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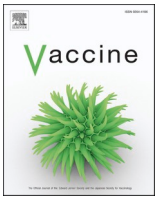

Comprehensive humoral and cellular immune responses to COVID-19 vaccination in adults with cancer

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ABSTRACT

Background: The COVID-19 pandemic has significantly impacted people with cancer. Initial vaccine studies excluded patients with malignancy. Immunocompromised individuals remain vulnerable to SARS-CoV-2, necessitating detailed understanding of vaccine response. The epidemiology of COVID-19 in Australia offered unique opportunities to study cancer populations with minimal community exposure to SARS-CoV-2.
Methods: SerOzNET prospectively examined previously unvaccinated patients with solid and haematological malignancies receiving up to five COVID-19 vaccine doses. Antibody response was measured by live virus neutralisation assay (neutralising antibody (NAb); positive titre ≥1:20; study primary endpoint) and commercial assay. T cell response was measured by cytometric bead array; positive defined as interferon gamma (IFN-γ) ≥10 pg/mL in response to Spike antigen. Patient and physician-reported adverse events were secondary endpoints.
Outcomes: 395 adults were enrolled prior to receiving mRNA vaccine (BNT162b2 = 347; mRNA-1273 = 1) or viral vector vaccine (ChadOx1-S = 43) for initial two-dose course, plus up to three additional doses. Median age was 58 years (range: 20–85); 60 % were female; 35 % had haematological malignancy, 2/395 (0.5 %) had

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baseline positive nucleocapsid antibody indicating prior SARS-CoV-2 exposure. NAb response post dose three was demonstrated in 84 % overall; 96 % of patients with solid cancers and 64 % with haematological cancer ($p < 0{\cdot}001$). Risk factors for non-response were haematological cancer and anti B-cell therapies. Some patients with haematological cancer seroconverted for the first time after the fourth or fifth dose. IFN-γ response was seen in many patients with haematological cancer who lacked NAb response. Serious adverse events were rare. COVID-19 infection occurred in 29 % with no deaths.

Interpretation: COVID-19 vaccination elicits B and T cell responses in patients with solid and haematological cancers, with an acceptable safety profile. A significant proportion of haematological cancer patients require >3 doses to elicit NAb, with many demonstrating T cell response, which may be an alternative pathway of immune protection.

1. Introduction

People with cancer were disproportionately impacted by the COVID-19 pandemic, with a case-fatality rate exceeding 25 % prior to availability of vaccination, and persistent worse outcomes compared to both non-cancer populations and people with cancer without SARS-CoV-2 infection [1–3]. Unfavourable outcomes of COVID-19 have been particularly noted in patients with haematological malignancies on active therapy, including higher rates of hospitalization, with a hazard ratio (HR) for death from any cause within four weeks of infection of 2·32 (95 % confidence interval (CI) 1·81–2·97) compared to healthy controls [3]. Patients with solid organ cancers also have increased risk of death (HR 1·43, 95 % CI 1·24–1·64) [3].

Optimal methods for assessment of COVID-19 vaccine correlates of protection for vulnerable populations remain undefined. Understanding the relative contributions of humoral and cellular immunity is particularly important in patients where one or more branches of the immune system is impaired by disease or therapy. Currently, neutralising antibody response (NAb) is the gold standard measure of response to vaccinations for most infectious diseases and correlates with protection against severe COVID-19 [4–6]. T cell response is also important, as demonstrated in antibody-deficient mice [7]. This is of particular interest for patients with inadequate antibody responses, including patients with B cell malignancies receiving anti-CD20 therapy [8].

The number and schedule of COVID-19 vaccine doses is particularly relevant to patients with cancer. Previous studies predominantly focussed on response to two-dose vaccination courses and were mainly performed early in the pandemic, in the context of overwhelming community transmission [9–12].

In contrast, the SerOzNET study reported here is a large prospective cohort study of immune responses to COVID-19 vaccination in patients with cancer, all but two of whom were infection-naïve. It allows for important and unique observations being conducted in the particular epidemiological context in Australia during the pandemic, where there was negligible community transmission in 2020–2021, followed by effective primary vaccination taken up by >90 % of the population by late 2021, then easing of public health restrictions and widespread community transmission (Supplementary Fig. 1). Thus, results are pertinent to vaccine induced protection and hybrid immunity with minimal infection exposure at baseline. Furthermore, this study adds significant detail to the limited studies in patients with cancer receiving four or more vaccinations. The comparison of antibody and T cell response additionally adds important data to shape ongoing vaccine policy.

2. Methods

2.1. Trial design and setting

The original protocol of this multicentre, single arm prospective study is published [13]. The protocol (Supplementary Appendix 1) was subsequently modified to include doses three, four, and five, and comply with changing Australian Government recommendations (Supplementary Fig. 1) [14].

The study was centrally approved by Monash Health Human Research Ethics Committee (RES-21-0000-337A), with local ethics approval at sites, and registered on Australia and New Zealand Clinical Trial Network Registry (ACTRN: 12621001004853). All participants provided written informed consent. Data were managed using REDCap® electronic data capture tool housed at Monash University, Melbourne [15,16].

Enrolment occurred from 26 June 2021 to 31 December 2022 at three Australian tertiary hospitals: Monash Health, Melbourne; Royal Perth Hospital, Perth; St Vincent's Hospital, Sydney. At trial commencement, patients over 60 years could receive either the available mRNA vaccine BNT162b2 or viral vector vaccine ChAdOx-1-S; patients under 60 were recommended only mRNA vaccine. Later in the study, mRNA-1273, NVXCoV-237 and elasomeran/davesomeran became available.

2.2. Eligibility

Participants reported here were aged over 19 years, COVID-19 vaccine naïve and belonging to one or more of the following cohorts: confirmed solid or haematological cancer currently receiving systemic anticancer therapy (chemotherapy, targeted or hormonal therapy, immunotherapy or combinations); completed cytotoxic chemotherapy within 12 months; or haematological cancer associated with immunocompromise regardless of treatment. Prior SARS-CoV-2 infection was not an exclusion but was rare. Persons unfit for serial blood collection,

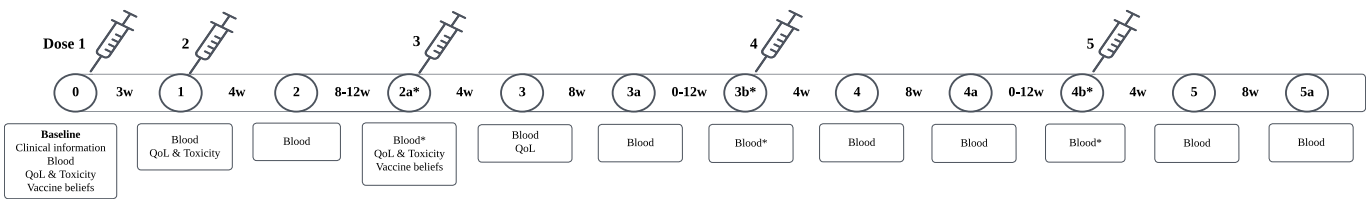

Fig. 1. SerOzNET study schema.
Legend: Numbers represent timepoints during study. QoL was collected before and 1 week after dose1, 2 & 3; patient-reported toxicity was collected 1 week after doses 1, 2 & 3; Vaccine beliefs were measured using Oxford Confidence and Complacency Scale; *Additional blood tests were taken at time of next vaccination if previous sample was>6w prior.
Abbreviations: w = weeks; QoL = Quality of Life;

not covered by Australia's Medicare program, prognosis of less than 12 months, or pregnant, were ineligible.

2.2.1. Role of funding source

The study funders were not involved in study design, collection, analysis, interpretation of data, or in writing of the report, or the decision to submit the paper for publication.

2.3. Study procedures

The study schema (Fig. 1) details assessments, which continued until three months after last vaccination, or six months if only two doses received.

Clinical measurements

SARS-CoV-2 infection: Participants were asked every visit if they had been diagnosed with COVID-19. Clinical details were recorded from patient reports and medical records.

