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Review

Neoantigen-Based and mRNA Therapeutic Cancer Vaccines: Clinical Status and Practical Bottlenecks

Karen Wang[1,*]

[1] Qingdao Grand International School, Qingdao, China
* Correspondence: Karen Wang, Qingdao Grand International School, Qingdao, China

Abstract: Therapeutic cancer vaccines seek to generate or expand adaptive immune responses against malignant cells, potentially complementing treatments that remove or reduce tumour burden. This narrative review examines personalised neoantigen vaccines and mRNA vaccine platforms through representative clinical studies and research on barriers to translation. These approaches overlap: neoantigens define the molecular targets, whereas mRNA provides one means of delivering them. Early studies in melanoma, glioblastoma and pancreatic cancer demonstrate that vaccination can induce mutation-specific T cells, sometimes with sustained memory. Randomised phase 2 evidence in resected high-risk melanoma provides a more direct signal of clinical benefit when an individualised mRNA vaccine is added to pembrolizumab, with supportive long-term follow-up. Nevertheless, most other studies remain small, uncontrolled or confounded by concurrent treatment. Three connected bottlenecks limit wider application. Predicted peptide binding does not establish natural antigen presentation or tumour recognition; immune exclusion and inhibitory mechanisms can prevent vaccine-induced cells from controlling disease; and individualised development requires timely tissue processing, antigen selection, manufacturing and quality assurance. Improvement therefore requires more than a stronger immune assay result. Priorities include clinically justified combinations with checkpoint blockade, prospectively validated antigen-selection methods, and manufacturing processes evaluated by the proportion of eligible patients who receive treatment on time. Shared mutation vaccines may reduce individual production requirements but apply only to biologically defined patient groups. The field has progressed from proof of immunogenicity towards evidence of clinical activity, while broad implementation still requires confirmatory trials, reliable delivery and transparent assessment of safety, cost and access.

Keywords: Therapeutic cancer vaccines; Neoantigens; mRNA vaccines; Tumour microenvironment; Clinical translation

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1. Introduction

Surgery, radiotherapy and systemic therapies can cure some cancers and extend survival in others, yet residual malignant cells and treatment resistance continue to cause recurrence. Their limitations depend on the tumour, disease stage and treatment regimen; toxicity and incomplete disease control should not be treated as uniform features of all conventional care. Therapeutic vaccination addresses a complementary problem: whether a patient's immune system can be directed towards tumour cells that persist after, or escape, initial treatment. Historical clinical evidence supports the principle without establishing that every vaccine platform will work. In a randomised phase 3 trial of sipuleucel-T in metastatic castration-resistant prostate cancer, overall survival improved

while time to objective disease progression did not. This experience also illustrates why the endpoint used to judge a vaccine matters [1].

Unlike prophylactic vaccines intended to prevent infection, therapeutic cancer vaccines are administered to patients with cancer or following treatment of an established malignancy. Their central purpose is to expand an effective repertoire of tumour-reactive T cells. Antigen-presenting cells must acquire vaccine-derived material, present relevant peptides through human leukocyte antigen (HLA) molecules and provide appropriate activation signals. The resulting cells must then encounter and recognise malignant tissue. CD8-positive T cells can mediate cytotoxicity, while CD4-positive responses can support immune coordination and memory. A successful response therefore requires several biological steps between administration and tumour control [2]. The presence of a mutation in sequencing data is only the beginning of this process.

Neoantigen targeting and mRNA delivery represent two influential developments within this broader strategy. Neoantigens arise from tumour-specific molecular alterations and can differ from the proteins encountered during immune tolerance. Personalised vaccination selects targets from an individual tumour rather than assuming that one antigen set is suitable for every patient. mRNA vaccines instead define a platform: cells translate an administered RNA sequence into antigenic material that can enter presentation pathways. A personalised neoantigen vaccine may use synthetic peptides or mRNA, and an mRNA vaccine may encode private mutations or antigens shared across patients. Treating these categories as mutually exclusive would obscure both the clinical evidence and the source of manufacturing constraints [3,4].

