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Insights for Oncology Trials Garnered From the Rapid Development of an mRNA COVID-19 Vaccine

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Abstract: The sudden emergence of the coronavirus disease 2019 (COVID-19) pandemic in early 2020 stimulated unprecedented scientific initiatives to rapidly develop effective treatments and vaccines. One example was the development of vaccines based on messenger RNA platforms, which received emergency use authorization in the United States less than 1 year after the primary sequence of the severe acute respiratory syndrome coronavirus 2 virus was published. Novel practices arose from the collaborative efforts and inclusive clinical studies that facilitated the vaccines' rapid development and clinical testing. I describe insights gained from the experience of mRNA-1273 vaccine development that may be applied to or adapted for oncology research. These insights include clinical study design, diversity and inclusion initiatives, speed, and real-world evidence generation, as well as close partnership among regulatory agencies, government, and pharmaceutical companies.

Key Words: COVID-19, mRNA, mRNA-1273, neoplasms, oncology, SARS-CoV-2, vaccine

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The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) necessitated an urgent, collaborative, and inclusive medical response. Within an accelerated time frame, this response resulted in the development and rollout of safe and effective vaccines,^{1–3} most notably the mRNA-based vaccines BNT162b2 (Comirnaty; Pfizer-BioNTech, New York, NY) and mRNA-1273 (Spikevax; Moderna, Inc., Cambridge, MA). The timely progression of mRNA vaccine development from viral sequence confirmation to phase III trials and emergency use authorization (EUA) in the same calendar year was an unprecedented and remarkable achievement. The success of COVID-19 vaccine development raises an intriguing question as to whether key learnings from this rapid process could be applied to the development of therapeutics for patients with time-sensitive unmet needs in other diseases such as cancer.

This review discusses key learnings from mRNA-1273 development during the COVID-19 pandemic and describes how these could be applied to oncology research to potentially deliver

improved patient outcomes. These combined insights include speed of implementation, open and frequent communication and information sharing, diversity and inclusivity, clinical study design, and use of real-world evidence.

KEY LEARNINGS FROM THE MRNA-1273 CLINICAL DEVELOPMENT PROGRAM

Speed and Agility of Implementation

Fundamental to the timely, safe, and effective development of mRNA-1273 was the application of a long-standing and scalable technology and the substantial previous global experience of targeting spike proteins of similar viruses as a vaccine strategy.⁴ Notably, the concept of mRNA-based therapeutics was not new but rather conceived 3 decades prior, with the goal of developing safe and versatile vaccines that were relatively easy to produce.^{5,6} In parallel, advances in drug delivery systems expedited preclinical development of mRNA therapeutics, which provided the basis for this new drug platform.^{7,8} Further research and development allowed mRNA vaccines to be manufactured in a cell-free manner, permitting rapid, scalable, and cost-effective production.⁴ In the case of mRNA-1273, this experience afforded an unprecedented 63-day turnaround between sequence finalization on January 13, 2020, to the first patient dosed on March 16, 2020, in a phase I study conducted by the National Institutes of Health (NIH; Fig. 1). Importantly, this timeline included the production, quality testing, and shipment of the first clinical batch of vaccine to the NIH by February 24, 2020. In essence, this flexible and versatile mRNA-based vaccine platform set the scene to deliver an immediate response to the challenges of SARS-CoV-2.

mRNA-1273 and BNT162b2, 2 mRNA-based COVID-19 vaccines, received EUA in late 2020 in the United States followed by additional approvals for use worldwide.^{9,10} While the immunizing antigenic sequence was identical, the nature of the mRNA transcripts, delivery vehicles (the lipid nanoparticles), and excipients differed considerably.⁴ These mRNA COVID-19 vaccines were evaluated within their respective large, randomized, prospective phase III clinical trials, resulting in primary vaccine efficacy estimates of 94% and 95% for mRNA-1273 and BNT162b, respectively.^{1,2} These results support the robustness of the mRNA vaccine platform as the consequence of decades of vigorous preclinical and developmental research. The success attributed to speed and agility of implementation of mRNA-based vaccine development in the COVID-19 pandemic is notably underpinned by this solid foundation of basic science and translational research.

