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Synergistic Antitumor Activity of Personalized mRNA Neoantigen Vaccines and PD-1/PD-L1 Inhibitor in Solid Tumors

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Abstract. Immunotherapy for cancer now represents a breakthrough in treatment of solid tumors. However, the clinical efficacy of immune checkpoint inhibitors is still limited by insufficient tumor-specific immune activation and multiple immune escape mechanisms. Personalized mRNA vaccines based on neoantigens offer an encouraging way to deal with such limitations, since they may elicit individualized T-cell activity against each person's specific tumor antigens. This paper reviews the synergistic anti-tumor potential of combining personalized mRNA neoantigen vaccines with Programmed Cell Death Protein-1/ Programmed Cell Death Ligand Protein-1(PD-1/PD-L1) inhibitors in solid tumors. Firstly, the complementary mechanisms underlying this combination are discussed. Current clinical evidence from melanoma, pancreatic ductal adenocarcinoma, renal cell carcinoma, and other solid tumor types shows that this strategy may elicit a durable tumor-specific immune response, which is particularly encouraging in the context of adjuvant therapy and minimal residual disease (MRD). However, due to differences in tumor mutation burden, antigen-presenting ability, immune cell infiltration, and the tumor microenvironment, treatment efficacy still varies among different tumor types. Moreover, clinical translation is also limited by the lack of large - scale clinical data, the scarcity of predictive biomarkers, the high complexity of personalized production, and challenges in cost and accessibility. Future advancements in neoantigen prediction, mRNA delivery technology, biomarker-based patient selection, and rational combination therapy will be essential for achieving more accurate treatment and for extending the use of personalized cancer immunotherapy in practice.

Keywords: mRNA Neoantigen Vaccines, PD-1/PD-L1 Inhibitor, Solid tumors, Cancer Immunotherapy, Personalized Antitumor Therapy Introduction

1. Introduction

Despite advances in the diagnosis and treatment of cancer, it remains one of the leading causes of death worldwide [1]. Traditional therapies such as surgery, chemotherapy, radiotherapy, and targeted therapies are used effectively and have improved survival for many patients, while durable disease control remains elusive in a substantial proportion of solid tumors, particularly those with advanced

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disease. Another hurdle to the challenge is the biological diversity of tumors, with those that have a low tumor mutational burden (TMB) and have an immunologically cold tumor microenvironment yielding weak antitumor immune responses and thus, a poor response to immunotherapy. The barriers stimulate scientists to look for methods to develop drugs that target the cancer cells as well as to achieve long-term immune surveillance to prevent disease progression and the recurrence of cancer.

Immune checkpoint inhibitors (ICIs) have been a turning point in cancer therapy, particularly the PD-1 and PD-L1 inhibitors. The ability of PD-1/PD-L1 blockade to restore exhausted T-cell function and the ability to induce durable clinical responses in several malignancies including several cancers such as melanoma, non-small-cell lung cancer, and renal cell carcinoma make it now a standard of care in several cancers. But not all patients enjoy these benefits. Not all patients will respond to treatment and acquired resistance will occur in some patients over time. In addition, immune checkpoint blockade has been shown to be associated with immune-related adverse events (irAEs), ranging from mild inflammation to more severe autoimmune-related adverse events. Long-lasting effects of checkpoint blockade are, however, limited by poorly expanded tumor-reactive lymphocytes and a very immunosuppressive tumor microenvironment suggesting that the blockade of PD-1/PD-L1 is often insufficient to induce durable responses [2].

One strategy that is attracting attention is personalized vaccination. Of the current vaccine platforms, mRNA vaccines have an added appeal as they can be manufactured relatively quickly, with multiple neoantigens being incorporated into a single vaccine and can be rapidly adapted to individualised vaccines [3]. The successful application of mRNA technology has also driven its application to oncology, with personalized mRNA neoantigen vaccines being one of the most actively studied precision cancer immunotherapy strategies [4].

Personalized mRNA neoantigen vaccines and PD-1/PD-L1 inhibitors have demonstrated promising therapeutic activity, but there is an increasing body of evidence that therapy with both these approaches together could yield better clinical results than with either approach in isolation. They have complementary therapeutic effects; vaccination could improve tumor specific immune responses and checkpoint blockade could help sustain vaccine-induced T-cell activity. Results of early clinical trials, such as the KEYNOTE-942 trial, indicate that using combination therapy may yield better clinical results and warrant continued investigation [5]. The evidence presented, however, is somewhat fragmentary, and most of the work presently available examines limited aspects of the treatment or particular types of tumors. Thus, questions regarding the broad applicability of the clinical effects in various solid tumors, the treatment-related toxicity and the biological explanations behind the differences in treatment response remain to be investigated in much greater detail.