The distinction also changes what counts as progress. An antigen-selection method can improve the relevance of vaccine cargo without resolving delivery, and a more efficient RNA formulation cannot compensate for targets absent from the tumour. Likewise, increased circulating T-cell numbers may coexist with poor tumour infiltration or impaired antigen presentation. Recent clinical development has consequently placed greater emphasis on the quality and persistence of responses, disease setting and endpoints that capture patient benefit [5]. For an adjuvant vaccine, prevention or delay of recurrence is more relevant than shrinkage of a lesion that has already been surgically removed. In advanced disease, response durability and survival must be interpreted alongside concurrent therapies.

The translational gap is thus partly a gap between different kinds of evidence. Cell and animal experiments can establish a mechanism under controlled conditions. Early human trials can test feasibility, safety and immunogenicity. A comparison with an appropriate control is needed to estimate the additional clinical effect of the vaccine within a treatment regimen. Manufacturing feasibility introduces a further requirement: a biologically active product cannot help a patient who deteriorates before it is available. These questions should be examined together, but they should not be answered with the same endpoint.

This review evaluates representative neoantigen and mRNA therapeutic vaccine studies, identifies the obstacles that connect their biological and practical limitations, and assesses feasible directions for improvement. It focuses on cancer treatment rather than infection prevention and on published evidence rather than projected commercial availability. The argument is that clinical translation depends on matching target quality, immune function and treatment timing. Progress in one component is valuable only when the remaining components allow that improvement to reach patients.

Review Scope and Evidence Assessment: This is a targeted narrative review of journal publications available by 6 October 2026. Retrieval from PubMed and publisher websites was complemented by reference tracking from recent reviews. Searches combined terms concerning therapeutic cancer vaccines, neoantigens, mRNA, clinical trials, antigen prediction and manufacturing. Studies were selected for their contribution to mechanisms, representative clinical development or the specified translation barriers. Primary trial reports were prioritised for patient numbers and outcomes; later reports from the same cohort were treated as follow-up rather than independent replication.

Reviews informed context, while preclinical experiments were identified explicitly. Meeting abstracts and inaccessible records were not used to establish patient benefit. Some mechanistic sources were available only as abstracts, and interpretation was restricted accordingly. This approach supports critical comparison but is not an exhaustive systematic review or meta-analysis; differences in populations, interventions and endpoints preclude a pooled efficacy estimate.

2. Clinical Progress of Representative Therapeutic Cancer Vaccines

2.1. Personalised Neoantigen Vaccines

Personalisation begins with tumour and matched normal material, followed by identification of somatic alterations, evidence of expression and selection of candidate peptides in relation to the patient's HLA molecules. The aim is to direct immunity towards malignant tissue while limiting recognition of normal cells. Multiple targets can be included to address tumour diversity, but the number of encoded mutations is not itself a measure of vaccine quality. Targets must remain expressed in clinically relevant tumour populations and support appropriate presentation by tumour cells or antigen-presenting cells [2].

The early melanoma study by Ott and colleagues established an influential proof of concept. Six patients received a synthetic long-peptide vaccine targeting up to 20 predicted personal neoantigens. The study detected mutation-specific CD4-positive and CD8-positive responses. Four vaccinated patients remained recurrence-free at a median follow-up of 25 months; two who developed recurrence subsequently received anti-PD-1 therapy and achieved complete tumour regression [6]. These observations supported feasibility and biological activity, but the small uncontrolled cohort cannot establish recurrence prevention. Responses after subsequent checkpoint treatment also cannot be assigned to vaccination alone.