Collective Urgency and Rapid, Effective Communication and Information Sharing

Reported SARS-CoV-2 cases increased rapidly from the outset of the COVID-19 pandemic. Consequently, even a minor delay in vaccine development would have had significant public health implications.¹¹ During the period when the proof-of-concept phase I clinical trials were underway, this collective sense of

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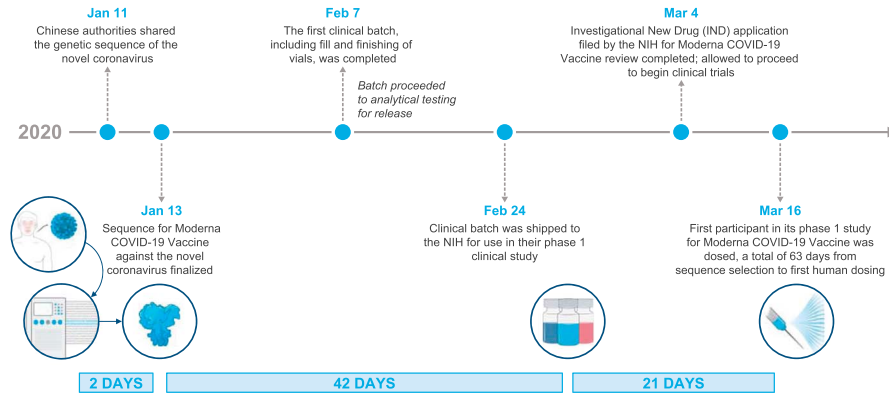


FIGURE 1. Timeline from virus sequence identification to the first clinical study. Following release of the SARS-CoV-2 genetic sequence, a candidate mRNA vaccine (mRNA-1273) was identified within 2 days. A clinical batch of vaccine was released to the NIH on February 24, 2020, and after further validation and IND submission, the first-in-human phase I study was initiated on March 16, 2020, only 63 days after sequence selection. IND indicates investigational new drug.

urgency, as illustrated by mRNA-1273 development, allowed collaborators, including the manufacturer (Moderna), the Biomedical Advanced Research and Development Authority, and a contract research organization (PPD Inc.), to chart a pathway to allow rapid evaluation and regulatory authorization (Fig. 2). This included important clarity from the Food and Drug Administration (FDA) regarding the acceptable endpoints and statistical assumptions to allow an EUA of a COVID-19 vaccine. Incorporating stringent and independently collaborative insights, studies could be executed rapidly with the support of multiple levels of expertise, safety oversight (including the investigators, the medical monitor, a weekly protocol review committee, and a data safety monitoring board), and frequent meetings, all of which enabled fast-paced decision making.

The design of the clinical studies of mRNA-1273 proposed by the sponsor met the FDA’s principles for safety and efficacy. Aided by the sense of urgency, external support and frequent communication and information sharing with regulators, the recruitment to the phases I, II, and III trials were overlapped to further speed development.^{12–14} Interim analyses built into the trial protocols also allowed for the rapid submission for a potential EUA. In addition, the control arm of the phase III (COVE) study, when unblinded at the end of part A (observer-blinded phase), became data-generating in part B (open-label phase) as patients were subsequently offered mRNA-1273 vaccination.^{1,14} Although an original time frame of 6 to 12 months was predicted, in reality, the phase III trial launched during a highly active pandemic within a period

of high transmission, which boosted enrollment and enabled an interim analysis within 4 months of dosing the first patient (Fig. 2).

Population Representation

To assess vaccination outcomes for a broad demographic population, mRNA-1273 enrollment for the pivotal phase III study was structured to ensure representation of the US population at risk of COVID-19 disease (mRNA-1273, n = 15,181; placebo, n = 15,170).¹ This included more than 6000 Hispanic participants and more than 3000 Black or African American participants; a significant number of older age participants (with 25% of participants ≥65 years old and ~39% who were 45–64 years old); and representation of individuals at an increased risk of COVID-19 exposure and infection (including educators, students, and workers in the health care, retail, restaurant, and hospitality sectors).¹

To provide a more accurate or realistic reflection of vaccine safety in populations with underlying medical conditions, there were a number of exceptions to standard exclusion criteria. Per standard vaccine trials, the COVE study exclusion criteria covered immunosuppression, bleeding disorders, acute febrile illness, conditions that might have interfered with immunogenicity or efficacy (use of blood products and immunoglobulins), allergies, history of previous SARS-CoV-2 infection, pregnancy, or inadequate contraception. However, unique in a pivotal vaccine efficacy trial and contrary to inclusion/exclusion criteria in most phases I and II studies, individuals living with HIV were included for part A of the COVE trial. Moreover, more than 26% of individuals enrolled

