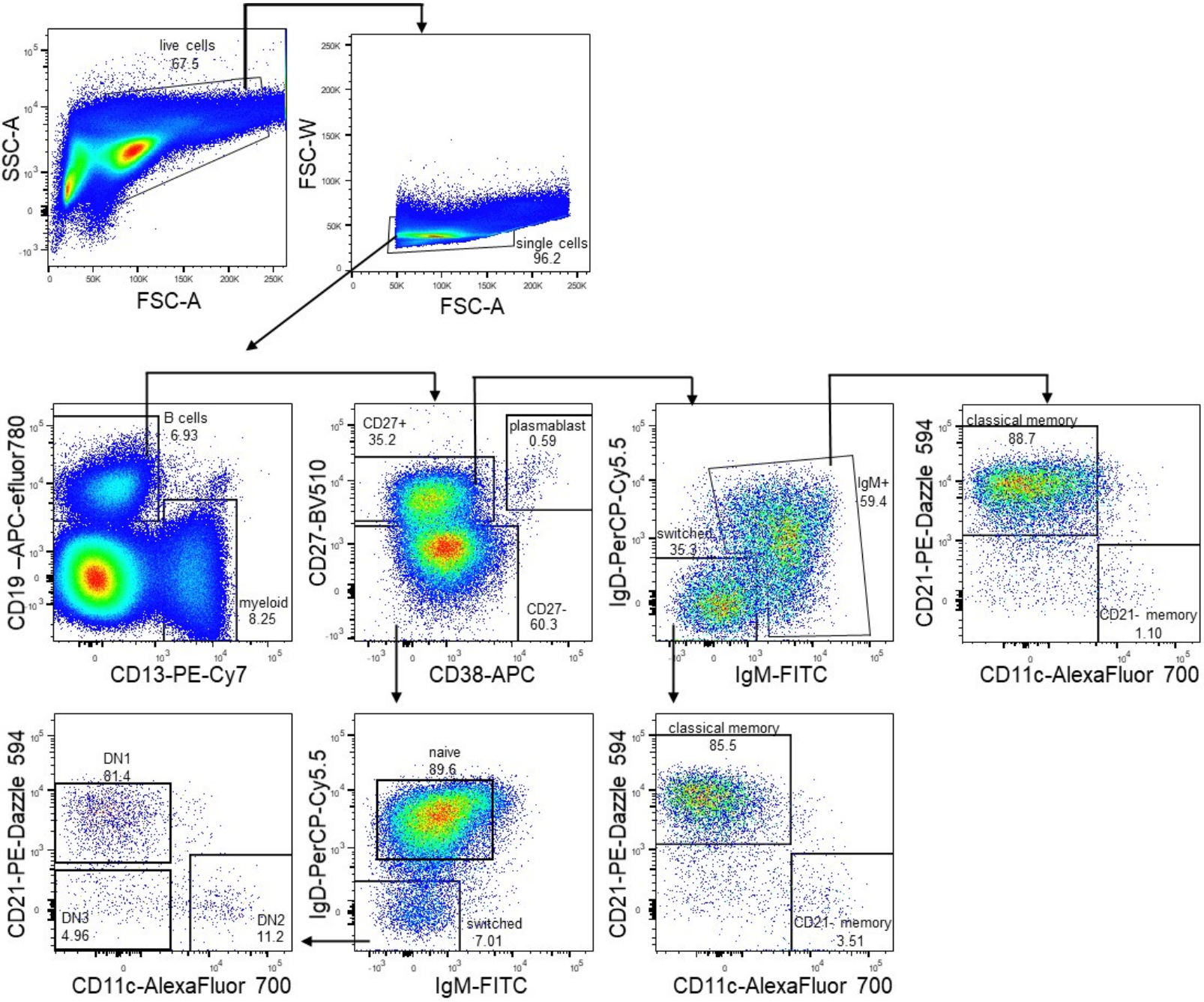
Supplementary Data Table 1. Chemotherapy Regimen and Groupings

