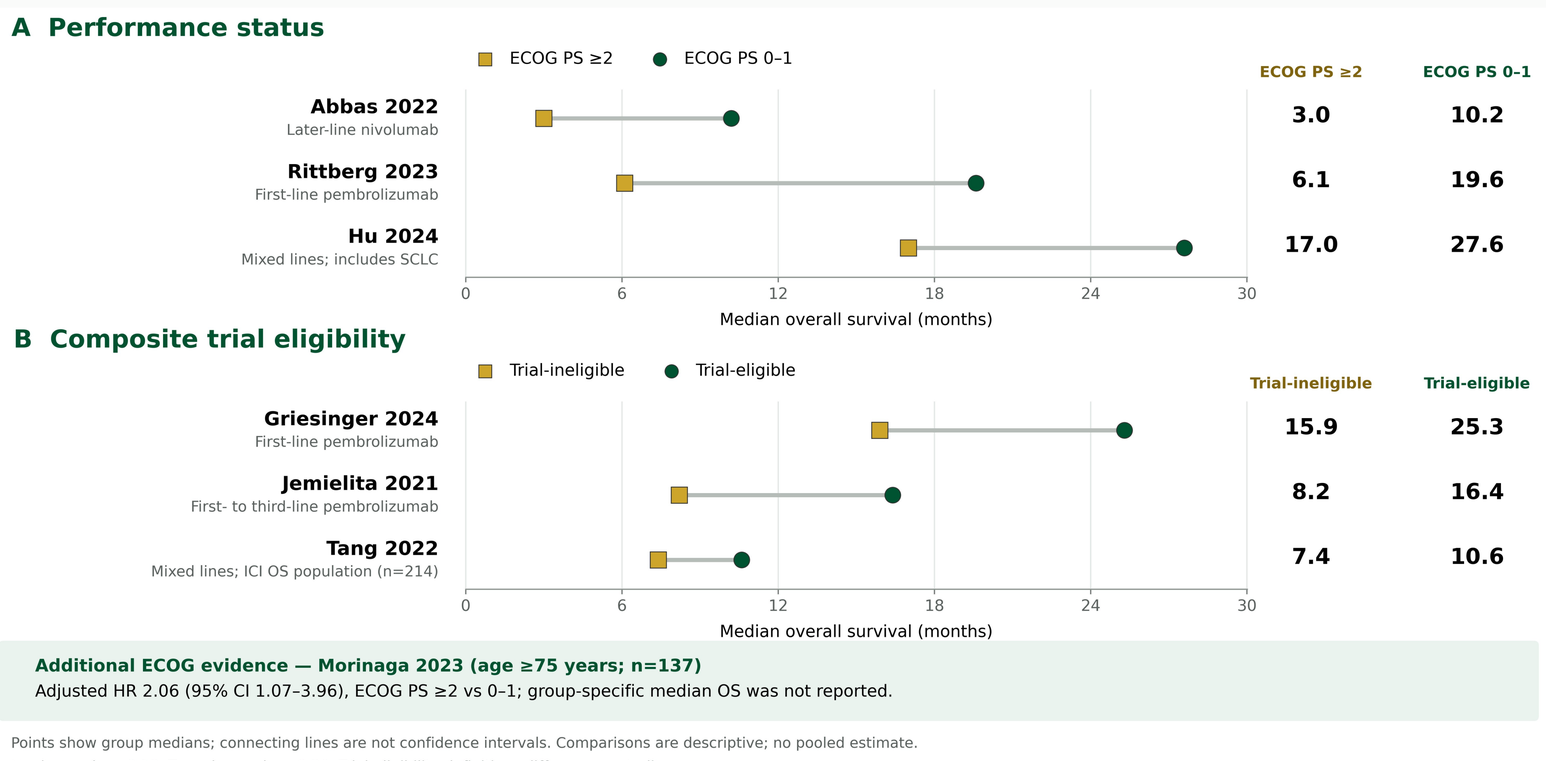
Study	ECOG PS ≥2	Brain metastases	Autoimmune disease	Corticosteroid use	Organ dysfunction
Griesinger 2024	16%	23%	—	—	—
Rittberg 2023	**39%***	9%	—	—	—
Abbas 2022	**39%***	26%	—	—	—
Tang 2022	20%	—	2%	15%	26%
Hu 2024	**35%***	**21%***	**13%***	—	—
Jemielita 2021[c]	*Criterion only*	—	—	—	*Criterion only*
Morinaga 2023	**19%***	—	—	8%†[d]	—
Domain reported	**7/7**	**4/7**	**2/7**	**2/7**	**2/7**
OS: median or HR	**4/7**	**1/7**	**1/7**	**0/7**	**0/7**
OS: curve only	**0/7**	**0/7**	**0/7**	**1/7**	**0/7**

Dark green (*): median OS or HR reported.
Light green: prevalence reported, without median OS or HR.
† Kaplan–Meier curve only. — Not reported.

