SUPPLEMENTARY MATERIALS

Supplementary Table S1. Type of antineoplastic treatment each cohort of cancer patients included in our study received

Cohort	Type of antineoplastic treatment received
1	- Not on active cancer therapy (i.e. patients on surveillance alone - Radiotherapy - Endocrine therapy (e.g. tamoxifen, letrozole)
2	Targeted therapy, including - TKIs/ small molecule inhibitors e.g. osimertinib, palbociclib, sorafenib - antibody drugs targeting pathways e.g. Herceptin, Pertuzumab, Cetuximab, Panitumumab and Bevacizumab
3	Immunotherapy, including patients on - Immunotherapy alone - Immunotherapy + TKI/small molecule inhibitors
4	Chemotherapy, including patients on - Chemotherapy alone - Chemotherapy + immunotherapy - Chemotherapy + antibody drugs targeting pathways e.g. FOLFOX+cetuximab, XELIRI + Bevacizumab - Chemotherapy + TKI/small molecule inhibitors e.g. Osimertinib, sorafenib
5	Haematological malignancies on active therapy, including leukaemia and lymphoma

TKI: Tyrosine kinase inhibitors

Supplementary Table S2. Proportion of cancer patients, stratified by type of treatment received, who seroconverted after each SARS-CoV-2 vaccine dose

No. seroconverted	Control	Targeted therapy	Immunotherapy	Chemotherapy	Haem on treatment
Post first dose	8/24 (33.3%)	6/20 (30.0%)	4/9 (44.4%)	10/19 (52.6%)	4/19 (21.1%)
Post second dose	39/47 (83.0%)	35/40 (87.5%)	16/17 (94.1%)	62/78 (79.5%)	14/27 (51.9%)
Post third dose	12/13 (92.3%)	13/15 (86.7%)	13/13 (100%)	31/32 (96.9%)	4/6 (66.7%)

Supplementary Table S3. Proportion of cancer patients, stratified by type of cancer, who seroconverted after each SARS-CoV-2 vaccine dose

No. seroconverted	**Haem**	**Gastrointestinal**	**Lung**	**Other**
Post first dose	4/22 (18.2%)	6/20 (20.0%)	6/12 (50.0%)	16/37 (43.2%)
Post second dose	19/32 (59.4%)	65/83(78.3%)	17/19 (89.5%)	65/75 (86.7%)
Post third dose	5/7 (71.4%)	31/33 (93.9%)	11/11 (100%)	26/27 (96.3%)

Supplementary Table S4. Post-SARS-CoV-2 vaccine antibody titres of haematological cancer patients

Antibody titres %	**Lymphoma (n=14)**	**Non-lymphoma, including leukaemias and myeloma (n=20)**
Post first dose (median, IQR)	0 [0, 0]	0 [0, 82.3]
Post second dose (median, IQR)	6.35 [0, 97.6]	52.01 [0, 96.4]
Post third dose (median, IQR)	Not applicable - no patients	72.5 [15.7, 95.4]
No. infected with COVID-19	9	5
% severe infections	11.1	20

IQR: interquartile range

Supplementary Table S5. Proportion of cancer patients, stratified by sex, who seroconverted after each SARS-CoV-2 vaccine dose

	Sex No. (%)	
No. seroconverted	Male	Female
Post first dose	6/34 (17.6)	26/56 (46.4)
Post second dose	74/101 (73.3)	91/106 (85.8)

Study Protocol

Department of Haematology-Oncology
National University Hospital, Singapore

A prospective study of seroconversion following COVID-19 vaccination in cancer patients

Table of contents

1. Introduction

Spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an ongoing global COVID-19 pandemic. As of 20 May 2021, there were over 160 million confirmed cases and over 3 million deaths. The morbidity and mortality from COVID-19 and its complications and large-scale economic disruption have prompted a race among mankind on vaccine development to manage this pandemic (Ali & Spinler, 2021; Berlin, Gulick & Martinez, 2020; Lin et al., 2021; Tian & Ye, 2020; Wang, Kream & Stefano, 2020). Vaccines approved for use in at least one country so far include mRNA vaccines (e.g. BioNTech-Pfizer and Moderna), protein subunit vaccines (e.g. RBD-Dimer), inactivated vaccines (e.g. Sinovac), and non-replicating viral vector vaccines (e.g. Ad26.COV2.S). In Singapore, the national vaccination exercise has begun with the use of Pfizer–BioNTech COVID-19 vaccine and Moderna mRNA-1273 vaccine, both mRNA vaccines.

