**Safety and Efficacy of Booster Doses of COVID-19 Vaccine in Immunocompromised Patients With a Cancer Diagnosis (Booster Dose Trial)**

Protocol ID: **2021-13204**
**NCT05016622**

**Title:** Safety and efficacy of booster doses of COVID-19 vaccine in immunocompromised patients with a cancer diagnosis

**IRB#:** 2021-13204

**Protocol version:** 21 January 2022

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## Background

It is now well-established that COVID-19 in patients with cancer carries a higher morbidity and mortality, especially in patients with hematologic malignancies[1,2] . Effective vaccines have been developed and authorized by the FDA to combat this pandemic[3-5]. However, emerging data suggests that despite these vaccines inducing high levels of immunity in the general population,patients with hematologic malignancies have lower rates of seroconversion for the SARS-CoV-2Spike antibody[6-9] . Our recent paper describing the seroconversion rates following COVID-19 vaccination amongst patients with cancer at Montefiore Medical Center revealed a seronegativerate of 15% (10/66 patients) in hematological malignancies vs. 2% (3/134 patients) in solid tumors . Evidence has also suggested that specific therapies, such as anti-CD20 antibodies, BTK-inhibitors and stem cell transplantation (SCT) have an association with lower rates of seroconversion. In our Montefiore Medical Center cohort, 30% (7/23) patients who received anti-CD20 therapy, 27% (7/26) patients who received SCT, and 100% (3/3) patients who received CAR-T cell therapy had negative anti-SARS-CoV-2 spike IgG following vaccination[6].

Novel immunization strategies such as booster dosing are urgently needed to protect this high-risk patient population. On Aug 12 2021, the FDA authorized an additional dose of mRNA vaccines (BNT162b2 or mRNA-1273) for certain patient populations with weakened immune systems[10]. Emerging data from patients with solid organ transplantation receiving a third dose of mRNA vaccine suggests higher immunogenicity in this patient population compared to the standard two-dose series[11,12]. There is however limited data of immunogenicity and safety of third dose of COVID-19 vaccine in cancer patients, currently evidenced by case reports only[13]. Additionally, the updated FDA/CDC recommendations do not apply to those that have received the Ad26CoV.2 S vaccine[14].
We propose a study to investigate the immunogenicity of the additional dose of the BNT162b2 or mRNA 1273 mRNA vaccine to patients with cancer who have a negative SARS-CoV-2 Spike IgG at least 14 days after 2 doses of the respective mRNA vaccines (BNT162b2/mRNA-1273) or who meet the CDC definition for immunocompromised status as a cancer patient. We also propose to administer an additional dose of mRNA vaccine (BNT162b2 or mRNA 1273) to cancer patients at least 28 days after receipt of the adenoviral based Ad26CoV2.S vaccine and perform laboratory based-tests to elucidate immunogenicity of such a vaccination strategy. Lastly, based on preliminary data from our first study cohort we will expand our study to include cohorts 2 and 3 - a randomized and prospective study of so-called “mix and match” vaccinations to assess the most effective vaccination strategy for poor responders to standard vaccination series.

## Study design and population

## Aims

Cohort 1
Our proposed study is a prospective single arm study which will aim in an exploratory/pilot fashion to assess the following variables in a population of patients with cancer with prior vaccination against COVID-19.

- To study the seroconversion for SARS-CoV-2 spike IgG in patients with cancer after administering a booster dose of the BNT162b2 or mRNA 1273 vaccine
- To study the spike antibody titers as well as T cell activation after a booster dose and compare them with the prior titer/baseline T cell activity
- To study safety and side effects from a booster dose of the BNT162b2 or mRNA 1273 COVID vaccine

**Inclusion Criteria**

Our target population consists of patients with a known diagnosis of cancer who were seen at the study site after Aug 1, 2021. Our study will employ the following inclusion criteria:

- Above the age of 18
- Meet one of the sub-criteria below:
  - Meet the CDC definition for immunocompromised status for cancer patients, i.e patients receiving active treatment for solid tumor or hematologic malignancy OR
  - Be a recipient of stem cell transplant or CAR-T cell therapy in the last 2 years OR
  - Have a negative SARS-CoV-2 spike IgG despite standard vaccination series, irrespective of active/inactive cancer status, on observation, or active therapy.
- Underwent an in-person encounter at a study facility during the study period
- Have received the second of the mRNA vaccines (BNT162b2 or mRNA 1273) or the adenoviral Ad26CoV2.S vaccine at least 28 days before the booster dose.