Accordingly, this review aims to collectively review the published evidence of the synergistic anti-tumoral effects of personalized mRNA neoantigen vaccines (PMNVs) and PD-1/PD-L1 inhibitors in solid tumors. This combination approach is explained and existing clinical evidence about efficacy, long-term outcome and safety is discussed. Finally, differences in therapeutic results between the various types of tumors, the clinical obstacles involved and future directions for optimization are compared. This review seeks to combine the latest mechanistic understanding with the most current clinical insights in order to give a clinically relevant and complete overview on the role of this combination strategy to design and clarify the therapeutic potential, the still existing hurdles, and the future translation opportunities of this combination approach to precision cancer immunotherapy.

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2. Theoretical rationale for mRNA neoantigen vaccines and PD-1 inhibitor

2.1. Mechanism of action of personalized mRNA neoantigen vaccines

Personalized mRNA neoantigen vaccines are used to activate tumor-specific immune responses by recognizing neoantigens produced from the somatic mutations of each individual's tumor. Differently from the usual tumor-associated antigens, these neoantigens do not exist in normal tissues and can therefore avoid central immune tolerance. This enables the immune system to regard them as foreign and special tumor markers [6]. With the help of the current sequencing and predicting techniques, it is now possible to detect effective neoantigens efficiently, which is beneficial for constructing personalized vaccines [4].

After the neoantigen selection, the corresponding mRNA sequences will be included in the vaccine preparation which is mainly delivered by lipid nanoparticles (LNPs) [3]. When taken up by antigen-presenting cells, especially dendritic cells, the neoantigens encoded in mRNA are processed and presented via MHC class I and class II pathways. This induces the activation of $CD8^+$ cytotoxic T-cells for tumor cell destruction and enhances the $CD4^+$ helper T-cell responses to promote the expansion and persistence of the immune system [7]. The entire process is illustrated in Figure 1. Compared to the traditional antigen-specific vaccines, the mRNA method allows for rapid production and the utilization of several neoantigens at the same time, making it suitable for personalized cancer immunotherapy [6].

Beyond the initial activation of T-cells, personalized vaccination can induce immunological memory and offer long-term immune surveillance against tumor recurrence by means of memory CD8+ T-cells [8]. However, the vaccine-induced T-cells may be inhibited in the suppressive tumor microenvironment and thus lose their persistence and function. Consequently, though mRNA neoantigen vaccines can effectively stimulate tumor-specific immunity, other approaches are necessary to preserve the immune response within the tumors, which provides the basis for the combination of vaccination with immune checkpoint blockade.

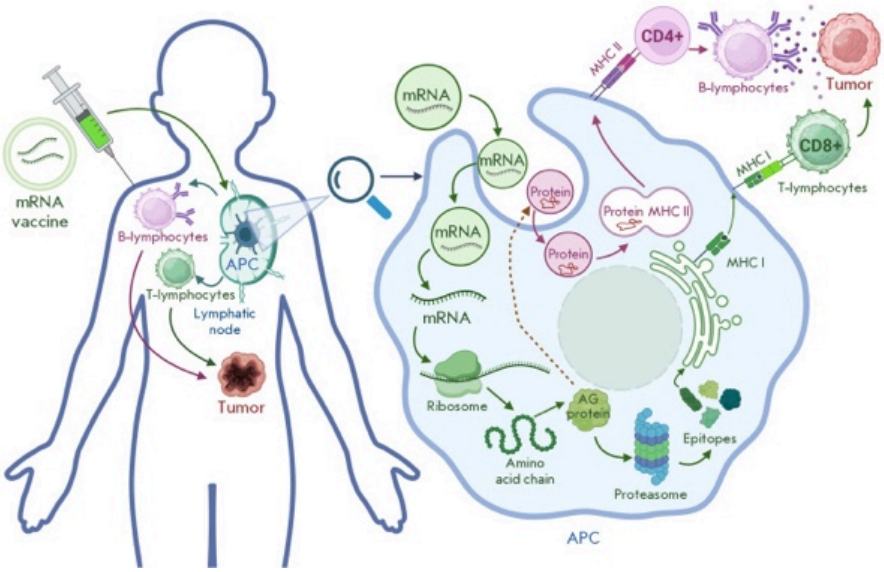


Figure 1. Mechanism of action of mRNA-based personalized neoantigen vaccines in antigen-presenting cells [9]

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2.2. Mechanism of PD-1/PD-L1 blockade in reversing tumor immune escape

Although personalized neoantigen vaccines can stimulate tumor-specific T-cells, the anti-tumor effect is usually restricted by the immune escape mechanisms in the tumor microenvironment (TME). Among these, the PD-1/PD-L1 pathway is an important immune checkpoint used by tumors to inhibit adaptive immune responses. PD-1 is a inhibitory receptor expressed on activated T-cells, while PD-L1 can be expressed continuously in both tumor cells and immune cells within the TME or be induced by IFN-γ. Continuous antigen stimulation results in the long-term maintenance of PD-1 signaling, which leads to T-cell exhaustion characterized by decreased proliferative ability, reduced cytokine secretion and decreased cytotoxic activity [2].