There have been ongoing studies to ensure efficacy and safety of vaccines in the general population. However, less is known about the efficacy and duration of immunity in cancer patients. Cancer patients are often immunocompromised as a result of both disease and treatment factors. The main immune deficit is neutropenia, where there is an abnormally low concentration of white blood cells. Common treatment modalities of cancer include radiotherapy, chemotherapy, and targeted immunotherapy such as tyrosine kinase inhibition.

Interim data have shown lower immune efficacy rates among cancer patients for COVID-19 vaccinations than healthy controls (Monin-Aldama et al., 2021). Immune efficacy of a single inoculum in solid cancer patients was lower (<40% efficacious) and much lower in haematological cancer patients (<15%) compared to healthy controls (>90% efficacious). The impact of immunocompromised states, including malignancies and primary and secondary immunodeficiencies, on the efficacy and immunogenicity of active vaccination is well established in literature on vaccinology. Seroconversion and seroprotective rates are lower in immunocompromised populations in comparison with healthy and immunocompetent populations. This is similar to what is seen in influenza vaccination, where there is lower seroconversion and seroprotection among the cancer patients (Beck et al., 2012).

Cancer patients also tend to suffer from higher morbidity and mortality from COVID-19. This may be more pronounced in patients suffering from a greater degree of immunocompromise as a result of their treatment (Erdal et al., 2021). This observational study groups patients into cohorts by the treatment modality received, allowing comparisons to be drawn between the efficacy and immunogenicity of vaccines and the treatment modality. Future studies can build upon these findings by potentially studying optimal dosage variations and dosage regimens for cancer patients.

2. Hypothesis

We hypothesise that the state of immunocompromise induced by malignancies and systemic antineoplastic therapy affects the efficacy of COVID-19 vaccines in patients. Furthermore, the degree of immunocompromise induced in patients varies by treatment modalities.

3. Aims of Research Proposal

1) To study the seroconversion rate of SARS-CoV-2 neutralising antibody in patients receiving treatment for malignancies.
2) To compare the seroconversion rate of SARS-CoV-2 neutralising antibody between patients receiving different treatment modalities for malignancies.
3) To compare the seroconversion rate SARS-CoV-2 neutralising antibody between a historical cohort of non-cancer patients and patients receiving different treatment modalities for malignancies.
4) To compare the rise in SARS-CoV-2 neutralising antibody before and after receiving each dose of COVID-19 vaccination.
5) To compare the incidence of adverse events to SARS-CoV-2 vaccines and their respective severity between healthy patients and patients receiving treatment for malignancies.
6) To compare the seroconversion rate of SARS-CoV-2 neutralising antibody in patients with cancer receiving different SARS-CoV-2 vaccines.

4. Outcomes

Primary outcome:

1. SARS-CoV-2 vaccine response at 12 weeks (Time frame: 12 weeks)
   Neutralising Anti-SARS-CoV-2 S-protein titre at 3 months as measured by GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits

Secondary outcomes:

1. SARS-CoV-2 vaccine response at 3 to 8 weeks (Time frame: 3 to 8 weeks)
   Neutralising Anti-SARS-CoV-2 S-protein titer at 3 to 8 weeks as measured by GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits

2. SARS-CoV-2 vaccine response at 6 months (Time frame: 6 months)
   Neutralising Anti-SARS-CoV-2 S-protein titre at 6 months as measured by GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits

3. SARS-CoV-2 vaccine response at 12 months (Time frame: 12 months)
   Neutralising Anti-SARS-CoV-2 S-protein titre at 12 months as measured by GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits
4. SARS-CoV-2 vaccine safety in the studied population [Time Frame: 12 months]

Incidence and severity of the adverse events after administration, including the peri-administrative period, of the SARS-CoV-2 vaccine

