Combination of mRNA Vaccines and Immune Checkpoint Inhibitors for Cancer Treatment

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Abstract

Messenger RNA (mRNA) vaccines have emerged as one of the most promising immunotherapies for cancer due to their treatment efficacy, safety profile, and low development costs. Through the mRNA vaccine, cells are instructed to produce proteins associated with specific mutations in tumors, prompting the immune system to identify and attack these mutations. While mRNA vaccines are considered a rising solution in the field of cancer research, monotherapy trials in general have yet to show significant clinical success. Due to tumors' ability to evade detection by the immune system, including impairing immune cell function and developing resistance to drugs, monotherapies are believed to be insufficient to treat multiple types of cancers. As a result, many scientists have shifted their strategies to prioritize the concept of combination therapy in order to maximize the benefits of clinical trials. The purpose of this paper is to evaluate the potential benefits of combining mRNA vaccines with immune checkpoint inhibitors for cancer treatment. Using data from past clinical trials combining mRNA vaccines with immune checkpoint inhibitors, as well as reviewing trials using immunotherapies alone, we will examine the design and procedures of the trials, as well as the results and data collected. Studies have demonstrated promising results from combining mRNA vaccines with immune checkpoint inhibitors, including improved distant metastasis-free survival (DMFS). These discoveries are vital to opening up a number of new avenues for the treatment of cancers of many types.

Tumor Immunity & Immunotherapy

Immunotherapy is a type of cancer treatment designed to strengthen a patient's immune system. These therapies aid in the detection and destruction of cancerous cells (*What Is Immunotherapy?*, 2022). Over time, the study of immunotherapy has progressed into just about every type of cancer, and immunotherapy has proven effective in treating certain cancers, such as skin, lung, and bladder (Bondhopadhyay, 2020). Unlike traditional, nonspecific cancer treatments such as chemotherapy, which target all dividing cells in the body including healthy tissues (S. Lee, 2021), immunotherapy works more directly and specifically at the level of the immune system (Mheslinga, 2023). This mitigates off-target toxicity and minimizes negative side effects (Mheslinga, 2023). Despite immunotherapy having few side effects, it is possible to experience side effects triggered by an overly active immune response that may affect the tissue or organs. The severity of side effects can range from mild to moderate to severe, and in rare circumstances, they can be life-threatening. Fortunately, immunosuppressive drugs such as steroids can safely manage most side effects when recognized early and treated effectively (Mheslinga, 2023). Consequently, every patient receiving immunotherapy should be appropriately monitored during and after treatment (Mheslinga, 2023).

While an increasing number of cancer patients are eligible to receive immunotherapy and experience effective and durable responses (Cercek et al., 2022), the vast majority of cancer patients do not respond (Bai et al., 2020). There are many differences between individuals, so people may not respond to the same treatments in the same manner (Sambi et al., 2019). Depending on their genetic makeup, some people metabolize drugs too slowly, causing the drug to accumulate in their bodies and be toxic (Lynch, 2023). In the case of others, the body may process drugs so quickly that even when they take a normal dose, the amount of drugs in the blood never reaches a level sufficient for the drug to be effective, potentially resulting in inadequate treatment (Lynch, 2023).

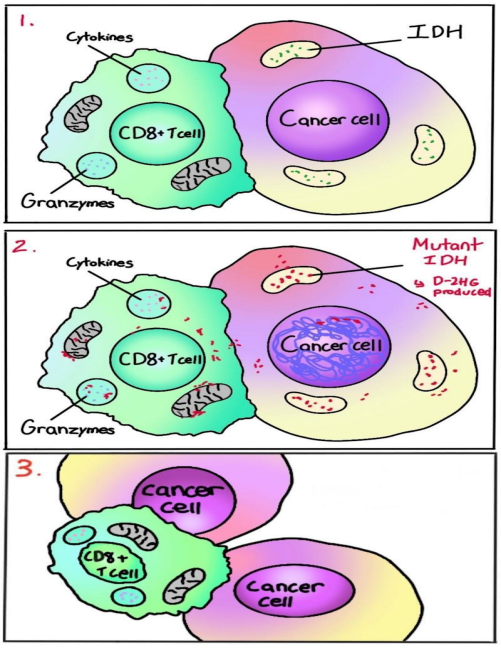
Additionally, drug resistance may also contribute to failed treatments, as seen in some patients with melanoma (Thornton et al., 2022). In some patients, immunotherapy for melanoma has been resisted by cancer cells over time (Thornton et al., 2022). Other times, scientists are unable to determine the exact reason why patients are not responding to immunotherapy (Bai et al., 2020).