Evidence from glioblastoma demonstrates why disease context matters. In the phase 1b study reported by Keskin and colleagues, personalised peptide vaccination was feasible in eight vaccinated patients. Among five patients evaluated after at least one booster, the two without dexamethasone during priming developed circulating neoantigen-specific responses, whereas the three exposed to dexamethasone did not. Analyses also linked vaccine-reactive T cells to the tumour compartment [7]. The findings make immune suppression during treatment a relevant translational variable. They do not prove that avoiding corticosteroids improves vaccine efficacy, because steroid exposure was not randomised and may reflect clinical differences between patients.

The NEO-PV-01 study combined personalised peptide vaccination with nivolumab in advanced melanoma, non-small-cell lung cancer and bladder cancer. Eighty-two patients were enrolled, but 60 received vaccine. Nivolumab began before vaccination, which occurred later in the treatment schedule. The study demonstrated vaccine-induced immune responses and provided evidence of changes in tumour-reactive immunity [8]. Its clinical outcomes are therefore evidence about a combination strategy in selected patients, rather than a controlled estimate of vaccine benefit. The gap between enrolment and vaccination also shows why feasibility should be reported for all enrolled patients, with reasons for nonreceipt, rather than only for those who completed manufacture and remained eligible.

Together, these studies support the ability to direct human T-cell responses against selected mutations. They do not establish a uniform clinical effect across cancers. Personalisation offers a rational way to match a vaccine to an individual tumour, but its advantage must ultimately be measured against a relevant alternative within the same disease setting. Differences in tumour burden, immune competence and accompanying treatment limit comparisons between small trials.

2.2. MRNA Vaccine Platforms and Overlapping Neoantigen Strategies

mRNA provides a programmable means of producing antigen inside cells. Formulation protects RNA and influences uptake, intracellular release and the tissues

exposed to the encoded material. Translation occurs in the cytoplasm, and vaccine RNA is transient. These properties facilitate redesign and multivalent antigen expression, but do not make formulations interchangeable. Route, carrier, RNA chemistry and dose influence both expression and inflammatory effects [3]. In particular, a clinical result obtained with one mRNA product should not be generalised to all lipid formulations or all encoded antigens.

Sahin and colleagues reported individualised RNA mutanome vaccination in 13 patients with melanoma, demonstrating responses against multiple mutation-derived targets [9]. This study belongs to both categories considered here: it used personalised neoantigens and an RNA platform. Its nonrandomised design established immunogenicity and supported further development, while leaving the size of the clinical benefit uncertain. By contrast, the BNT111 programme used RNA to encode four shared tumour-associated antigens rather than patient-specific mutations. Its early melanoma study assessed safety in 89 patients and exploratory clinical activity in 42 patients with measurable disease and follow-up imaging. It documented antigen-specific immune responses with vaccination alone or alongside PD-1 blockade. Related adverse events included frequent fever and chills, grade 3 events and one grade 4 decrease in lymphocyte count [10]. BNT111 therefore illustrates the flexibility of RNA delivery, not the equivalence of shared self-antigens and neoantigens.

In pancreatic ductal adenocarcinoma, Rojas and colleagues evaluated adjuvant autogene cevumeran alongside atezolizumab and modified FOLFIRINOX after surgery. Sixteen patients received vaccine, and eight developed high-magnitude vaccine-induced T-cell responses. Immune responders had a longer recurrence-free interval than nonresponders at the reported analysis [11]. This was a phase 1 study without a randomised control, and immune-response groups were defined after treatment. The association cannot establish that vaccination caused the difference in recurrence. Subsequent analysis of the same cohort showed persistent, functional vaccine-induced CD8-positive T-cell populations approximately three years after vaccination, extending the evidence for durable immune memory [12]. It remains follow-up of the same patients, not confirmation in an independent trial.

The randomised phase 2b KEYNOTE-942 study provides a stronger test of added clinical value. Patients with completely resected high-risk stage IIIB–IV melanoma were allocated to individualised mRNA-4157/V940 plus pembrolizumab or pembrolizumab alone. Among 157 randomised patients, the initial recurrence-free survival hazard ratio was 0.561, with a 95% confidence interval of 0.309–1.017. The reported two-sided P value was 0.053 [13]. The prespecified phase 2 design used a one-sided significance level of 0.10. The result met that criterion, although the 95% confidence interval crossed 1 and the two-sided P value exceeded 0.05. It supplied a comparative efficacy signal that earlier uncontrolled vaccine studies could not provide, while leaving confirmatory evaluation necessary.

