Clinical Outcomes Associated with Pembrolizumab Immunotherapy in Mesothelioma: A Systematic Review

CO48

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INTRODUCTION

- Mesothelioma is a rare, aggressive cancer with poor prognosis, where standard chemotherapy offers limited benefit, especially in non-epithelioid subtypes.
- Rapid progression, scarce second-line options, and biological heterogeneity highlight the need for real-world outcomes data to guide treatment strategies.
- Pembrolizumab has shown meaningful clinical activity across early-phase trials and real-world studies. However, comprehensive clinical synthesis is limited, and variability in reported outcomes makes it challenging to clearly define its therapeutic value.
- Robust clinical outcomes research is needed to clarify pembrolizumab's role, identify responsive subgroups, and support evidence-based decision-making.

OBJECTIVE

- To summarize current evidence on pembrolizumab in mesothelioma, highlighting efficacy, safety, and predictive biomarkers across disease subtypes and treatment settings.

METHODS

Databases Searched:

- PubMed – Peer-reviewed, full-text articles
- ClinicalTrials.gov – Registered clinical trials

Search Timeline:

- Last 5 years

Search Strategy:

- Keywords: **pembrolizumab, mesothelioma**
- Filters applied:
  - Language: English
  - Access: Free full-text availability

Data Extraction and Synthesis

- Two reviewers independently screened titles, abstracts, and full texts for inclusion. Discrepancies were resolved by consensus.
- Extracted data included study type, mesothelioma subtype (pleural/peritoneal), treatment line, pembrolizumab regimen, and key outcomes: **ORR**, **PFS**, **OS**, **adverse events**, and **biomarker associations**.
- Clinicaltrials.gov retrieval results were analyzed based on six parameters: trial status, study type, nature of study, type of therapy, outcome measurement feasibility and regulatory relevance, and population.
- Due to heterogeneity in study designs and endpoints, findings were summarized using **qualitative synthesis**.

Eligibility Criteria

Studies were screened based on predefined inclusion and exclusion criteria related to **record characteristics** (population, intervention, study design, outcomes) and **report characteristics** (language, accessibility, publication type, and date), as shown below:

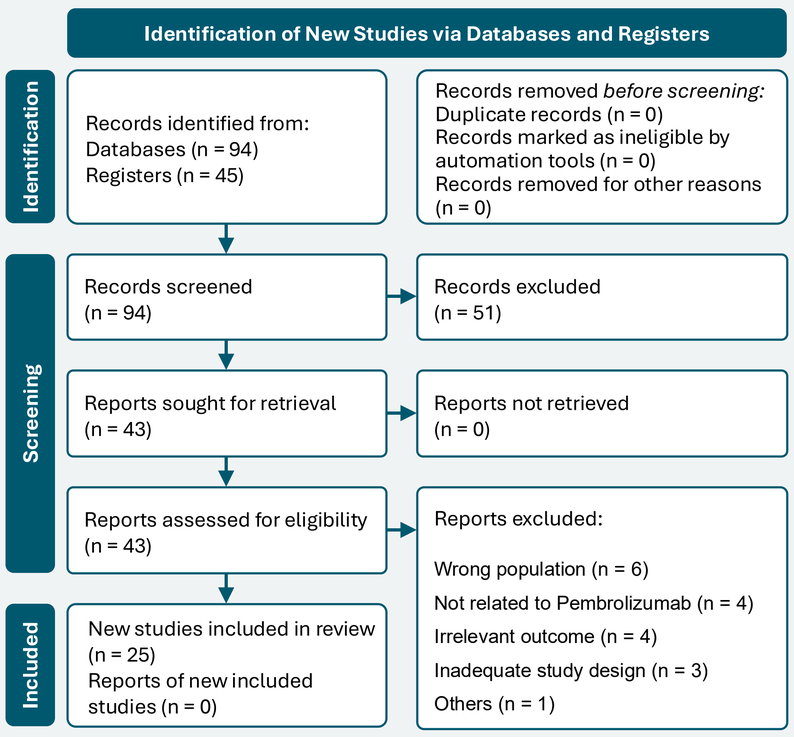
Report Characteristics

Characteristic	Inclusion Criteria	Exclusion Criteria
Language	English	Non-English publications
Accessibility	Free full-text available via PubMed or ClinicalTrials.gov	Subscription-based or paywalled content
Publication Type	Full-text original articles or full trial records	Conference abstracts without full-text, duplicate or interim reports superseded by later publications
Publication Date	January 1, 2015 to May 31, 2025	Studies published outside the defined time window

