Personalized mRNA Cancer Vaccines: Advances, Limitations, and the Promise of mRNA-4157 (V940)

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Abstract. mRNA-4157 (V940) is an individualized cancer vaccine designed to stimulate potent immune responses against patient-specific tumor neoantigens. Building on the rapid design capability, safety profile, and immunogenicity demonstrated by mRNA vaccines during the COVID-19 pandemic, V940 represents a significant advance in personalized immunotherapy. It is generated through sequencing of tumor and matched normal tissues, computational prediction of up to 34 top-ranked neoantigens, and formulation of an optimized mRNA construct in lipid nanoparticles. Once delivered, the mRNA is translated in host antigen-presenting cells, initiating antigen processing, presentation, and activation of $CD8^+$ and $CD4^+$ T cells that target tumor cells carrying those mutations. Advantages include rapid design cycles, polyepitope targeting, and a non-integrating platform, while challenges include time-sensitive manufacturing, cold chain requirements, imperfect neoantigen prediction, reduced efficacy in low-mutation-burden tumors, and the immunosuppressive tumor microenvironment. Current development focuses on refining antigen prediction algorithms, combining with synergistic therapies such as checkpoint inhibitors, radiation, or innate agonists, and expanding use into earlier-stage cancers. V940's modular, mutation-guided approach offers a template for future cancer vaccines and the potential to transform treatment paradigms across multiple malignancies.

Keywords: mRNA-4157 (V940), Personalized cancer vaccines, Neoantigens, Immunotherapy, Tumor microenvironment.

1. Introduction

Cancer vaccines are an emerging form of immunotherapy that aims to train the immune system to recognize and destroy tumor cells by presenting tumor-associated antigens. Unlike prophylactic vaccines against infectious diseases, most cancer vaccines are therapeutic, targeting existing malignancies to boost anti-tumor immunity and prevent recurrence [1].

The COVID-19 pandemic accelerated both the development and public awareness of messenger RNA (mRNA) vaccine technology, demonstrating its rapid design capability, high safety profile, and potent immune activation properties. The unprecedented success of mRNA-based SARS-CoV-2 vaccines has catalyzed efforts to apply the same platform to oncology, where the flexibility of mRNA allows for rapid encoding of multiple tumor antigens and personalization to an individual's cancer profile.

One of the most advanced examples of this approach is mRNA-4157 (V940), a personalized cancer vaccine developed by Moderna, Inc. in collaboration with Merck KGaA [2]. This vaccine is designed to induce targeted immune responses against patient-specific neoantigens—mutated proteins found only on tumor cells—thereby minimizing damage to healthy tissue [3]. By tailoring the antigen sequence to each patient's tumor mutational signature and delivering it via lipid nanoparticles, mRNA-4157 seeks to elicit strong, precise T cell–mediated immunity capable of reducing tumor burden and preventing relapse [1, 3].

2. Mechanism of Action of mRNA-4157

mRNA-4157 is a personalized neoantigen vaccine engineered from a patient's unique tumor mutation profile, encoding up to 34 neoantigens [2].

The process begins with sequencing tumor and matched normal tissue to identify somatic mutations. Bioinformatics pipelines then predict which mutated peptides are most likely to bind patient's MHC molecules, be processed effectively, and stimulate T cells [2]. Up to 34 of the highest-priority neoantigens are selected and encoded in a single, optimized mRNA containing nucleoside modifications such as a 5′ cap, and a poly(A) tail, to enhance stability and translation.

Formulated in LNPs and administered intramuscularly, the mRNA enters antigen-presenting cells such as dendritic cells. Host ribosomes translate the mRNA into a poly-neoantigen protein, which is processed into peptides and displayed on MHC class I and II molecules. This triggers expansion of tumor-specific $CD8^+$ cytotoxic T cells, supported by $CD4^+$ helper T cells, enabling precise elimination of tumor cells harboring those mutations and promoting immunologic memory [4-6].

Compared with peptide vaccines, which often include limited epitopes and require adjuvants, and dendritic cell vaccines, which are labor-intensive and poorly scalable, this approach is designed to be more comprehensive and scalable. Unlike chemotherapy or small molecules, V940 is mutation-guided and designed to adapt to evolving tumor targets, while avoiding the broad cytotoxicity of conventional therapies [2].

3. Manufacturing and Personalization Process

The development of V940 begins with obtaining a tumor biopsy and matching normal tissue or blood sample. These specimens undergo next-generation whole-exome and RNA sequencing to define the tumor's mutational landscape [2]. Advanced algorithms integrate HLA genotyping, predicted peptide processing, and expression data to rank candidate neoantigens. The selected sequences are concatenated into a single mRNA, manufactured under GMP conditions, and encapsulated in LNPs [7].

This design–build–test cycle can be completed in a matter of weeks, offering a major time advantage in personalized oncology. However, production is highly time-sensitive: delays would miss the optimal adjuvant treatment window and exclude patients with rapidly recurring disease [4]. Current research focuses on compressing sequencing, computational design, and GMP production aim to further shorten "vein-to-vaccine" intervals.