Safety assessments: These are described in detail elsewhere (preprint) [17]. Briefly, patient reported adverse effects (AE) were collected by electronic survey seven days after the first three vaccine doses and graded according to Patient Reported Outcomes Common Terminology Criteria for Adverse Events version 1·0 (PRO-CTCAE v1·0) [18]. Investigator reported AE were collected from medical records in two time periods: baseline to one month post dose two, and dose three to one month post dose three.

Laboratory methods

Blood collection: Approximately 45 mL of peripheral blood was collected into serum-separating tubes (SST) and acid citrate dextrose (ACD) tubes and processed within four hours. Serum was extracted from SST following centrifugation. Peripheral blood mononuclear cells (PBMC) were extracted from ACD tubes via density gradient centrifugation using SepMate tubes with Lymphoprep density gradient media (STEMCELL Technologies, Vancouver, Canada), according to manufacturer instructions. Extracted samples were stored at -80 °C for batch processing.

Serological response: NAb were determined via high content fluorescent live SARS-CoV-2 neutralisation assay against early-2020 clade (D614G for initial 282 samples until October 2021, then A2.2) SARS-

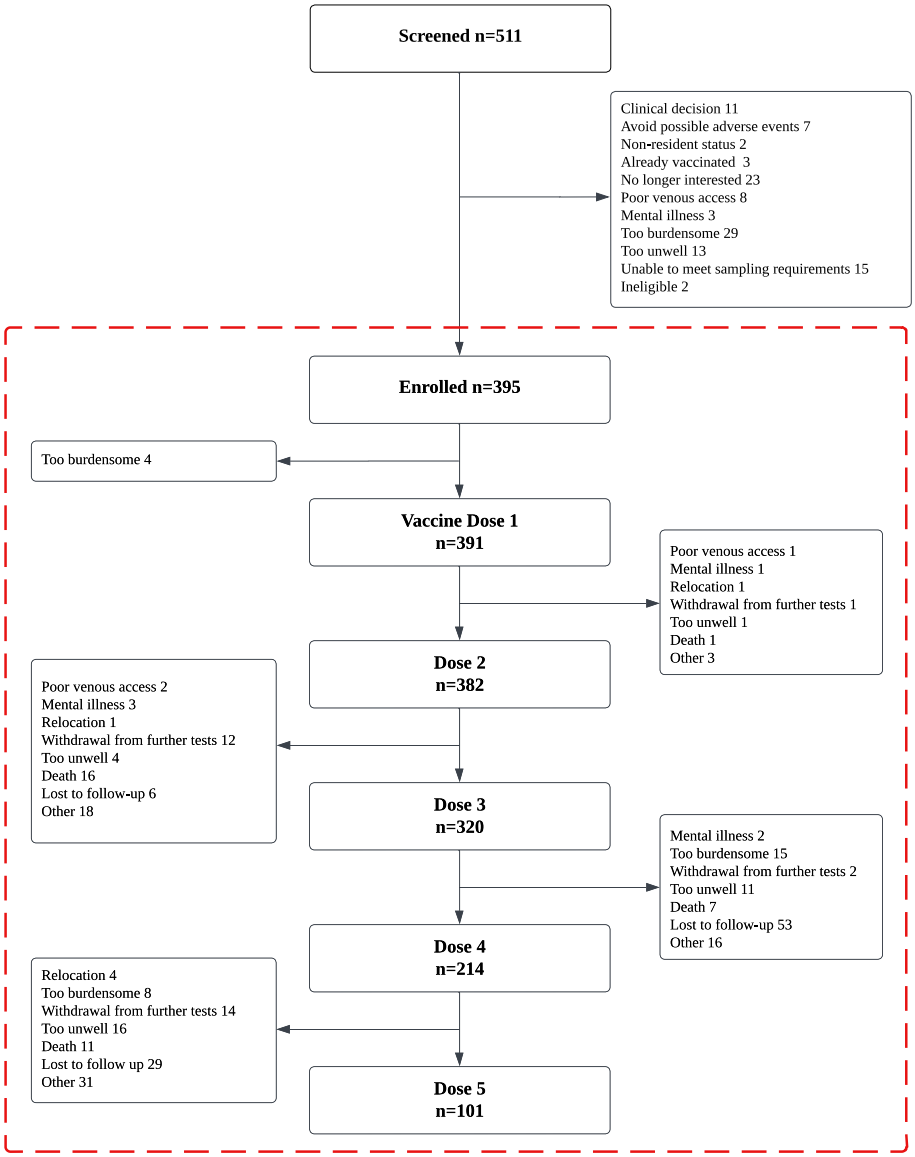

Fig. 2. CONSORT diagram.
Legend: Dotted line represents patients included in SerOzNET study.Other: received vaccination elsewhere without having blood draw; travelling; recent COVID-19 infection so waiting for recovery.

CoV-2 viral cultures as described [19–21]. Response was defined as titre ≥1:20 and grouped as low (1:20–1:40), moderate (>1:40–1:80), high (>1:80–1:320) and very high (>320), based on quartiles of response range across all timepoints. Nucleocapsid antibody titre was quantified by Architect SARS-CoV-2 IgG chemiluminescent microparticle assay (Abbott Diagnostics Division, Illinois, USA), measured as an index (chemiluminescent signal: calibrator). Values ≥1·4 were interpreted as positive, as per manufacturer instructions. Antibodies to Spike protein (anti-S IgG) were measured by Architect AdviseDx SARS-CoV-2 IgG II assay (Abbott Diagnostics Division, Illinois, USA) as per manufacturer instructions and reported as arbitrary units (AU) per millilitre (mL), with positive being ≥50 AU/mL.

2.3.1. T cell response

PBMC were phenotyped using flow cytometry to assess the proportion of live $CD45^+$ $CD4^+$ and $CD8^+$ T cells and $CD19^+$ B cells. SARS-CoV-2-specific immunity was assessed by incubating total PBMC with SARS-CoV-2 Spike peptide pools encompassing the glycoprotein C- and N-terminus regions (Mimitopes, Victoria, Australia) as published [22]. Control conditions included negative (no peptide) and two positive control stimulations: Phytohaemagglutinin (PHA) and a mixed peptide pool containing Epstein-Barr virus and Cytomegalovirus peptides. Following overnight incubation, tissue culture supernatants (TCSN) were collected from each individual stimulation condition and stored at −80 °C degrees. A cytometric bead array (CBA) was used to assess TCSN and to quantify the production of T-cell cytokines including interferon gamma (IFN-γ). CBA was performed using a Flex-set (BD Biosciences, Franklin Lakes, NJ, USA). Flow sample acquisition was performed on a BD LSRFortessa machine with FACSDiva software (BD Biosciences, Franklin Lakes, NJ, USA). Post-acquisition analysis was performed using FCAP array (BD Biosciences, Franklin Lakes, NJ, USA). IFN-γ was selected as the most informative cytokine to define response [23,24]. A positive result was defined as IFN-γ production in response to Spike antigen stimulation of ≥10 pg/mL. For pragmatic reasons related to labour intensive procedures, only a randomly selected subset was analysed after timepoint three, constituting 32 % and 58 % of samples from patients with solid and haematological cancer respectively. Results were grouped into low (10–40 pg/mL), moderate (>40–120 pg/mL), high (>120–200 pg/mL) and very high (>200 pg/mL), based on quartiles of response range across all timepoints.

2.4. Study endpoints

The original primary endpoint was the proportion of patients with positive NAb response one month after two vaccine doses. After updated government recommendations to a minimum of three doses for the healthy population, the protocol and statistical analysis plan were revised to the more relevant primary endpoint of the proportion of patients with positive NAb response one month after three vaccine doses.

Secondary endpoints were: quantification of serological and immunological responses after each vaccine dose; comparison of response with healthy controls; comparison between cohorts with different cancer diagnoses and treatment; detailed QoL and adverse events. Exploratory outcomes were: patterns of response over time; effect of anti B-cell therapy on response.

2.5. Statistical methods

Sample size was based on serological response and designed to have >80 % power (β of 0·80) to detect at least a 10 % lower NAb seroconversion rate in any defined clinical cohort (compared with assumed non-cancer population incidence of 95 %) with 95 % confidence (α of 0·05), as outlined in the statistical analysis plan (Supplementary Appendix 2).