Preventing the interaction between PD-1 and PD-L1 releases inhibitory signals and partly reactivates the function of exhausted T-cells, thus restoring the anti-tumor immune function [2]. It can induce the enlargement of T-cells, increase cytokine secretion and the capacity to destroy tumor cells, which can effectively improve the clinical effect in many patients with malignant tumors. However, the success of immune checkpoint blocking mainly depends on the existence of specific tumor T-cells and their adequate amounts. Tumors with low immune invasion or insufficient spontaneous antigen response are generally called immunologically cold tumors and usually show little response to the inhibition of PD-1/PD-L1 [10].

Hence, while checkpoint blockade is a powerful tool to stop a key mode of tumor immune evasion, its function has been limited to the presence of functional antitumor T-cells.This limitation provides a strong rationale for combining PD-1/PD-L1 inhibitors with personalized neoantigen vaccines, which can simultaneously introduce and expand tumor-specific immune responses.

2.3. Synergistic antitumor logic of the combination strategy

Even though personalized neoantigen vaccines can trigger tumor-specific T-cells, the anti-tumor effect is usually restricted by the immune escape mechanisms in the TME. Among these mechanisms, the PD-1/PD-L1 pathway is an important immune checkpoint which tumors use to inhibit the adaptive immune responses. PD-1 is an inhibitory receptor expressed on activated T-cells, while PD-L1 can be constantly expressed in both tumor cells and immune cells in the TME, or be induced by IFN-γ. Constant antigen stimulation results in the long-term maintenance of PD-1 signaling, causing T-cell exhaustion characterized by the reduction of proliferation ability, decrease in cytokine production and decline in cytotoxic activity [2].

After vaccination, tumor-specific T-cells may up-regulate inhibitory receptors such as PD-1 under continuous antigen stimulation, leading to functional exhaustion in the tumor microenvironment [2]. The inhibition of PD-1/PD-L1 can partially restore their proliferative ability, cytokine secretion and cytotoxicity, thus maintaining the anti-tumor effects caused by vaccination. This cooperative mechanism can produce a larger and longer-lasting number of functional T-cells which are effective against tumors than each treatment can achieve individually [7].

In addition, personalized vaccination might improve the sensitivity of low-infiltration tumors to checkpoint blockade by modifying their immune system. Preclinical experiments indicate that novel antigen vaccines based on mRNA can increase the number of $CD8^+$ T-cells and intensify the inflammatory reaction in the tumor microenvironment. For instance, Fournier et al. [10] reported that an mRNA vaccine system could convert "cold" tumors into those activated by T-cells, thus enhancing the effect of PD-1/PD-L1 inhibitors.

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3. Clinical evidence and safety of combination therapy

3.1. Efficacy outcomes and long-term follow-up trends

Clinical studies across different tumor types, treatment settings, and study designs have shown a range of efficacy patterns, with several key consistencies emerging. In each of these three cancer types (melanoma, pancreatic ductal adenocarcinoma, renal cell carcinoma), personalized neoantigen vaccination has generated long-term, neoantigen-specific T-cell responses, with the durability of the response tending to improve with the higher the number of neoantigens used [5, 8, 11, 12]. The efficacy of these immunologic reactions to the tumor, however, seems to be related to tumor biology and disease stage.

Clinical benefit has been seen more consistently in the adjuvant setting or in patients with minimal residual disease, and is more variable in advanced and metastatic disease. The KEYNOTE-942 trial shows this: patients who received the combination therapy after complete surgical resection had substantial benefit for outcomes related to recurrence, and there is limited and inconsistent evidence of benefit in advanced disease. The reason may be that patients with lower tumour burden are less immunosuppressed and so the T-cells created by the vaccine can multiply and work more effectively.

Similar results have been observed in pancreatic ductal adenocarcinoma (PDAC) and clear-cell renal cell carcinoma (RCC), albeit the clinical presentation varies between the two types of cancer. A PDAC model was used to test this approach, and RNA neoantigen vaccines produced tumor-specific T-cell responses that were sustained in the vaccinees, with those who had a T-cell response having longer recurrence-free survival [8, 12]. Finally, in RCC, Braun et al. [11] also reported that vaccine-induced neoantigen-specific T-cells could be sustained, thus showing that personalized vaccination can generate long-lasting adaptive immunity in even those tumors that have previously demonstrated low sensitivity to immunotherapy.