Despite this, immunotherapy remains as a viable option for eradicating cancer since it addresses factors such as cancer evasion from the immune system more effectively. (Koury et al., 2018).

For example, the illustration shown in Figure 1 is just one way tumors may evade the immune system to multiply and grow.

Figure 1

Mutations in IDH Result in Cancer Immune Evasion



Note. Using cytokines and granzymes, CD8+ T cells combat cancer cells containing IDH (Figure 1A). When IDH is mutated, D-2HG is produced and begins to alter the DNA of cancer cells. Then, the T cell absorbs D-2HG (illustrated in red) (Figure 1B). When D-2HG is absorbed, it deactivates the T cell and the cancer cell divides and grows (Figure 1C).

In cancer cells, a metabolic enzyme called isocitrate dehydrogenase (IDH), is often mutated, causing cancer cells to produce an oncometabolite known as D-2HG (Harvard Medical School, 2022). Research has demonstrated that D-2HG causes epigenetic dysregulation inside cancer cells, altering their DNA (Harvard Medical School, 2022). Normally, cytotoxic CD8+ T cells release cytokines and granzymes, which are molecules that kill cancerous cells. T cells can also absorb D-2HG produced by cancerous cells (Harvard Medical School, 2022). Once inside, D-2HG disrupts the release of cytokines and granzymes, and reduces T cells' ability to fight cancer (Harvard Medical School, 2022). In this way, cancer cells can grow and evade immune cells.

Types of Immunotherapies

There are a variety of immunotherapies that can improve the immune system's overall ability to fight cancer, including chimeric antigen receptor (CAR) T-cell therapy (*T-cell Transfer Therapy - Immunotherapy*, 2022). As part of CAR T-cell therapy, T cells from a patient are engineered in the lab to produce CAR proteins before they are expanded and reinfused back into the patient (*T-cell Transfer Therapy - Immunotherapy*, 2022). These CARs enable T cells to better identify and attach to specific proteins on the surface of cancer cells, thereby increasing the effectiveness of their attack (*T-cell Transfer Therapy - Immunotherapy*, 2022).

Another type of immunotherapy, cytokine therapy, uses cytokines to enhance the immune system's capability to fight cancer (S. Lee, n.d.). Cytokines are chemicals produced by the body that activate the immune system to combat disease or germs that enter the body (S. Lee, n.d.). They can also be engineered in a laboratory to be used as cancer treatments (S. Lee, n.d.). Cytokines stimulate immune effector cells that elicit an immune response at tumor sites (Lee & Margolin, 2011). Effector cells, such as those of cytotoxic CD8+ T cells, can identify and target cancerous cells that bear specific antigens while sparing neighboring healthy cells (Janeway, 2001).