Anti-cancer treatment was recorded at enrolment. Steroid doses were considered as none (including physiological replacement), low (short course premedication for allergy or emesis) and high (daily doses >10

Table 1
Demographic and baseline characteristics.

	All $N = 395$	Solid cancer $N = 257$	Haematological cancer $N = 138$
Age in years: median (range)	58 (20–85)	57 (20–83)	61·5 (20–85)
Female (%)	236 (60)	170 (66)	67 (49)
Ethnicity* (%)			
Oceanian	27 (7)	21 (8)	6 (4)
European	250 (63)	148 (58)	102 (74)
African and Middle Eastern	18 (5)	10 (4)	8 (6)
Asian	86 (22)	68 (26)	18 (13)
American**	12 (3)	10 (4)	2 (2)
English spoken at home (%)	295 (75)	176 (69)	119 (87)
BMI (kg/m^2) median [IQR]	26·9 (24·2–31·0)	27·3 (24·6–32·2)	26·3 (23·6–29·2)
ECOG (%)			
0	238 (62)	158 (62)	80 (61)
1	129 (33)	86 (34)	43 (33)
2, 3	20 (5)	11 (4)	9 (7)
Cancer origin (%)			
Gastrointestinal		60 (23)	–
Thoracic		19 (7)	–
Breast		84 (33)	–
Gynaecologic		35 (13)	–
Genitourinary		32 (12)	–
Other solid malignancy***		27 (11)	–
Lymphoma		–	74 (54)
Myeloma		–	25 (18)
Lymphoid Leukemia		–	25 (18)
Myeloid Leukemia		–	10 (7)
Other hematologic malignancy		–	3 (2)
Stage** **** (%)**			
I	33 (9)	18 (7)	15 (12)
II	61 (16)	46 (18)	15 (12)
III	67 (17)	49 (19)	18 (14)
IV	179 (47)	140 (54)	39 (31)
Not applicable◆	44 (12)	3 (1)	41 (32)
Treatment intent (%)			
Palliative	189 (48)	141 (55)	48 (35)
Curative	98 (25)	19 (7)	79 (57)
Adjuvant	86 (22)	83 (32)	3 (2)
Neoadjuvant	14 (4)	14 (5)	0 (0)
Surveillance■	7 (2)	0 (0)	7 (5)
Type (%)			
Chemotherapy	152 (38)	117 (46)	35 (25)
Chemotherapy + immune checkpoint inhibitor	8 (2)	8 (3)	0 (0)
Chemotherapy + anti-CD20	38 (10)	0 (0)	(28)
Immune checkpoint inhibitor without chemotherapy	41 (10)	41 (16)	0 (0)
Anti-CD20 without chemotherapy	15(4)	0 (0)	15 (11)
Hormone therapy	55 (14)	55 (21)	0 (0)
Targeted therapy only▲	56 (14)	27 (12)	29 (21)
Allogeneic stem cell transplant	7 ((2)	0 (0)	7 (5)
Supportive therapy only▲▲	23 (6)	9 (4)	14 (10)
Steroid use at baseline•(%)			
Nil	231 (59)	166 (65)	65 (47)
Low dose	124 (32)	81 (32)	43 (31)
High dose	39 (10)	10 (4)	29 (21)

Legend: *Patient reported, classified using Australian Standard Classification of Cultural and Ethnic Groups (Australian Bureau of Statistics 2019); ** includes North, Central, South America ***cancers of head and neck ($N = 12$), brain ($N = 2$), skin ($N = 5$), connective tissue (N = 1); neuroendocrine ($N = 7$); ****Using American Joint Committee on Cancer (AJCC) Staging Manual, 7th Edition; ◆Alternative system used for this malignancy; ■ Patients with low grade haematological malignancy not requiring systemic treatment, ▲Includes 9 patients on anti-B cell agents (Bruton Tyrosine Kinase (BTK) inhibitors (7),

blinatumomab (2), ▲▲Includes bone modifying agents; •Steroid doses: Nil = none or physiological replacement dose; Low dose = short course e.g. premedication for allergy or emesis; high dose = daily supraphysiologic doses (>10 mg prednisolone equivalent) or pulsatile high dose steroids as per haematological cancer treatment regimens.
Abbreviations: N = number; BMI = body mass index; IQR = Interquartile range; ECOG = Eastern Cooperative Oncology Group performance status.

mg prednisolone equivalent or pulsatile high dose steroids in treatment regimens).

Statistical analyses were conducted using R (v4.3, Vienna, Austria). Patient characteristics and AEs were summarized using descriptive statistics. Efficacy analyses included all enrolled patients receiving at least one vaccine dose. NAb and quantitative anti-S IgG responses and T-cell response by IFN-γ production were compared between patients by age, sex, Eastern Cooperative Oncology Group performance status (ECOG), and treatment type using *t*-tests, ANOVA, and multivariate logistic regression. Multivariate logistic regression of factors contributing to response was pre-planned to be undertaken on results from one month post dose 3, in line with the primary endpoint. Serological response in patients who became infected with SARS-CoV-2 compared to those uninfected was also compared using these methods. Safety analyses included all enrolled patients who received at least one vaccination and completed at least one PRO-CTCAE survey, or any person with a medical safety case report form.

3. Results

3.1. Patient population

Patients were enrolled between June 2021 and December 2022. Of 395 patients consented, 391 received an initial vaccine dose, with at least three doses received by 320 participants (81 %) and four and five doses received by 214 (54 %) and 101 (26 %) respectively (Fig. 2). For doses one and two, 348/391 (89 %) of participants received two doses of an mRNA vaccine (347 BNT162b2, 1 mRNA-1273), and 42/391 (11 %) received ChadOx1-S. From dose three, 97 % received BNT162b2 (618 doses; Supplementary Table 1). The median interval between doses one and two was 21 days, doses two and three 70 days, doses three and four 95 days, and doses four and five 125 days. Clinical and disease characteristics are shown in Table 1. Two patients had positive baseline nucleocapsid antibody indicating prior SARS-CoV-2 exposure, of whom only one had a known prior infection. Fifty percent (198/395) of patients were on cytotoxic chemotherapy, alone or in combination with other agents, 49 (12 %) were on immune checkpoint inhibitors with or without chemotherapy, and 53 (13 %) received anti-CD20 antibodies.

3.2. Neutralising antibody response

After the first vaccine dose, 70/227 (31 %) of patients with solid cancer and 12/116 (10 %) of patients with haematological cancer had positive NAb response ($p < 0.0001$). One month after the second dose, 192/229 (84 %) of patients with solid cancer and 48/111 (43 %) of patients with haematological cancer had positive NAb response ($p < 0{\cdot}001$). This increased to 96 % and 64 % respectively, after dose three ($p < 0{\cdot}001$) and continued to rise with subsequent doses (Fig. 3). After dose four, 118/120 (98 %) of patients with solid cancer had positive NAb, all of whom had seroconverted after dose three. By contrast, 51/72 (78 %) of patients with haematological cancer had positive NAb after four doses, five of whom for the first time. Of these, four had received prior rituximab (anti-CD20 therapy), with mean time from cessation of 12 months, and one patient had received ibrutinib (Bruton Tyrosine Kinase (BTK) inhibitor), ceased eight months prior.