**Exclusion Criteria**

- Patients who have had a serious adverse reaction to any prior COVID-19 vaccines resulting in emergency room visit or hospitalization, had events related to myocarditis, thrombosis and thrombocytopenia syndrome or anaphylaxis to any prior dose of the COVID-19 vaccines.
- Patients who have had a documented COVID-19 infection in the 90 days prior to starting the study

**Outcomes**

We will be studying the following primary outcome:

- Rates of seroconversion for SARS-CoV-2 spike antibody after 4 weeks after a booster dose of BNT162b2/mRNA-1273 COVID Vaccine in patients that were initially seronegative after standard vaccine series

We will be studying the following secondary outcomes:

- Safety of booster dose of BNT162b2 and mRNA 1273 vaccines
- Correlation between malignancy type and prior treatment type and seroconversion
- Correlation between timing of most recent cancer-directed treatment and seroconversion
- Correlation between the total number of cancer-directed treatments received andseroconversion
- Differences between booster efficacy dependent on prior vaccine type (mRNA vs. adenoviral, BNT162b2 versus mRNA-1273)
- T cell responses at baseline and 4 weeks following vaccination
- Antigen neutralization assay results at baseline and 4 weeks following vaccination

Duration of sustained immunogenicity following vaccination in seropositive patients following our cohort for 24 months following booster vaccinations

<u>Cohort 2</u>

There is emerging data that a mix and match strategy of boosting with a different COVID-19 vaccine could yield a more robust response. In addition, recent data from Johnson & Johnson demonstrate good safety and an excellent secondary immune response with 9-fold increase in neutralizing antibody levels with a booster dose of the Ad26CoV2.S vaccine. Preliminary results from cohort 1 of our study do indeed show that while a significant percentage of patients respond to a booster dose of an mRNA vaccine, however many patients either do not respond or respond with very low antibody titers suggestive of low level immunity. This poses the question whether a switch vaccine approach might be more effective at achieving

strong anti-Covid immunity. Thereby, our study in cohort 2 will address the key question of achieving a detectable immune response in poor responders to prior series of mRNA vaccinations by a randomized study design randomizing eligible patients between the Pfizer BNT162b2 vs the AdCoV2.S vaccine with reaching positive SARS-CoV-2 Spike IgG titers above a pre-established threshold by 4 weeks following vaccinations as the primary endpoint with further secondary endpoints regarding safety, neutralization antibody and T cell assays and durability of response with assessments at 3, 6, 12 and 24 months.

Our proposed study is a prospective randomized study which will aim in an exploratory/pilot fashion to assess the following variables in a population of patients with cancer with poor response to prior vaccination against COVID-19.

- 1. To study the seroconversion for SARS-CoV-2 spike IgG in patients with cancer after administering an additional booster dose of the BNT162b2 or AdCoV2.S vaccine determined in a randomized fashion
- 2. To study safety and side effects from an additional booster dose of the BNT162b2 or AdCoV2.S vaccine

**Cohort 2**

Our target population consists of patients with a known or previous diagnosis of cancer who had received three prior doses of one of the mRNA based COVID-19 vaccines including a booster dose

**Inclusion criteria:**

Above the age of 18
Have a diagnosis of prior or active malignancy- either hematological or solid tumor
Have a negative or low-level SARS-CoV-2 spike IgG after at least 14 days of booster vaccination series irrespective of active/inactive cancer status, on observation, or active therapy.
Have received an FDA authorized booster dose of mRNA (BNT162b2 or mRNA 1273) vaccine at least 28 days before study enrollment

**Exclusion Criteria**

Patients who have had a serious adverse reaction to any prior COVID-19 vaccines resulting in emergency room visit or hospitalization, had events related to myocarditis,thrombosis and thrombocytopenia syndrome or anaphylaxis to any prior dose of the COVID-19 vaccines.
Patients who have had a documented COVID-19 infection in the 90 days prior to study enrollment

**Outcomes**

Primary outcome: Rates of seroconversion for SARS-CoV-2 spike antibody after 4 weeks following an additional booster dose of BNT162b2/AdCov2.S COVID vaccine in patients that had a poor serological response after standard vaccine series (allowing additional booster dose)

Secondary outcomes: Safety of booster dose of BNT162b2 and AdCov2.S vaccines, correlation between malignancy type and prior treatment type and seroconversion, correlation between timing of most recent cancer-directed treatment and seroconversion, correlation between the total number of cancer-directed treatments received and seroconversion, differences between booster efficacy dependent on prior vaccine type (BNT162b2 versus mRNA-1273), T cell responses at baseline and 4 weeks following vaccination, Antigen neutralization assay results at baseline and 4 weeks following vaccination, duration of sustained immunogenicity following vaccination in seropositive patients, correlations with baseline immune status correlates such as lymphocyte subsets/immune globulin levels

**Safety monitoring.**

Patients who have met all eligibility criteria will then be randomized 1:1 to receive either the BNT162b2 or AdCov2.S and then will be scheduled to receive their study dose at the Montefiore Vaccine Center. Each patient will be observed for a minimum of 15 minutes after their vaccination to monitor for any adverse

effects in the Montefiore Vaccine Center as per the Vaccine Center protocol.