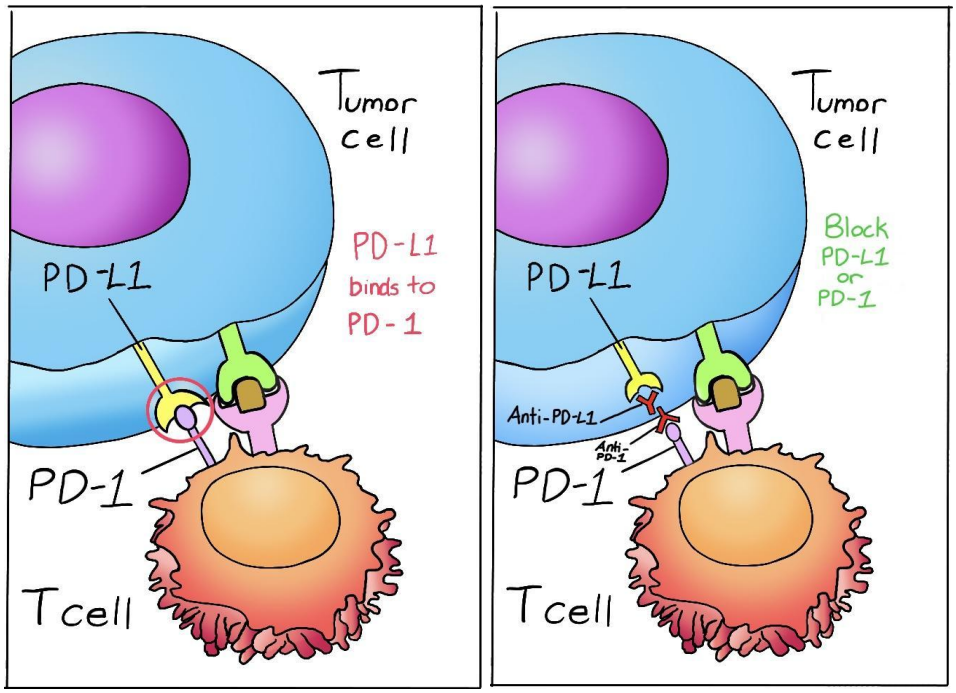
A specific class of cytokines made by the body are called interferons (Zaidi & Merlino, 2011). Interferons play a crucial role in initiating a stronger immune response against cancer cells as well as slowing their growth or inducing cell death (Di Franco et al., 2017). There are two types of interferon approved by the FDA for adjuvant treatment of cancers such as melanoma: interferon α-2b (Intron A) and a pegylated version of α-2b (Sylatron) (Chiarion-Sileni et al., 2006; Sondak & Kudchadkar, 2012). Due to this pegylation, Sylatron remains in the blood for a longer period of time, which allows it to be administered at lower doses (*Interferon for Melanoma Adjuvant Therapy*, n.d.).

Among the other types of immunotherapy, immune checkpoint inhibitors are also important for the treatment of cancer (Carlino et al., 2021). An immune checkpoint protein in the body assists

in preventing the immune system from overreacting and destroying healthy cells (Stirling et al., 2022).

Figure 2

PD1/PDL1 Antibodies: How They Work



Note. By binding PD-L1 to PD-1, T cells are prevented from killing tumor cells (left image). An immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) can block the PD-L1-PD-1 interaction and allow T cells to kill tumor cells (right image).

For instance, the cell surface receptor programmed death-1 (PD-1) on T cells and its corresponding ligand PD-L1 on tumor cells are examples of checkpoint proteins that assist to prevent and/or tune an immune response (Ghosh et al., 2021).When PD-L1 binds to its receptor PD-1 on the surface of a T cell, this can suppress T cell activation and prevent it from killing tumor cells (Ghosh et al., 2021). This is another mechanism by which tumors evade the immune system, thereby allowing cancer to grow and spread.

Immune checkpoint inhibitors prevent checkpoint proteins from binding with their cognate ligands by forming a barrier between them (Stirling et al., 2022). By blocking the interaction between PD-L1 and PD-1, for example, immune checkpoint inhibitors allow T cells to exert their effector function and kill the malignant tumor cells (Yi et al., 2022).

At present, eight immune checkpoint inhibitors are approved by the FDA, including atezolizumab, pembrolizumab, and ipilimumab (J. B. Lee et al., 2022). Atezolizumab is a monoclonal antibody that targets PD-L1 on cancer cells (Herbst et al., 2020); pembrolizumab is an anti-PD-1 humanized monoclonal antibody (Khoja et al., 2015); and ipilimumab is