Chemotherapy Regimen	Cancer Cohort (N)	Chemotherapy Group	Booster Group (N)
5-FU, Irinotecan, and Leucovorin	3	Fluoropyrimdine-based	2
5-FU/Leucovorin	1	Fluoropyrimdine-based	1
Nab-paclitaxel	2	Taxane/other antimicrotubule-based	
AIM	1	Anthracycline-based	
Avastin and Navelbine	1	Taxane/other antimicrotubule-based	
Capecitabine	3	Fluoropyrimdine-based	
Capecitabine + Bevacizumab	1	Fluoropyrimdine-based	2
Doxil	1	Anthracycline-based	
Enhertu	1	Other Targeted Cytotoxics	1
Eribulin	1	Taxane/other antimicrotubule-based	
Faslodex + Abemaciclib	1	Oral CDK4/6-based	
Faslodex + Palbociclib	1	Oral CDK4/6-based	1
FLOT	1	Fluoropyrimdine-based	
Folfirinox	2	Fluoropyrimdine-based	1
Folfirinox + CPI-613	1	Fluoropyrimdine-based	1
FOLFOX	1	Fluoropyrimdine-based	
FOLFOX + Bevacizumab	1	Fluoropyrimdine-based	
Fulvestrant + Palbociclib	1	Oral CDK4/6-based	
Gem/cis/nab-paclitaxel	5	Gemcitabine-based	5
Gemcitabine and nab-paclitaxel	4	Gemcitabine-based	3
Gemcitabine and Cisplatin	4	Gemcitabine-based	2
Ibrance and Anastrazole	1	Oral CDK4/6-based	
Letrozole + Ibrance	2	Oral CDK4/6-based	
Paclitaxel and Carboplatin	2	Taxane/other antimicrotubule-based	
Palbociclib	1	Oral CDK4/6-based	2
Sacituzumab govitecan	1	Other Targeted Cytotoxics	
Stivarga	1	Other Targeted Cytotoxics	1
T-DM1 + Palbo	1	Oral CDK4/6-based	
Taxol	3	Taxane/other antimicrotubule-based	
Topotecan + Bevacizumab	1	Other Targeted Cytotoxics	
ZN-C5 and Palbociclib	2	Oral CDK4/6-based	

Supplementary Figure



THE UNIVERSITY OF ARIZONA
Cancer Center

Supplementary Appendix

Study Title:
Immune Response to the COVID-19 Vaccine

Clinical Study Sponsor	University of Arizona Cancer Center 1515 N. Campbell Ave Tucson, AZ 85724-5024 United States
Principal Investigators	Rachna T. Shroff, MD, MS 1515 N. Campbell Ave., Tucson, AZ 85724, USA. +1 (314) 853-1185 rshroff@arizona.edu
Sub-Investigators	Pavani Chalasani, MD, MPH, Deepta Bhattacharya, PhD, Bonnie LaFleur, PhD, Daniel Pennington
Study Site:	The University of Arizona Cancer Center North Campus 3838 N. Campbell Ave. Tucson, AZ 85719-1454
Protocol Version(s) and Date(s)	Version 1.0 – 5/27/2021 Version 2.0 – 6/18/2021

Investigator Agreement

I have read, understand, and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.

I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

_____ _____
Signature Date (MM/DD/YY)

_____
Name of Principal Investigator

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1. STUDY DESIGN

1.1 Introduction

In recent work performed by our team, 59 patients with a known diagnosis of a solid tumor malignancy on active immunosuppressive cancer therapy were enrolled and had blood sampled through the University of Arizona Cancer Center during their routine care to better understand the immune response to the Pfizer COVID-19 vaccine. Our results demonstrated that the cancer patients had a statistically significant diminished immune response to the vaccine when compared to a healthy control cohort. We are amending this study to explore the effects on immune response to include a potential third vaccine for the cancer cohort. This will increase the visits required to approximately two more visits. It will require two additional blood samples, one 48 hours prior to third vaccine and the second, 5-11 days after the third vaccine. Subjects will also be called at 14 (+/- 3) days and 4-week (+/- 7 days) post third vaccination for AE review. The following protocol will be for the subjects that decide to continue onto a third vaccination.