Cohort 3

On December 16, 2021 the CDC published updated recommendations regarding use of the Ad26.COV2.S (Johnson & Johnson) vaccine (https://www.cdc.gov/media/releases/2021/s1216-covid-19-vaccines.html) due to the rare but persistent adverse event thrombosis with thrombocytopenia syndrome (TTS) seen with the Ad26.COV2.S vaccine alone. They expressed a clinical preference for individuals to receive an mRNA COVID-19 vaccine over an Ad26.COV2.S vaccine, however, reaffirmed that receiving any vaccine is better than being unvaccinated. This recommendation, however, did not specify stipulations for our currently immunosuppressed patients with cancer population who have already received three prior mRNA COVID-19 vaccines with minimal or no response. Given our patient population remains at high-risk for severe COVID-19 despite three prior mRNA COVID-19 vaccines, we feel the administration and efficacy evaluation of Ad26.COV2.S (Johnson & Johnson) vaccine as a mix and match strategy for booster vaccination continues to remain warranted as part of our study. In fact, a recent study from South Africa does suggest excellent efficacy of a booster Ad26.COV2.S vaccine corroborating this approach[15].

Some patients, however, remain hesitant to receive an Ad26.COV2.S given its rare but potentially severe adverse event as outlined above. Thereby, for study candidates who prefer not be randomized in cohort 2, participation in cohort 3 will be offered. Cohort 3 will be a prospective, non-randomized cohort to address the question of whether a switch mRNA vaccine approach might be more effective at achieving an increased immune response in poor responders to a prior series of three mRNA vaccinations (mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BioNTech)). Eligible patients will be prospectively followed to receive a BNT162b2 vaccine as a fourth dose evaluating their increase in mean SARS-CoV-2 Spike IgG titers above a pre-established threshold by 4 weeks following vaccination as the primary endpoint with further secondary endpoints regarding safety, neutralization antibody and T cell assays and durability of response with assessments at 3, 6, 12 and 24 months. As it is anticipated that about 60-70% of study candidates will have previously received BNT162b2 and 30-40% mRNA-1273, this cohort will allow an assessment of a switch approach in a non-randomized single arm fashion.

Our proposed study is a prospective single arm study, which will aim in an exploratory/pilot fashion to assess the following variables in a population of patients with cancer with prior vaccination against COVID-19.

- To study the difference in mean titers for SARS-CoV-2 spike IgG in patients with cancer after administering an additional (fourth) booster dose of the BNT162b2 vaccine in patients that had a poor serological response after standard homologous (BNT162b2 → BNT162b2) vs. heterologous (mRNA-1273 → BNT162b2) vaccine series (including a third dose).
- To study safety and side effects from an additional booster dose of the BNT162b2 COVID vaccine

**Inclusion criteria:**

Our target population consists of patients with a known or previous diagnosis of cancer who had received three prior doses of one of the mRNA based COVID-19 vaccines including a booster dose. Our study will employ the following inclusion criteria:

- Above the age of 18
- Have a diagnosis of prior or active malignancy- either hematological or solid tumor
- Have a negative or low-level SARS-CoV-2 spike IgG after at least 14 days of booster vaccination series irrespective of active/inactive cancer status, on observation, or active therapy.
- Have received an FDA authorized booster dose of mRNA (BNT162b2 or mRNA 1273) vaccine at least 28 days before study enrollment

- Decline to participate in cohort 2 requiring randomization of BNT162b2 and Ad26.CoV2.S vaccines

**Exclusion Criteria**

- Patients who have had a serious adverse reaction to any prior COVID-19 vaccines resulting in emergency room visit or hospitalization, had events related to myocarditis, thrombosis and thrombocytopenia syndrome or anaphylaxis to any prior dose of the COVID-19 vaccines.
- Patients who have had a documented COVID-19 infection in the 90 days prior to study enrollment

**Outcomes**

Primary outcome: To compare the increase in mean titers for SARS-CoV-2 spike antibody after 4 weeks following a homologous (BNT162b2 → BNT162b2) vs. heterologous (mRNA-1273 → BNT162b2) additional booster dose of COVID vaccine in patients that had a poor serological response after standard vaccine series (including a third dose).