Five doses were received by 57 patients with solid cancer and 44

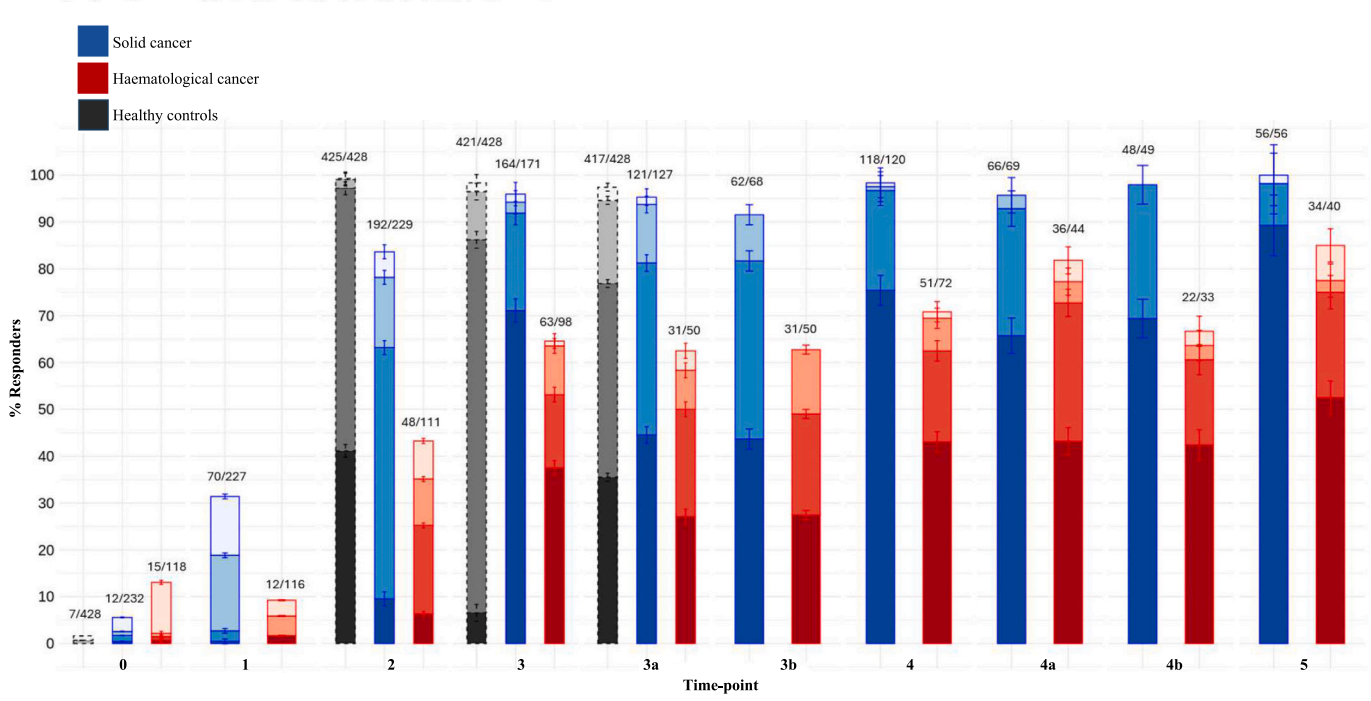

Fig. 3. Neutralising antibody response over time.
Legend: Neutralising antibody to SARS-CoV-2 Clade A.2.2 measured at various time points as per study schema (Fig. 1). Absolute values are given on top of each bar (numerator is absolute number of responders; denominator is total number of samples analysed. Depth of colour (light to dark) reflects absolute value categorised into levels of low (1:20–1:40), moderate (>1:40–1:80), high (>1:80–1:320), very high (>320) based on quartiles of response range across all timepoints. Healthy controls were enrolled in a separate parallel study (The Australian Vaccine, Infection and Immunology Collaborative Research cohort (VIIM)). Samples were collected at analogous timepoints to those in the SerOzNET study and analysed for neutralising antibody response in the same laboratory using the same methods as for patients enrolled in the SerOzNET study.

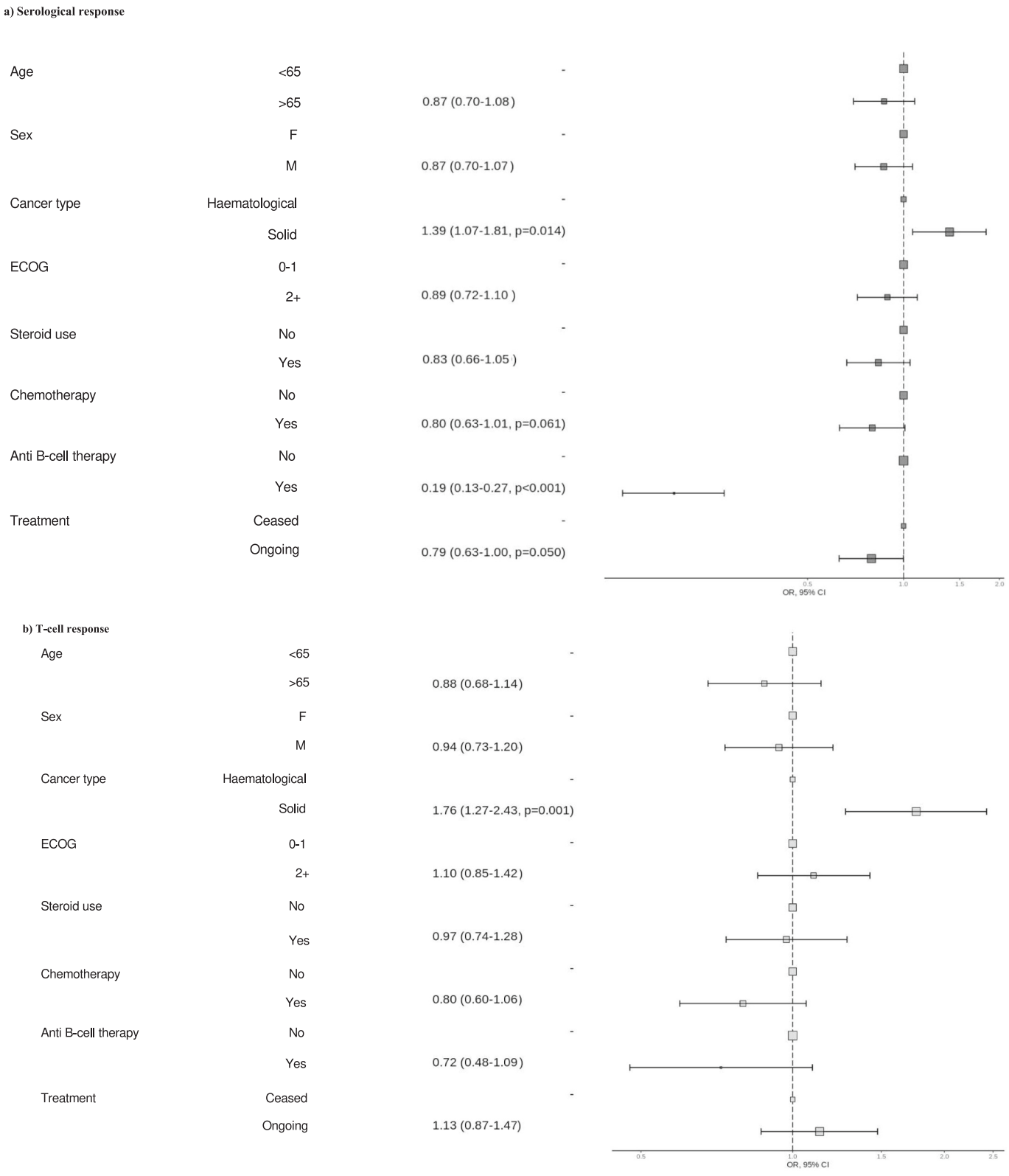

Fig. 4. Multivariate analysis for predictors of response following 3 doses of vaccine.
a) Serological response.
b) T cell response.
Legend: Serological response was defined as neutralising antibody titre ≥1:20 to early clade (D614G or A2.2) SARS-CoV-2 live virus after dose 3. T-cell response defined as IFN- $\gamma\gamma$ production ≥10 pg/mL in response to wild-type Spike antigen. Treatment type documented at time of enrolment. Steroid use was defined as "yes" for patients on daily doses >10 mg prednisolone equivalent or pulsatile high dose steroids in treatment regimens.
Abbreviations: F = female; M = male; ECOG = Eastern Cooperative Oncology Group Performance Status Score.

