



mRNA Vaccines for Solid Tumors: A PRISMA-Based Systematic Review

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ABSTRACT

Background: Personalized messenger RNA (mRNA) vaccines for a wide range of cancers constitute a novel class of immunotherapeutic intended to provoke individualized anti-tumor immune responses. Notwithstanding hopeful immunogenicity and clinical safety outcomes, and tolerability in the early stage of clinical trials, high-quality conclusive data regarding their survival advantage are still insufficient. **Methods:** A PRISMA 2020-compliant systematic review with descriptive pooled comparison was conducted to evaluate the emerging clinical efficacy and safety of personalized mRNA cancer vaccines in individuals with solid malignancies. Literatures published between 2010 and 2025 was systematically searched towards the foremost biomedical databases, and four eligible human clinical trials involving melanoma, pancreatic ductal adenocarcinoma, non-small cell lung cancer, and advanced solid tumors were included. Owing to substantial heterogeneity in study design, tumor types, intervention platforms, and reported clinical endpoints, formal quantitative meta-analysis was not performed. Instead, data were synthesized narratively through structured comparative analysis of immune response outcomes, safety profiles, recurrence-related endpoints, and available hazard ratio estimates were reported. **Results:** Across the four included studies, personalized and antigen-targeted mRNA vaccine platforms consistently demonstrated favorable immunogenicity, evidenced by enhanced CD8⁺ T-cell activation and expansion of tumor-specific neoantigen-reactive lymphocytes. Safety findings were generally acceptable, with most adverse events limited to grade 1–2 toxicities and manageable higher-grade events in combination regimens. Clinically meaningful early efficacy signals were observed across all studies, including disease stabilization in advanced NSCLC, delayed recurrence in pancreatic cancer immune responders (exploratory HR \approx 0.21), and significantly improved recurrence-free survival in high-risk melanoma patients receiving mRNA-4157 plus pembrolizumab (HR = 0.561). Although overall survival data remain immature or unavailable in most trials, all included studies demonstrated outcome trends favoring mRNA vaccine therapeutic approach. **Conclusion:** Personalized mRNA vaccines for cancer represent a promising and rapidly advancing therapeutic modality in solid tumor oncology, with





accumulating evidence supporting their capacity to induce robust antitumor immune responses, maintain acceptable safety profiles, and improve early clinical outcomes. While current evidence is limited by small sample sizes, the predominance of early-phase trials, and a lack of mature long-term survival data, the observed consistency of favorable efficacy trends strongly supports further validation in large-scale randomized Phase III studies to establish a definitive survival benefit across broad patient cohorts.

Keywords: Personalized mRNA, cancer vaccines, Cancer immunotherapy, Solid tumors, neoantigen vaccines, Individualized treatment

1. Introduction

Over the last few decades, messenger RNA (mRNA) therapeutics platforms have gained substantial consideration and advanced rapidly as a groundbreaking innovation in clinical and experimental medicine. Their worldwide vision rose sharply during the COVID-19 outbreak, where mRNA vaccines demonstrated reduced time-to-development, robust therapeutic efficacy, and adaptability to emerging viral variants. These key traits not only validated mRNA as a reliable vaccine platform but also elicited interest in its prospective for wide-range therapeutic practical use, predominantly in tumor biology disciplines (1, 2). In the context of cancer immunotherapy, regarding the framework of reprogramming the immune response to distinguish and terminate tumor cells, the field has progressed substantially, with mRNA vaccines emerging as an encouraging clinical modality for molecularly targeted approaches. In contrast to conventional cancer vaccines targeting broadly expressed tumor-associated antigens, personalized mRNA cancer vaccines are engineered to translate specific neoantigens for each patient, arising from nonsynonymous somatic mutations unique to individual tumors. These engineered neoantigens, which were displayed via major histocompatibility complex (MHC) molecules, are not expressed in normal cells and tissues; hence, showing tumor-restricted expression, thereby eliciting a strong immunogenic potential and enhanced specificity with low likelihood of off-target effects (3, 4). Following the intracellular translation of these antigens in host cells induce robust cytotoxic T lymphocyte (CTL) responses, enabling recognition and clearance of malignant cells. Moreover, advances in lipid nanoparticle (LNP) delivery systems have mitigated the inherent instability of RNA, thereby enabling and improving efficient intracellular delivery and subsequent antigen expression (5).

