

Cytokine release syndrome in a patient with colorectal cancer following vaccination with BNT162b2 (tozinameran)

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Abstract

We present a case of cytokine release syndrome (CRS) that occurred five days after vaccination with BNT162b2 (tozinameran), an mRNA COVID-19 vaccine, in a patient with colorectal cancer on long-standing anti-PD-1 monotherapy. The CRS was evidenced by raised inflammatory markers, thrombocytopenia, elevated cytokine levels (IFN- γ /IL-2R/IL-18/IL-16/IL-10), and steroid responsiveness.

Main Text

Cytokine release syndrome (CRS) is a systemic inflammatory response, characterised by excessive cytokine release. CRS may develop following infection (including coronavirus disease 2019 [COVID-19]), or due to iatrogenic causes most notably chimeric antigen receptor T-cell (CAR-T) therapy, and less frequently cytotoxic chemotherapy or stem cell transplantation.¹⁻³ Extremely rarely, it occurs following immune checkpoint inhibitor (ICI) therapy,⁴ and, to the best of our knowledge, it has not been reported following administration of any vaccine. Here, we report a case of CRS following vaccination with BNT162b2 (tozinameran), an mRNA COVID-19 vaccine.

A 58-year-old male commenced anti-PD-1 monotherapy (an investigational ICI within an ongoing clinical trial) in February 2019 for the treatment of mismatch repair deficient colorectal cancer (MMRd CRC) metastatic to mesentery and rectus muscle (**Figure 1a**). Two months following treatment initiation he experienced a neurological immune-related adverse event (irAE), with worsening ataxia (grade 1 to grade 2 and MRI changes in pons, medulla, and cerebellum) on the background of pre-existing spinocerebellar ataxia of unknown aetiology. ICI was suspended and he was commenced on 1 mg/kg prednisolone (tapered over one month) and ataxia returned to grade 1 (baseline). Anti-PD-1 therapy was re-started in June 2019 (**Figure 1a**), with stable disease as per immune related Response Evaluation Criteria in Solid Tumors (irRECIST). In March 2020 (13 months after commencing ICI), he developed an endocrine irAE (grade 1 hypocortisolemia from adrenocorticotrophic hormone deficiency; **Fig 1a**) and was commenced on physiological doses of corticosteroid replacement (prednisolone 3 mg daily). Disease control was maintained and the last ICI dose was administered in December 2020, 27 days prior to BNT162b2.

The patient had no history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and had negative SARS-CoV-2 serological tests in June and October 2020. He received the first dose of BNT162b2 vaccine on 29 December 2020 (**Figure 1a**) without immediate adverse events, except for grade 1 inflammation at the vaccination site. Five days later (32 days after last anti-PD-1 dose), he presented with myalgia, two days history of diarrhoea (grade 1), and one day history of fever (38.4°C), despite anti-pyretics (ibuprofen) use. On admission to hospital, his vital signs were: oxygen saturation: 100% on room air; respiratory rate: 18/min; blood pressure: 111/71 mmHg; heart rate: 86 bpm; temperature: 36.7°C. Laboratory investigations revealed elevated inflammatory markers (C-reactive protein [CRP]: 125 mg/l [normal: <6]; serum lactate dehydrogenase [LDH]: 184 U/l [normal range: 120-246]), and thrombocytopenia (68x10⁹ cells/l [normal range: 150-410]; confirmed on microscopy) (**Figure 1b**). Empirical treatment with broad-spectrum intravenous antibiotics was commenced, however, blood and

urine cultures were negative, as was SARS-CoV-2 RT-PCR of serial naso-pharyngeal swabs (**Figure 1a**). Computed tomography of thorax, abdomen and pelvis revealed no nidus of infection and stable disease. Over the next five days, fevers up to 39.8°C continued, with worsening thrombocytopenia (28×10^9 cells/l), increasing inflammatory markers (CRP: 317 mg/l, LDH 849 U/l), including significantly elevated ferritin (6,010 µg/l [normal range: 18-464]) (**Figure 1b**). At this point (five days post-admission), CRS was suspected and he was commenced on 1 mg/kg intravenous methylprednisolone (IVMP), and antibiotics were ceased three days later. Biochemical and haematological indices normalised within seven days of IVMP initiation (**Figure 1b**), and the patient was afebrile and asymptomatic upon discharge home with a weaning corticosteroid regimen. He remained well and was re-challenged with anti-PD-1 on 8 February 2021 (36 days after initial presentation) without any adverse events (**Figure 1a**).