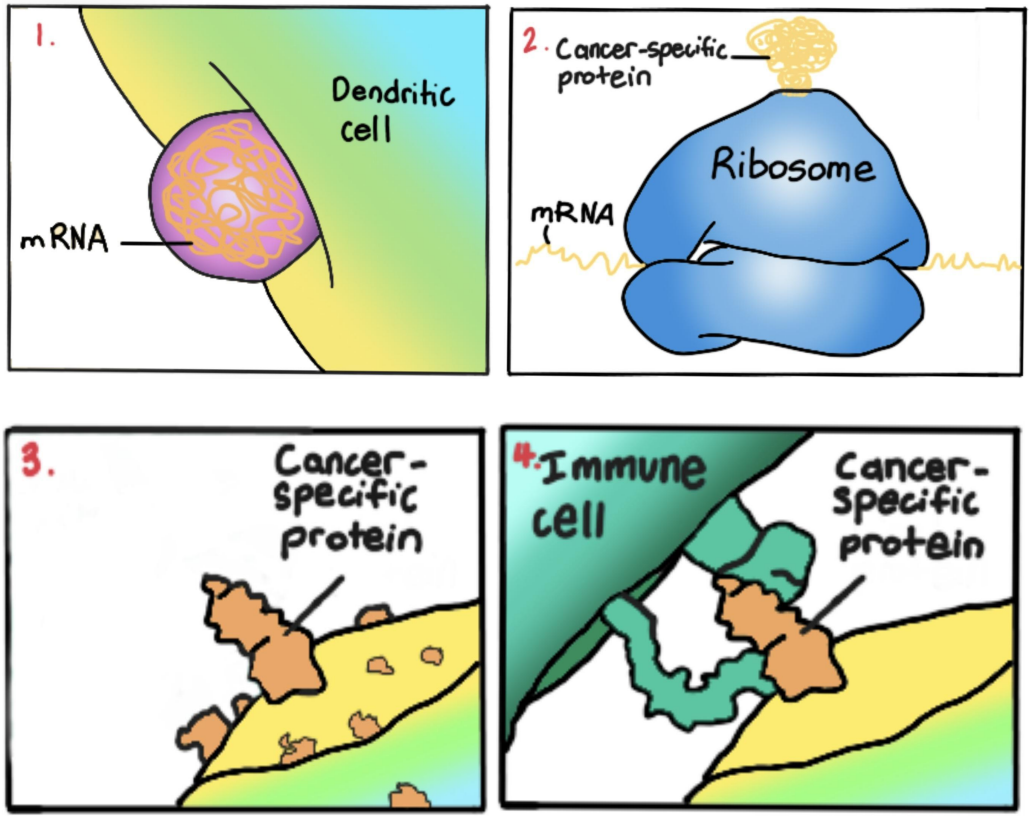
anti-CTLA-4 (i.e. another immune checkpoint protein) (Touboul & Bonavida, 2021). Several immune checkpoint inhibitors are being tested for cancers such as head and neck, aiming to improve long-term survival rates and extend progression-free survival times in early stages (Kwapisz, 2020).

Messenger RNA (mRNA) vaccines

An mRNA vaccine can encode for any protein, for instance, it may introduce a piece of mRNA that corresponds to a viral protein or cancer-specific antigen (Sockrider & Krishnan, 2021; Vishweshwaraiah & Dokholyan, 2022). Shown in Figure 3 is a step-by-step illustration of how an mRNA vaccine encoding a cancer-specific protein works.

Figure 3

mRNA Vaccine: Step by Step



Note. Dendritic cells, a type of immune cell, take up mRNA wrapped in a fat particle layer (Figure 3A). After entering these cells, mRNA remains in the cytoplasm, where ribosomes read it to produce cancer-associated proteins (Figure 3B). Then, on the surface of dendritic cells, these proteins are displayed (Figure 3C). As the dendritic cells migrate to nearby lymph nodes,

they present the proteins they possess to other immune cells. The cells will then produce antibodies in order to fight the cancer (Figure 3D).

A special type of immune cell called a dendritic cell takes up mRNA, and once inside the dendritic cell, the mRNA remains in the cytoplasm - it does not enter the nucleus of the cell (Children's Hospital Of (C.H.O.) Philadelphia, n.d.). Following this, the ribosome reads the mRNA to create pieces of cancer-associated proteins (Children's Hospital Of (C.H.O.) Philadelphia, n.d.). The dendritic cells will have pieces of the protein on their surfaces and travel to a lymph node nearby, where they will present the proteins to other immune cells (Children's Hospital Of (C.H.O.) Philadelphia, n.d.). In response, other immune cells will begin to produce antibodies (Children's Hospital Of (C.H.O.) Philadelphia, n.d.). In order to protect the body against infection, antibodies recognize individual viruses or other pathogens, attach to them, and mark them for destruction by the immune system (Sockrider & Krishnan, 2021). After the body has rid itself of the pathogen, antibodies remain in the body, allowing the immune system to rapidly respond to a potential subsequent infection (Sockrider & Krishnan, 2021).