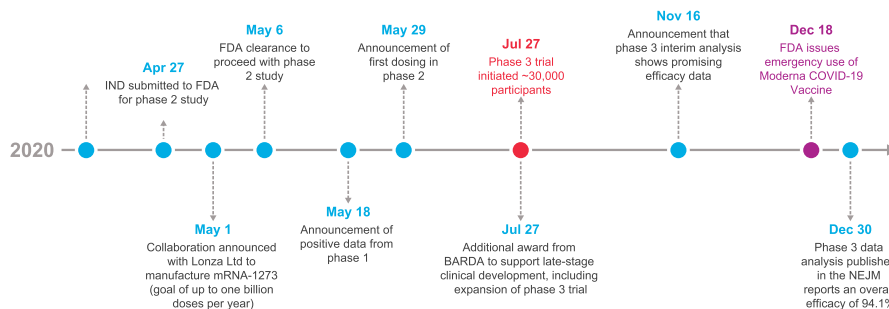


FIGURE 2. Timeline from the finalized sequences identification to the first clinical study. Rapid clearance of a phase II study was achieved in early May 2020, along with agreements to provide a large supply of vaccine, if approved. At the end of July 2020, a phase III clinical study was initiated that reported positive interim data on November 16, 2020. The mRNA-1273 vaccine received EUA on December 18, 2020, less than 1 year after publication of the SARS-CoV-2 genetic sequence. BARDA indicates Biomedical Advanced Research and Development Authority; IND, investigational new drug.

in the COVE study had an underlying chronic illness. The COVE clinical study was also designed to target those at high risk of infection across a wide distribution of zip codes, which provided a diverse geographic representation in the United States. In addition, any participants who developed severe COVID-19 disease during the study were permitted access to other investigational agents (such as antivirals and monoclonal antibodies).¹

Vaccine efficacy of mRNA-1273 in the representative COVE study was 94.1% (95% confidence interval, 89.3%–96.8%) with respect to preventing COVID-19 illness, including severe disease.¹ The validity of this finding and enrollment approach have been confirmed by similar results in multiple real-world studies.^{15,16} For example, results from a prospective matched cohort study conducted in the United States that included more than 700,000 individuals demonstrated a vaccine effectiveness of 87.4% (95% confidence interval, 84.8%–89.6%) at a time when SARS-CoV-2 variants of concern were emerging.¹⁷ The similarity of the clinical trial vaccine efficacy findings to vaccine effectiveness results in numerous and evolving real-world settings supports the effort and value of recruiting demographically representative clinical study populations at risk of the disease of interest.

INSIGHTS FOR ONCOLOGY NEEDS FROM COVID-19 VACCINE RESEARCH

Unmet Needs in Oncology

For oncology, the therapeutic approach is highly individualized, based on tumor histology, stage, prognostic and predictive biomarkers, and patient factors, including performance status, comorbidities, preferences, and care goals.¹⁸ In the absence of curative therapy, prolonging the time until disease progression or extending the

duration and quality of life is the goal of treatment. For both patients and their health care providers, there is an urgency for access to life-prolonging treatment, and in many cases, there is a willingness of patients to participate in clinical trials, be treated with novel therapies, or to try therapies that have been approved with limited or only surrogate evidence.

The concordance of registrational and real-world data that demonstrate the safety and effectiveness of COVID-19 vaccines shows that it is possible to conduct clinical trials that are more representative of patient populations. However, it has been recognized that there is a lack of diversity and inclusivity in oncology clinical trials.^{19–23} Emerging evidence has shown that the data generated in these studies may not align with the real-world performance of newly approved oncology drugs.²⁴ It should also be noted that a potentially confounding barrier to assessing the performance of oncology drugs postapproval is the lack of high-quality real-world data studies.²⁵