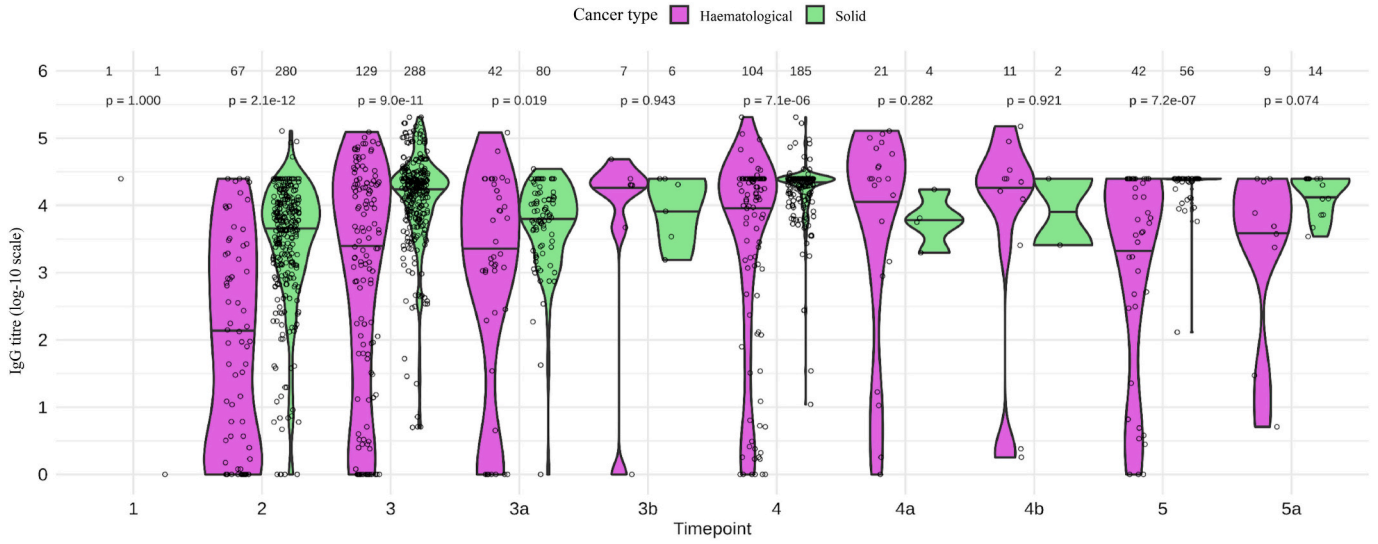

Fig. 5. Anti-S IgG quantitative antibody response by cancer type.
Legend: Antibody response was measured by commercial assay (Anti-S IgG; Architect AdviseDx SARS-CoV-2 IgG II, Abbott Diagnostics) according to manufacturer instructions. Circles reflect individual titres. Total number of samples tested at each timepoint are recorded above the plots. Timepoints defined as per study schema (Fig. 1).

with haematological cancer, with NAb results available for 56 and 40 patients respectively. All 56 patients with solid cancer had ongoing positive NAb response, however of the 34/40 patients with haematological cancer with positive NAb, 4 seroconverted for the first time. Three of these had been on rituximab at or just prior to initial vaccination but then ceased. The mean time from cessation to dose five was 10·3 months. The remaining patient received continuous investigational BTK inhibitor and B-cell-lymphoma-2 (Bcl-2) inhibitor, and had a mild COVID-19 infection just prior to dose five. Of all patients receiving anti B-cell therapies at enrolment (anti-CD20 agents, BTK inhibitors, blinatumomab, Bcl-2 inhibitors), NAb non-response was noted in 35/54 (65 %) after three doses, 21/41 (51 %) after four doses and 5/22 (23 %) after five doses.

Pre-planned multivariate logistic regression at one month post dose 3

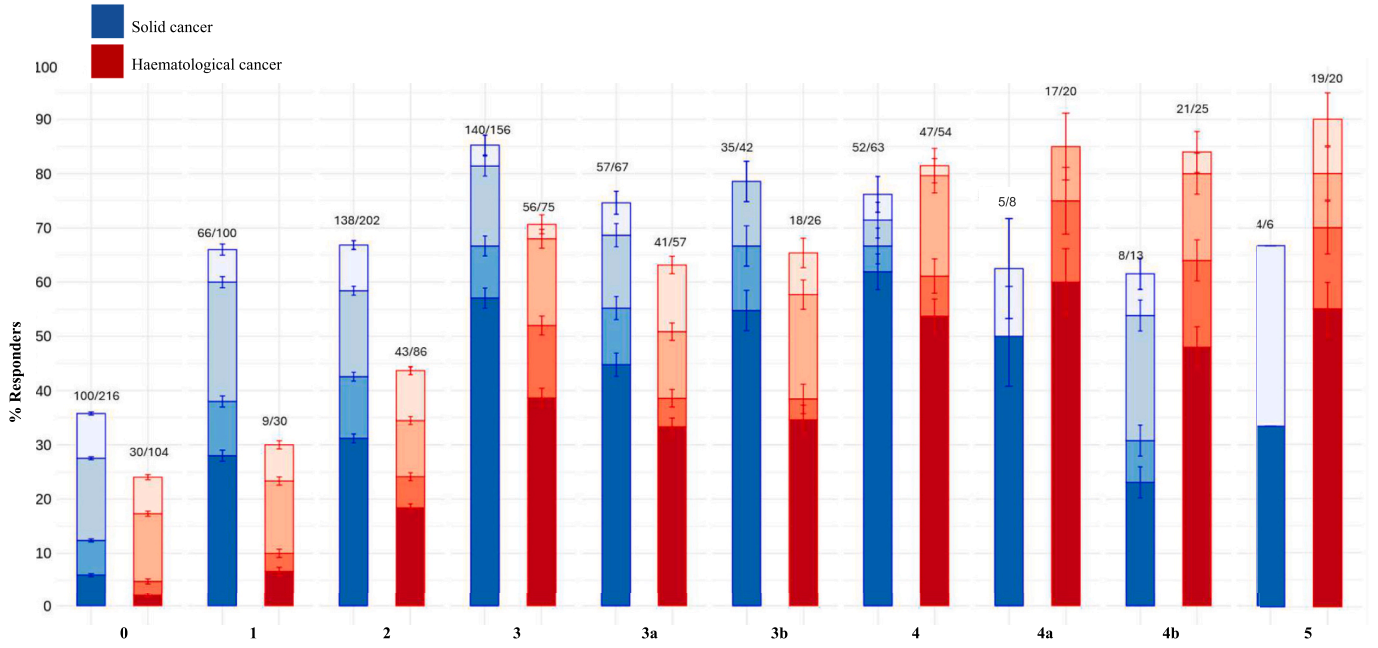

Fig. 6. T-cell response over time.
Legend: T-cell response by interferon-$\gamma\gamma$ production in response to Spike antigen peptide stimulation, with positive response defined as ≥10 pg/mL. Absolute values are given on top of each bar (numerator is absolute number of responders; denominator is total number of samples analysed). Depth of colour (light to dark) reflects absolute value categorised into levels of low (10–40 pg/mL), moderate (40–120 pg/mL), high (120–200 pg/mL), very high (>200 pg/mL) based on quartiles of response range across all timepoints. Timepoints defined as per study schema (Fig. 1).