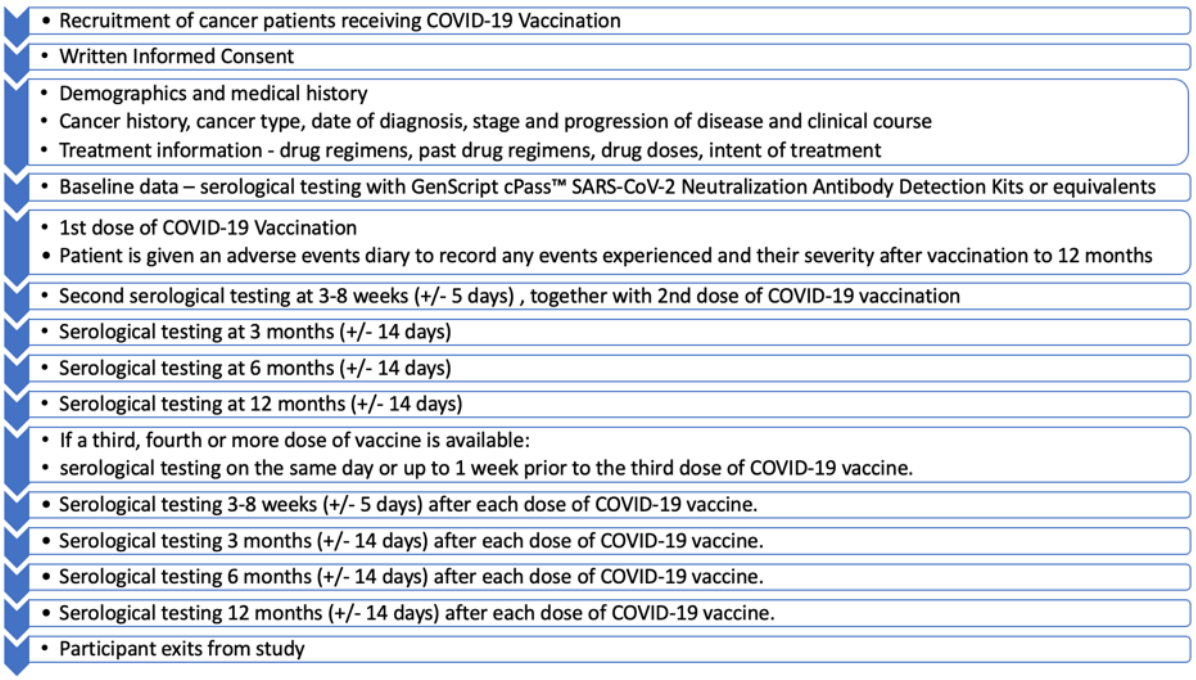
Exploratory outcomes:

1. Transcriptomic properties
   To assess changes in gene expression in peripheral blood myeloid cells.

2. Cancer-related mortality and outcomes (e.g. Progression Free Survival, Disease Free Survival) for vaccinated patients
   To compare cancer-related mortality and outcomes between vaccinated patients and unvaccinated cancer patients .

5. Proposed Methodology

5.1. Study schema



5.2. Recruitment of study subjects

Patients will be recruited from the National University Cancer Institute Cancer Centre and Ng Teng Fong General Hospital. Any individual who is going to receive or has received a COVID-19 vaccine and has a personal history of malignancy is eligible. Written informed consent will be obtained. Recruitment and consent taking will be performed by study coordinators from the Haematology-Oncology Research Group and Ng Teng Fong General Hospital.

Blood will be drawn for baseline tests and serology before the first dose of COVID-19 vaccine. Up to 15mL blood will be collected from each subject at each timepoint. The following will be taken: one plain tube for serology and one PAXgene tube for serial transcriptomics.

At the time of recruitment, demographic characteristics, cancer history, and past and present cancer treatment history of the study subject will be collected.

- Demographic information includes ethnicity, height, weight and smoking status
- Personal medical history will include medical comorbidities, Eastern Cooperative Oncology Group Physical Status, drug allergies and any known hypersensitivity to anti-neoplastic agents will be collected.
- Cancer history that will be collected includes the type, date of diagnosis, stage and progression of disease and clinical course.
- Treatment information that will be collected includes the drug regimen, drug doses, and intent of treatment.
- Additional information will be collected, including treatment (and the dates) given before the 1st vaccine, treatment between the two vaccines and after the 2nd vaccine, use of anti-pyretics in the 1st 7 days post vaccination
- History of COVID-19 vaccination will also be collected. While it is preferred for patients to enroll in the study prior to their first dose of COVID-19 vaccine, in unique circumstances, patients can also enroll in between first and second vaccine doses after discussion with the principal investigator (PI).

After the dose of a COVID-19 vaccine is administered, patients will be monitored for incidence and severity of any adverse events.