1.2 Number of centers

Single Center: University of Arizona Cancer Center

1.3 Number of subjects

Up to 1000 subjects will be enrolled.

1.4 The subject participation time period

Subjects will be given a third SARS-COV2 Pfizer vaccination. There will be a blood draw at baseline (up to 2 days prior to third vaccine), and a secondary blood draw 5-11 days after 3rd vaccination. Subject will also have a 2 week (+/- 3 days) and 4 week (+/- 7 days) post-vaccine phone call for AE review.

2. OBJECTIVESs

2.1 Primary Objective

- To understand immune response to a second COVID-19 vaccination booster (3rd vaccine) in patients with solid tumor malignancies on immunosuppressive cancer therapies.

2.2 Secondary Objectives

- To understand the safety profile of a second booster (third SARS-COV2 vaccination).

3. BACKGROUND AND RATIONALE

The COVID-19 pandemic has led to over 150 million infections worldwide and claimed over 3 million lives to date. While non-pharmaceutical public health interventions managed to control outbreaks in certain countries, most of the global population will depend upon vaccines to mitigate the pandemic. Since the identification of SARS-CoV-2 as the causative agent of COVID-19 in January 2020[1,2], vaccines with very high efficacy have been developed and deployed with remarkable speed. Independent clinical trials demonstrated 94-95% vaccine efficacy against symptomatic disease caused by SARS-CoV-2 for both the Pfizer/BioNTech and Moderna mRNA-based vaccines[3,4]. Based on these data, in December 2020, both the Pfizer/BioNTech and Moderna vaccines were granted emergency use authorization by regulatory agencies in the United Kingdom and North America. Subsequent observational studies after authorization have shown that these vaccines also have high effectiveness against asymptomatic infections and suppress viral loads in breakthrough infections[5–8]. These data portend a marked overall reduction in community transmission once widespread vaccination is achieved.

These clinical trials, however, largely excluded immunocompromised individuals, including patients on immunosuppressive therapies to control chronic inflammatory conditions, primary immunodeficiencies, organ transplant recipients, and cancer patients on cytotoxic chemotherapy. As the number of deaths from this devastating virus has exceeded 575,000 in the US[9], concern about its impact on cancer patients has been high. This is especially true since a study from the COVID-19 Cancer Consortium showed a 13% 30-day all-cause mortality from COVID-19 in a study of 928 patients[10]. Importantly, the investigators noted a higher risk of death in patients with active cancer.

Beyond the obvious direct benefits to these patients, vaccine-induced protection of immunocompromised individuals is of substantial indirect benefit to the general population. Some highly transmissible SARS-CoV-2 variants of concern that partially evade antibody responses are suspected to have arisen following prolonged evolution within immunocompromised patients[11–16]. Even partial vaccine-induced immunity is likely to reduce within-host viral population size and duration of within-host viral persistence and evolution, thereby slowing the emergence of future problematic variants[17]. Yet protective immune correlates of antibodies and memory B and T cells remain to be quantitatively defined. Thus, optimal strategies are needed to elevate post-vaccination immunity in vulnerable immunocompromised populations to similar levels observed in healthy individuals. For individuals who cannot mount such an immune response, widespread community vaccination and targeted strategies to immunize close contacts will be required for indirect protection.

In recent work performed by our team, 59 patients with a known diagnosis of a solid tumor malignancy on active immunosuppressive cancer therapy were enrolled through the University of Arizona Cancer Center during their routine care. Participants in the control cohort were enrolled through the State of Arizona's COVID-19 vaccine point of

distribution site at the University of Arizona during the phase 1B vaccination program. Eligible control cohort participants were enrolled while in the observational waiting area after their first vaccine shot. We followed serological and cellular immune responses following mRNA vaccination of individuals in these cohorts[18]. Using live SARS-CoV-2 assays, neutralizing antibodies were detected in 67% and 80% of cancer patients after the first and second immunizations, respectively, with a 3-fold increase in median titers after the booster. Similar trends were observed in serum antibodies against the receptor-binding domain (RBD) and S2 regions of Spike protein, and in IFNγ+ Spike-specific T cells. The magnitude of each of these responses was markedly diminished relative to the control cohort.