To explore the features of his presentation further, we performed longitudinal cytokine analysis, pre- and post-IVMP. An exaggerated type 1 helper T-cell (Th1) response is a frequent feature of CRS,¹ and the initial profile (day 3 of admission; **Figure 2a**) indicated activation of Th1 cells (elevated MIG, IL-2R, IL-16, IFN-γ, IL-18) and macrophages (elevated MCP-1, MIP, IL-8, IL-18, MIG). IL-10 inhibits pro-inflammatory cytokine responses limiting exuberant inflammatory responses³, and while we observed elevated IL-10 on days 3 to 8 of admission it evidently failed to suppress hyperinflammation in this case. Majority of cytokines decreased substantially during IVMP treatment, but persistent elevation of IL-2R, IL-2, IL-16, and IL-18 day 12 of admission (**Figure 2a**) indicate sustained T-cell activation.

SARS-CoV-2 reactive and neutralising antibodies were detectable seven days post-vaccination (**Figure 2b**), and the titres continued to rise during IVMP treatment, suggesting a robust vaccine-induced immune response. However, S-specific CD4⁺ and CD8⁺ T-cells were undetectable on days 17 and 40 post-vaccination (**Figure 2c,d and Figure S1a,b**), consistent with weak/absent T-cell responses observed in healthcare workers following the first dose of BNT162b2.⁵

To identify antibody-binding epitopes we performed a serum epitope repertoire analysis (SERA) and protein-based immunome wide association study (PIWAS), using a bacterial display system coupled with next-generation sequencing. Post-vaccine profile was comparable to that of healthcare workers after COVID-19 mRNA vaccine (data not shown), with a rise in positive signal against spike but not non-spike proteins (vs SARS-CoV-2 positive subjects)⁶ (**Figure S2**). This was consistent with the lack of prior SARS-CoV-2 infection as a potentially contributor to the clinical presentation.

The laboratory findings in CRS are variable and relate to the underlying cause, although CRP elevation is universal and correlates with severity.¹ Elevated ferritin and thrombocytopenia are also common abnormalities.¹ Whilst there are no defined cytokine profiles that confirm CRS, raised IFN-γ, IL-2R, IL-18, IL-6, and IL-10 are considered key in establishing the diagnosis.^{1,2} All bar IL-6 were elevated in this case. Whereas transient cytokine elevation (IFN-α, IFN-γ, IL-6, IFN-inducible protein-10, and IL-12 p70) was observed following mRNA cancer vaccines co-administered with ICI in melanoma patients,⁷ they manifest as self-limiting mild flu-like symptoms.

Less than 0.01% of irAEs reported in the context of anti-PD-1 monotherapy involve CRS⁴ and to date no CRS events have been reported following BNT162b2. ICI-related CRS typically develops a median of 4 weeks after ICI initiation (range: 1-18 weeks),⁴ making CPI as the sole cause of CRS unlikely in this patient who commenced anti-PD1 treatment 22 months prior. The close temporal association of vaccination and clinical presentation favours the vaccine as potential trigger of CRS in this case.