Secondary outcomes: Safety of additional booster dose of BNT162b2 vaccine, correlation between malignancy type and prior treatment type and change in mean titer, correlation between timing of most recent cancer-directed treatment and change in mean titer, correlation between the total number of cancer-directed treatments received and change in mean titer, T cell responses at baseline and 4 weeks following vaccination, Antigen neutralization assay results at baseline and 4 weeks following vaccination, duration of sustained immunogenicity following vaccination in seropositive patients, correlations with baseline immune status correlates such as lymphocyte subsets/immune globulin levels

**Safety monitoring**

Patients who have met all eligibility criteria as part of cohort 3 will receive the BNT162b2 vaccine study dose at the Montefiore Vaccine Center. Each patient will be observed for a minimum of 15 minutes after their vaccination to monitor for any adverse effects in the Montefiore Vaccine Center as per the Vaccine Center protocol.

**Methods**

We will employ several methods for patient identification/recruitment.

- Using EPIC EMR and Montefiore Einstein Cancer-Center's Quality 360 team, we will identify patients that have undergone SARS-CoV-2 spike antibody testing. Patients with a test will then be checked if they have completed the full vaccination series for one of the FDA's Emergency Use Authorized COVID vaccines (i.e. 2 doses of the mRNA-based mRNA- 1273 (Moderna) or BNT162b2 (Pfizer/BioNTech) or a single dose of the adenovirus- based Ad26.COV2.S (Johnson & Johnson) vaccine and at least 14 days have passed since the second dose of the mRNA-based vaccines (Moderna or Pfizer/BioNTech) or 28 days have passed since the adenovirus-based Johnson & Johnson vaccine. If patients meet the above criteria, they will be offered participation in our study.

- We will also be screening patients self-referred or referred by their Montefiore providers as well as from other institutions referred for study participation. We anticipate that approximately half of the patients accrued will be patients being managed at Montefiore Health System. We also anticipate external referrals from institutions in the NYC area as well as the Leukemia Lymphoma Society given heightened interest in the study nationally as well as established funding by the LLS- an organization that has just completed a study of patients with hematological malignancies and has defined a vulnerable patient population some of whom will now qualify for the booster shot per FDA/CDC criteria and would likely qualify for our study. These patients will then be scheduled for a consenting visit and patients who consent for participation in the study via a carefully conducted and documented informed consent process to participate in the study will be screened for study eligibility.

- At each blood draw, we will collect six tubes of blood from each patient for testing

We will plan to use the AdviseDx SARS-CoV-2 IgG II assay (CLIA certified) to assess for the primary endpoint of assessing a response to the booster dose. We note that although this spike IgG antibody is specific to the receptor binding domain (RBD) of the spike protein, it might still not necessarily correlate with virus neutralizing activity. Therefore, in addition in the present study we will also utilize an assay to assess T cell response and determine virus neutralizing activity. We will plan to use the EUROIMMUN SARS-CoV-2 IGRA stimulation tube set (EUROIMMUN order no. ET 2606-3003) and Interferon-gamma ELISA (EUROIMMUN order no. EQ 6841-9601) for these assays. These T cell response assays are for Research Use Only and are not CLIA certified assays.

The SARS-CoV-2 spike antibody and T cell assays will all be processed at Montefiore Medical Center laboratories as per Abbott and EUROIMMUN's instructions for use. The SARS-CoV-2 IgG II assay results will be made available in Epic for review by the research team, primary oncologist, and patient when available, however, the T cell assays will be used for research purposes only and documented in an Excel Data Collection Sheet as below. For the neutralization assay, we will be utilizing Genscripts' "SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (RUO)" and running the test on stored serum samples. The neutralization assay is also a research assay and the results will be documented in the aforementioned Excel Data Collection Sheet.

The protocol when initially approved (version date July 23 2021) included a safety-run in phase for the 3rd dose of vaccine. So far we enrolled 4 patients into the safety run-in phase that received booster dose before FDA authorization and have not noted safety concerns in these patients. However, given that FDA has authorized a third dose for patients with compromised immune systems, we propose to close the run-in phase early for the mRNA vaccines and move ahead with enrolling patients based on the modified inclusion criteria in line with FDA guidance. Patients that have received the Ad26.CoV2.S vaccine will be offered participation in the study and will have a run-in phase where 3 patients will receive the vaccine first and followed closely with symptom check at 48 hours and 1 week post-vaccination. Once safety of booster mRNA vaccine post adenoviral vaccine is established, further enrollment onto the adenoviral vaccine arm will occur.