Record Characteristics

Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years) with histologically confirmed pleural or peritoneal mesothelioma	Studies involving only non-human subjects, preclinical models, or non-mesothelioma malignancies
Intervention	Treatment with pembrolizumab, either as monotherapy or in combination with other agents	Studies not involving pembrolizumab as a therapeutic agent
Study Design	- Interventional trials (Phase I–III) - Observational studies (prospective/retrospective) - Real-world evidence (RWE) reports	Case reports, systematic/narrative reviews, editorials, letters, or commentaries
Outcomes	Must report at least one of: - Objective Response Rate (ORR) - Progression-Free Survival (PFS) - Overall Survival (OS) - Adverse Events (AEs) - Predictive biomarkers (e.g., PD-L1, TMB)	No clinical outcomes or biomarker data reported

RESULTS AND DISCUSSION



Note: As ClinicalTrials.gov results were specifically retrieved using Pembrolizumab and Mesothelioma keywords, they were not subjected to any further screening despite their mention in PRISMA.

Trial Status Distribution

- Most trials were either terminated (27%) or recruiting (24%), with fewer in active, completed, or other status categories.

Study Type Uniformity

- All 43 studies (100%) were interventional, with no observational or registry-based entries.

Outcome Measure Feasibility & Regulatory Relevance

- About 60% of trials used early endpoints for accelerated approval decisions, while <40% targeted confirmatory outcomes like OS or durability.

Sponsorship Landscape

- The majority of studies (76%) were academically or publicly sponsored, with a smaller portion (24%) supported by industry partners.

Combination vs Monotherapy Orientation

- Most studies (~70–75%) evaluated pembrolizumab in combination regimens, while a smaller share (~25–30%) investigated it as monotherapy.

Patient Demography and Eligibility Scope

- All trials enrolled adult and older adult populations across both sexes, with no pediatric or adolescent studies identified.

First Line MPM

1. **KEYNOTE-483:** Improved OS/ORR; strongest in non-epithelioid; FDA-approved (Sept 2024).
   Manageable AEs; neoadjuvant studies ongoing.

Second Line MPM

2. ORR 18–21%, OS ~21 mo in PD-L1 ≥ 50% or non-epithelioid.
   PROMISE-meso: No PFS gain; ~40% real-world disease control.

DISCUSSION & CONCLUSION

- Combination regimens featuring pembrolizumab have successfully crossed the threshold from experimental to frontline use in MPM, demonstrating that rare cancers can achieve regulatory traction when anchored in well-powered, histology-informed trials.
- Evidence from real-world and phase II settings highlights that even modest response rates can be clinically meaningful in rare diseases when aligned with biologically enriched subgroups such as non-epithelioid or PD-L1–high cases.
- The inconsistent predictive value of PD-L1, TMB, and MSI-H underscores the need for rare cancer–specific biomarker strategies rather than reliance on pan-tumor assumptions.
- The dominance of early-readout endpoints (ORR, PFS, safety) illustrates how accelerated pathways can be leveraged in low-incidence settings where traditional OS-based trials are often infeasible.
- Immunotherapy-related toxicity patterns in MPM show that safety is manageable even in fragile populations, supporting feasibility of combination approaches in rare tumor trials.
- Future programs should adopt histology-driven and composite biomarker frameworks to enhance precision and reduce trial attrition in rare cancers.
- Embedding both early decision endpoints and durability measures can balance regulatory acceleration with long-term value demonstration.
- Adaptive platforms, rational combos, and real-world data integration offer scalable models for pembrolizumab-like agents across other rare malignancies.

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