Receptor occupancy associated with anti-PD-1 agents is 2–3 months⁸ and it remains possible that CRS was triggered by the vaccine on a background of immune activation secondary to PD1 blockade which results in T-cell proliferation and increased effector function⁹. We did not detect S-reactive T-cells in the periphery, however vaccine-activated T-cells that contributed CRS could be resident within tissue or lymph nodes and evade detection in the blood.¹⁰ T-cell cross-reactivity, as a result of sequence similarity between spike protein and tumour neoantigens is an alternative though a less likely cause of CRS in this case. Cross-reactivity to cardiac tissue was reported as a mechanism of ICI-related myocarditis¹¹, and this patient's history of irAEs and the high neoantigen load (typical of MMRD CRC)¹² could in theory increase the likelihood of T-cell cross-reactivity.¹³

Given patients with cancer were excluded from SARS-CoV-2 vaccine studies and are currently prioritised in COVID-19 vaccination programs globally, this case motivates prospective pharmacovigilance regarding the safety profile of COVID-19 vaccines in cancer patients. However, this being an isolated case, the benefit-risk profile for COVID-19 vaccination remains strongly in favour of vaccination in the cancer population who are generally more vulnerable to COVID-19.^{14,15} Current empirical recommendations regarding the timing of COVID-19 vaccination suggest administering “on availability” in cancer patients on systemic anticancer treatments including ICI, cytotoxic chemotherapy, and hormone therapy; and avoiding vaccination within 48–72 h of investigational products to minimise misattribution of adverse event causation.¹⁶

Methods

CAPTURE design, study schedule, and follow-up

During admission, the patient was enrolled in CAPTURE (NCT03226886), an observational prospective study of the immune response to SARS-CoV-2 in cancer patients that opened for recruitment in May 2020 at the Royal Marsden NHS Foundation Trust. The study design has been previously published.¹⁷ Adult patients with current or history of invasive cancer are eligible for enrolment, irrespective of cancer type, stage, or treatment. Primary and secondary endpoints relate to patient characteristics of those with and without SARS-CoV-2 infection, and the impact of COVID-19 on long-term survival and ICU admission rates. Exploratory endpoints pertain to characterising clinical and immunological determinants of COVID-19 and vaccine response in cancer patients. Clinical data and sample collection for participating cancer patients are performed at baseline, and at clinical visits per standard-of-care management during the first

year of follow-up; frequency varies depending on in- or outpatient status and systemic anti-cancer treatment regimens. CAPTURE was approved as a substudy of TRACERx Renal (NCT03226886). TRACERx Renal was initially approved by the NRES Committee London - Fulham on January 17, 2012. The TRACERx Renal sub-study CAPTURE was submitted as part of Substantial Amendment 9 and approved by the Health Research Authority on April 30, 2020 and the NRES Committee London - Fulham on May 1, 2020. CAPTURE is conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements.

Handling of whole blood samples

For indicated experiments, serum or plasma samples were heat-inactivated at 56°C for 30 minutes prior to use.

Plasma and PBMC isolation

Whole blood was collected in EDTA tubes (VWR) and stored at 4°C until processing. All samples were processed within 24 hours. Time of blood draw, processing, and freezing was recorded for each sample. Prior to processing tubes were brought to room temperature (RT). PBMC and plasma were isolated by density-gradient centrifugation using pre-filled centrifugation tubes (pluriSelect). Up to 30 ml of undiluted blood was added on top of the sponge and centrifuged for 30 minutes at 1000 x g at RT. Plasma was carefully removed then centrifuged for 10 minutes at 4000 x g to remove debris, aliquoted and stored at -80°C. The cell layer was then collected and washed twice in PBS by centrifugation for 10 minutes at 300 x g at RT. PBMC were resuspended in Recovery cell culture freezing medium (Fisher Scientific) containing 10% DMSO, placed overnight in CoolCell freezing containers (Corning) at -80°C and then stored in liquid nitrogen.

Serum isolation

Whole blood was collected in serum coagulation tubes (Vacuette CAT tubes, Greiner) for serum isolation and stored at 4°C until processing. All samples were processed within 24 hrs. Time of blood draw, processing, and freezing was recorded for each sample. Tubes were centrifuged for 10 minutes at 2000 x g at 4°C. Serum was separated from the clotted portion, aliquoted and stored at -80°C.