After patients consent they will be scheduled to receive a booster dose of the BNT162b2 or mRNA-1273 (Pfizer/BioNTech/Moderna) vaccine at the Montefiore Vaccine Center by an experienced team of vaccinators. Each patient will be observed for a minimum of 15 minutes after their vaccination to monitor for any adverse effects in the Montefiore Vaccine Center as per the Vaccine Center protocol.

Each patient enrolled in the study will also be provided 24-hour contact information to call in case of an emergency or for any other after hour concerns.

Patients will undergo spike antibody testing at D0 of the study and then return for a study visit four weeks after their booster vaccine to complete a SARS-CoV-2 spike antibody test and T cell response assays to determine virus neutralizing activity. Side effects to the booster dose will be noted via a questionnaire that patients would fill out at this visit which will collect data pertaining to side effects and their severity compared to prior vaccine doses. Patients will return for a final study visit five to six months after their booster vaccine to assess for long-term side effects and to obtain SARS-CoV-2 spike antibody test and T cell response assays in patients who became seropositive after 4 weeks to determine if immunogenicity is sustained.

**Follow up tests for cohorts 2 and 3:** Patients will undergo spike antibody testing as well as baseline laboratory studies including CBC, lymphocyte subsets, quantitative immunoglobulins, T-cell response and neutralizing activity at enrollment. Patients will then receive their 4th booster vaccine (D0). Patients will return for a study visit at least 28 days after their booster vaccine to complete a SARS-CoV-2 spike antibody

test including follow-up laboratory studies as listed above. Side effects to the booster dose will be noted via a questionnaire that patients would fill out at this visit which will collect data pertaining to side effects and their severity compared to prior vaccine doses. Patients will the return for further study visits at 3 months, 6 months and 12 months and then a final study visit 24 months after their booster vaccine to assess for long-term side effects and to obtain SARS-CoV-2 spike antibody test, T cell response assays, and other laboratory studies as above in patients who became seropositive after 4 weeks to determine if immunogenicity is sustained.

**Sample size**

**Cohort 1.** For a 1 sample test of proportions our hypothesis is that booster vaccine dosing will induce detectable immunity by the spike IgG assay in at least 20% of individuals. Null hypothesis is a positivity rate of 10% to account for some test variability and therefore the alternative hypothesis is $p > 30\%$. Our planned sample size of up to 250 will have ample power (>95%) to detect such a difference in our primary endpoint and will still retain 80% power and 5% significance in the secondary preplanned subset analyses as long as cohort sizes per subset are >26. We anticipate the large majority of patients will be hematologic malignancy patients and such preplanned subset analyses will include two cohorts, the highly immune suppressed (prior anti- CD20, CAR-T, or SCT therapy), and all others (solid tumor/hematologic malignancy patients) who do not fall into the first cohort. We anticipate cohort sizes of at least 26 per cohort based on the numbers of seronegative patients identified in our prior study.

**Cohort 2.** Our null hypothesis is that the additional homologous booster vaccine dosing will induce detectable immunity (positive spike IgG test result higher than the predefined threshold for seropositivity– i.e. >1000 AU/ml) by the spike IgG assay in at least 25% of individuals. Alternate hypothesis is that heterologous vaccination with the AdCov2.S vaccine will increase this seroconversion rate by an additional 25%- that is to 50%. With an alpha of 0.05 and 80% power to detect the difference, we would require a sample size of 46 in each group. Accounting for 5% dropout rate, we will thus use a planned sample size of up to 100 subjects. We anticipate the large majority of patients will be hematologic malignancy patients and such preplanned subset analyses will include two cohorts, the highly immune suppressed (prior anti-CD20, CAR-T, or SCT therapy), and all others (solid tumor/hematologic malignancy patients) who do not fall into the first cohort.

**Cohort 3.** Our null hypothesis is that the additional homologous booster vaccine dosing with the BNT162b2 after prior BNT162b2 vaccination will increase mean titers in the spike IgG assay by at least 300%. Alternate hypothesis is that heterologous vaccination with the BNT162b2 after prior mRNA-1273 vaccination will increase mean titers by an additional 300%- that is to 600%. To achieve 80% power at a significance level alpha = 0.05, a one sided two sample t-test would require 22 samples per group to detect differences in mean titers of 750 AU/mL and 1500 AU/mL at an estimated standard deviation of 1000 AU/mL. Given we estimate 30-40% patients with have had prior mRNA-1273 vaccination and accounting for 5% dropout rate, we will thus use a planned sample size of 80.