3-8 weeks (+/- 5 days) after the first dose of COVID-19 vaccine, up to 15mL blood will be collected from each subject, timed with the second dose of COVID-19 vaccine.

3 months (+/- 14 days) after the first dose of COVID-19 vaccine, up to 15mL blood will be collected from each subject.

6 months (+/- 14 days) after the first dose of COVID-19 vaccine, up to 15mL blood will be collected from each subject.

12 months (+/- 14 days) after the first dose of COVID-19 vaccine, up to 15mL blood will be collected from each subject.

Patients who have been vaccinated but who were not recruited before they received their first dose may still be recruited. Serological testing will be done at the same time points as defined for the other cohorts.

Serological timepoints for this group of patients

A. 3-4.5 months after first dose of COVID-19 vaccine
B. 6 months (+/- 14 days) after first dose of COVID-19 vaccine
C. 12 months (+/- 14 days) after first dose of COVID-19 vaccine

As a third dose of vaccination has been made available to the patients, serological testing will also be done on the same day or up to 1 week before the third dose is administered and at 3-8 weeks, 3 months, 6 months and 12 months after the third dose.

Patients who have already been recruited into the study will be given an amended informed consent form to allow for further blood draws after booster.

Patients who will be recruited into the trial for the three doses of vaccine will have serological testing done at the following timepoints:

1. Baseline investigation before administration of first dose of COVID-19 vaccine.
2. 3-8 weeks (+/- 5 days) after first dose of COVID-19 vaccine (timed with second dose of vaccine).
3. 3 months (+/- 14 days) after first dose of COVID-19 vaccine.
4. 6 months (+/- 14 days) after first dose of COVID-19 vaccine.
5. 12 months (+/- 14 days) after first dose of COVID-19 vaccine.
6. Same day or up to 1 week prior to the third dose of COVID-19 vaccine.
7. 3-8 weeks (+/- 5 days) after third dose of COVID-19 vaccine.
8. 3 months (+/- 14 days) after third dose of COVID-19 vaccine.
9. 6 months (+/- 14 days) after third dose of COVID-19 vaccine.
10. 12 months (+/- 14 days) after third dose of COVID-19 vaccine.

If any of the timepoints from timepoints 6-10 are within 2 weeks of the timepoints of 3-5, the timepoints will be merged.

Similarly, should a fourth or more dose of vaccination be made available to the patients, serological testing will also be done on the same day or up to 1 week before the additional dose is administered and at 3-8 weeks, 3 months, 6 and 12 months after the additional dose.

Patients who have already been recruited into the study will be given an amendment informed consent form to allow for further blood draws after the fourth dose of vaccine.

Patients who will be recruited into the trial for the fourth, or subsequent, doses of vaccine will have serological testing done at the following timepoints:

1. Baseline investigation before administration of the first dose of COVID-19 vaccine.
2. 3-8 weeks (+/- 5 days) after the first dose of COVID-19 vaccine (timed with the second dose of vaccine).
3. 3 months (+/- 14 days) after the first dose of COVID-19 vaccine (timed with the third dose of vaccine).
4. 6 months (+/- 14 days) after the first dose of COVID-19 vaccine.
5. 12 months (+/- 14 days) after the first dose of COVID-19 vaccine.
6. Same day or up to 1 week prior to the third dose of COVID-19 vaccine.
7. If patient has not received a fourth dose yet, 3-8 weeks (+/- 5 days) after the third dose of COVID-19 vaccine.
8. If patient has not received a fourth dose yet, 3 months (+/- 14 days) after the third dose of COVID-19 vaccine.
9. If patient has not received a fourth dose yet, 6 months (+/- 14 days) after the third dose of COVID-19 vaccine.
10. If patient has not received a fourth dose yet, 12 months (+/- 14 days) after the third dose of COVID-19 vaccine.

For each subsequent dose of COVID-19 vaccine, such as the fourth, the following timepoints will be used with respect to the latest dose of COVID-19 vaccine:
11. Same day or up to 1 week prior to the subsequent dose of COVID-19 vaccine.
12. 3-8 weeks (+/- 5 days) after the subsequent dose of COVID-19 vaccine.
13. 3 months (+/- 14 days) after the subsequent dose of COVID-19 vaccine.
14. 6 months (+/- 14 days) after the subsequent dose of COVID-19 vaccine.
15. 12 months (+/- 14 days) after the subsequent dose of COVID-19 vaccine.