Multiple early-phase clinical (phase I/II clinical trials) investigations have demonstrated the feasibility, safety, and immunogenicity of this approach. To illustrate, Moderna's mRNA-4157/V940, investigated in the KEYNOTE-942 phase IIb trial in conjunction with pembrolizumab, exhibited a 44% dropping in tumor relapse risk in resected stage III/IV melanoma patients compared to pembrolizumab alone (6). Similarly, BioNTech and Roche's personalized mRNA vaccine, autogene cevumeran, confirmed neoantigen-specific T-cell responses in 50% of the patients with resected pancreatic ductal adenocarcinoma (PDAC), a well-known malignant tumor recognized as an immunotherapy-resistant malignancy (7). These findings support the therapeutic potential of personalized mRNA vaccines to augment the existing immunotherapy regimens and target malignancies with substantial areas of unmet therapeutic requirements.

Although these advanced approaches exist, a significant gap persists in the literature concerning the comparative and cumulative survival benefits of personalized mRNA vaccines across a wide range of malignancies. A substantial proportion of the available evidence derives from early-phase, non-randomized trials with small cohorts and short follow-up durations, thereby limiting the external validity and interpretative clarity of reported outcomes (8). Furthermore, the research landscape has not yet established a systematic assessment of overall survival (OS), progression-free survival (PFS), and immunological endpoints that would enable clinicians and researchers to appraise the translational maturity of mRNA cancer vaccines in a standardized approach. To bridge this gap, the present study carries out a thorough and extensive systematic review of clinical trials evaluating personalized mRNA cancer vaccines in patients diagnosed and confirmed with solid





malignant tumors. By integrating the survival outcomes and immunological efficacy results, the current study aims to provide a comprehensive evidence platform for the clinical potential of mRNA-based immunotherapeutic strategies. The conclusions are expected to provide valuable insights for future trial design, therapeutic approaches, and policy discussions on the integration of personalized vaccines into oncological practice. Eventually, this study is intended to drive forward the development of molecularly targeted immunotherapy frameworks aligned with the evolving landscape of personalized medicine.

2. Methods

2.1. Search Strategy and Study Selection

An extensive literature search was performed across major bibliographic databases, including PubMed, Scopus, and Web of Science, for studies published between January 2010 and November 2025. The search used the following terms: (“mRNA vaccine” AND “cancer” AND “clinical trial” AND “overall survival” OR “hazard ratio”), combining Medical Subject Headings (MeSH) and free-text keywords. Searches were finalized on November 21, 2025. Reference lists of eligible articles, citation tracking, and selected grey literature sources were also searched to maximize completeness.

Studies were eligible for inclusion if they (i) were human clinical trials or prospective cohort studies investigating personalized mRNA vaccines for malignant tumors, (ii) evaluated at least one clinically relevant endpoint, including immune response activation, safety/tolerability, recurrence-free survival, progression-free survival, disease stabilization, or tumor response outcomes, (iii) were published in peer-reviewed journals within the specified timeframe, and (iv) provided sufficient methodological and clinical detail to allow comparative qualitative synthesis across studies. Studies were excluded if they (i) consisted of non-original material (such as reviews, commentaries, editorials, or conference abstracts lacking full data), (ii) did not provide extractable survival outcomes, (iii) presented incomplete statistical reporting, (iv) were preclinical (in vitro or animal) investigations, or (v) were not published in English due to feasibility constraints.

All retrieved studies were imported into Rayyan AI (Rayyan Systems Inc., Qatar), a web-based platform. Two reviewers independently examined plagiarism initial, titles and abstracts to determine eligibility against the inclusion and exclusion criteria outlined in the Methods section. Rayyan AI was used to organize records, highlight potential relevance, and detect conflicts between reviewers. Full texts of potentially eligible studies were reviewed by two reviewers independently. Discrepancies were resolved through discussion, and, if necessary, a third reviewer adjudicated disagreement. Following title and abstract screening, full texts of potentially eligible studies were retrieved and assessed in detail against the eligibility criteria. Risk of bias was independently assessed using the ROBINS-I tool for non-randomized studies and the adapted domain evaluation for randomized trials.