Recent studies have shown a strong correlation between the levels of vaccine-induced neutralizing antibodies and overall efficacy[19]. These antibodies prevent viral entry and/or fusion with endosomal compartments of target cells. These data are further supported by non-human primate experiments in which passively transferred convalescent plasma protects against severe disease and overall infections[20]. Similarly, neutralizing monoclonal antibody therapies have shown efficacy in COVID-19 patients if provided soon after symptom onset[21]. The Pfizer/BioNTech and Moderna vaccines have approximately 95% efficacy against symptomatic disease caused by the parental SARS-CoV-2 strain. When considering some viral variants of concern that have recently arisen and become predominant, such as B.1.351, vaccine efficacy drops to approximately 75%. Based on these data, one can predict that those with the lowest 25% of neutralizing antibody responses after vaccination may be at elevated risk for symptomatic disease. Antibody responses by a large fraction of our cancer patients fall within this bottom quartile. In settings of low antibody levels, symptomatic breakthrough infections can be prevented from progressing to severe disease by virus-specific T cells[20,22]. Yet T cells were also negatively impacted in our cancer patients[18]. Together, these data strongly suggest susceptibility to symptomatic infections and severe disease in our cancer cohort despite vaccination.

We therefore quantified RBD- and Spike S1-specific memory B cell subsets as predictors of anamnestic responses to viral exposures or additional immunizations. After the second vaccination, Spike-specific plasma cell-biased memory B cells were observed in most cancer patients at levels similar to those of the control cohort after the first immunization. These data suggest that a third immunization might elevate antibody responses in many cancer patients to levels seen in healthy individuals after the second dose.

Investigational Products

SARS-COV2 Vaccination

Refer to the Pfizer EUA fact sheet for details on nonclinical and clinical studies.

4. INVESTIGATIONAL PRODUCT, INTERVENTION, DEVICE

Investigational Products, supply, components, composition, storage, and administration
SARS-COV2 Pfizer vaccine.

SARS-COV2 Pfizer vaccine will be supplied by the Arizona Department of Health Services (ADHS), specifically, for the purpose of this study. The ADHS has approved the repurpose of the POD's vaccine for this protocol.

Refer to the Pfizer SARS-COV2 EUA fact sheet for detailed instructions on drug preparation, components, composition, storage, and administration.

Dose modifications are not applicable for this study.

5. SUBJECT ELIGIBILITY

Investigators will maintain an electronic subject log (in the UACC OnCore system) of all potential (i.e., consented) study subjects, which will include as applicable demographics, informed consent, eligibility, on treatment, off treatment, follow up and off study dates.

5.1 Inclusion Criteria

1. Patients must have active solid tumor malignancy diagnosis
2. On active chemotherapy (which includes patients receiving chemotherapy within the last 3 months)
3. Received two prior SARS-COV2 Pfizer vaccines
4. Age ≥ 18 years
5. Ability to understand and the willingness to sign a written informed consent
6. Agree to comply with study procedures
7. Subjects previously enrolled under the main study
8. Patients must be able to speak and read English

5.2 Exclusion Criteria

1. History of HIV or organ/bone marrow transplant
2. Actively receiving immunotherapy
3. On active, chronic immunosuppression (>10 mg daily dose of prednisone equivalent)
4. Currently incarcerated or residence of another state

5.3 Enrollment

All subjects who agree to continue in the study will maintain their previously used unique sequential subject ID. This number will continue to be used to identify the subject throughout the clinical study and will be used on all applicable study documentation related to that subject. The subject identification number will remain constant throughout the study.

The written informed consent document(s) must be signed and personally dated by the subject or by the subject's legally authorized representative and completed to a fully executed informed consent document and processed per the institution standard operating procedures.