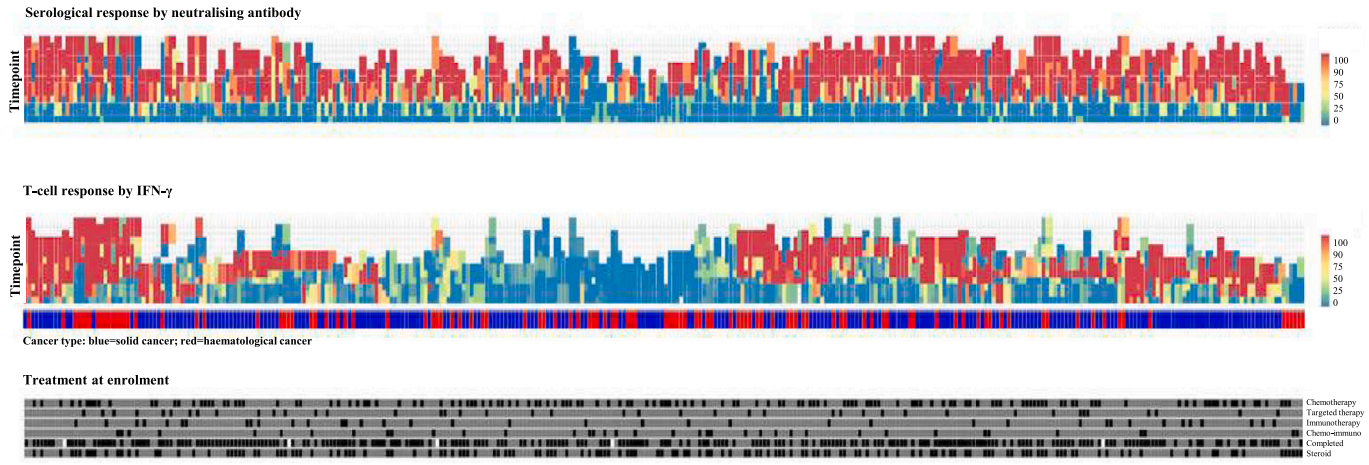

Fig. 7. Comparison of individual Serological and T cell responses to serial vaccination.
Legend: Heatmap generated by unsupervised clustering of serology response by neutralising antibody to early clade (D614G or A2.2) SARS-CoV-2 live virus. T cell response was measured by IFN-γ production in response to wild-type Spike antigen. Each column represents an individual patient, timepoints increase from bottom to top of graph. Colours in the response graphs represent normalised response, with blue being nonresponse and red being highest response category (>200 pg/mL for IFN-γ and > 1:80 for NAb. Treatment of each patient at study enrolment is indicated by black = yes, grey = no, white = missing for each type. Abbreviations: IFN-γ = interferon gamma; NAb = neutralising antibody; Chemo-immuno = combined chemotherapy and immunotherapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

demonstrated greater odds of NAb response in patients with solid compared with haematological malignancies (odds ratio (OR) 1·39; 95 % CI 1·07–1·81; $p = 0·014$), and lower odds of response for patients on anti B-cell therapy (OR 0·19, 95 % CI 0·13–0·27, $p < 0·001$) and on any treatment compared to having completed therapy (OR 0·79, 95 % CI 0·63–1·00, p = 0·050). There was a non-significant trend toward reduced response in patients on cytotoxic chemotherapy (OR 0·80, 0·63–1·01, p = 0·061). Age, gender, performance status and steroid use were not predictive of NAb response (Fig. 4a).

3.3. Quantitative anti-S IgG response

Quantitative anti-IgS was measured to assess consistency of clinical associations compared to NAb response, and correlation between NAb response and the commercial assay, as this test is readily available and reproducible.

Median quantitative anti-S IgG titre measured by commercial assay increased after each dose in all patients until after dose four, with no subsequent increment (Fig. 5). Where patients had a delayed interval between doses (>3 months), comparison of results taken one month after previous vaccination with the extra sample at time of the delayed dose showed slight waning of median anti-S titre.

Univariate comparisons of key patient groups are shown in Supplementary Figs. 2 to 5. The anti-S titre was lower in patients older than 65 after two vaccinations (median 4365 AU/mL vs.1778 AU/mL, $p = 0·004$), but this difference did not persist. Patients on anti B-cell therapies had lower anti-S titres than other patients with haematological cancer. Anti-S titre was lower in patients on steroids at several timepoints. For patients with solid cancers, no effect of cytotoxic chemotherapy was seen. This was not assessed for patients with haematological cancer because cytotoxics were frequently (46 %) combined with anti B-cell therapy.

3.4. Correlation of NAb and anti-S IgG

NAb results generated using gold standard viral co-cultures correlated well with commercial testing ($R^2 = 0·66$). Low-level binding antibodies were seen at baseline, with positive commercial anti-S noted in some patients with negative NAb. After two and three doses respectively, 90 % and 96 % of patients with positive anti-S IgG also had positive NAb (Supplementary Fig. 6).

3.5. T cell responses

The proportion of IFN-γ responders after each dose is shown in Fig. 6. IFN-γ response to Spike antigen was detectable at baseline in 100/216 patients with solid cancers and 30/104 patients with haematological cancers, likely due to cross-reactivity with circulating coronaviruses. However, the intensity of response at baseline (median IFN- γ in responders 48 pg/mL) was lower than post-vaccination, where the majority of patients had high or very high response (median IFN-γ in responders at all later timepoints 210 pg/mL). After three doses, 140/156 (90 %) patients with solid cancer and 56/75 (75 %) with haematological cancers had positive IFN-γ response, with little increase after further doses.

Multivariate analysis demonstrated greater odds of IFN-γ response one month after dose three in patients with solid compared to haematological cancer (OR 1·76; 95 % CI 1·27–2·43; $p = 0·001$). Age, gender and treatment were not predictive of T-cell response (Fig. 4b).

3.6. Correlating B and T cell response

To explore the interaction between B and T cell responses, a heatmap analysis using unsupervised clustering by NAb response demonstrated that the majority of patients developed strongly positive responses in NAb and IFN-γ after sequential vaccinations, however distinct groups

Table 2
Patient and investigator reported adverse effects.

Patient-reported adverse effects	Vaccine Dose		
	1	2	3
Any local symptom n/N (%)	240/369 (65)	245/365 (67)	196/286 (69)
Any severity, most frequent Pain at injection site	224/371 (60)	229/367 (62)	180/288 (63)
Severe or serious, most frequent Pain at injection site	3/371 (<1)	5/367 (1)	7/288 (2)
Systemic symptom n/N (%)	178/353 (50)	217/351 (62)	159/273 (58)
Any severity, most frequent			
Fatigue	70/369 (19)	102/367 (28)	–
Muscle pain	–	–	68/282 (24)
Severe or serious, most frequent Fatigue	15/369 (4)	29/367 (8)	26/285 (9)
Investigator reported SAE n/N (%)			
Grade 1–2	9 (3)		0
Grade 3–4	34 (9)		8 (3)
Grade 5	2 (1)		0
SAE, relation to vaccine n/N (%)			
All	45/382 (12)		8 (3)
Unlikely	41/45 (91)		8/8 (100)
Possible	4/45 (9)		0
Definite	0		0
Thrombotic event n/N (%)			
All	5/382 (1)		0
Deep vein thrombosis	1*		0
Pulmonary embolism	1*		0
Superficial vein thrombosis	2*◆		0
Cerebrovascular event	1*		0

Legend: Adverse effects reported by patients 1 week after vaccine dose 1,2 & 3; and by investigators for the period from baseline until 1 month post dose 2, and from dose 3 until 1 month post dose 3. Patient events were recorded with the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE®) version 1.0 questionnaire whilst Investigator reported events used Common Terminology Criteria for Adverse Events version 5.0. Not all questions needed to be answered. Relation to vaccine was determined by the treating team; n = number reporting symptom; N = total number of responses for that question; SAE = Serious Adverse Event; *after BNT162b2 ◆after ChAdOx1-S.

with deficient responses in one or both parameters can be identified (Fig. 7). Amongst patients with solid cancer, both NAb and IFN-γ were positive in most patients after doses three to five, however in patients with haematological cancer, a significant proportion of NAb non-responders had positive IFN-γ (Supplementary Table 2).

3.7. Impact of SARS-CoV-2 infection

During the study, 116 (29 %) patients acquired COVID-19 (Supplementary Table 3). The median time from first vaccine until infection was 7·3 months, with median of three doses prior to infection. Only five patients required hospitalization due to COVID-19, none required oxygen or intensive care and none died. At the timepoint prior to their infection three of these patients had negative NAb and two had low-positive titres; two had absent IFN-γ response (Supplementary Table 4).

The pattern of serological response following infection shows higher quantitative IgG titres at all timepoints compared to non-infected patients who had received the same number of vaccine doses (Supplementary Fig. 7). Of 109 patients with a NAb result prior to infection, 22 (20 %) had negative titres. Of these, eight of 16 with available results seroconverted at next testing post infection. For IFN-γ, of 79 results available prior to infection, 30 were negative, from which seven of 21 with available results converted to positive at next test. Seven of eight patients with persistently negative NAb and 12 of 14 patients with persistently negative IFN-γ post infection had haematological malignancies.

3.8. Adverse events and QoL

Patient and physician reported AEs are presented in Table 2. Detailed AE and QoL data have been analysed, showing the majority of patients reported localized symptoms, without QoL change (results presented separately, preprint) [17]. Only four of the 53 (8 %) SAE reported were assessed as possibly attributable to vaccination; none were definitively attributable.