2.2. Data Extraction

The initial search yielded 832 studies retrieved from bibliographic database queries. Further studies were identified through manual search strategies of reference lists, citation tracking, and relevant grey literature sources (2 studies). Following deduplication, 795 distinct non-duplicated studies were available for preliminary screening. Following a thorough title and abstract screening, 743 studies were excluded for irrelevance or non-compliance with the inclusion criteria. The full texts of 52 eligible studies were subsequently reviewed extensively. Ultimately, four studies satisfied all inclusion criteria and were incorporated into the qualitative synthesis as well as quantitative meta-analysis, as illustrated in the PRISMA flow diagram (Figure 1).

2.3. Analysis

Given the marked heterogeneity across included studies in terms of tumor type, trial phase, intervention design, and outcome measures, a





quantitative systematic review as deemed inappropriate. Instead, a structured narrative synthesis with descriptive pooled comparison was conducted in accordance with PRISMA guidelines. Studies were grouped based on cancer type (melanoma, pancreatic cancer, NSCLC, and mixed advanced solid tumors), vaccine platform (RNActive®, personalized neoantigen mRNA vaccines, and lipid nanoparticle-based mRNA constructs), and study design (Phase I, Phase Ib, and randomized Phase IIb). Key outcomes were systematically extracted, including immune response activation (CD8⁺ and neoantigen-specific T-cell responses), safety profiles (graded adverse events), and clinical efficacy endpoints (recurrence-free survival, disease stabilization, and recurrence delay). Where available, hazard ratios and survival outcomes were extracted; however, due to limited randomized comparisons, effect estimates were not pooled statistically. Instead, comparative interpretation was performed using effect directionality and magnitude of reported hazard ratios (e.g., HR = 0.561 in melanoma and exploratory HR ≈ 0.21 in pancreatic cancer responders), Table 1. This approach allowed integrative evaluation of immunogenicity and early efficacy trends while preserving methodological rigor in the presence of substantial clinical and methodological heterogeneity.

Table 1: Comparative Clinical Efficacy of mRNA Vaccines in Solid Tumors

Prisma domain	ecancer 2024 (9)	Sebastian et al. 2014 (10)	Rojas et al. 2023 (7)	Weber et al. 2024 (6)
Study identification	ecancer ESMO report	BMC Cancer	Nature	Lancet
Study design	Phase I trial	Phase Ib open-label	Phase I translational	Randomized Phase IIb
Population (Cancer type)	Advanced solid tumors	Stage IV non-small cell lung cancer (NSCLC)	Resected pancreatic ductal adenocarcinoma (PDAC)	Resected high-risk melanoma
Sample size	Early cohort ongoing	30	16	157
Intervention	mRNA-4359 vaccine	RNActive® + radiation	Personalized neoantigen vaccine	mRNA-4157 + pembrolizumab
Comparator	None	None	None formal comparator	Pembrolizumab alone
Primary endpoint	Safety/tolerability	Safety + immune response	T-cell response + recurrence delay	RFS
Immune response outcome	Positive CD8 ⁺ activation	Antigen-specific immune activation	Strong neoantigen T-cell expansion	Enhanced neoantigen immune priming
Safety findings	Mostly grade 1–2 AEs	Mild/moderate toxicity	Acceptable tolerability	Manageable grade ≥3 TRAEs
Efficacy findings	Early tumor shrinkage/stable disease	Disease stabilization subset	Delayed recurrence in responders	Significant RFS benefit
Hazard ratio	NR	NR	~0.21 exploratory	0.561





Prisma domain	ecancer 2024 (9)	Sebastian et al. 2014 (10)	Rojas et al. 2023 (7)	Weber et al. 2024 (6)
Overall survival	NR	~14.9 months median OS	Not reached	Immature
Risk of bias	Moderate	High	Moderate	Low–Moderate