For instance, in a patient with esophageal squamous cell carcinoma, the combination of an mRNA neoantigen vaccine with PD-1 blockade has exhibited encouraging immune responses and disease control in one case [13]. However, these findings are only based on single cases and cannot be directly applied to a greater number of patients.

According to the available information, personalized mRNA neoantigen vaccines, when used together with PD-1/PD-L1 inhibitors, might produce long-lasting anti-tumor immune responses in various solid tumor cases. A summary of the representative clinical studies is given in Table 1. However, the amount of clinical evidence differs greatly among different types of tumors. Melanoma is confirmed by randomized clinical trials, but the evidence for most other solid tumors is mainly based on preliminary studies with small patient groups. The higher immunogenicity and more permissive immune microenvironment in melanoma may partially explain the stronger evidence, while the dense stromal and immunosuppressive microenvironment in pancreatic adenocarcinoma (PDAC) could hinder the infiltration and function of the vaccinated T-cells even if systemic immune activation is detected [2, 4]. Therefore, larger prospective clinical trials are needed to evaluate the efficiency and applicability of this treatment method in different kinds of cancers.

Table 1. Representative clinical studies of personalized neoantigen vaccines combined with PD-1/PD-L1 inhibitors

Tumor	mRNA Vaccine	PD-1 inhibitor	Phase
Melanoma [5]	mRNA-4157 (V940)	Pembrolizumab	IIb

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Table 1. (continued)

PDAC [8, 12]	Autogene cevumeran	± PD-1*	I
RCC [11]	Personalized neoantigen mRNA vaccine	Nivolumab	I
ESCC [13]	Personalized neoantigen mRNA vaccine	Tislelizumab	Case Report

* In the pancreatic cancer studies, PD-1 blockade was administered only in a subset of patients as part of the adjuvant treatment strategy rather than as the primary intervention.

3.2. Safety characteristics and immune-related adverse events

3.2.1. Types and clinical characteristics of adverse events

Personalized neoantigen vaccines in combination with PD-1/PD-L1 inhibitors have been tested in a variety of early phase clinical trials and are known to be manageable. In general, the adverse events observed with treatment are relatively frequent, and are mostly of low intensity; studies so far indicate no consistent pattern of unexpected adverse events beyond that reported for mRNA vaccines and immune checkpoint blockade [5, 11].

Common side effects of vaccine use are injection site reactions, fatigue, fever, chills, or myalgia [5]. These reactions are mainly due to innate immune activation caused by mRNA delivery, lipid nanoparticle formulations and not to specific immune toxicity, as suggested in figure 2 [3]. Therefore, they do not usually result in the suspension of vaccines, and have not significantly prevented their use in ongoing clinical trials [3, 4].