One impediment to inclusive participation in oncology clinical trials is the comorbidity associated with late-stage and or metastatic disease where patients may be too ill to travel for clinical assessments.²⁶ Therefore, such patients may be ineligible to participate in traditional randomized clinical trials, which are typically highly monitored site-based studies.²⁷ This subsequently restricts study demographics and the number of individuals that can be enrolled (even if patients are willing), leading to skewed diversity and less inclusivity within studied populations. For example, the strict criteria currently used in oncology clinical research exclude patients with comorbidities that may accurately represent a real-world population but may confound safety assessments.²⁸ In addition, cancer treatment options are usually specific to the type or subtype of tumors and the stage of the disease, leading to lower patient recruitment, particularly in studies of targeted

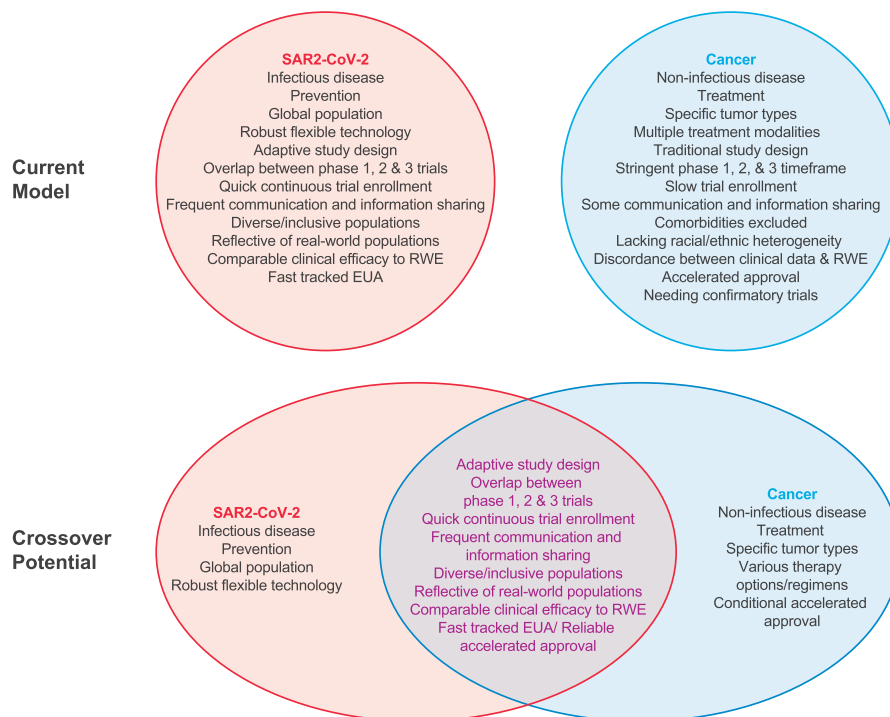


FIGURE 3. Potential insights for oncology research development of the mRNA-1273 vaccine. Conducting vaccine clinical trials during emergent pandemics or in oncology has unique considerations specific to each therapeutic area. However, learnings from the rapid authorization of COVID-19 vaccines, in terms of speed, open communication and information sharing, diversity and inclusiveness, and real-world data generation, could be applied to oncology drug development. RWE indicates real-world evidence.

therapies for rare tumor mutations. This means that there may be few patients eligible to receive a particular therapy within the geographical reach of a centralized trial site.

It has also been recognized that the use of academic centers, along with economic, language, and literacy barriers, reduces collaborative efforts and compounds the lack of population heterogeneity within cancer research.^{27,29} Among oncology studies conducted between 2018 and 2020 associated with FDA approval of 45 new cancer drugs, 68% to 73% of study participants were White, 14% to 18% were Asian, 4% to 5% were Black or African American, 4% to 6% were Hispanic, 44% to 59% were 65 years or older, and 24% to 41% were from the United States.^{19–21}

A diverse population profile is important when considering the pharmacokinetic, pharmacodynamic, and toxicity profiles of currently approved cancer drugs. Differences have been demonstrated across various racial and ethnic groups, with varying effects on drug metabolism, therapeutic efficacy, and safety outcomes in minority patient groups, as well as disparities in treatment options for these patients in terms of access and availability.^{22,30–34} To improve diversity and inclusion in oncology drug development, some centers have identified best practices,²⁵ including strong diverse leadership and commitment (focusing on a number of aspects, including metrics, process improvement, and notable practices), investigator hiring and mentoring practices (reflective of geographic area and cultural competency), community engagement practices, patient engagement (guiding a patient's willingness to participate in a clinical trial), and operational practices (how a clinical study will be carried out).