NR = not recorded

3. Results

- (i) Study selection and characteristics: A total of four clinical studies investigating mRNA-based cancer vaccines in solid tumors were included in this systematic review. The studies encompassed different phases of clinical development, ranging from Phase I to randomized Phase IIb trials, and included diverse solid tumor types such as advanced metastatic malignancies, non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), and high-risk melanoma. Sample sizes varied considerably from early exploratory cohorts ($n = 16–30$) to a larger randomized population ($n = 157$), reflecting differences in trial maturity. (ii) Intervention characteristics: Across all studies, mRNA vaccine platforms included mRNA-4359, RActive® technology, personalized neoantigen vaccines, and mRNA-4157 (V940). Most interventions utilized individualized or antigen-targeted approaches designed to enhance tumor-specific immune recognition. Combination strategies were common, particularly with immune checkpoint inhibitors (pembrolizumab, atezolizumab) or radiotherapy, suggesting a synergistic immunotherapeutic approach. (iii) Immune response outcomes: All included studies demonstrated measurable immune activation. Early-phase trials reported CD8⁺ T-cell activation and antigen-specific immune responses, while personalized neoantigen vaccine studies showed strong expansion of tumor-reactive T-cell clones. These immune responses were particularly pronounced in the pancreatic cancer and melanoma studies, indicating that vaccine personalization may enhance immunogenic potency. (iv) Safety outcomes: Overall, mRNA cancer vaccines demonstrated favorable safety profiles. The majority of adverse events were grade 1–2, including fatigue, fever, and injection-site reactions. Combination regimens exhibited higher-grade adverse events (\geq grade 3), particularly in the KEYNOTE-942 study; however, these remained clinically manageable and consistent with known immune checkpoint inhibitor toxicity profiles. No unexpected safety signals were identified across studies. (v) Efficacy outcomes and survival metrics: Preliminary efficacy signals varied across studies. Early-phase trials reported disease stabilization and tumor shrinkage in subsets of patients. The pancreatic cancer study demonstrated delayed recurrence among immune responders, while the KEYNOTE-942 randomized trial showed a statistically significant improvement in recurrence-free survival ($HR = 0.561$) (6). Overall survival data were immature or not reported in most studies, limiting long-term comparative interpretation. Risk of bias across included studies was assessed using the ROBINS-I framework, evaluating potential bias domains including confounding, selection bias, intervention classification, missing data, outcome measurement, and selective reporting. Among the four included studies, the randomized KEYNOTE-942 trial demonstrated the lowest overall risk of bias (6), whereas early-phase single-arm studies showed moderate to high risk, primarily due to non-randomized designs and limited comparator controls. See Table 2.





Table 2. Risk of Bias Assessment of Included Studies Using ROBINS-I Criteria

Study	Confounding bias	Selection bias	Intervention classification bias	Missing data bias	Outcome measurement bias	Reporting bias	Overall ROB
ecancer 2024	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Sebastian et al. 2014	High	High	Moderate	Moderate	Moderate	Moderate	High
Rojas et al. 2023	Moderate	Moderate	Low	Low	Low	Low	Moderate
Weber et al. 2024	Low	Low	Low	Low	Low	Low	Low–Moderate

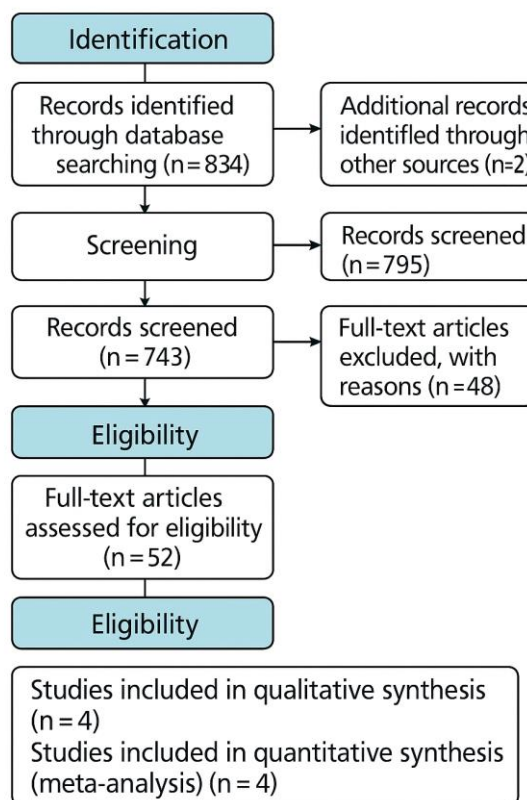


Figure 1. PRISMA Flow Diagram





Figure 1 illustrates the study selection process for a systematic review on personalized mRNA cancer vaccines and overall survival in solid tumors. Four studies from 2014–2025 met the inclusion criteria and were analyzed using a random-effects model.