If any of the above timepoints are within 2 weeks apart, the timepoints will be merged. If they are planned to receive the fourth dose, it means that points 7-10 would be optional or not applicable, but they will have points 11-15 testing instead.

While these time points and window periods are ideal for blood draws for analysis purposes, in order to balance patient convenience and maximal follow-up, blood draws will be permitted to be matched to patient regular blood draws, but not more frequently than 3 monthly (excluding the initial blood draws surrounding first, second dose of vaccines). Missed blood draws will not be considered protocol deviations as the study has achieved the primary objective and remaining follow-ups are secondary/exploratory endpoints.

5.3. Confidentiality issues

Information pertaining to the patient that arises from the research will not become part of the patient's medical record. Case record forms will be kept under lock and key in the Department of Haematology-Oncology, National University Hospital (NUH). Each patient recruited into the study will be assigned a unique patient number (UPN), with no direct reference to the patient's other identifying information. Information from the case record forms will be

transcribed onto an electronic database that is password protected using a user designated and password protected computer in the Department. Personnel in the laboratory have no direct access to the clinical history database or other patient information.

5.4. Blood handling

Venepuncture will be co-ordinated with other blood work required for clinical indication whenever possible to prevent an unnecessary procedure to the patient. However, if there are no regular blood draws planned, a separate blood draw for the purpose of the study may also be permitted. The blood samples will be stored at 2-8°C in the refrigerator at the collection site for no longer than 3 days before transferring to the laboratory for DNA extraction.

5.5. Serology testing

Serology will be tested using GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits, which perform rapid detection of total neutralising antibodies against SARS-CoV-2 or equivalent assays. Tests will be performed on the same sample of blood drawn and no additional blood will be drawn from these patients. Serology will be performed by trained laboratory personal at NUH. Seroconversion will be defined as a Geometric Mean Titre of at least four-fold increase from baseline. Additional analyses may also be performed at the Agency for Science, Technology and Research or Duke-NUS Medical School.

Serological timepoints will be:

1. Baseline investigation before administration of first dose of COVID-19 vaccine
2. 3-8 weeks (+/- 5 days) after first dose of COVID-19 vaccine (timed with second dose of vaccine)
3. 3 months (+/- 14 days) after first dose of COVID-19 vaccine
4. 6 months (+/- 14 days) after first dose of COVID-19 vaccine
5. 12 months (+/- 14 days) after first dose of COVID-19 vaccine

Patients who have been vaccinated but who were not recruited before they received their first dose and were subsequently recruited will have serological testing done at the following timepoints:

1. 3-4.5 months after first dose of COVID-19 vaccine
2. 6 months (+/- 14 days) after first dose of COVID-19 vaccine
3. 12 months (+/- 14 days) after first dose of COVID-19 vaccine

As a third dose of vaccination is made available to the patients, serological testing will also be done on the same day or up to 1 week before the third dose is administered and at 3-8 weeks, 3 months, 6 months and 12 months after the third dose.

Patients who have already been recruited into the study will be given an amendment informed consent form to allow for further blood draws after the third dose.

Patients who will be recruited into the trial for the three doses of vaccine will have serological testing done at the following timepoints:
1. Baseline investigation before administration of first dose of COVID-19 vaccine
2. 3-8 weeks (+/- 5 days) after first dose of COVID-19 vaccine (timed with second dose of vaccine)
3. 3 months (+/- 14 days) after first dose of COVID-19 vaccine.
4. 6 months (+/- 14 days) after first dose of COVID-19 vaccine.
5. 12 months (+/- 14 days) after first dose of COVID-19 vaccine.
6. Same day or up to 1 week prior to the third dose of COVID-19 vaccine.
7. 3-8 weeks (+/- 5 days) after third dose of COVID-19 vaccine.
8. 3 months (+/- 14 days) after third dose of COVID-19 vaccine.
9. 6 months (+/- 14 days) after third dose of COVID-19 vaccine.
10. 12 months (+/- 14 days) after third dose of COVID-19 vaccine.

If any of the timepoints between timepoints 6-10 are within 2 weeks of the timepoints of 3-5, the timepoints will be merged.

Similarly, should a fourth or more dose of vaccination be made available to the patients, serological testing will also be done on the same day or up to 1 week before the additional dose is administered and at 3-8 weeks, 3 months, 6 and 12 months after the additional dose.