**Statistical analysis**

To assess our goals as outlined above, statistical analysis will be done in the R software environment. The primary aim of cohorts 1 and 2 examining the seroconversion rates after 4 weeks will be checked with a one sample z test of proportions. The primary aim of cohort 3 examining the increase in mean Spike IgG titers will be checked with a one sided two sample t-test. Secondary aims involving the significance of associations between certain malignancies and the rates of seroconversion in our prospective single arm study will be measured by Fisher's exact and Cochran- Mantel-Haenszel tests depending on if analysis is conducted by a stratified variable (Cochran- Mantel-Haenszel) or not (Fisher's exact). The more complicated relationship between patients' seroconversion rates, their recent receival of medical treatment, and additional factors such as history of malignancy will be examined through a multivariate logistic

regression model. After addressing the appropriateness of interaction terms, a Wald test will be used to consider the statistical significance of all included variables at the $p < 0.05$ level.

**Duration**

Our study will follow patients from Aug 1, 2021 through November 2023, which will allow for sufficient time to assess follow-up serologies after COVID-19 vaccination infection in patients with cancer (24 months follow up).

**Matching**

Cohort 1
Patients would serve as their own control. Baseline seropositivity rate by definition is 0% for the cohort but anticipating natural and laboratory variation we have based on statistical null hypothesis around a 10% seropositivity rate at 4 weeks and anticipate that booster vaccination will increase this to higher than 30%.

**Planned intervention**

Cohort 1
The planned intervention is to administer a booster dose of the BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) vaccine to patients that meet FDA/CDC criteria of cancer on active therapy or patients that have received a stem cell transplantation or CAR-T cell therapy in the last 2 years or those that have a negative spike IgG after having = completed one of the FDA's Emergency Use Authorized vaccination series for COVID-19 (i.e. 2 doses of the mRNA-based mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNTech), or a single dose of the adenovirus-based Ad26.COV2.S (Johnson & Johnson) vaccine, following completion of their vaccination series.

Cohort 2
The planned intervention is to administer an additional booster dose of the BNT162b2 (Pfizer/BioNTech) or Ad26.COV2.S (Johnson & Johnson) vaccine to patients that meet eligibility criteria for cohort 2 in a 1:1 randomization fashion with negative spike antibody vs. low positive antibody level serving as a stratification factor to ensure controlling for key confounder.

Cohort 3
The planned intervention is to administer an additional booster dose of the BNT162b2 (Pfizer/BioNTech) vaccine to patients that meet eligibility criteria for cohort 3 in a prospective single arm fashion in patients that had a poor serological response after standard vaccine series (including a third dose).

**Participant recruitment**

The study will both utilize data from the electronic health record to identify patients meeting the above inclusion criteria and enroll them on to the study and accept patients self-referred or referred by their provider at Montefiore Medical Center or external institutions. A consenting visit will be scheduled with each prospective patient. Following a carefully conducted and documented informed consent process subjects who consent for study participation will then be screened. Patients who qualify for booster COVID-19 vaccination as per FDA/CDC guidance and study criteria will then participate in our study.

**Data and Safety Monitoring Plan**

In the prior version of the protocol (version July 23 2021), we had outlined a careful detailed data safety monitoring plan which we have changed in light of the FDA authorization for booster dosing with the BNT162b and mRNA1273 vaccines. For patients that have received one of these mRNA vaccination series who have consented to participate in the study, data for side effects will be collected via a questionnaire that is administered at the 4 week visit.

For patients that have received adenoviral vaccine, we plan for a safety run-in when only 3 subjects from the adenoviral vaccine type will be dosed and monitored for an extended period following dosing as well as monitored closely for one week. Only if no unexpected or severe side effects (such as adverse events leading to emergency room visit, anaphylaxis, hospitalization or death) are noted during this period, will further patients be allowed to be dosed. Weekly study team meetings will be held during the initial study period while vaccinations are being performed and for at least 4 weeks afterwards to review available safety data and alert IRB and DSMC according to institutional protocols if any serious AEs are identified. In addition, our study will be monitored by the Montefiore/Einstein Cancer Center DSMC.

Due to the updated CDC recommendations published on December 16, 2021 regarding use of the Ad26.COV2.S (Johnson & Johnson) vaccine given its rare but persistent serious adverse event thrombosis with thrombocytopenia syndrome (TTS), patients in Cohort 2 will continue to fill out and receive safety questionnaires at each study visit during follow-up to screen for this rare adverse event.