For some time, researchers have studied and worked with mRNA vaccines due to their potential to treat cancer and their convenience for clinical trials (Vishweshwaraiah & Dokholyan, 2022). However, despite promising results in clinical trials, no mRNA vaccine has yet received FDA approval for treating cancer (Lorentzen et al., 2022). As noted by Vishweshwaraiah and Dokholyan (2022), mRNA can be produced using readily available materials and as a result can be developed much more quickly than traditional methods. Once developed, this enables large-scale clinical trials to be conducted for experimental purposes. As an additional benefit, since mRNA vaccines are versatile, they can quickly be adapted to prevent new variants, enabling clinical trials to be done as soon as possible to evaluate the immune response to the variant (Vishweshwaraiah & Dokholyan, 2022).

In recent years, scientists have explored the efficacy of mRNA vaccines against various types of cancers including melanoma ("Precision Medicine Meets Cancer Vaccines," 2023), pancreatic cancer (Huang et al., 2022), and other advanced solid tumors. In addition, personalized mRNA cancer vaccines are currently being studied in different clinical trials in combination with other immunotherapies as they may improve in distant metastasis-free survival (DMFS) (Khattak et al., 2023). In personalized mRNA cancer vaccines, a patient's own neoantigens are encoded, which are proteins that form on cancer cells when mutations occur (Huang et al., 2022). Manufacturing begins with the identification of genetic mutations in tumor cells of a patient that may give rise to neoantigens (Huang et al., 2022). Using computer algorithms, it is possible to predict which neoantigens will most likely bind to receptors on T cells and stimulate the immune system (Huang et al., 2022).

As an example, mRNA-5671 is a personalized KRAS-targeted vaccine that codes for four of the most common mutations in KRAS: G12D, G12V, G13D, and G12C (Asimgil et al., 2022). According to Xu et al. (2019), the KRAS mutation occurs in normal cells as a result of an error in the protein. KRAS controls the proliferation of healthy cells by acting as an on-off switch. To do this, it binds the KRAS-activating molecule GTP and converts it to GDP, which inactivates the protein. Mutations of the KRAS gene, however, can allow cells to grow uncontrolled, ultimately resulting in cancer (Xu et al., 2019). KRAS mutations are found in about 25% of tumors, making

them one of the most commonly occurring mutations in cancer and colorectal cancer in particular (Beganovic, 2010). Additionally, other mRNA vaccines, like CV9104 encode for prostate cancer encode antigens such as PSA, PSMA, PSCA, STEAP1, PAP, and MUC1 (Stenzl et al., 2017).

Researchers have tested the effectiveness of immune checkpoint inhibitors alone or combined with mRNA vaccines. For example, mRNA-5671 in combination with pembrolizumab is under clinical development by Moderna for colorectal cancer. It is necessary to note that drug resistance is often apparent in monotherapy (*Benefits of Combination Immunotherapy and Reducing Harms*, n.d.). In some cases, cancer cells may adapt to a drug while it is administered, acquiring molecular changes that allow them to evade its effects (*Why Do Cancer Treatments Stop Working?*, 2016). Thus, many researchers believe combining different drugs to treat patients may be an effective way to overcome or delay resistance (*Why Do Cancer Treatments Stop Working?*, 2016). With combination therapy, pathogens or tumors are less likely to resist multiple drugs at the same time (*Why Do Cancer Treatments Stop Working?*, 2016). Because of this, many trials are still being conducted to determine whether combination therapy will result in better outcomes for cancer patients than monotherapy.