Patients who will be recruited into the trial for the fourth or subsequent doses of vaccine, will have serological testing done at the following timepoints:

1. Baseline investigation before administration of the first dose of COVID-19 vaccine
2. 3-8 weeks (+/- 5 days) after the first dose of COVID-19 vaccine (timed with the second dose of vaccine)
3. 3 months (+/- 14 days) after the first dose of COVID-19 vaccine (timed with the third dose of vaccine.)
4. 6 months (+/- 14 days) after the first dose of COVID-19 vaccine.
5. 12 months (+/- 14 days) after the first dose of COVID-19 vaccine.
6. Same day or up to 1 week prior to the third dose of COVID-19 vaccine.
7. If patient has not received a fourth dose yet, 3-8 weeks (+/- 5 days) after the third dose of COVID-19 vaccine.
8. If patient has not received a fourth dose yet, 3 months (+/- 14 days) after the third dose of COVID-19 vaccine.
9. If patient has not received a fourth dose yet, 6 months (+/- 14 days) after the third dose of COVID-19 vaccine.
10. If patient has not received a fourth dose yet, 12 months (+/- 14 days) after the third dose of COVID-19 vaccine.

For each subsequent dose of COVID-19 vaccine, such as the fourth, the following timepoints will be used with respect to the latest dose of COVID-19 vaccine:
11. Same day or up to 1 week prior to the subsequent dose of COVID-19 vaccine.

12. 3-8 weeks (+/- 5 days) after the subsequent dose of COVID-19 vaccine.
13. 3 months (+/- 14 days) after the subsequent dose of COVID-19 vaccine.
14. 6 months (+/- 14 days) after the subsequent dose of COVID-19 vaccine.
15. 12 months (+/- 14 days) after the subsequent dose of COVID-19 vaccine.

If any of the above timepoints are within 2 weeks apart, the timepoints will be merged. If they are planned to receive the fourth dose, it means that points 7-10 would be optional or not applicable but they will have points 11-15 testing instead.

While these time points and window periods are ideal for blood draws for analysis purposes, in order to balance patient convenience and maximal follow-up, blood draws will be permitted to be matched to patient regular blood draws, but not more frequently than 3 monthly (excluding the initial blood draws surrounding first, second dose of vaccines). Missed blood draws will not be considered protocol deviations as the study has achieved the primary objective and remaining follow-up are secondary/exploratory endpoints.

Safety assessments include local and systemic events and the use of anti-pyretics in the first seven days after administration of the vaccine. Acute reactions that occur in the first 30 minutes will be documented in the medical records and in the adverse events case report form. Each subject will be asked to record local reactions at the injection site and systemic effects in a diary for the first seven days following each vaccination. Hard copies of the diaries will be provided to patients. The filled adverse events diaries will be collected back from patients at their first follow-up visit for blood draw from 3-8 weeks (+/- 5 days) after the first dose of COVID-19 vaccine. If a local reaction persists beyond this period, the subject is requested to report that information. If a grade 3+ local reaction is reported, the subject should contact the study team to ascertain further details and determine if a clinic visit is indicated.

The grading of safety assessments is based on the US Food and Drug Administration Center for Biologics Evaluation and Research guidelines on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Tables 1A and 1B).

Table 1A. Local reaction grading scale

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalisation for severe pain

Redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Swelling	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Table 1B. Systemic event grading scale

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	1 – 2 episodes in 24 hours	More than 2 episodes in 24 hours	Requires outpatient intravenous (IV) hydration	Emergency room (ER) visit or hospitalisation for hypotensive shock
Diarrhoea	2 – 3 loose stools in 24 hours	4 – 5 stools or in 24 hours	6 or more watery stools or requires outpatient IV hydration	ER visit or hospitalisation for severe diarrhoea
Headache	No interference with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalisation for severe headache
Fatigue/ tiredness	No interference with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalisation for severe tiredness
New or worsened muscle pain	No interference with activity	Some nterference with activity	Prevents daily routine activity	ER visit or Hospitalizstion for severe new or worsened muscle pain

New or worsened joint pain	No interference with activity	Some interference with activity	Prevents daily routine activity	ER visit or Hospitalisation for severe new or worsened joint pain
Fever (oral)	38.0 – 38.4°C	38.5 – 38.9°C	39.0 – 40.0°C	> 40.0°C

5.6 Patient diary

At the beginning of a study, study staff shall explain to each subject the importance of the diary and how the subject should record data within it. Site staff shall review the diary at each visit; deficiencies and attempts to correct these deficiencies should be noted in source records. Site staff must ensure that the diaries are returned at the time designated in the trial protocol. If a patient diary is not returned, the site should make several attempts to retrieve it. These attempts should be documented in the subject's medical record.