Before subjects may be entered into the study, a copy of the written institutional review board (IRB) approval of the protocol, informed consent form (ICF), and all other applicable subject information and/or recruitment material must be on file at the institution.

6. STUDY PROCEDURES

6.1 Screening/Baseline

Subjects will enter this portion of the study after a completely executed informed reconsent has been obtained.

During the Pre-treatment (prior to 3rd vaccine), "baseline" period, subjects are reconsented and qualified (screened) for the study. Informed reconsent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

Previously collected medical history and concurrent medications will be updated to accurately reflect any changes since initial questionnaire was completed. Blood sampling (approximately 40 mL, three tubes, same as previous) will be collected up to 48 hours prior to the third vaccine. This can also be collected on the day of treatment, prior to third vaccination.

6.2 Registration

All regulatory requirements must be in place prior to subject registrations.

Patients will already have identification numbers assigned from previous involvement in the study. They will maintain their subject ID.

6.3 Treatment Visit

During this period, patients will have their new baseline, pre-third vaccine blood drawn if not already collected in screening. Treatment visit should occur within 28 days of reconsenting. If past the 28-day time period, patients can continue after further reconsenting. Patient will then receive their third (2nd booster) Pfizer vaccine at the UA POD (same place as prior) by volunteers. A training email will be sent out to the UA POD volunteers. An MD will be present at the vaccination site to monitor for any issues. The MD will be aware these subjects are research subjects. Subjects will be given a "Golden Ticket" stating the patients are participating in a clinical trial and are eligible to receive the third vaccination. Subjects should be instructed to immediately inform the Investigator of any new AEs.

The Treatment Period ends when a subject receives his or her third vaccine shot; the subject then enters the Post-Treatment Period.

6.4 Follow up

Subjects will return to the study site approximately 5-11 days after their 3rd vaccine for a blood draw (approximately 40 mL, three tubes, same as previous) and AE review. Patients will then be called for AE review at 14 days (+/-3 days) post third vaccine and at 4 weeks (+/- 7 days) post third vaccine. There will be no further follow-up in this study.

6.5 Off Study

Subjects will be considered off study when all planned treatment, early termination, and follow-up visits have been completed, unless death or withdrawal of consent to continue participation occurs.

6.6 General Considerations

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

7. Immune Analyses

7.1 Antibody analyses

Serum will be collected from non-heparinized blood collection tubes. These serum samples will be used for enzyme-linked immunosorbent assays to quantify antibodies that recognize the receptor binding domain of the SARS-CoV-2 spike protein. In addition, these serum samples will be used to quantify antibodies that can prevent SARS-CoV-2 from infecting target cells.

7.2 T cell quantification

Plasma and peripheral blood mononuclear cells will be harvested from heparinized blood collection tubes. Plasma will be frozen as a backup for replicates of antibody assays described in 7.1 should they be required. Using enzyme-linked immunospot assays, peripheral blood mononuclear cells will be tested for T cell reactivity and interferon-gamma production in response to peptides from SARS-CoV-2 spike protein.

8. DATA AND SAFETY MONITORING PLAN

8.1 Identification of the DSMB obligated for oversight responsibilities:

The University of Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial. This study has been assigned a Low Risk level by the DSMB.

8.2 Identification of the entity obligated for routine monitoring duties:

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program quarterly to ensure that the investigation is conducted according to protocol design and regulatory requirements.

This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues. Investigator will review AE logs if applicable. If reportable AEs (as mentioned in section 8.5) are identified, the investigator will sign off on the UACC AE log.

8.3 Monitoring progress and data review process:

Routine monitoring of subject data will be conducted at least quarterly.
The first routine monitoring visit will include at a minimum:

- Informed consent – 50% of cases enrolled;
- Subject eligibility – 10% of cases, up to two subjects;
- Data review – 10% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. The monitor will request additional source documentation, clarification, information, or corrections to the CRF and/or regulatory records from the Clinical Research Coordinator (CRC) or other applicable staff responsible for the study and resolution of queries/findings. Documentation of such a request will be maintained with a copy of the monitor's visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the

subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms will be created to include study data points and the adverse event forms and be completed using the institution database or other acceptable data formats. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents will be conducted at least annually.