Clinical Trials Evaluating mRNA Vaccines in Cancer: Two Case Study Methods

Phase I/IIB trial of the novel mRNA-based prostate cancer vaccine CV9104 in patients with metastatic castration-resistant prostate cancer:

According to Stenzl et al. (2017), patients with mCRPC who were asymptomatic or oligosymptomatic were randomized 2:1 to receive intradermal CV9104 or a placebo. A 2:1 randomization, for example, would mean that for every three patients, two would receive CV9104 and one would receive a placebo. A double-blind trial, in which neither the experimenters nor the participants knew which treatment was given (David, 2022), was continued beyond initial progression until progression under a subsequent standard of care (SOC) or toxic effects occurred (Stenzl et al., 2017). The primary endpoint was overall survival, while secondary endpoints included radiographic progression-free survival (rPFS), time to symptom progression (TTSP) (Stenzl et al., 2017). According to Halabi et al. (2021), rPFS is measured from the date of random assignment to death from any cause or disease progression on CT or TC scan, whichever occurs first. The time to symptomatic progression (TTSP) refers to the period of time before symptoms worsen (Bouchard et al., 2018).

Phase 2 mRNA-4157-P201/KEYNOTE-942 distant metastasis-free survival results:

As stated by Khattak et al. (2023), mRNA-4157-p201 is currently being tested in a multicenter, open-label, randomized Phase II study in patients with high-risk Stage IIIB/C/D and IV cutaneous melanoma that has been completely resected. Patients were stratified, that is, divided into subgroups based on shared characteristics or attributes, in this case cancer stage. Within each subgroup, patients were then assigned to receive either mRNA-4157 in combination with pembrolizumab (anti-PD-1) or pembrolizumab alone within each subgroup using a 2:1 randomization. 157 patients were randomized to receive mRNA-4157 and pembrolizumab

together (n = 107) or pembrolizumab monotherapy (n = 50). Every three weeks, mRNA-4157 (1 mg) was administered intramuscularly for a total of nine doses, and pembrolizumab (200 mg) was given intravenously for up to eighteen cycles. In this study, the primary endpoint was recurrence-free survival (RFS) (Khattak et al., 2023), which is the time from the date of curative surgery until the date of recurrence or death (Yan et al., 2018). After determining a positive RFS, the secondary endpoint of DMFS was pre-specified and hierarchically tested. In the context of DMFS, it is the period of time between randomization and the development of distant metastases or death (Amabile et al., 2021).

Two Case Study Results

Phase I/IIB trial of the novel mRNA-based prostate cancer vaccine CV9104 in patients with metastatic castration-resistant prostate cancer (mCRPC):

CV9104 represents an advancement of CV9103 (which encodes for the antigens PSA, PSCA, PSMA, and STEAP1) (Rausch et al., 2014). As part of CV9104 immunotherapy, two additional antigens are encoded, namely PAP and Mucin 1 (MUC1) (Rausch et al., 2014).

In the majority of cases, cancer treatments cause cancer cells to undergo apoptosis (Nath & Mukherjee, 2014). However, cancer cells may acquire defects in the apoptosis pathway and, as a consequence, do not respond to these treatments (Nath & Mukherjee, 2014). MUC1 is a glycoprotein that will prevent the activation of the intrinsic apoptotic pathway in cancer cells, which helps them evade cell death (Nath & Mukherjee, 2014). The overexpression of MUC1 will result in cancer cells to spread (Hosseinzadeh et al., 2022). In this regard, it is important to determine whether combining CV9104, which targets specific genes like MUC1, with standard of care (SOC) might result in a longer overall survival for patients with metastatic CRPC than placebo and standard of care (Stenzl et al., 2017).

Table 1

Summary Table of mCRPC Study Results

Group	# of Patients	Median OS (months)	Incidence of grade >= 3 AEs (%)	Incidence of serious AEs (%)
mRNA vaccine CV9104	134	35.5	51.1	44.5
Placebo	63	33.7	59.7	43.5

Note. This table compares the treatment of mCRPC patients with CV9104 versus placebo.

As part of the trial, 197 patients were randomly assigned 2:1 to receive CV9104 (n = 134) or placebo (n = 63) (Stenzl et al., 2017). In terms of sample size, the 197 patients represented in the study are an appropriate and sufficient number, since normal Phase I trials need a total of around 20-80 subjects, and phase II trials that investigate the treatment's effects seldom require more than 100-200 subjects (Pourhoseingholi, 2013).