S1-reactive IgG ELISA

Ninety-six-well MaxiSorp plates (Thermo Fisher Scientific) were coated overnight at 4°C with purified S1 protein in PBS (3 µg/ml per well in 50 µl) and blocked for 1 hour in blocking buffer (PBS, 5% milk, 0.05% Tween 20, and 0.01% sodium azide). Sera were diluted in blocking buffer (1:50). Fifty microliters of serum were then added to the wells and incubated for 2 hours at RT. After washing four times with PBS-T (PBS, 0.05% Tween 20), plates were incubated with alkaline phosphatase-conjugated goat anti-human IgG (1:1000, Jackson ImmunoResearch) for 1 hour. Plates were developed by adding 50 µl of alkaline phosphatase substrate (Sigma Aldrich) for 15-30 minutes after six washes with PBS-T. Optical densities were measured at 405 nm on a microplate reader (Tecan). CR3022 (Absolute Antibodies) was used as a

positive control. The cut-off for a positive response was defined as the mean negative value multiplied by 0.35 times the mean positive value.

Neutralising antibody assay

Confluent monolayers of Vero E6 cells were incubated with SARS-CoV-2 virus and two-fold serial dilutions of heat-treated serum or plasma samples starting at 1:40 for 4 hrs at 37°C, 5% CO₂, in duplicates. The inoculum was then removed and cells were overlaid with viral growth medium. Cells were incubated at 37°C, 5% CO₂. At 24 hours post-infection, cells were fixed in 4% paraformaldehyde and permeabilized with 0.2% Triton X-100/PBS. Virus plaques were visualized by immunostaining, as described previously¹⁸ for the neutralisation of influenza viruses using a rabbit polyclonal anti-NSP8 antibody used at 1:1000 dilution and anti-rabbit-HRP conjugated antibody at 1:1000 dilution and detected by action of HRP on a tetramethyl benzidine-based substrate. Virus plaques were quantified and ID50 was calculated.

T-cell stimulation

PBMC for *in vitro* stimulation were thawed at 37 °C and resuspended in 10 ml of warm complete medium (RPMI, 5% human AB serum) containing 0.02% benzonase. Viable cells were counted and 2x10⁶ cells were seeded in 200 µl complete medium per well of a 96-well plate. Cells were stimulated with 4 µl/well PepTivator SARS-CoV-2 S, M, or N pools (representing 1 µg/ml final concentration per peptide; Miltenyi Biotec, Surrey, UK). Staphylococcal enterotoxin B (Merck, UK) was used as a positive control at 0.5 µg/ml final concentration, negative control was PBS containing DMSO at 0.002% final concentration. PBMC were cultured for 24 hrs at 37°C, 5% CO₂.

Activation-induced marker assay

Cells were washed twice in warm PBMC. Dead cells were stained with 0.5 µl/well Zombie dye V500 for 15 minutes at RT in the dark, then washed once with PBS containing 2% FCS (FACS buffer). A surface staining mix was prepared per well, containing 2 µl/well of each antibody for surface staining (**Supplementary Table 1**) in 50:50 brilliant stain buffer (BD) and FACS buffer. PBMC were stained with 50 µl surface staining mix per well for 30 minutes at RT in the dark. Cells were washed once in FACS buffer and fixed in 1% PFA in FACS buffer for 20 min, then washed once and resuspended in 200 µl PBS. All samples were acquired on a Bio-Rad Ze5 flow cytometer running Bio-Rad Everest software v2.4 and analysed using FlowJo v10 (Tree Star Inc.) analysis software. Compensation was performed with 20 µl antibody-stained anti-mouse Ig, k / negative control compensation particle set (BD Biosciences, UK). Up to 1x10⁶ live CD19-/CD14- cells were acquired per sample. Gates were drawn relative to the unstimulated control for each donor. Gating strategy is shown in **Figure S2c**. T-cell response is displayed as a stimulation index by dividing the percentage of AIM-positive cells by the percentage of cells in the negative control. When S, M, and N stimulation were combined the sum of AIM-positive cells was divided by the three times the percentage of positive cells in the negative control.