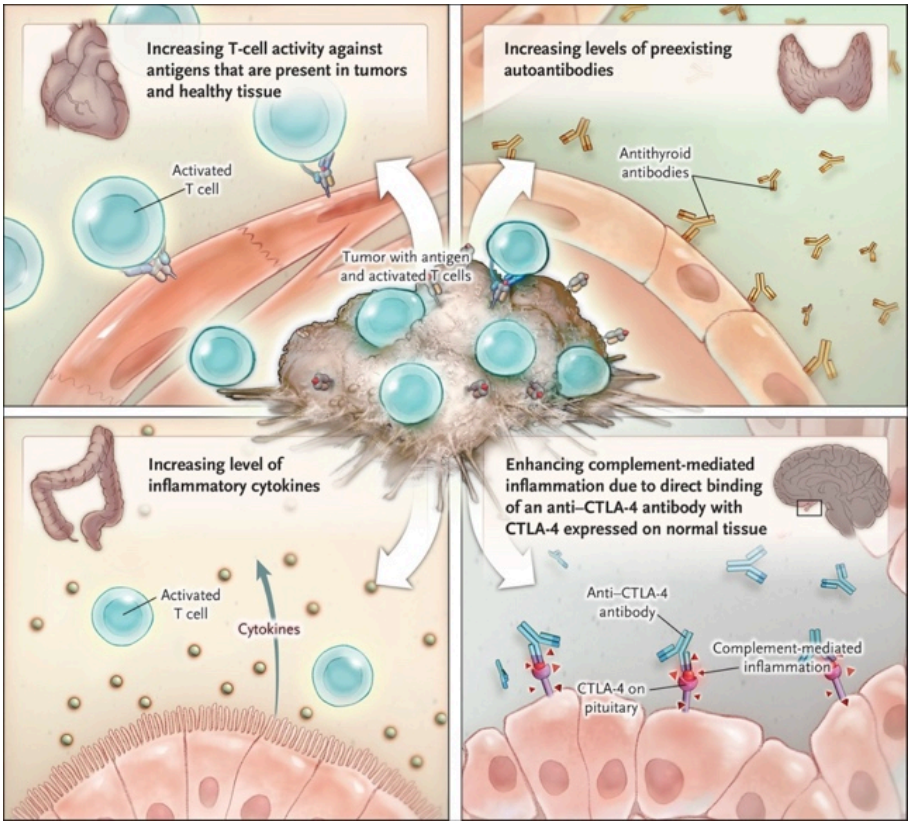


Figure 2. Possible mechanisms underlying immune related adverse events [15]

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By contrast, irAEs are primarily caused by peripheral immune tolerance defects following the administration of PD-1/PD-L1 inhibitors and can affect various systems, such as the skin, endocrine system, liver, gastrointestinal tract and lungs [14]. T-cell activation exacerbated by excessive immunisation is seen against the antigens found in both the tumour and normal tissue, and inflammatory cytokines, auto-antibodies and complement-mediated inflammation can also lead to tissue injury, as shown in Figure 2. There are currently no data showing that vaccination in combination with immune checkpoint inhibitors has altered the incidence or severity of the associated toxicities compared with immune checkpoint inhibitors used as single agents, suggesting that personalized vaccination does not fundamentally alter the toxic properties of immune checkpoint blockade [2, 15].

3.2.2. Occurrence pattern of high-grade adverse events

Although the overall safety of combination therapy seems satisfactory, most grade ≥3 adverse events are mainly related to immune checkpoint inhibition rather than the vaccine component. No consistent increase in serious vaccine-induced toxicities has been found, but the interpretation is restricted by the small scale of the present clinical trials.

In the KEYNOTE-942 trial, the incidence of grade ≥3 treatment-related adverse events was higher in the combination arm than in the pembrolizumab monotherapy arm. However, the types and characteristics of these toxicities were similar to the previously reported safety profile of PD-1 blockade, and no new vaccine-specific safety signals were detected during the extended follow-up.

Similar patterns have also been observed in other kinds of solid tumors. Studies on renal cell carcinoma and pancreatic cancer have shown persistent immune activation with no substantial increases in side effects caused by the vaccine [8, 11, 12]. In conclusion, the above results suggest that personalized vaccination mainly improves anti-tumor immunity without noticeably changing the toxicity pattern determined by checkpoint inhibition.

Moreover, the interpretation of high-grade toxicity is restricted due to the preliminary stage of the present clinical investigations. Variations in tumor kind, disease stage, previous treatments and different treatment regimens make a direct evaluation of the trials inconvenient. When personalized vaccine-based therapies enter into larger clinical trials, it will be necessary to have a longer follow-up and a wider range of patients to determine their long-term safety. In addition, the advantage of combination therapy lies in the equilibrium between the survival benefit and the possibility of serious immune-related toxicities, particularly in the increased number of patients.

3.2.3. Clinical management considerations and implications for combination therapy

This difference is especially significant for the proper handling of clinical cases, because the two therapeutic parts have different toxic effects. It is necessary to maintain the treatment continuity and to reduce the unnecessary interruptions. The adverse reactions occurring during vaccination are usually mild and can recover by themselves; nevertheless, the immune-mediated adverse reactions should be observed and dealt with promptly to prevent serious complications.

The management approach currently focuses on early diagnosis (according to clinical indications), early severity assessment and early commencement of immunosuppressive therapy. In general, mild toxicity can be controlled with monitoring and discontinuation of treatment is required for grade 3 or more severe immune-related adverse events and systemic glucocorticoids may be used [14, 15]. The standardisation of care protocols significantly improves the safety of checkpoint inhibitors and is highly applicable to therapeutic combinations involving vaccines.

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The main issue with combination therapy is maintaining the anti-tumor effects of using the vaccine while controlling the immune-related side effects of the other therapy. While current clinical evidence does not indicate that the use of appropriate management of irAEs is likely to adversely affect overall treatment efficacy, glucocorticoids and other immunosuppressive agents can suppress T-cell activity. Early detection and treatment of irAEs with clinical guidance can preserve lasting antitumor immunity. These results are consistent with the idea that effective toxicity management is not a zero-sum game with regard to therapeutic benefit. Personalized mRNA neoantigen vaccines are on the rise, and individual monitoring and the discovery of predictive biomarkers for toxicity risk will likely be more of a benefit in patient management. The aim of practical clinical application is thus to maintain vaccine-induced anti-tumor immunity while minimizing treatment toxicity by tailoring monitoring and management to the individual patient.