The five-year KEYNOTE-942 report strengthens the durability of that signal while retaining the limitations of a phase 2 cohort. At a median planned follow-up of 60.3 months, the recurrence-free survival hazard ratio was 0.510 (95% confidence interval 0.294–0.887). The exploratory overall-survival estimate remained uncertain, with a hazard ratio of 0.471 (95% confidence interval 0.165–1.345). These were descriptive analyses of the original randomised cohort [14]. Evidence of sustained recurrence reduction is more informative than a transient immune response, but it does not establish benefit in other malignancies or replace confirmatory evidence in larger populations. Similarly, the contribution of the vaccine to a combination is distinct from a claim that vaccination can substitute for checkpoint blockade.

Table 1 summarises the main evidence and the interpretation each design permits. The studies are organised by target and delivery method rather than placed in an efficacy ranking. Response rates and recurrence estimates across different cancers should not be compared as though they arose from one population.

Table 1. Representative Clinical Evidence and Limits of Interpretation. Numbers Distinguish Enrolled or Randomised Populations from Vaccinated Populations Where Relevant.

Study and approach	Design and population	Main inference and limitation
Ott; personalised peptides [6]	Early melanoma study; 6 vaccinated	Mutation-specific responses; recurrence observations lack a control.
Keskin; personalised peptides [7]	Phase 1b glioblastoma; 8 vaccinated	Systemic and intratumoural immune findings; corticosteroid association is nonrandomised.
NEO-PV-01; peptides plus nivolumab [8]	Phase 1b, three cancers; 82 enrolled, 60 vaccinated	Combination immunogenicity; prior nivolumab and selection complicate attribution.
Sahin; personalised RNA [9]	Early melanoma study; 13 treated	Responses to multiple neoantigens; no randomised efficacy comparison.
BNT111; shared-antigen RNA [10]	Phase 1 melanoma; 89 in safety cohort	Shared tumour-associated targets; exploratory activity does not establish a neoantigen effect.
Autogene cevumeran; personalised mRNA [11] [12]	Phase 1 resected pancreatic cancer; 16 vaccinated	8 immune responders and durable T cells; responder comparison is associative.
V940 plus pembrolizumab [13] [14]	Randomised phase 2b melanoma; 157 randomised	Comparative recurrence signal with long follow-up; later analyses descriptive.

3. Practical Bottlenecks Restricting Clinical Application

3.1. Selecting Targets That Are Presented and Immunogenic

Neoantigen prediction combines measurements and estimates that answer different questions. Sequencing identifies an alteration; RNA evidence suggests that the altered sequence is expressed; peptide-processing and HLA models estimate presentation; and T-cell assays test recognition under specified experimental conditions. Failure at any stage can make a computationally attractive candidate clinically irrelevant. Consequently, a single universal false-positive rate is inappropriate unless the definition of a positive target, the candidate pool and the validation assay are specified.

The Tumor Neoantigen Selection Alliance benchmark assessed predictions against experimentally tested candidates and demonstrated substantial differences between approaches. Features beyond binding affinity helped distinguish immunogenic candidates [15]. The practical lesson is to validate an entire selection procedure against an explicit endpoint, rather than describing high HLA affinity as proof of immunogenicity. For targets intended to support direct cytotoxic recognition, a response to peptide-loaded cells is less direct evidence than recognition of tumour cells that naturally process the antigen.

Mass-spectrometry-informed approaches offer one way to improve this process. Bulik-Sullivan and colleagues integrated immunopeptidomic information into neoantigen prediction, connecting algorithm development more closely to the peptides actually presented by cells [16]. Such approaches remain constrained by the tissues, HLA alleles and experimental conditions represented in their training data. Absence from a mass-spectrometry dataset does not necessarily prove absence from a tumour, and presentation alone does not guarantee an available, functional T-cell repertoire. Prospective validation must therefore retain separate measures of presentation and immune recognition.