**Informed consent**

Patients will be scheduled for a consenting visit with a member of the research group listed as consenting provider on the IRB protocol. Study rationale, alternatives, potential risks/benefits, confidentiality issues will be carefully reviewed and voluntary nature of study participation emphasized. Ample time will be provided for questions and the consenting process will be documented. If patients sign the ICF, screening will be initiated, and a copy of the consent will be given to the patient.

**Risk/Benefit**

As of Aug 12 2021, the BNT162b2 (Pfizer/BioNTech) and mRNA 1273 (Moderna) vaccines are authorized for booster dosing for those that have received similar prior vaccines. Despite the authorization, there is real potential risk for mild, moderate, and/or severe adverse effects after receiving the booster vaccine. An initial safety profile of BNT162b2 has been shown in a Phase 1/2 two-part, dose-escalation trial that enrolled 60 participants (Study BNT162-01). The Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study (Study C4591001) has enrolled approximately 46,000 participants, 12 years of age or older with ongoing safety data. Adverse reactions following the Pfizer-BioNTech COVID-19 vaccine in these studies included injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, and malaise. Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), diarrhea, vomiting, pain in extremity (arm),myocarditis, and pericarditis have also been reported following administration of the Pfizer- BioNTech COVID-19 Vaccine outside of clinical trials *(see Full EUA Prescribing Information)*[16]. A recent case report, case series, and observational cohort study does suggest some efficacy of such booster dosing with Emergency Use Authorized COVID-19 vaccines without any new safety signals identified[11-13] . We do acknowledge that there may be other risks which could be severe to using BNT162b2 (Pfizer/BioNTech) as a booster vaccine that are currently unknown.

Similarly, the mRNA 1273 vaccine underwent dose finding and safety phase 1 (NCT04283461) and phase 2 (NCT04405076) trials after which in the phase 3 trial of mRNA 1273 vaccine (COVE study), approximately 30,000 participants were recruited in a randomized manner that received 2 doses of 100µg 1 month apart. The most common solicited adverse reactions (ARs) after the two-dose series was injection site pain (86.0%). Solicited systemic adverse events occurred more often in the Moderna COVID-19 vaccine group (54.9% and 79.4%) than in the placebo (42.2% and 36.5%) group after both the first dose and the second dose respectively and were most commonly headache, fatigue and myalgia. While the majority of these ARs were mild (grade 1) or moderate (grade 2), there was a higher occurrence of severe (grade 3) reactions in the Moderna COVID-19 Vaccine group after the first (2.9%) and second (15.8%) injections. The majority of local solicited ARs occurred within the first one to two days after injection and generally persisted for a

median of one to two days. Similar to the BNT162b2 vaccine, some reports of myocarditis and pericarditis have been reported post-mRNA 1273 vaccination (*see Full EUA Prescribing Information*[17]). A recent randomized controlled trial of three vs two doses of mRNA 1273 vaccine in solid-organ transplant recipients, reported that any local and systemic events were slightly more common after the third dose of mRNA-1273 than after the dose of placebo, but no grade 3 or 4 events and no cases of acute rejection occurred[18].

As to safety of the Ad26.COV2.S vaccine in study COV3001, the most common local solicited adverse reaction (≥10%) reported was injection site pain (48.6%). The most common systemic adverse reactions (≥10%) were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%) (see Tables 1 to 4). Severe allergic reactions, including anaphylaxis, have been reported following administration of the Janssen COVID-19 vaccine.
Severe allergic reactions (including anaphylaxis), thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome, and capillary leak syndrome have been reported following administration of the Janssen COVID-19 Vaccine during mass vaccination outside of clinical trials. On December 16, 2021 the CDC published updated recommendations regarding use of the Ad26.COV2.S (Johnson & Johnson) vaccine (https://www.cdc.gov/media/releases/2021/s1216-covid-19-vaccines.html) due to the rare but persistent adverse event thrombosis with thrombocytopenia syndrome (TTS) seen with the Ad26.COV2.S vaccine alone. They expressed a clinical preference for individuals to receive an mRNA COVID-19 vaccine over an Ad26.COV2.S vaccine, however, reaffirmed that receiving any vaccine is better than being unvaccinated and no recommendations were outlined with respect to use in immunocompromised patients after previous three dose vaccination series with prior mRNA vaccines.

To reduce the risk of serious adverse effects from the booster vaccine, we will include a safetyrun-in phase for those that have received prior adenoviral vaccine with close monitoring as described in the methods above.

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, hematoma and, rarely, infection or fainting. To reduce the risk of injury from a fall, each subject will be phlebotomized in a sitting or recumbent position, closely monitored and asked about these symptoms before being allowed to stand up post- phlebotomy.