4. Tumor-specific efficacy variability and future directions

4.1. Manifestation of efficacy differences across solid tumors

The clinical results show that the effect of personalized mRNA neoantigen vaccination and PD-1/PD-L1 inhibitors is different for various solid cancers. Present evidences do not approve the application of the combination as a general treatment for all cancers, but indicate that there is a high dependence on the local immune environment, immunogenicity and tumor load for its effectiveness.

Tumors having a higher stromal and/or immunosuppressive condition hinder the effective action of T-cells, and melanoma is an ideal example where this method can work well. This is important since a strong systemic immune response does not necessarily ensure that T-cells can enter the tumor, maintain their functions and eliminate the abnormal cells. Even if vaccination can induce T-cells specific to neoantigens, the clinical results may vary among different types of tumors.

The variations in tumor types indicate the necessity to refrain from considering immune activation as the final goal for therapeutic effectiveness. In some tumors, the T cells induced by the vaccine may proliferate and persist in the tumor, but their action might be limited by the adjacent microenvironment. Nevertheless, if the specific neoantigens targeted are sufficiently immunogenic, even tumors with less mutation can still be cured. This suggests that the efficiency of the immune response and its capacity to operate within the tumor microenvironment may have as important a role as the number of potential neoantigens present in the vaccine.

Generally, the differences in therapeutic results are due to the joint influence of the vaccine, tumor and immunological backgrounds, not because of the inefficiency of the vaccine. Individualized vaccination can offer tumor-specific targets, and PD-1/PD-L1 blockade can preserve the activity of T-cells, but neither method can eliminate all the biological obstacles to effective anti-tumor immunity. The specific characteristics of tumor immunity indicate that it is necessary to examine particular patients for the combination.

4.2. Underlying causes of inter-tumor efficacy variability

The varied clinical effects observed in different solid tumors indicate that the effectiveness of mRNA neoantigen vaccines in conjunction with PD-1/PD-L1 inhibitors depends on several biological factors, which may not be limited to the production or existence of tumor-specific T-cells. Not only the induction of anti-tumor immune responses is necessary; the activation and effector functions of the immune system in the tumor microenvironment should also be maintained for a successful treatment.

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A important factor is TMB which influences the number of potential neoantigens that can be recognized by a vaccine [6]. A higher number of mutations in a tumor leads to more immunogenic neoantigens that can be attacked by specific T-cells induced by the vaccine. For example, highly mutated tumors such as melanoma might explain the strong immune response observed in these cases. However, the variety of neoantigen candidates is significantly decreased in tumors with low TMB, thus reducing the extent and intensity of immune activity caused by the vaccine. Nevertheless, TMB should not be regarded as the only marker for therapeutic effect. In clinical trials, it has been found that tumors with a relatively low mutation load (e.g., PDAC) can still elicit clinically significant immune responses after vaccination with neoantigens, indicating that both the quality and immunogenicity of neoantigens and their quantity are important factors.

Another important factor is the baseline immune status of the tumor microenvironment. PD-1/PD-L1 inhibition depends on pre-existing tumor-specific T-cells, which can be reactivated after being inhibited by the checkpoint. Therefore, immunostimulatory (or "hot") tumors are usually more responsive, while immunosuppressive or immunologically cold tumors tend to benefit less. Personalized vaccination can partially overcome this limitation by introducing new tumor-specific T-cells and promoting immune infiltration; however, severe immunosuppression in the tumor microenvironment may still limit the function of T-cells.

Effective anti-tumor immunity is influenced by proper antigen presentation. If there are defects in MHC expression, antigen processing pathways or alterations in immune recognition, even though vaccine-induced T-cells are successfully produced, the tumor cells cannot be recognized. Thus, defects in antigen presentation function may serve as an important mechanism for either acquired or congenital tolerance of individualized neoantigen vaccines.

In addition, the tumor microenvironment includes several immunosuppressive factors such as regulatory T-cells, myeloid-derived suppressor cells, tumor-associated macrophages and inhibitory cytokines. These factors jointly inhibit the activation, proliferation and survival of T-cells [16]. These inhibitory processes usually occur simultaneously and strengthen each other, resulting in a strong immunosuppressive condition which consequently affects the therapeutic effect of combined immunotherapy.

The variations in therapeutic effects are due to the interactions between the availability of new antigens, immune cell penetration, antigen presenting ability and the inhibition in microenvironment. It is important to clarify these factors in order to find the predictive marker and to select the patients appropriately for the individualized vaccine treatment.