In addition, the characteristics of the patients, the median number of administrations, and the first subsequent SOC therapy were also well balanced within the arms (Stenzl et al., 2017). No significant differences were observed in overall survival (Stenzl et al., 2017). The median overall survival in the CV9104 arm was 35.5 months compared to 33.7 months in the placebo arm (Stenzl et al., 2017). Although the treatment group had a median overall survival of 1.8 months longer, the study indicated a hazard ratio (HR) of 1.1. A hazard ratio represents the ratio of the hazard rates in the treated group to the control group (Barraclough et al., 2011). According to Barraclough et al. (2011), a HR of 1 implies equal risks for both groups; the HR is less than 1 if the experimental treatment group performs better than the control group, and greater than 1 if the experimental group performs worse. This trial's HR of 1.1 indicates that the HR in the treatment group is 10% higher than the rate in the control group. This suggests that those who died in the treatment group did so sooner than those in the control group. In the study, researchers were also 95% confident that the true hazard ratio would fall between 0.70 and 1.76 (Stenzl et al., 2017). As indicated by the confidence interval of the hazard ratio, the hazard ratio may fall below one or above one, indicating that the results of effectiveness between the two groups are not significantly different. Further, the study concluded with a p-value of 0.33 (Stenzl et al., 2017). Since the p-value was greater than 0.05, this also suggests that there were no significant differences between the treatment and control groups in terms of overall survival (Stenzl et al., 2017).

As for the rPFS endpoints and time to symptom progression, no notable differences were observed (Stenzl et al., 2017). The results revealed that grade ≥3 adverse events (AEs) (51.1% vs. 59.7%) and serious AEs (44.5% vs. 43.5%) were similar between the two arms, while injection site reactions and flu-like symptoms were more frequent in the CV9104 arm (Stenzl et al., 2017). The study concluded that CV9104 did not improve overall survival in comparison to a placebo (Stenzl et al., 2017).

Phase 2 mRNA-4157-P201/KEYNOTE-942 distant metastasis-free survival results:

mRNA-4157 encodes at least 34 neoantigens that are uniquely tailored to a patient's tumor mutations (Khattak et al., 2023). Neoantigen-directed therapy can enhance endogenous neoantigen T-cell responses, resulting in epitope spread to novel antigens that can drive antitumor activity and maintain memory with cytolytic properties (Seymour, 2023). In this way, disease control can be more effectively maintained (Seymour, 2023).

Table 2

Summary Table of Melanoma Study Results

Group	# of Patients	Median follow-up RFS events	18-month RFS rates	18-month DMFS rates	Distant recurrence or death
Combination (mRNA-4157 + Pembrolizumab)	107	22.4% (24/107) in 23 months	78.6% 95% CI: (69.0%, 85.6%)	91.8% 95% CI: (84.2%, 95.8%)	8.4 % (9/107)
Pembrolizumab	50	40% (20/50) in 24 months	62.2% 95% CI: (46.9%,74.3%)	76.8% 95% CI: (61.0%, 86.8%)	24% (12/50)

Note. This table compares monotherapy versus combination therapy for melanoma patients.

In this study, a total of 157 patients were treated with mRNA-4157, either in combination with pembrolizumab (n = 107) or as a monotherapy with pembrolizumab (n = 50) (Khattak et al., 2023). There is a statistically significant and clinically meaningful improvement in RFS in combination therapy compared to pembrolizumab monotherapy, with a reduction in the risk of recurrence or death of 44% (Khattak et al., 2023). Based on the trial, the HR was calculated at 0.561 with a 95% confidence interval between 0.309 and 1.017 for the true HR (Khattak et al., 2023). The p-value of 0.0266 (Khattak et al., 2023) indicates that there are significant differences in RFS between the combination and monotherapy groups, as it is less than 0.05. Upon completion of a minimum of 12 months on study, the primary analysis of the primary endpoint was conducted and 44 RFS events were observed (Khattak et al., 2023). In the primary analysis, there were 22.4% (24/107) RFS events reported in the combination arm at a median follow-up of 23 months and 40% (20/50) events reported in the monotherapy arm at a median follow-up of 24 months (Khattak et al., 2023). As of 18 months, the overall RFS rate was 78.6%, and researchers were 95% confident that the RFS rate in the combination arm would be between 69%-85.6%, compared to 62.2% (46.9%,74.3%) in the monotherapy arm (Khattak et al., 2023).