Another foreseeable risk is that of inadvertent disclosure of HIPAA protected information. As a measure to minimize such risks the collected data will be accessed only by approved individuals, will be collected onto the Excel Data Collection Sheet, and stored on encrypted Montefiore Secure Drive, MonteBox.

Patients may or may not receive personal, direct benefit from taking part in this study. The possible benefits of taking part in this study include developing an immune response to the COVID vaccine, which may help prevent infection and/or severe illness from COVID-19 including death. Participation in this study, however, does not guarantee these direct benefits.

**Compensation**
Patients will not be offered compensation for participating in our study but might be offered reimbursement for limited travel expenses not exceeding $100.

**Study calendar cohort 1**

| Assessment | | Screening | Initial visit | Vaccine day (D0) | D28 | D150-180 |
|---|---|---|---|---|---|---|
| **Informed consent** | ICF | X | X | | | |
| **Demographics** | Demographics | X | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Medical history | X | | | | |
| | COVID vaccine history | X | | | | |
| | Inclusion/Exclusion Criteria | X | | | | |
| | SARS-CoV-2 Spike antibody | X | | | | |
| **Safety** | Vital signs | | X | | X | X |
| | SpO2 | | X | | X | X |
| | Physical exam | | X | X | X | X |
| | Document Side effects | | | | X | X |
| | Side Effect Questionnaire | | | | X | |
| **Intervention** | Vaccine administration | | | X | | |
| | Vaccine questionnaire | | | | X | |
| **Outcome** | SARS-CoV-2 Spike antibody | | X | | X | X |
| | SARS-CoV-2 Neutralization assay | | X | | X | X |
| | EUROIMMUN T-cell assay | | X | | X | X |

**Study calendar cohort 2**

| **Assessment** | | **Screening** | **Initial visit** | **Vaccine day (D0)** | **D28** | **D90** | **D180** | **D365** | **D730** |
|---|---|---|---|---|---|---|---|---|---|
| **Informed consent** | ICF | X | X | | | | | | |
| **Demographics** | Demographics | X | | | | | | | |
| | Medical history | X | | | X | X | X | X | X |
| | COVID vaccine history | X | | | X | X | X | X | X |
| | Inclusion/Exclusion Criteria | X | | | | | | | |
| | SARS-CoV-2 Spike antibody | X | | | | | | | |
| **Intervention** | Vaccine administration | | | X | | | | | |
| | Vaccine/safety questionnaire | | | | X | X | X | X | X |
| **Outcome** | SARS-CoV-2 Spike antibody | | X | | X | X | X | X | X |
| | SARS-CoV-2 Neutralization assay | | X | | X | X | X | X | X |
| | EUROIMMUN T-cell assay | | X | | X | X | X | X | X |

For study visits a 7 day window will be allowable for the 4 week follow up visit, a 14 day window will be allowable for the day 90 visit and 28 day window will be allowable for the rest of the study visits.

**Study calendar cohort 3**

| Assessment | | Screening | Initial visit | Vaccine day (D0) | D28 | D90 | D180 | D365 | D730 |
|---|---|---|---|---|---|---|---|---|---|
| **Informed consent** | ICF | X | X | | | | | | |
| **Demographics** | Demographics | X | | | | | | | |
| | Medical history | X | | | X | X | X | X | X |
| | COVID vaccine history | X | | | X | X | X | X | X |
| | Inclusion/Exclusion Criteria | X | | | | | | | |
| | SARS-CoV-2 Spike antibody | X | | | | | | | |
| **Intervention** | Vaccine administration | | | X | | | | | |
| | Vaccine/safety questionnaire | | | | X | X | X | X | X |
| **Outcome** | SARS-CoV-2 Spike antibody | | X | | X | X | X | X | X |
| | SARS-CoV-2 Neutralization assay | | X | | X | X | X | X | X |
| | EUROIMMUN T-cell assay | | X | | X | X | X | X | X |

For study visits a 7 day window will be allowable for the 4 week follow up visit, a 14 day window will be allowable for the day 90 visit and 28 day window will be allowable for the rest of the study visits.

**External Site**

| Institution | Point of Contact | Role |
|---|---|---|
| EUROIMMUN | Maite Sabalza, maite.sabalza@euroimmun.us | Reagents and supplies, running samples. |
| International Cancer Covid Vaccination Consortium | Crick Legal<br>lgc@crick.ac.uk | Data Sharing with ICCV. DUA will be reviewed and executed to account for this activity. |

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