8.4 Process to implement study closure when significant risks or benefits are identified:

If deemed unsafe in the opinion of the investigator, or with DSMB review, the study will be discontinued.

8.5 Description of adverse events and reporting procedures:

ADVERSE EVENTS
An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AE's will only be reported on UACC adverse event record form if deemed related to the vaccine, by the investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:
"How have you felt since your last clinic visit?"
"Have you had any new or changed health problems since you were last here?"

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events deemed unexpected by the investigator, and any deaths will be reported within 24 hours of notification of the event to the sponsor and, if applicable, any collaborating entity. All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter, Table 5: Adverse Event Reporting. We have discussed with the FDA that the 2nd booster (3rd vaccine) is IND exempt. Additionally, we have had discussions with the FDA and Pfizer to ensure communication lines are open for management of unexpected safety adverse events that may occur.

All submitted serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and then reviewed by the DSMB Chair. The assigned QA/QC Monitor will review the SAE reporting process to confirm reporting requirements are met.

AE/SAE REPORTING TIME

AE/SAEs will be collected as above, from the time of third vaccination until the 4-week (+/- 7 days) post third vaccination visit.

8.6 Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB on a quarterly basis, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);

- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least annually.

8.7 Identification of the sponsor or funding agency, as applicable:

The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study.

A copy of this correspondence will also be forwarded to the DSMB and the SRC.

8.8 Risks Associated with SARS-COV2 Pfizer Vaccine

The most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever. Of note, more people experienced these side effects after the second dose than after the first dose, so there is a possibility that side effects may be even more pronounced with the third dose. This is unknown.

Refer to the SARS-COV2 Pfizer vaccine fact sheet for a detailed description of anticipated safety risks for SARS-COV2 Pfizer vaccine.

9. QUALITY ASSURANCE MEASURES

Per the UACC DSMB Charter, Internal *Ad Hoc* audits may be performed on any UACC clinical trial if identified for audit, the audit will be conducted by an identified audit team per the UACC DSMB Charter. A QA/QC representative will coordinate the audit team functions and a written audit report will be provided to the principal investigator and the DSMB.

10. REMOVAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational products. If the subject withdraws, no further procedures will be collected.

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

11. STATISTICAL CONSIDERATIONS

11.1 General

The original observational study[18], that is the basis of this interventional study, was powered to test a non-inferiority hypothesis. The resulting sample size recommendation was 55 participants in each cancer and control cohorts (n=110). This sample size was based on neutralizing antibodies measured through $PRNT_{90}$ that ensured that we would have sufficient power to demonstrate vaccine non-inferiority in immunocompromised cancer individuals allowing for a 0.3 difference in $PRNT_{90}$ (on the log10, or a titer difference of 200) between mean values. Further, this sample size was sufficient to ensure ~ 80% of the cancer cohort have log_{10} $PRNT_{90}$ values of above 50 (log_{10} 1.7), a clinically significant level for which 95% of the cancer cohort would have detectible titers above a 4-fold increase, if all other assumptions were met. The assumptions for this sample size are listed below and the mean and standard deviations for these assumptions are based on data from three preliminary studies done for the Moderna TX, Inc. (mRNA-1273) vaccine[23, 24, 25]; one preliminary study for the Pfizer (BNT162b1) vaccine[26]; and study on severe inpatient and COVID-19 community infected individuals performed at the University of Arizona[27].

1. Clinically significant mean $PRNT_{90}$ value is likely lower than $log_{10}(2)$
2. Standard deviation of 0.5; the recommended sample size does allow for a slightly higher standard deviation (0.6) in the cancer cohort.
3. Mean of the control cohort is 2.7 and mean level of the cancer cohort is at least 2.4 (difference in means is = 0.3).
4. Noninferiority margin of 0.6.
5. Power of at least 0.80.