5.7. Study population and cohorts

Inclusion Criteria:
- Patients with a personal history of malignancy and/or currently undergoing antineoplastic therapy of any type (chemotherapy, immunotherapy, biologic therapy, targeted therapy, radiotherapy, hormonal therapy)
- Patient deemed by primary physician to be suitable to receive COVID-19 vaccination
- Age ≥ 21 years
- Informed consent has been provided

Exclusion Criteria:
- Patients with no personal history of malignancy

There will be a total of 3 main cohorts planned for this study.
1. Patients who have yet to receive a dose of COVID-19 vaccine but will be receiving one in the future
2. Patients who have received at least 1 dose of COVID-19 vaccine already
3. Patients who have provided signed consent to participate in this study before 15 September 2021

The following 5 subcohorts are planned for this study, recruiting a total of 400 patients with 80 patients in each subcohort:

1. Cancer patients not on active cancer therapy (this may include those who are at least 3 months post adjuvant chemotherapy on surveillance, those on adjuvant hormone therapy, or those on radiotherapy alone)
2. Cancer patients on tyrosine kinase inhibition
3. Cancer patients on immunotherapy. This includes patients on combination therapy with radiotherapy, chemotherapy, or targeted therapy.
4. Cancer patients on systemic chemotherapy
5. Cancer patients with haematological malignancies on active therapy

6. Data Analysis and Statistical Considerations

6.1 Data quality assurance

Data integrity will be assured by matching and verifying with the data source. The PI will be subjected to Health Sciences Authority and Domain Specific Review Board (DSRB) audits when needed.

6.2 Data entry and storage

A Research Electronic Data Capture (REDCap) database will be established specifically to collect the data for the registry. Each patient recruited into the study will be assigned a UPN, and the patient's biosamples will be labelled using the UPN, with no direct reference to the patient's other identifying information. Information from the source documents will be transcribed onto an electronic database that is password protected in a user designated and password protected computer in the Department. Personnel in the laboratory have no direct access to the clinical history database or other patient information. Information pertaining to the patient that arises from the research will not become part of the patient's medical record. All records will be kept for a minimum period of 6 years following the date of study closure according to International Committee on Harmonization of Good Clinical Practice guidelines, or longer as applicable per institution guidelines.

6.3 Determination of sample size

We expect to recruit 400 patients into this observational study over 1 year. There will be 80 patients recruited into each of the 5 subcohorts. This is based on an estimated seroconversion rate of 90% in our control group (patients without active cancer) and seroconversion of 65% in the other subcohorts, for a power of 90%. 3 primary comparisons will be made between subcohort 1 versus subcohort 2, subcohort 1 versus subcohort 3 and subcohort 1 versus subcohort 4, resulting in a split alpha of 0.0167.

Remaining comparisons would be secondary endpoints, and will not be included in the sample size calculation.

More subcohorts may be added to the study in future updates to the study protocol.

The efficacy as measured by immunogenicity and seroconversion rates at the aforementioned timepoints will be compared between subcohorts receiving different treatment modalities for malignancies and between patients receiving treatment for malignancies and patients not undergoing active treatment for malignancies. Demographic characteristics of participants in the subcohorts will also be controlled for.

Correlations will be drawn between the treatment modality administered for the malignancies. The differences in incidence, type and severity of adverse events will also be compared.

6.4 Statistical and analytical plan

All analyses will be performed using SPSS 26.0 or R V4.0.3 with statistical significance set at 2-sided $P < 0.05$.

Primary outcome:
The SARS-CoV-2 vaccine response at 12 weeks (Time frame: 12 weeks) and
Neutralising Anti-SARS-CoV-2 S-protein titre at 3 months as measured by GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits will be reported as n (%) with 95% confidence interval.

3 primary comparisons will be made between subcohort 1 versus subcohort 2, subcohort 1 versus subcohort 3, and subcohort 1 versus subcohort 4, resulting in a split alpha of 0.0167.