4.3. Current limitations in clinical application

Despite the preliminary clinical results, the use of personalized mRNA neoantigen vaccines in conjunction with PD-1/PD-L1 inhibitors is still restricted in general medical practice because of some technical and biological difficulties. These restrictions include the problems in vaccine production, insufficient clinical trial evidence about the therapeutic efficiency and the absence of effective biomarkers for patient selection.

Personalized cancer treatments, on the other hand, require the production of the treatment per patient, ranging from sequencing cancer genomes, predicting neoantigens, designing vaccines, manufacturing, and quality control [3]. In some parts of the procedure, new sequencing and mRNA technologies have been incorporated to streamline the process, but it remains lengthy and challenging, and sometimes not finished within the treatment "windows" required for the most aggressive forms of cancer. The widespread adoption of this technology is not easy due to this specialised infrastructure and production costs. They also make it more complex to standardize

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procedures, and to get clinical adoption of the regulations, slowing the speed of regulatory approval. Despite potential improvements in clinical efficacy, there may be barriers to widespread adoption of the treatment including manufacturing capacity, cost and access to state-of-the-art medical facilities.

The difficulty is the absence of large-scale and high quality clinical information of various kinds of tumors.While the randomized phase 2b trial data for melanoma is presented in the KEYNOTE-942 trial, almost all other indications have been studied in small early phase trials. There are a number of differences across studies and trials regarding vaccine types, dosage regimens, and endpoints, making it difficult to undertake cross-trial comparisons, and highlighting the need for large, well-designed randomized controlled trials to establish whether such approaches actually produce a therapeutic benefit.

Currently available predictive biomarkers are not enough to select those patients who will clinically benefit from combination therapy. Many factors were assessed such as tumor mutational load, neoantigen immunogenicity, immune cell infiltration, PD-L1 expression, and none of these factors alone is predictive [4]. Therefore there is a need to combine genome and immune information for patient selection and for targeting for maximum therapeutic benefit.

4.4. Future optimization directions

There are defined opportunities for improving mRNA neoantigen vaccines, including designing vaccines, delivery technology, combination regimens, and patient stratification, given the current clinical and biological barriers of these approaches. To be useful in treating not only selected tumors but all kinds of malignancies, optimization of these parameters is needed.

Now the identification and prioritization of neoantigens can be greatly refined. Current prediction methods are largely not able to accurately predict clinically relevant and immunogenic neoantigen candidates, which can be identified by Next-Generation sequencing. Incorporating these technologies, such as artificial intelligence, immunopeptide-omics and multi-omics profiling into prediction models, is expected to increase accuracy [4, 6].

Improvements in the delivery of mRNA and in its manufacture help to make clinical use more feasible. The optimized lipid nanoparticle formulations allow higher expression of the antigens and therefore higher immune response, and the streamlined production processes shorten manufacturing times and costs. These advances are particularly relevant in the case of those who have rapidly progressing cancers.

A rational combination therapy regime may be more practical than continued vaccination for increasing the immune system to overcome resistance than vaccines alone. If the blockade of PD-1/PD-L1 is not effective, other targets of the immune checkpoint could be used and personalized vaccination could also be combined with other interventions that promote infiltration of immune cells and/or modification of the tumor microenvironment for immunologically 'cold' tumors. Matching the additional treatment to the particular barrier to T-cell function, instead of assuming one type will function in any tumor, is the key [10].

To identify patients most likely to benefit from combined treatment, the ability to produce predictive biomarkers is needed. Tumor genomics, characteristics of neoantigen, immune cell composition and spatial distribution analysis may provide a more accurate evaluation of the response to treatment than current single "markers."

The ongoing development of neoantigen prediction, mRNA engineering, delivery methods and the selection of patients on the basis of biomarkers has the potential to greatly broaden the therapeutic potential of this combination immunotherapy approach. Importantly, technological innovation will not be the only driver of advancement; progress will also depend on a deeper

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understanding of tumor immunobiology and the dynamic crosstalk within the tumor microenvironment. The progress made to date suggests that mRNA neoantigen vaccines, when combined with PD-1/PD-L1 blockade, can deliver broader therapeutic benefits across a wider range of solid malignancies.

5. Conclusion

The biological argument, clinical evidence, safety profile and tumour-specific variability of mRNA neoantigen vaccines in combination with PD-1/PD-L1 inhibitors have been reviewed. The results overall seem to be encouraging, but as yet insufficient to conclude that this approach is a reliable method for treatment of solid tumours in a general way.

The strongest clinical clue to date is in situations where tumor burden is low, such as following surgical resection. This is significant as it indicates that the potential benefits of personalised vaccination may not only be to reduce established tumour burden but also to provide immune surveillance in limited residual disease. In parallel, the evidence outside melanoma is less mature and durable immune responses should not be assumed to indicate long-term clinical benefit.