Tumour evolution adds another constraint. McGranahan and colleagues linked clonal neoantigens with T-cell reactivity and sensitivity to checkpoint blockade, providing a rationale for considering whether a target is widely distributed among malignant cells [17]. However, evidence obtained in checkpoint-treated populations is not direct

validation of a vaccine-ranking algorithm. For vaccination, targeting expressed clonal alterations may reduce the chance that untreated subclones dominate, but the relevant claim still requires testing. Sampling across tumour regions and estimates of tumour purity affect inferred clonality, whereas HLA loss can prevent presentation of an otherwise suitable target.

Alternative splicing expands the potential antigen repertoire beyond conventional coding substitutions. The recent review by Wu and Gui describes how aberrant splicing can generate cancer-associated neoantigen candidates [18]. This is a plausible route for tumours with few conventional mutation-derived targets, but each candidate still requires evidence of tumour specificity, presentation and recognition. Expanding the candidate list without improving validation could increase uncertainty rather than improve a vaccine.

3.2. Immune Suppression and Failure to Reach Malignant Tissue

A peripheral immune response does not establish that effector cells reach viable tumour tissue or remain functional there. Stromal organisation, suppressive signalling and inhibitory receptor pathways can interfere with this transition. The clinical relevance of immune exclusion is illustrated by Mariathasan and colleagues, who connected a fibroblast TGF-beta response signature with lack of response to PD-L1 blockade in a defined tumour context. Their accompanying mouse experiments supported a mechanism in which combined pathway inhibition improved T-cell access [19]. This supports the rationale for addressing exclusion, but it is not clinical proof that adding TGF-beta inhibition to a cancer vaccine improves outcomes.

Tumour escape may also occur at the level of recognition. In melanoma progressing after PD-1 blockade, Zaretsky and colleagues identified defects involving interferon signalling or beta-2-microglobulin, including loss of surface MHC class I in one case [20]. These observations matter for vaccine design because generating additional antigen-specific cells may not restore direct CD8-positive T-cell recognition when MHC class I presentation is absent. Checkpoint inhibition and antigen vaccination act at different points in the immune response; neither necessarily repairs a missing molecular target or presentation pathway.

The practical consequence is that vaccine evaluation should include the tumour compartment where feasible, not only blood-based assays. Paired tissue, spatial measurements and functional recognition studies can help distinguish insufficient priming from exclusion, loss of the target or impaired presentation. The glioblastoma findings further indicate that immune-modulating concomitant medication belongs in this assessment [7]. These measurements must remain proportionate to tissue availability and patient burden. Their purpose is to explain failure and select a plausible next intervention, rather than to create a larger biomarker panel without a decision it can inform.

3.3. Manufacturing Constraints and Treatment Access

Personalised production connects a unique biological input to a patient-specific clinical schedule. Tumour procurement and transport precede sequencing, HLA typing, candidate selection, product manufacture, release testing and delivery. Whole-exome sequencing is therefore one cost component rather than a complete estimate of treatment cost. Specialist labour, bioinformatic review, formulation, failed or repeated processing, quality control and treatment administration also affect resource use. The reviewed trials do not provide a sufficiently comparable cost base to justify a universal per-patient price.

The programmable structure of mRNA creates manufacturing opportunities, but the distinction between platform scalability and individual batch production is essential. Jackson and colleagues describe reusable production principles, including in vitro transcription, purification and release testing [21]. Those principles can reduce the need to redesign the whole process when the encoded sequence changes. They do not remove the requirement to establish identity, purity, potency and safety for an individual product, or guarantee that every patient-specific sequence behaves identically during production.