Extrapolating COVID-19 Vaccine Lessons to Aid Cancer Research

Ultimately, there may be more differences than similarities between COVID-19 and cancer research and drug development in terms of populations, benefit-risk profiles, trial endpoints, and preventive versus treatment aims. Nonetheless, the primary goal of improving health care aligns across both disciplines. Extrapolation of key successful strategies developed during the rapid deployment of COVID-19 vaccines during the pandemic offers novel opportunities for clinical oncology research. These include improving the speed with which individuals are enrolled into clinical studies, fostering stronger collaboration between centers, regulatory agencies, and the patients themselves, and increasing diversity and inclusivity to better reflect real-world populations (Fig. 3). These best practices can help to narrow the gap between data obtained from clinical trials and the real-world oncology setting. Such strategies may also help to ameliorate the growing issue of oncology agents that receive accelerated approval based on surrogate endpoints only to be voluntarily withdrawn, or have their authorizations revoked, upon failure to show overall clinical benefit in phase III studies.³⁵

For mRNA-1273, timely development was characterized by the rapid flow of information and risk management, with frequent and open communication and information sharing between industry, academia, governmental, and regulatory authorities. This formed part of a solution that enabled the EUA and provided a fast and efficient response against a global disease. While cooperative oncology clinical study groups provide leadership, they lack the widespread urgency of the COVID-19 pandemic as a motivating and focusing common cause.

The COVID-19 vaccine approach has also demonstrated the effectiveness of having small, highly controlled pilot studies prior to expanding to larger, more diverse populations, with the option of continuous enrollment. A potentially comparable approach in oncology that deliberately and aggressively broadens the eligibility criteria over time to include patients with comorbidities, poten-

tially allowing for remote assessment, and continuous enrollment, could expand participation in oncology studies to reflect a more real-world patient base.

The overt differences in the 2 clinical areas of vaccinology and oncology means approaches used must also accommodate these distinctions. For example, in the COVE study, there was added value from the control arm in this phase III trial that subsequently became data-generating when participants were later offered mRNA-1273 vaccination.^{1,14} In phase III oncology trials, crossover may confound the endpoints that regulatory bodies require for approval.³⁶ Moreover, as COVID-19 vaccinations are preventive strategies and cancer trials are treatment-based, the benefit-risk profile and trial endpoints are necessarily different. In addition, unless curative, cancer treatments may require long-term treatment and assessment, whereas vaccination involves a priming dose regimen followed by further booster doses (taking into account potential waning immunity and virus variants that may emerge). Safety assessment is also different, with strict safety guidelines in vaccination studies, with events following vaccination typically occurring in generally healthy individuals within a 7-day window compared with cancer patients who are generally much sicker with chronic symptoms and adverse events following treatment that may emerge over a prolonged course of therapy. While there are untapped crossover opportunities, fundamental differences remain between vaccinology and oncology that affect the specific practicalities of enrollment, execution, follow-up, endpoints analysis, and regulatory approval.

CONCLUSIONS

In 2020, the COVID-19 pandemic was a broad and compelling call to arms answered by multiple stakeholders working toward a clear and common goal that enabled the EUA of COVID-19 vaccines such as mRNA-1273 and BNT162b2 in the United States in less than 12 months after the virus was sequenced.^{17,35} Standard principles of efficacy and safety that underpin drug development were followed; timelines from initiation of clinical trials to public availability were accelerated based in part on transparency and frequent dialogue with drug manufacturers and regulatory agencies. While recognizing differences between preventive and treatment strategies, the development of mRNA-1273 within the COVID-19 pandemic has also highlighted potential approaches that may enhance oncology clinical research and real-world studies. These approaches include establishing frequent communication and information sharing among stakeholders, increased diversity and inclusivity in clinical studies that closely align with real-world populations, reducing barriers to enrollment by minimizing inclusion and exclusion criteria, and swifter trial initiation, which will result in quicker generation of clinical data and faster patient access to novel treatment options.

The COVID-19 pandemic has influenced practical changes in the way in which cancer treatments can be administered and how patients can be monitored, including remote assessments and telehealth.^{37–39} A shift to identify and apply transferable approaches learned from the COVID-19 vaccine strategy may enhance practical steps to further cancer treatment development. Lessons extrapolated from the COVID-19 pandemic may help to adapt oncology studies to proceed more rapidly with greater representation of patients from diverse demographic backgrounds and disease states.

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