Multiplex immune assay for cytokines and chemokines

The preconfigured multiplex Human Immune Monitoring 65-plex ProcartaPlex immunoassay kit (Invitrogen, Thermo Fisher Scientific, UK) was used to measure 65 protein targets in plasma on the Bio-Plex platform (Bio-Rad Laboratories, Hercules, CA, USA), using Luminex xMAP technology. Analytes measured included APRIL; BAFF; BLC; CD30; CD40L; ENA-78; Eotaxin; Eotaxin-2; Eotaxin-3; FGF-2; Fractalkine; G-CSF; GM-CSF; Gro-alpha; HGF; IFN-alpha; IFN-gamma; IL-10; IL-12p70; IL-13; IL-15; IL-16; IL-17A; IL-18; IL-1alpha; IL-1beta; IL-2; IL-20; IL-21; IL-22; IL-23; IL-27; IL-2R; IL-3; IL-31; IL-4; IL-5; IL-6; IL-7; IL-8; IL-9; IP-10; I-TAC; LIF; MCP-1; MCP-2; MCP-3; M-CSF; MDC; MIF; MIG; MIP-1alpha; MIP-1beta; MIP-3alpha; MMP-1; NGF-beta; SCF; SDF-1alpha; TNF-beta; TNF-alpha; TNF-R2; TRAIL; TSLP; TWEAK; VEGF-A. All assays were conducted as per the manufacturer's recommendation.

Serum epitope repertoire analysis

Patient serum samples were screened and analysed using the previously published serum epitope repertoire analysis (SERA) pipeline.¹⁹ Briefly, sera were screened with a randomised bacterial peptide display library and plasmids from antibody-bound bacteria were isolated and sequenced. Protein-based Immunome Wide Association Studies (PIWAS) was applied to identify epitopes and antigens for the SARS-CoV-2 proteome.²⁰

Declarations

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Author contributions

S.T., L.A., S.S., and A.F. contributed to study design. L.A., K.R., A.F., and S.T. drafted the manuscript. S.S., A.F., and L.A. contributed to the collection and processing of clinical specimens. A.F., K.W., and M.C. performed laboratory analysis. A.F. and L.A. contributed to visualisations. S.S., L.A., N.J-H., D.L., I.C., N.S., and C.F. provided clinical data. All authors critically reviewed the manuscript for intellectual content, approved the final version of the manuscript for submission, and agreed to be accountable for all aspects of the work.

Competing interests declaration

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Data availability

All requests for raw and analysed data, materials, and CAPTURE study protocol will be reviewed by the CAPTURE Trials Team, Skin and Renal Clinical Trials Unit, The Royal Marsden NHS Foundation Trust (CAPTURE@rmh.nhs.uk) to determine if the request is subject to confidentiality and data protection obligations. Data and materials that can be shared will be released via a material transfer agreement.