Secondary outcomes:
The above will also be reported for SARS-CoV-2 vaccine response at 3 to 8 weeks, 6 months and 12 months; for Neutralising Anti-SARS-CoV-2 S-protein titre at 6 and 12 months, SARS-CoV-2 vaccine safety in the studied population (Time frame: 12 months) and Incidence and severity of the adverse events after administration of the SARS-CoV-2 vaccine.

Comparison of the percentage differences across the 4 cohorts for numerical variables will be assessed using one-way analysis of variance when normality and homogeneity assumptions were satisfied, otherwise Kruskal Wallis will be used. For binary outcomes, chi-square or Fisher's Exact tests, and adjusting for demographic and relevant covariates in a Poisson regression with relative risk reported.

7. Informed Consent, Ethical Review, and Regulatory Considerations

7.1. Informed consent

No investigator may involve a human being in research unless the investigator has obtained the legally effective informed consent of the patient or the patient's legally authorised representative. An investigator shall seek such consent only under circumstances that provide the prospective patient or the patient's legally authorised representative sufficient opportunity to consider whether or not to participate, and minimise the possibility of coercion or undue influence. The information that is given to the patient or the representative shall be in a language understandable to the patient or representative.

Before implementing any study procedure, informed consent will be documented in the participant case histories and by the use of a written consent form approved by the DSRB, and signed and dated by the patient or the patient's legally authorised representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorised representative. The original, signed consent will be maintained by the investigator and available for inspection by the regulatory authority at any time. In obtaining and documenting informed consent, the investigator will comply with the Singapore Guideline for Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki.

The patient will be informed about the background and aims of the study. The patient will be told of her right to withdraw from the study at any time without any penalty with regards to the continuation of care at this institution and by the same physicians as she chooses. The patient will be told that tissue and blood samples obtained will be assigned UPN to ensure patient confidentiality.

7.2. Patient information

The responsible physician will inform the patient about the background and aims of the study. The patient will be told of his or her right to withdraw from the study at any time without any penalty with regards to the continuation of care at this institution and by the same physicians as he/she chooses. The patient will be told that tissue and blood samples obtained for genetic studies will be assigned UPN to ensure patient confidentiality.

7.3. Ethical review

This protocol and the associated informed consent documents will be sent to review and approval by the National Healthcare Group DSRB (domain B).

The investigator will supply the following to the study site's ethical review board(s):

- The study protocol

- Informed consent document
- Relevant curricula vitae

7.4. Regulatory considerations

Protection and privacy of the personal data of individuals are covered under the Personal Data Protection Act 2012. Patient medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The patient may request in writing that medical information be given to his/her personal physician.
The investigator/institution will permit direct access to source data and document by regulatory authorities. The access may consist of study-related monitoring, audits, DSRB reviews and regulatory authority inspection.

A REDCap database will be established specifically to collect data for the registry. Each patient recruited into the study will be assigned a UPN, and the patient's biosamples will be labelled using the UPN, with no direct reference to the patient's other identifying information. Information from the source documents will be transcribed onto an electronic database that is password protected in a user designated and password protected computer in the Department. Personnel in the laboratory have no direct access to the clinical history database or other patient information. Information pertaining to the patient that arises from the research will not become part of the patient's medical record. All records will be kept for a minimum period of 6 years following the date of study closure according to International Committee on Harmonization of Good Clinical Practice guidelines, or longer as applicable per institution guidelines.

Information collected includes demographic characteristics, cancer history and pathological information, past and present cancer treatment history of the study participant, date and type of COVID-19 vaccination, serologic response to vaccination as measured by blood draws, and adverse events to vaccination. Additional clinical records including post-vaccination diagnosis of COVID-19 infection, ICU admission and mortality will also be collected where applicable.

8. Publication

The research team will submit the study results for publication in peer-reviewed scientific journals. No personal health identifiers will be published.

9. Retention of Study Documents

Source documents

Original documents, data and records (e.g. medical records, raw data collections forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical study will be adequately prepared and maintained. These documents are designed to record all observations and other pertinent data for each participant enrolled in this clinical study. Source records will adequately reconstruct all data entered into the case report forms, which will be completed in English.

Archival of records

The investigators will retain records required to be maintained under this part for a period of 15 years following the completion or discontinuation of the study. The investigators will retain protocols, amendments, Institutional Review Board approvals, copies of the signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

10. References

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