The key question is not just whether a vaccine is able to elicit tumour-reactive T-cells, but whether they can maintain their function within the tumour environment. The response to treatment can be difficult to predict as TMB, neoantigen quality, antigen presentation, infiltration and immunosuppressive mechanisms can interact. This is also the reason that a single biomarker is not likely to be enough for patient selection and future studies will need to link molecular features to the actual immune state of the tumor.

In addition, there are practical limitations that cannot be overlooked. Because the treatments are more challenging and expensive than standard treatments, each personalised vaccine must be sequenced from the tumour, selected for neoantigens, manufactured and quality-controlled. Requirements are particularly significant in cases of patients with rapidly advancing disease, where a biologically promising treatment that may take a long time or be difficult to manufacture may not be of much practical use.

Further improvement will rely on increasing the selectivity and efficacy of the treatment. Advanced neoantigen prediction, optimized mRNA delivery and production, and the development of an integrated biomarker that combines genomic and immune context will help identify patients most likely to benefit from mRNA vaccine treatment. Combination regimens should also be tailored to the predominant resistance mechanism of each tumor, and not given in a one-size-fits-all approach.

In this regard, the key is not that personalized mRNA neoantigen vaccination has already overcome the limitations of cancer immunotherapy, but that it has enabled a more biologically targeted approach to treatment. The next step is to identify patient populations, tumour types and treatment combinations that will provide meaningful clinical results from that biological rationale.

References

[1] Bray, F., et al. (2024). Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 185 countries. *CA: A Cancer Journal for Clinicians*.

[2] Ribas, A., & Wolchok, J. D. (2018). Cancer immunotherapy using checkpoint blockade. *Science, 359*(6382), 1350–1355.

[3] Shariati, A., et al. (2024). mRNA cancer vaccines from bench to bedside: A new era in cancer immunotherapy. *Biomark Res, 12*, 157.

[4] Garg, P., Salgia, R., & Singhal, S. S. (2026). mRNA-based cancer vaccines: A new frontier in personalized immunotherapy. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1881*(3), 189577.

DOI: 10.54254/2753-8818/2026.36956

[5] Gao, Y., et al. (2024). mRNA-based personalized cancer vaccines: Opportunities, challenges and outcomes. *Journal of Hematology & Oncology, 17*(1).
[6] Li, X., et al. (2026). Next-generation neoantigen mRNA vaccines: Immuno-engineering strategies for precision cancer immunotherapy. *Cellular Oncology, 49*(2), 72.
[7] Chen, H., et al. (2022). Personalized neoantigen vaccine combined with PD-1 blockade increases CD8+ tissue-resident memory T-cell infiltration in preclinical hepatocellular models. *Journal for Immunotherapy of Cancer, 10*(9), e004389.
[8] Sethna, Z., Guasp, P., Reiche, C., et al. (2025). RNA neoantigen vaccines prime long-lived CD8+ T cells in pancreatic cancer. *Nature, 639*, 1042–1051.
[9] Kabut, J., et al. (2025). mRNA-based neoantigen vaccines in pancreatic ductal adenocarcinoma (PDAC)—a promising avenue in cancer immunotherapy. *International Journal of Molecular Sciences, 26*(22), 10988.
[10] Fournier, C., et al. (2025). Nanostructured lipid carriers based mRNA vaccine leads to a T cell-inflamed tumour microenvironment favourable for improving PD-1/PD-L1 blocking therapy and long-term immunity in a cold tumour model. *eBioMedicine, 112*.
[11] Braun, D. A., Moranzoni, G., Chea, V., et al. (2025). A neoantigen vaccine generates antitumour immunity in renal cell carcinoma. *Nature, 639*, 474–482.
[12] Rojas, L. A., et al. (2023). Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature, 618*(7963), 144–150.
[13] Wang, B., et al. (2024). Personalized mRNA vaccine combined with PD-1 inhibitor therapy in a patient with advanced esophageal squamous cell carcinoma. *American Journal of Cancer Research, 14*(8), 3896–3904.
[14] Brahmer, J. R., et al. (2018). Management of immune-related adverse events associated with immune checkpoint inhibitor therapy. *Journal of Clinical Oncology, 36*(17), 1714–1768.
[15] Postow, M. A., et al. (2018). Immune-related adverse events associated with immune checkpoint blockade. *New England Journal of Medicine, 378*(2), 158–168.
[16] Chen, D. S., & Mellman, I. (2013). Oncology meets immunology: The cancer-immunity cycle. *Immunity, 39*(1), 1–10.