4. Discussion

This large cohort study provides detailed immune assessment highlighting benefits of serial SARS-CoV-2 vaccination in patients with solid and haematological malignancies and adds important data to previous studies, which were conducted under significantly different pandemic conditions (Table 3) [9–12,25–30]. For the majority of patients with solid cancers, three doses appeared protective, while those with haematological cancer benefited from additional doses at short interval. Studies in immunocompetent people show waning of SARS-CoV-2 immunity over time, periodic booster doses will be required for both groups [31,32].

The study identifies subgroups who did not respond to serial vaccine doses. In particular, 65 % of patients receiving B-cell depleting therapies did not develop an antibody response after a three-dose primary course, consistent with others' findings [28,29,33,34]. However, most of these (71 %) had T cell response as measured by IFN-γ, the hallmark of T-helper-1 cell activity and a central signalling molecule in adaptive immunity, which may confer a degree of immune protection [8,35]. Additionally, continued vaccination up to five doses was useful for initial non-responders in the haematological cancer population, with a small but relevant group seroconverting late, coinciding with longer time after completion of B cell suppressing therapy, confirming others' observations [29]. Patients previously on anti-CD20 agents did not respond despite serial doses until more than ten months after cessation, suggesting other means of protection should be reinforced in the year after treatment and additional booster vaccinations should be given after this period.

The role of antibody testing in routine care remains controversial, incurring costs and lacking current guidelines on adaptation of vaccination schedules based on results. However, for patients with significant vulnerability to COVID-19, selective testing may be useful to individualise care. Of importance here is the demonstration of strong correlation between a commercial quantitative antibody test and presence of neutralising antibodies measured in a gold standard testing laboratory. One concern with commercial tests however is their coverage of the evolving COVID-19 variant landscape.

T cell response likely plays a crucial part in vaccine-induced immunity, both in patients with suboptimal humoral immune responses, and in the context of novel variants; where T cell response is preserved despite antibody response being evaded by changes in the spike protein, providing an alternative means of protection [36]. In SerOzNET, the proportion of T cell responders was marginally higher in solid compared to haematological cancer patients after three vaccine doses, with equivalence after four doses.

T cell functional assays are labour intensive, hence are frequently omitted, or performed only in subsets of patients, including in our study from dose four onward. All samples are stored in a biobank, available for further research. Validation of simpler methods to assess T cell response, such as assessment of activated T cell subsets, will allow larger scale assessment [28].

An important result from this study is that hybrid immunity resulted in higher antibody titres than exclusive vaccine induced immunity. In healthy healthcare workers, hybrid immunity provided similar protection to booster vaccination against subsequent infection [37]. This result gives some reassurance to patients with cancer although clearly, avoidance of infection is preferable.

Table 3
Major studies of COVID-19 vaccine response in patients with cancer.

Study acronym, reference	Type of cancer	Number of patients	Vaccine doses	Vaccine type	Antibody measurement	T-cell measurement	Main Findings
VOICE (9)	Solid; patients on steroids excluded	551	2	mRNA-1273	BAb	Spike-specific IFN-γ production assessed in a subset (n = 175)	▪ Detectable BAb response in >97 % after 2 doses ▪ T-cell response in 53–67 %
CAPTURE (10)	Solid & Haematological	585	2	BNT162b2, ChadOx1-S	NAb NAb to VoC	Spike-specific IFN-γ production	▪ NAb in 59 % haematological and 85 % solid cancer patients ▪ T-cell response for both in 79 %
CANVAX (11)	Solid & Haematological	762	2	mRNA-1273, BNT162b2, Ad26CoV2-S	NAb QAbT	–	▪ Reduced NAb in patients on chemotherapy ▪ Primary endpoint was comparison of vaccine type
Vax-On (12, 25)	Solid	372	2–3	BNT162b2	QAbT	–	▪ >89 % seroconversion after 2 doses
VOICE follow up (26)	Solid, only if suboptimal response to primary course	48	3	mRNA-1273	BAb BAb to VoC	Spike-specific IFN-γ production	▪ No non-responders after 3 doses ▪ T-cell response increased after dose 3
CAPTURE follow up (27)	Solid & Haematological	199	3	BNT162b2	NAb NAb to VoC	Spike-specific IFN-γ production	▪ NAb detectable after dose 3 in previous non responders ▪ T-cell response increased after dose 3
CAPTURE follow up 2 (28)	Haematological	80	4	BNT162b2	NAb NAb to VoC	Activated T- cell subsets	▪ More responders after 4 doses ▪ T-cell response increased after dose 4
COBRA KAI (29)	Haematological	414	4	RNA-1273, BNT162b2	NAb BAb NAb to VoC:	–	▪ 19 % did not seroconvert after 4 doses ▪ More responses to dose 3 and 4 if B-cell compartment recovering post treatment
Ehmsen et al. (30)	Solid & haematological	395	4	mRNA-1273	QAbT	–	▪ After dose 4, all solid cancer patients seroconverted versus 87 % haematological patients

Abbreviations: BAb = Binding antibody; NAb = Neutralising antibody; IFN-γ = Interferon gamma; VoC = Variant(s) of concern; QAbT = Quantitative antibody titre.

There was minimal effect of other influences on immune response, including age, steroids, and cytotoxic chemotherapy. These may have a small impact on response to dose one and two (reduced anti-S IgG titre noted), however the effect was minimised by serial dosing and eclipsed on multivariate analysis by the much larger effect size of anti B-cell therapy and haematological cancer type. Age has been noted by others to correlate with reduced serological and T cell responses after one dose, with comparable response after second vaccination, consistent with our findings [38].

Adverse effects were overall mild, with no QoL deterioration or impact on planned cancer therapy (preprint) [17]. Patients who developed COVID-19 infections on study had favourable outcomes, which may be explained by the relative preservation of T cell response amongst vaccinated patients, particularly with haematological cancer. Other factors may also have contributed, such as antiviral therapy and protective immune effects from vaccination in unmeasured cellular pathways.

IgG subclasses are important in COVID-19 immunity, with different subclass ratios associated with severity of infection. [39] Repeated mRNA vaccination is associated with increased IgG4 class switching, which is of uncertain clinical implication. [40,41] In future, evaluation of our stored specimens for IgG subclasses may further contribute to the understanding of IgG subclasses post repeated vaccination.

Study strengths include its size, real-world conduct, correlation of B and T cell responses and documentation of the impact of hybrid immunity. Challenges included frequent adaptations to changing vaccine schedule recommendations. Dropout was observed as expected for any cancer cohort study, due to underlying illness and time commitments. This may have been non-random, with unwell patients more likely to end participation, leaving more robust patients in the study, and may have influenced the very high rate of vaccine response seen at later timepoints.

5. Conclusion

COVID-19 vaccination for patients with solid and haematological cancers is highly effective for inducing both neutralising antibody and T cell response to the SARS-CoV-2 Spike antigen. A third dose is essential to ensure maximal response amongst patients with cancer, with some haematological cancer patients benefiting from fourth and fifth doses. Patients with cancer with frequently boosted vaccination experience mild COVID-19 infection, attributable to a combination of humoral and cellular immunity.

Data sharing statement

Monash Health, as sponsor of the SerOzNET study, is the sole and exclusive owner of Study Data and Study Results and all intellectual property rights pertaining to such Study Data and Study Results. Data sharing will be considered upon reasonable request, after consideration of a written scientific proposal by the requesting institution.

Authorship

All authors attest they meet the ICMJE criteria for authorship.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Author SO has received institutional funding (Monash Health) for clinical research unrelated to this study from AstraZeneca. Author WR received laboratory kits from Abbott. Author SS commenced work on this study whilst employed at Queensland Institute of Medical Research Berghofer, but during manuscript preparation has commenced work at Sanofi ANZ. Author CRM has received research funding to her institution from Sanofi and Moderna, honoraria from Sanofi and Janssen (paid to institution) and has provided consulting to Bavarian Nordic, Sanofi and Seqirus (payment to institution). The remaining authors declare that they have no conflict of interest.

Data availability

Data will be made available on request.