Time should be measured from a clinically meaningful starting point. Reporting the interval after an antigen sequence is finalised omits delays in biopsy, specimen adequacy and analysis. The enrolment-to-vaccination difference in NEO-PV-01 and the sequential treatment pathway in the pancreatic study show why full patient flow matters [8] [11]. Nonreceipt can have biological, clinical or logistical causes; it should not automatically be labelled manufacturing failure. Conversely, reporting only the vaccinated population can overstate how readily a programme can be delivered to all initially eligible patients.

A multicentre study of autogene cevumeran in advanced solid tumours illustrates this distinction. Lopez and colleagues screened 550 patients and enrolled 213; 94 screening exclusions were attributed to manufacturing-related reasons. The reported 28-day turnaround was a best-case interval from approval or receipt of a complete sample set to completion of manufacture, rather than a median biopsy-to-treatment interval [22]. This identifies constraints in a particular development programme without establishing a universal failure rate or typical production time.

For health systems, access requires more than a technically successful batch. Centres need reliable tissue pathways, secure transfer of genomic information and coordination between laboratories and oncology services. A useful implementation study would report total turnaround distributions, reasons for nonreceipt, release failures, treatment interruptions and resource use. These are proposed evaluation requirements, rather than evidence that one manufacturing model is already the most efficient. They would make it possible to judge whether shorter production times improve actual treatment access.

4. Feasible Directions for Improvement

4.1. Combining Vaccination with Checkpoint Blockade

Checkpoint blockade offers a biologically coherent partner when vaccine-induced T cells encounter inhibitory signalling. The strongest clinical justification in the studies reviewed comes from the randomised V940 comparison, not from the general assumption that two immunotherapies must be synergistic [13] [14]. Future trials should retain an active comparator appropriate to the disease setting and isolate the incremental value of vaccination. Timing also requires investigation: priming, expansion and tumour exposure may occur under different treatment conditions, so giving agents together is not automatically the optimal sequence.

Combination development must evaluate harm with the same care as efficacy. In the primary KEYNOTE-942 report, grade 3 or higher treatment-related adverse events occurred in 25% of the combination group and 18% of the pembrolizumab group [13]. Checkpoint-associated immune toxicities can affect organs beyond the tumour, while vaccination can add systemic or local reactions. Attribution is particularly difficult in multidrug regimens. Relevant outcomes include grade, duration, reversibility, corticosteroid requirements and discontinuation, rather than only a statement that treatment was tolerated. Immunological rationale should support dose and sequence testing, not replace it.

Additional immune support remains an experimental direction. Liu and colleagues investigated a tumour-targeted circular RNA-encoded dimeric IL-15 prodrug combined with a neoantigen mRNA vaccine in preclinical models [23]. The work extends the possible design space beyond antigen delivery alone, but animal tumour control does not establish a human benefit–risk balance. Cytokine expression, duration, distribution and systemic inflammation require their own assessment. Such strategies should be distinguished from the existing clinical evidence for particular vaccine–checkpoint combinations.

4.2. Improving Antigen Selection and Validation

Algorithm improvement should be judged by whether selected targets support meaningful tumour recognition in new patients. Better ranking on a retrospective benchmark is useful but insufficient. Evaluation should separate patients between training and testing, examine performance across HLA backgrounds and report the

consequences of candidate-selection thresholds. Models trained on well-represented alleles may not transfer equally to other populations. The TESLA and immunopeptidomic studies provide complementary starting points for this work [15] [16].

A practical strategy is to combine evidence of expression and presentation with target clonality and functional testing for a manageable subset of candidates. This does not imply that every target can undergo every assay before treatment; excessive validation can itself delay access. The relevant optimisation is to identify which additional test most reduces consequential uncertainty within the clinical time available. Prospective studies should record why a target was selected and test whether those criteria predict immune and clinical outcomes. Reporting unsuccessful candidates is particularly valuable because training only on recognised epitopes can conceal the reasons prediction fails.