The CAPTURE consortium

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Figures

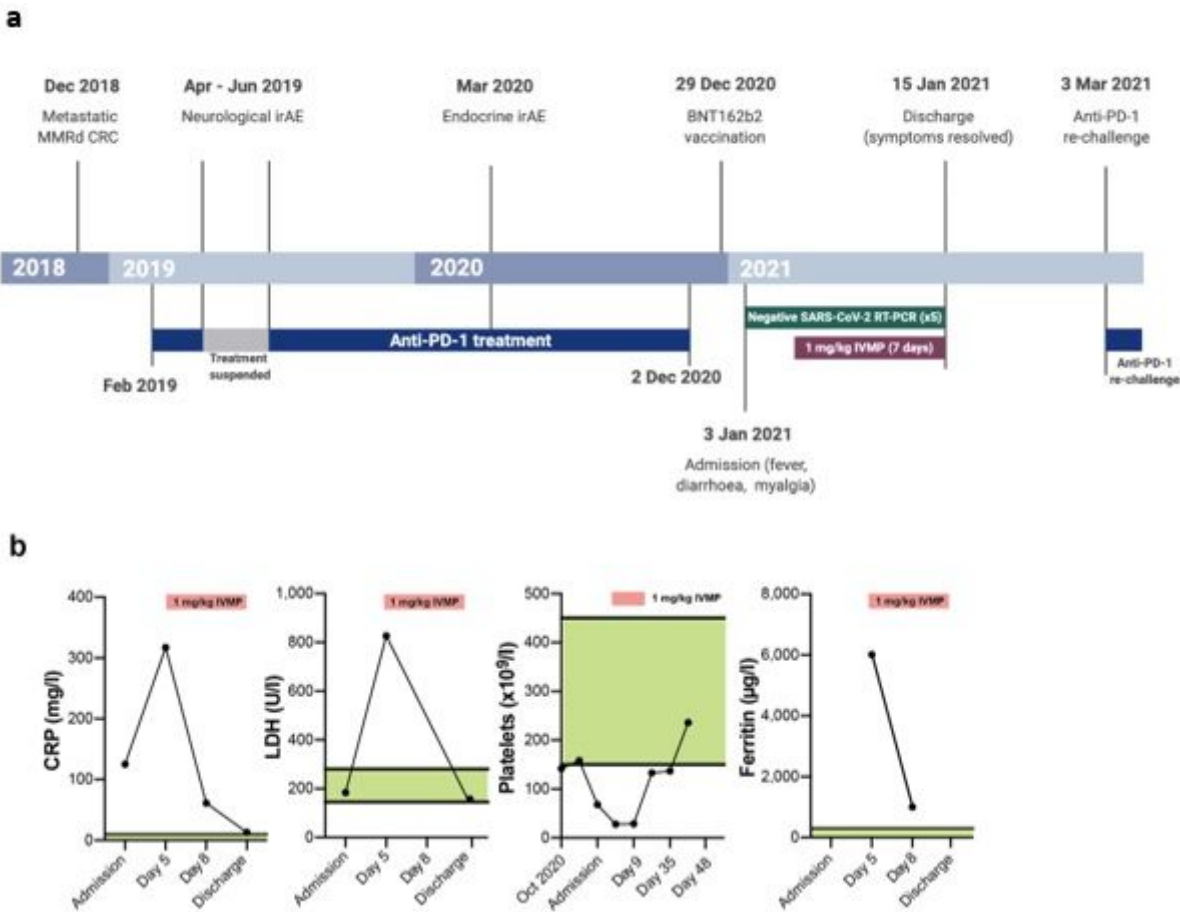


Figure 1

Clinical course from cancer diagnosis and inflammatory markers during CRS a) Clinical timeline from diagnosis of metastatic MMRd CRC to CRS after one dose of BNT162b2 vaccine. Created with BioRender.com. b) CRP, LDH, platelet count and ferritin levels during the course of admission. Normal ranges are indicated in green. Treatment with IVMP is indicated in red. CRP, C-reactive protein; CRS, cytokine release syndrome; IrAEs, immune-related adverse events; IVMP, intravenous methylprednisolone; LDH - lactate dehydrogenase; MMRd CRC, mismatch repair deficient colorectal cancer