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Appendix. Supplementary data

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References

[1] Tagliamento M, Agostinetto E, Bruzzone M, et al. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2021;163:103365.
[2] Wang W, Kaelber DC, Xu R, et al. Breakthrough SARS-CoV-2 infections, hospitalizations, and mortality in vaccinated patients with Cancer in the US between December 2020 and November 2021. JAMA Oncol 2022;8(7):1027–34.
[3] Gong IY, Vijenthira A, Powis M, et al. Association of COVID-19 vaccination with breakthrough infections and complications in patients with Cancer. JAMA Oncol 2023;9(3):386–94.
[4] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603–15.
[5] Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med 2021;385(25):2348–60.
[6] Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27(7):1205–11.
[7] Fumagalli V, Ravà M, Marotta D, et al. Antibody-independent protection against heterologous SARS-CoV-2 challenge conferred by prior infection or vaccination. Nat Immunol 2024;25:633–43.
[8] Bange EM, Han NA, Wileyto P, et al. CD8+ T cells contribute to survival in patients with COVID-19 and hematologic cancer. Nat Med 2021;27(7):1280–9.
[9] Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol 2021;22(12):1681–91.
[10] Fendler A, Shepherd S, Au L, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. Nat Can 2021;2:1305–20.
[11] Naranbhai V, Pernat CA, Gavralidis A, et al. Immunogenicity and Reactogenicity of SARS-CoV-2 vaccines in patients with Cancer: the CANVAX cohort study. J Clin Oncol 2022;40(1):12–23.
[12] Nelli F, Giannarelli D, Fabbri A, et al. Immunogenicity and early clinical outcome after two or three doses of SARS-CoV-2 mRNA-BNT162b2 vaccine in actively treated cancer patients: results from the prospective observational Vax-on-Third study. Ann Oncol 2022;33(7):740–2.
[13] Body A, Ahern E, Lal L, et al. Protocol for SARS-CoV-2 post-vaccine surveillance study in Australian adults and children with cancer: an observational study of safety and serological and immunological response to SARS-CoV-2 vaccination (SerOzNET). BMC Infect Dis 2022;22(1):70.
[14] Australian Federal Government Department of Health. Australian Technical Advisory Group on Immunisation (ATAGI) Clinical guidance on use of COVID-19 vaccine in Australia in 2021 (v3.0). Available from: https://webarchive.nla.gov.au/awa/20210605013610/https://www.health.gov.au/resources/publications/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021. [Accessed 11 June 2024].
[15] Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.
[16] Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
[17] Body A, Donoghoe M, Lal L, Wakefield C, Ahern E, Anazodo A, et al. Vaccine beliefs, adverse effects, and quality of life in patients with cancer undergoing routine COVID-19 vaccination. Pre-print, available from, https://www.medrxiv.org/content/10.1101/2024.06.02.24308345v1.full-text. [Accessed 11 June 2024].
[18] National Cancer Institute Division of Cancer Control and Population Sciences. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). 2023. Available from, https://healthcaredelivery.cancer.gov/pro-ctcae/. [Accessed 11 February 2023].
[19] Tea F, Stella AO, Aggarwal A, et al. SARS-CoV-2 neutralizing antibodies: longevity, breadth, and evasion by emerging viral variants. PLoS Med 2021;18(7). e1003656-e1003656.
[20] Shen Y, Freeman JA, Holland J, et al. COVID-19 vaccine failure in chronic lymphocytic leukaemia and monoclonal B-lymphocytosis; humoural and cellular immunity. Br J Haematol 2022;197(1):41–51.
[21] Aggarwal A, Stella AO, Walker G, et al. Platform for isolation and characterization of SARS-CoV-2 variants enables rapid characterization of Omicron in Australia. Nat Microbiol 2022;7(6):896–908.
[22] Lineburg KE, Srihari S, Altaf M, et al. Rapid detection of SARS-CoV-2-specific memory T-cell immunity in recovered COVID-19 cases. Clin Transl Immunol 2020;9(12):e1219.
[23] Lineburg KE, Crooks P, Raju J, et al. Breakthrough SARS-COV-2 infection induces broad anti-viral T cell immunity. Iscience 2023;26(12).
[24] Lineburg KE, Neller MA, Ambalathingal GR, et al. Rapid whole-blood assay to detect SARS-CoV-2-specific memory T-cell immunity following a single dose of

AstraZeneca ChAdOx1-S COVID-19 vaccine. Clini Transl Immunol 2021;10(8):e1326.
[25] Nelli F, Fabbri A, Onorato A, et al. Six month immunogenicity of COVID-19 mRNA-BNT162b2 vaccine in actively treated cancer patients: updated results of the Vax-on study. Ann Oncol 2022;33(3):352–4.
[26] Oosting SF, van der Veldt AAM, Fehrmann RSN, et al. Immunogenicity after second and third mRNA-1273 vaccination doses in patients receiving chemotherapy, immunotherapy, or both for solid tumours. Lancet Oncol 2022;23(7):833–5.
[27] Fendler A, Shepherd STC, Au L, et al. Immune responses following third COVID-19 vaccination are reduced in patients with hematological malignancies compared to patients with solid cancer. Cancer Cell 2022;40(2):114–6.
[28] Fendler A, Shepherd ST, Au L, et al. Functional immune responses against SARS-CoV-2 variants of concern after fourth COVID-19 vaccine dose or infection in patients with blood cancer. Cell Reports Med 2022;3(10).
[29] Hofsink Q, Haggenburg S, Lissenberg-Witte BI, et al. Fourth mRNA COVID-19 vaccination in immunocompromised patients with haematological malignancies (COBRA KAI): a cohort study. EClinicalMedicine 2023;61:102040.
[30] Ehmsen S, Asmussen A, Jeppesen SS, et al. Increased antibody titers and reduced seronegativity following fourth mRNA COVID-19 vaccination in patients with cancer. Cancer Cell 2022;40(8):800–1.
[31] Park HJ, Gonsalves GS, Tan ST, et al. Comparing frequency of booster vaccination to prevent severe COVID-19 by risk group in the United States. Nat Commun 2024;15(1):1883.
[32] Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med 2021;385(24):e84.
[33] Kohn M, Delord M, Chbat M, et al. A third anti-SARS-CoV-2 mRNA dose does not overcome the pejorative impact of anti-CD20 therapy and/or low immunoglobulin levels in patients with lymphoma or chronic lymphocytic leukemia. Haematologica 2022;107(6):1454–9.
[34] Candon S, Lemee V, Leveque E, et al. Dissociated humoral and cellular immune responses after a three-dose schema of BNT162b2 vaccine in patients receiving anti-CD20 monoclonal antibody maintenance treatment for B-cell lymphomas. Haematologica 2022;107(3):755–8.
[35] Ivashkiv LB. IFNγ: signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy. Nat Rev Immunol 2018;18(9):545–58.
[36] Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize omicron. Nature 2022;603(7901):488–92.
[37] Carazo S, Skowronski DM, Brisson M, et al. Protection against omicron (B.1.1.529) BA.2 reinfection conferred by primary omicron BA.1 or pre-omicron SARS-CoV-2 infection among health-care workers with and without mRNA vaccination: a test-negative case-control study. Lancet Infect Dis 2023;23(1):45–55.
[38] Collier DA, Ferreira IATM, Kotagiri P, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 2021;596(7872):417–22.
[39] Yates JL, Ehrbar DJ, Hunt DT, et al. Serological analysis reveals an imbalanced IgG subclass composition associated with COVID-19 disease severity. Cell Reports Med 2021;2(7). https://doi.org/10.1016/j.xcrm.2021.100329.
[40] Kiszel P, Sík P, Miklós J, et al. Class switch towards spike protein-specific IgG4 antibodies after SARS-CoV-2 mRNA vaccination depends on prior infection history. Sci Rep 2023;13(1):13166. https://doi.org/10.1038/s41598-023-40103-x.
[41] Irrgang P, Gerling J, Kocher K, et al. Class switch toward noninflammatory, spike-specific IgG4 antibodies after repeated SARS-CoV-2 mRNA vaccination. Sci Immunol 2023;8(79):eade2798. https://doi.org/10.1126/sciimmunol.ade2798.