4.3. Shared Targets and More Accessible Production

Nonpersonalised products could reduce repeated antigen discovery and enable manufacture before an individual patient is identified. However, shared tumour-associated antigens and shared mutation-derived neoantigens raise different issues. BNT111 exemplifies the first category, whereas recurrent driver mutations can supply targets for the second [10]. A shared target is not a universal target: eligibility still depends on the molecular alteration, its expression and presentation, and the immune capacity to recognise it.

The IDH1(R132H) peptide programme illustrates vaccination against a recurrent mutation. The initial NOA16 study established safety and immunogenicity in a defined group of patients with mutant glioma [24]. Its final analysis supplies longer-term observations, but the single-arm setting and accompanying standard treatment limit causal interpretation [25]. In another setting, the phase 1 AMPLIFY-201 study evaluated a lymph-node-targeted vaccine against shared mutant KRAS antigens in pancreatic and colorectal cancer with minimal residual disease detected by circulating tumour DNA or serum tumour markers. The reported immune and biomarker findings support further clinical development, while the absence of randomisation limits claims about recurrence prevention [26]. Final follow-up documented persistent immunity and antigen spreading in the same 25-patient cohort. Associations between stronger immune responses and longer survival remained exploratory and did not provide a vaccine-versus-control treatment effect [27].

Shared products should therefore be developed as options for molecularly defined groups, alongside individualised approaches for patients whose tumours lack suitable shared targets. The trade-off concerns coverage as well as production efficiency. A readily available product with a narrow eligible population cannot substitute for every personalised programme, and a broadly configurable platform may remain inaccessible if turnaround is too slow. Comparative implementation studies should examine these trade-offs directly, including the consequences for patients who never reach vaccination.

Table 2 translates the review into a set of testable development priorities. Each proposed solution is linked to the failure it addresses and to an outcome that would indicate whether it has helped.

Table 2. Practical Bottlenecks and Proposed Evaluation Requirements. This Table Synthesises the Preceding Analysis and Does Not Report New Experimental Findings.

Bottleneck	Feasible response	Evidence needed to judge improvement
Predicted targets do not support tumour recognition	Combine expression, presentation, clonality and functional evidence	Prospective recognition of naturally presented targets in independent patients
Primed cells fail in the tumour environment	Use mechanism-informed combinations and assess tumour tissue where feasible	Added clinical benefit against an appropriate

		comparator, with toxicity and resistance analysis
Production exceeds the clinical treatment window	Standardise reusable processes and document the complete patient pathway	Time from tissue acquisition to administration; reasons for nonreceipt and failed release
Individual production limits access	Develop shared mutation products for eligible groups	Molecular and HLA coverage, clinical benefit, resource use and equitable access

5. Conclusion

Personalised neoantigen vaccines have established that selected tumour mutations can be used to induce human T-cell responses, and mRNA offers a flexible platform for delivering either individualised or shared antigen sets. These developments have produced durable immune responses in several early clinical studies and a comparative recurrence signal in resected high-risk melanoma. Their interpretation remains disease-specific. Immunogenicity, association with recurrence and randomised evidence of added clinical benefit represent different levels of progress.

Three bottlenecks continue to shape translation. Antigen selection must identify naturally processed tumour-derived targets that support functional tumour-reactive T-cell responses. The tumour environment and escape mechanisms must permit those cells to act. Finally, personalised production must deliver an acceptable product within the patient's treatment window at a resource cost that health systems can support. Solving any one of these problems does not ensure that the others have been resolved.

The most credible path forward combines controlled evaluation of vaccine–checkpoint regimens, prospective testing of antigen-selection methods and transparent measurement of manufacturing and access. Shared mutation vaccines may widen availability for defined patient groups, while individualised approaches retain a role for tumours without suitable common targets. Broad clinical use will depend on reproducible patient benefit, manageable toxicity and dependable delivery, rather than on the magnitude of an immune response alone.

Data Availability: This article reviews published literature and reports no newly collected patient data. All clinical observations are attributed to their original publications.

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