Percentages are prevalence in the full study cohorts, not the proportion classified as trial-ineligible. Criterion only: used in a composite eligibility classification; separate prevalence not reported. Morinaga OS analyses were restricted to patients aged ≥75 years.[d] Shading and symbols indicate reporting type, not prevalence magnitude or statistical significance.

- ECOG PS was addressed in all seven studies, but numeric domain-specific OS estimates were available in only four. Outcome reporting for other domains was sparse.
- In two studies assessing trial eligibility at ICI initiation, 46–47% of ICI recipients were classified as trial-ineligible.[e]

Figure 2. Median overall survival by performance status and trial eligibility



Additional ECOG evidence — Morinaga 2023 (age ≥75 years; n=137)
Adjusted HR 2.06 (95% CI 1.07–3.96), ECOG PS ≥2 vs 0–1; group-specific median OS was not reported.

Points show group medians; connecting lines are not confidence intervals. Comparisons are descriptive; no pooled estimate.
Hu: log-rank p=0.18. Tang: log-rank p=0.20. Trial-eligibility definitions differ across studies.

- Median OS was shorter with ECOG PS ≥2 and among trial-ineligible patients in all six studies reporting group medians, although statistical significance was not consistently demonstrated.
- One study reported OS by autoimmune disease status, with no statistically significant difference (not reached vs 22.7 months, p=0.79).[b]
- No study reported median OS or HR estimates for corticosteroid use or organ dysfunction. One study presented a Kaplan–Meier comparison by prednisolone dose.[d]

Limitations

- Definitions, treatment lines, and populations varied; some OS analyses were restricted to subgroups, and one cohort included SCLC.
- Observational OS differences do not establish differences in the treatment benefit of ICIs.

Conclusions

- Reporting of trial-eligibility–related characteristics was uneven across real-world ICI studies.
- ECOG PS was the most consistently reported domain, and poorer performance status was associated with shorter survival estimates. Outcome evidence for other domains was sparse.
- More consistent definitions and outcome reporting for autoimmune disease, corticosteroid use, and organ dysfunction are needed to inform treatment and coverage decisions for patients treated outside pivotal-trial eligibility criteria.

References

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3. Abbas MN, et al. Cancer Rep. 2022;5(3):e1487.
4. Tang M, et al. Lung Cancer. 2022;166:40–48.
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6. Jemielita T, et al. JCO Clin Cancer Inform. 2021;5:849–858.
7. Morinaga D, et al. Cancer Med. 2023;12:11525–11541.

Notes

[a] Tang 2022 was counted as first-line in the submitted abstract and reclassified as mixed on full extraction (72.2% first-line, 27.8% second-line or later).
[b] Hu 2024 cohort includes SCLC (16.8%).
[c] Jemielita 2021 used ECOG PS and organ function in a composite eligibility classification but did not report their separate prevalence.
[d] Domain-specific OS was counted as numeric when median OS or HR was reported. Morinaga 2023 presented OS by prednisolone dose (≥10 vs <10 mg/day or none) in patients ≥75 y as a Kaplan–Meier curve (log-rank p=0.0935) without median OS or HR; the 8% prevalence reflects any steroid use at ICI initiation in the full cohort and does not correspond to the ≥10 mg/day group.
[e] Among cohorts classifying eligibility at ICI initiation (Griesinger 46.0%, Jemielita 47.1%). Tang 2022 (assessed at diagnosis): 56.5% of ICI recipients were not trial-typical.

Abbreviations

ECOG PS, Eastern Cooperative Oncology Group performance status; **EHR**, electronic health record; **HR**, hazard ratio; **ICI**, immune checkpoint inhibitor; **KM**, Kaplan–Meier; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **SCLC**, small cell lung cancer.

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