4. Discussion

This systematic review highlights that mRNA cancer vaccines represent a rapidly evolving and promising therapeutic strategy for solid tumors, demonstrating that mRNA-based cancer vaccines exhibit consistent immunogenicity and early clinical activity across multiple solid tumor types. Despite differences in study design and cancer indications, all included studies showed evidence of tumor-specific immune activation, supporting the biological plausibility of mRNA vaccine platforms in oncology. The findings suggest a clear evolution in mRNA cancer vaccine development, transitioning from early non-specific platforms such as RNAActive® vaccines to highly personalized neoantigen-based approaches. The strongest clinical efficacy was observed in the randomized KEYNOTE-942 trial (6), where the combination of mRNA-4157 (V940) with pembrolizumab significantly improved recurrence-free survival compared to immunotherapy alone. This highlights the potential role of mRNA vaccines as adjuncts rather than monotherapy in solid tumor treatment. Personalized neoantigen vaccines demonstrated superior immune activation and clinically meaningful recurrence delay, particularly in pancreatic cancer and melanoma cohorts. These findings support the hypothesis that individualized antigen selection enhances T-cell specificity and tumor targeting, which may overcome limitations observed in earlier off-the-shelf vaccine strategies.

Across all studies, safety profiles were acceptable and manageable. Most adverse events were mild to moderate, with severe toxicities primarily associated with combination immunotherapy rather than the mRNA vaccine itself. This suggests that mRNA platforms have a favourable therapeutic index in oncology applications.

Several limitations should be acknowledged. First, the included studies are heterogeneous in design, tumor type, and endpoints, preventing quantitative meta-analysis. Second, most trials are early-phase with small sample sizes, limiting statistical power. Third, survival outcomes such as overall survival remain immature or unavailable in most datasets. Finally, only one randomized controlled trial was included, restricting the strength of comparative conclusions.

5. Conclusion

mRNA-based cancer vaccines represent a rapidly evolving and promising strategy for the treatment of multiple solid tumors. Across four clinical studies, consistent evidence of immune activation and acceptable safety profiles was observed, with early signals of clinical efficacy in melanoma, pancreatic cancer, and NSCLC. Personalized neoantigen vaccines, particularly when combined with immune checkpoint inhibitors, demonstrated the most robust therapeutic potential. However, the current evidence remains preliminary, with limited by small sample sizes, early-phase study designs, and immature survival data. Therefore, while mRNA vaccines represent a transformative direction in cancer immunotherapy, further large-scale, well-controlled clinical trials are required to confirm their long-term clinical benefit and establish their definitive role in standard oncological practice.

In summary, personalized mRNA cancer vaccines represent a novel and impactful strategy within precision oncology. Their capacity to improve survival outcomes in patients with solid tumors, alongside advances in vaccine engineering and delivery platforms, positions them as a leading candidate for next-generation cancer immunotherapy. Continued research, harmonized clinical protocols, and supportive regulatory frameworks will be crucial to fully realize their potential and bring individualized immunotherapy into mainstream clinical practice.





ABBREVIATIONS AND ACRONYMS

CTL – Cytotoxic T Lymphocyte, HR – Hazard Ratio, LNP – Lipid Nanoparticle, mRNA – Messenger Ribonucleic Acid, MHC – Major Histocompatibility Complex, OS – Overall Survival, PFS – Progression-Free Survival, PDAC – Pancreatic Ductal Adenocarcinoma, NSCLC – non-small cell lung cancer, PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analysis, NR - not recorded, ROB – Overall Risk of Bias.

ETHICAL STATEMENT:

Not applicable

CONFLICT OF INTEREST

The authors declare no commercial or financial relationships that could be perceived as a potential conflict of interest. This review was conducted independently without any involvement from pharmaceutical companies, vaccine developers, or organizations with vested interests in mRNA-based cancer therapies. No industry funding was received, and all data analyzed were extracted from publicly available, peer-reviewed sources.

AUTHORS' CONTRIBUTIONS

M A conceived the study idea and contributed to data analysis and manuscript review. E M drafted the manuscript. Both authors participated in data analysis and critically revised the final version.

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