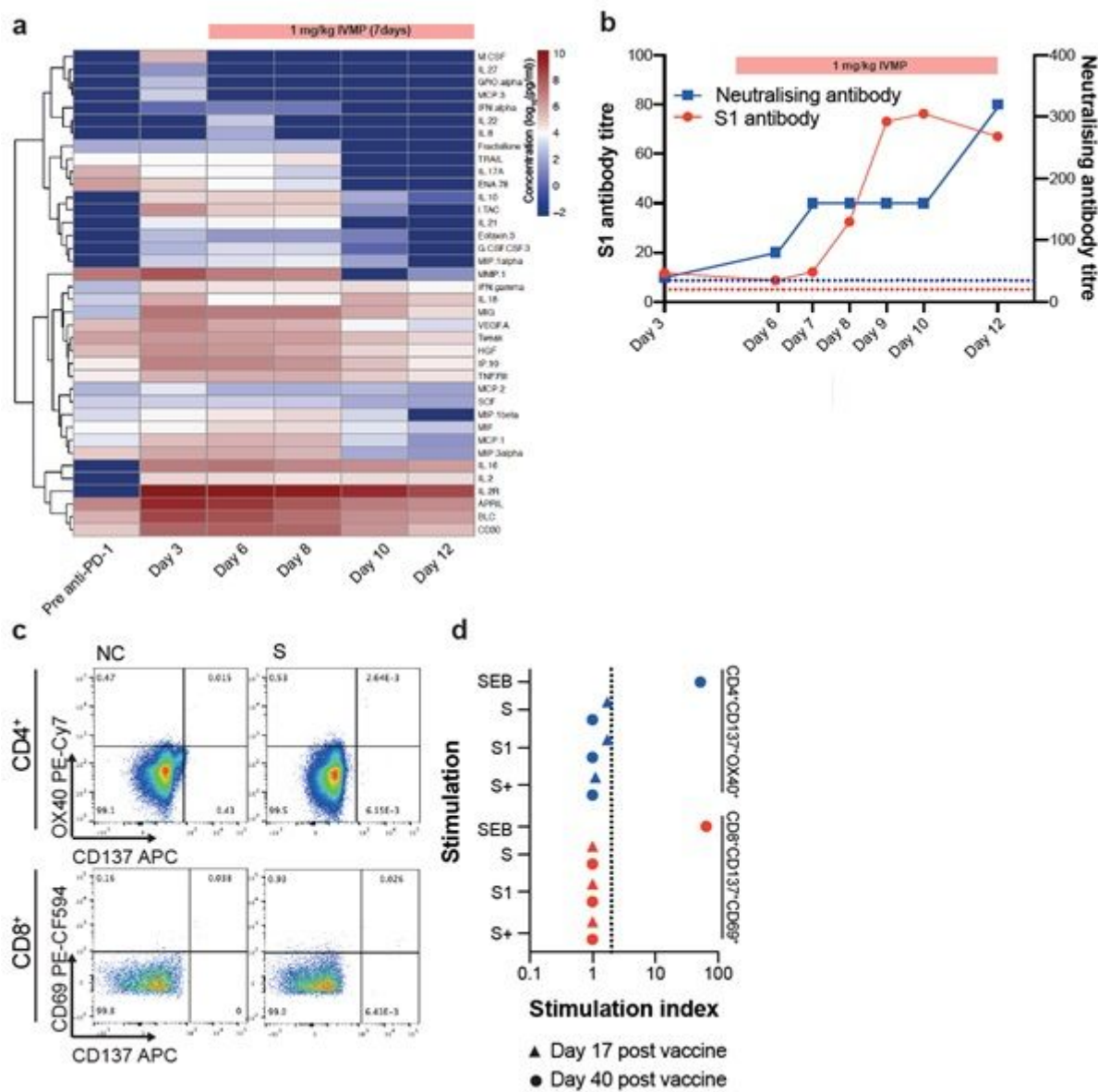


Figure 2

Cytokine profile and immune response to BNT162b2 vaccine a) Cyto/chemokine levels were measured using the human immune monitoring 65-plex ProCartaPlex immunoassay in consecutive plasma samples. Samples were measured in duplicates. Data are presented as the log₁₀ of the concentration in pg/ml. b) Kinetics of S1-reactive and neutralising antibody responses post-BNT162b2. Data are presented as the reciprocal dilution of the last detected sample. IVMP treatment is indicated in red. c) SARS-CoV-2 specific CD4+ and CD8+ T-cell response in exemplary samples after stimulation of PBMCs

with spike (S) peptide pool. d) PBMCs were stimulated with S, S1, and S+ peptide pools representing the full length of the spike protein. SEB was used as a positive control. Data are presented as a stimulation index indicating the ratio of the frequency of CD4+CD137+OX40+ or CD8+CD137+CD69+ T-cells in the sample and the negative control. IVMP, intravenous methylprednisolone; PBMC, peripheral blood mononuclear cells; SEB, Staphylococcal enterotoxin B

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