Furthermore, combination therapy improved DMFS compared to pembrolizumab monotherapy both statistically and clinically (Khattak et al., 2023). With a hazard ratio of 0.347 (Khattak et al., 2023), this indicates that the combination arm has 65.3% less chance of developing distant metastases or death than the monotherapy group. A 95% confidence interval was also provided for the hazard ratio, suggesting that the true hazard ratio would likely lie between 0.145 and 0.828 (Khattak et al., 2023). As the hazard ratio range remained below 1.0, the combination therapy group was achieving better DMFS rates than the monotherapy group. In addition, there

was a p-value of 0.0063, and any p-value below 0.05 indicates a statistically significant difference between the combination and monotherapy groups (Khattak et al., 2023).

In the combination arm, the DMFS rates were 91.8% with 95% confidence that the true rate would be between 84.2% and 95.8%, while in the monotherapy arm, DMFS rates were 76.8% (61.0%, 86.8%) (Khattak et al., 2023).Viewing the combination arm, patients experienced a distant recurrence, which means cancer spread far from its original site, or died in 8.4% (9/107) of cases, and in 24% (12/50) of cases in the monotherapy group (Khattak et al., 2023).

Researchers concluded that mRNA-4157, in combination with pembrolizumab, significantly prolonged DMFS in patients with resected high-risk melanoma compared to pembrolizumab alone (Khattak et al., 2023). Accordingly, these findings support the hypothesis that combining mRNA vaccines with immune checkpoint inhibitors may be beneficial to outcomes for cancer patients (Khattak et al., 2023). Patients with melanoma will soon be enrolled in a phase 3 randomized trial (Khattak et al., 2023).

Conclusion

In this paper, two major trials were examined, which supported the idea that mRNA vaccines combined with immune checkpoint inhibitors offer greater potential than monotherapy alone. In the trial of mCRPC patients receiving CV9104 vaccine or a placebo, CV9104 did not improve OS in comparison to the placebo group (Stenzl et al., 2017). While the median overall survival rate in the treatment group was 1.8 months longer, the study indicated a hazard ratio of 1.1 (Stenzl et al., 2017), which indicates that the hazard rate is 10% higher than the rate in the control group. Further evidence of the non-significant difference between the treatment and control groups was provided by statistics such as the 95% confidence interval for the hazard ratio (0.70 and 1.76) and the p-value (0.33) (Stenzl et al., 2017). In the study with melanoma patients, combination therapy improved the RFS statistically significantly compared to pembrolizumab monotherapy, resulting in a 44% reduction in recurrence or death (Khattak et al., 2023). Additionally, researchers found that patients with resected high-risk melanoma who received pembrolizumab along with mRNA-4157 had a better DMFS rate than patients who received pembrolizumab alone (Khattak et al., 2023). With a hazard ratio of 0.347 (Khattak et al., 2023), the combination arm has 65.3% fewer chances of developing distant metastases or dying compared to the monotherapy group.

While mRNA vaccines combined with immune checkpoint inhibitors are more effective than monotherapy in the two examined studies, further trials are needed. As there are few detailed clinical trials evaluating mRNA vaccines and immunotherapy for cancer treatment, finding appropriate studies to compare combination therapy with monotherapy was challenging. We were therefore limited to early-stage trials. Phase 3 trials, where more patients are included in the study to verify the benefits of combination and monotherapy, are necessary to further compare the effectiveness of these therapies (Cancer Research UK, 2023). Moreover, these therapies should be investigated in diverse types of cancer, since different cancers may respond differently to different treatments. By doing so, a clearer picture will emerge of whether mRNA vaccines in combination with immune checkpoint inhibitors are more effective than either alone.

mRNA vaccines for cancer may have a role outside of immunotherapy as well. Research is ongoing regarding potential methods of using mRNA to induce cancer cell destruction without immune cells at Tel Aviv University (Tasleem & Tasleem, 2023). mRNA vaccines are an important area of active cancer research with the potential for significant benefits to patients.

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