4. Clinical Trial Progress

In the randomized Phase IIb KEYNOTE-942 trial in completely resected stage IIIB–IV cutaneous melanoma, mRNA-4157 in combination with pembrolizumab achieved an 18-month recurrence-free survival (RFS) of 79% versus 62% for pembrolizumab alone (HR 0.561; 95% CI 0.309–1.017) [2]. The safety profile was manageable, with mostly grade 1–2 adverse events and immune-mediated toxicity rates like monotherapy. Extended follow-up showed sustained improvement in both RFS and distant metastasis–free survival (DMFS), indicating durable clinical benefit [2].

Latest developments include two Phase III programs in resected non-small cell lung cancer (NSCLC): INTerpath-002 (adjuvant V940 + pembrolizumab after surgery and chemotherapy) and a perioperative program following neoadjuvant pembrolizumab plus chemotherapy [7]. V940 is also under evaluation in HPV-related malignancies, including head and neck cancers, where early-phase trials report immunogenicity and preliminary activity. A global double-blind Phase III melanoma trial (INTerpath-001) is underway to validate KEYNOTE-942 findings [2].

5. Advantages Over Traditional Cancer Vaccines

mRNA-4157 offers several advantages positioning it as a next-generation cancer vaccine. Its design-and-manufacturing cycle can be completed within weeks after tumor sequencing, enabling rapid personalization that is particularly valuable in time-sensitive settings such as the adjuvant window. By encoding up to 34 neoantigens in a single construct, it achieves broad polyepitope targeting that reduces the risk of tumor immune escape through antigen loss. In situ synthesis of these

antigens within host antigen-presenting cells drives strong $CD8^+$ and $CD4^+$ T cell activation, producing robust and durable anti-tumor immunity. As a non-infectious, non-integrating platform with transient expression, it avoids risks associated with viral vectors or DNA-based approaches, including insertional mutagenesis and chronic inflammation. Compared with peptide vaccines, which often include a limited number of short epitopes and depend on adjuvants to boost immunogenicity, and dendritic cell vaccines, which are labor-intensive and difficult to scale, mRNA-4157 combines high immunogenic potential with manufacturing scalability. Relative to conventional cancer treatments, it provides much more specificity than chemotherapy while also providing better longevity and breadth than monoclonal antibodies [2, 7, 8].

6. Limitations and Challenges

Despite its promise, mRNA-4157 faces several limitations. Manufacturing is highly time-sensitive, requiring tumor and normal sequencing, computational neoantigen prediction, and individualized GMP production; timelines of several weeks can delay adjuvant treatment and may exclude patients with rapid recurrence [8, 9]. The LNP formulation necessitates frozen storage and controlled distribution, imposing cold chain constraints that limit community and global accessibility while increasing operational complexity [8, 10]. Neoantigen prediction algorithms, although improving, remain imperfect, often including targets that are poorly immunogenic or clonally irrelevant, leading to interpatient variability in immune responses. Efficacy may also be attenuated in "cold" tumors with low mutation burden, where fewer neoantigens and weaker baseline T-cell priming blunt benefit compared with highly mutated melanoma. Furthermore, an immunosuppressive tumor microenvironment—rich in regulatory T cells, myeloid-derived suppressor cells, exhausted T cells, and inhibitory cytokines such as TGF-β—can impair intratumoral trafficking and activity of vaccine-primed T cells despite evidence of systemic immunogenicity. Finally, the need for individualized sequencing, computational design, GMP manufacturing, multiple clinic visits, and strict cold chain maintenance creates significant logistical and cost barriers to large-scale implementation.

7. Future Outlook

Development of mRNA-4157 is progressing in three main areas. The first focuses on improving AI-based neoantigen prediction to better select targets that are both highly immunogenic and clonally expressed [1]. This is done by integrating multiple features — including HLA binding affinity, likelihood of antigen processing, expression levels, and predicted T-cell receptor recognition. Second, rational combination strategies are being tested to overcome tumor immune resistance, including the addition of toll-like receptor agonists, myeloid-modulating agents, or radiation therapy to promote in situ antigen release and enhance dendritic cell priming [7]. These combinations hold particular promise for extending benefit into "cold," low–tumor-mutation-burden cancers where vaccine efficacy has historically been limited [1, 4]. Third, clinical development is moving into earlier-stage, perioperative settings—both adjuvant and neoadjuvant—where tumor burden is lower and immune competence is higher. The encouraging adjuvant signal in resected stage IIIB–IV melanoma from the KEYNOTE-942 trial has spurred multiple Phase III programs in melanoma and resected NSCLC, all using pembrolizumab as a backbone. With its modular design, adaptability, and potential for integration with next-generation delivery systems, mRNA-4157 could serve as a template for future personalized cancer vaccines if its efficacy is confirmed and operational challenges are addressed [6], [11, 12]. Logistical demands, cold-chain and cost constraints, and the need to overcome a hostile tumor microenvironment remain significant barriers to broad adoption, and confirmatory trial results will be essential to define its place alongside—and potentially ahead of—current therapeutic modalities.

8. Conclusion

mRNA-4157 stands as a milestone in personalized immunotherapy, pairing promising early clinical outcomes with a mechanistic approach that directly encodes patient-specific tumor mutations to drive targeted immunity. While manufacturing timelines, cold chain requirements, imperfect antigen prediction, and the immunosuppressive TME remain obstacles, the vaccine marks a paradigm shift toward mutation-guided, patient-specific cancer treatment. If ongoing Phase III trials confirm efficacy and operational hurdles are overcome, V940 could redefine the standard of care in select cancers and lay the groundwork for future individualized cancer vaccines.

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