Rationale for the current interventional study is based on data from the observational study that showed that the non-inferiority hypothesis was not necessary as the levels of $PRNT_{90}$ for the control cohort was clearly, and statistically, superior to those found in the cancer cohort ($p < 0.0001$) with a log_{10} mean level of 2.78 in the control cohort versus 1.61 in the cancer cohort.

11.2 ANALYSIS

The primary endpoint will be the paired change in $log_{10}(PRNT_{90})$ from the interventional baseline titer (draw 4 since start of the observational study) to one week post the third Pfizer shot (draw 5). The primary hypothesis will be that there is an increase in $log_{10}(PRNT_{90})$ levels between these two blood draws. The test statistic will be a two-sided paired t-test. A sample size of at least 35 participants will achieve a power of 0.80 to detect a pairwise difference of 1.17 $log_{10}(PRNT_{90})$ at a 0.05 level of significance; this sample size assumes a pairwise SD of 2.39 as seen in the observational study. Secondary endpoints will include neutralizing antibodies, RBD titers, and T cell ELISPOTs.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

Before a subject's participation in the clinical study, the investigator or identified designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures or investigational products are administered or initiated.

12.2 Institutional Review Board

A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the institution before recruitment of subjects into the study.

The investigator is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments; except changes to eliminate an immediate hazard to study subjects, and changes to the informed consent document from the IRB prior to implementation.

The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other serious adverse event reports occurring at or received from participating centers as applicable for multi-center trials following the IRB policies and procedures.

13. ADMINISTRATIVE PROCEDURES

13.1 Investigator Responsibilities

The PI will conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

13.2 Data and Safety Monitoring Board Protocol Review

Initial DSMB protocol review will be conducted prior to SRC and IRB submissions.

Any protocol revision or amendment that includes a potential change to any section of data and safety monitoring plan must be reviewed and approved by the DSMB ***prior to* the protocol amendment submission to the IRB**.

13.3 Conditions for Modifying the Protocol

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the Principal Investigator.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (e.g., change in monitor or change of telephone number).

13.4 Conditions for Terminating the Study

At any time, the study may be terminated by the Principal Investigator or the Principal Investigator's institution. Should this be necessary, the Principal Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Principal Investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the Principal Investigator and all Investigator(s) shall cease enrolling subjects into the study and shall discontinue conduct of the study as soon as is medically practicable.

14. SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

15. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

16. DATA

Applicable data as specified as required in the protocol will be reported/submitted in the case report form (CRF). Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. **CRFs will be completed via REDCAP.**

Additional procedures and assessments may be performed as the institution's standard of care; however, these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to a serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational product/intervention/device or employed as a control in the investigation.

17. PROTOCOL DEVIATIONS

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

The investigator should not implement any deviation from, or changes of, the protocol without prior review and documented IRB approval of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), change of telephone number(s). A waiver of inclusion/exclusion criteria granted by the sponsor-investigator must be documented and IRB approved prior to implementation.

18. COMMON TOXICITY CRITERIA (CTCAE)

CTCAE Version: 5.0

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP

homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

19. STUDY SCHEDULE

	Baseline	Treatment	Post-treatment	
Informed Consent	X		5-11 days after vaccine	D14 (+/- 3 days) and 4 weeks (+/- 7 days) post vaccine
Medical History and Demographics	X			
Blood Sample Collection	X_a	X_a	X_b	
Pfizer Vaccine Administration		X		
Concomitant Medications	Continuously			
Adverse Events	Continuously			
Footnotes: [a]To be collected up to 48 hours prior to the Pfizer study vaccine administration. [b]To be collected 5-11 days after the Pfizer study vaccine administration.				

20. ABBREVIATIONS

AE	Adverse Event
ASCO	American Society of Clinical ‘Oncology
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ESMO	European Society for Medical Oncology
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factors
G-MDSCs	Granulocytic Myeloid-Derived Suppressor Cells
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
PD-1	Programmed Death- 1
PD-L1	Programmed Death Ligand -1
QA/QC	Quality Assurance/Quality Control
SAE	Serious Adverse Event
SRC	Scientific Review Committee
UACC	University of Arizona Cancer Center

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