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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: 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; published online Nov 9. http://dx.doi.org/10.1016/S1470-2045(21)00574-X.

Appendix

Section 1: Supplemental methods

1.1 Supplemental laboratory assessments

SARS-CoV-2 Spike S1-specific IgG concentrations in serum were determined using a previously published fluorescent bead-based immune assay.[1,2] The assay's specificity (99·7%) and sensitivity (91·6%) for Spike S1 protein were determined using a heterogeneous sample set. This set included asymptomatic and mild to severe COVID-19 cases as representative of COVID-19 cases in the general population and as negative controls samples of pre-pandemic population and persons infected with various viruses, including endemic coronaviruses.[1,2] Concentrations were interpolated from a reference consisting of pooled sera using a 5-parameter logistic fit that was calibrated against the NIBSC/WHO COVID-19 reference serum 20/136 and expressed as international binding antibody units per ml (BAU/mL). A BAU/mL value of >10 was considered positive.

Neutralising antibodies were measured with the plaque reduction neutralisation test (PRNT). In the PRNT, we tested serum samples for their neutralisation capacity against SARS-CoV-2 D614G, as previously described.[3] SARS CoV-2 D614G was isolated from a diagnostic specimen at the Department of Viroscience, Erasmus MC, cultured and subsequently sequenced to rule out additional mutations in the S protein: D614G (GISAID: hCov-19/Netherlands/ZH-EMC-2498). Heat-inactivated sera were 2-times diluted in Dulbecco modified Eagle medium supplemented with NaHCO3, HEPES buffer, penicillin, streptomycin, and 1% foetal bovine serum, starting at a dilution of 1:10 in 60 µL. After that, 60 µL of virus suspension (400 plaque-forming units) was added to each well and incubated at 37 °C for 1 hour. Next, the mixtures were transferred onto Vero E6 cells and incubated for 8 hours. Next, the cells were fixed with 10% formaldehyde and stained with polyclonal rabbit anti-SARS-CoV antibody (Sino Biological) and a 472 secondary peroxidase-labelled goat anti-rabbit IgG (Dako). The signal was developed using a precipitate forming 3,3′,5,5′-tetramethylbenzidine substrate (True Blue; Kirkegaard and Perry Laboratories). The number of infected cells per well was counted using an ImmunoSpot Image Analyzer (CTL Europe GmbH). The serum neutralisation titre is the reciprocal of the highest dilution resulting in an infection reduction of >50% ($PRNT_{50}$).

PBMCs were isolated within 24 hours from 60 mL blood with density gradient centrifugation using Ficoll-Paque Plus (GE Healthcare) and SepMateTM tubes (STEMCELL). The PBMCs were washed 2 times with phosphate-buffered saline, counted using Türk's solution, and checked for viability with trypan blue. Vials containing PBMCs in 50% RPMI (Gibco), 20% foetal calf's serum (LPS), and 10% DMSO (Sigma Aldrich) medium were cryopreserved in liquid nitrogen until further use. SARS-CoV2 Spike-specific T cells were measured using IFNγ ELISpot assays. In short, multiScreen® HTS IP filter plates (Millipore) activated with 35% ethanol were coated with anti-human IFNγ antibody (1-D1K, Mabtech; 5 µg/mL) and incubated overnight at 4 °C. Next, the plates were blocked with X-VIVO (Lonza) medium + 2% human AB serum (HS; Sigma) and incubated for 1 hour at 37 °C and 5% CO_2. PBMCs were thawed, dissolved in 4 °C IMDM (Gibco) medium and 10% foetal calf's serum, centrifuged for 7 minutes at 375 g, and washed two times. In X-VIVO+2%HS, PBMCs were brought to a concentration of 4 x 10^6 cells/mL and rested for 1 hour at 37 °C and 5% CO_2. The PBMCs were counted using trypan blue and checked for viability. SARS-CoV-2 S1 and S2 peptide pools (JPT Peptide Technologies) consisting of 0·5 µg/mL 15-mer peptides overlapping 11 amino acids covering the sequence of the viral protein served to stimulate the PBMCs. The dilutions were performed in X-VIVO+2%HS, and all stimulations were executed in triplicate. DMSO 0·4% served as negative control and PHA (Remel Europe Ltd; 4 µg/mL) as a positive control. PBMCs (2 x 10^5) were seeded per well and cultured for 20-24 hours at 37 °C and 5% CO_2. The next day, ELISpot plates were washed with phosphate-buffered saline and 0·05% Tween 20. Anti-human biotinylated IFNγ antibody (7-B6-1, Mabtech; 1:1000) in 0·05% Poly-HRP buffer (ThermoFisher) diluted in phosphate-buffered saline was added for 1·5 hours. At room temperature, washing was repeated, followed by the addition of streptavidin poly-HRP (Sanquin; 1:6000) in 0·05% Poly-HRP buffer for 1 hour at room temperature in the dark. After an additional washing step, spots were visualized using TMB substrate (Mabtech). Spot forming cells (SFC) were quantified with the AID ELISpot/Fluorospot reader and expressed as SFCs/10^6 PBMCs. The average of the DMSO negative control was subtracted per stimulation. The total Spike-specific SFC was defined by summing up the SFCs of the separate S1 and S2 peptide pools. An antigen-specific response was defined as at least a 2-times increase in the number of spots from pre- to 28 days after the second vaccination and ≥50 IFNγ producing spot-forming cells (SFC) per 10^6 PBMCs 28 days after the second vaccination. This was based on experience in other infectious diseases using values in unvaccinated and uninfected healthy controls.[4] Samples were excluded when the positive control PHA was negative.

1.2 Supplemental statistical methods

Power calculation

At the time of designing the trial and performing the power calculations, there was only preliminary data published on antibody response after vaccination with mRNA-1273 from a phase I study in 45 healthy adults aged 18-55 years.[5] All these individuals had seroconversion. Because we anticipated to enrol an older, less healthy cohort of individuals without cancer, the anticipated true response rate to COVID-19 vaccine was estimated at 90% for those without cancer, and for patients with cancer undergoing treatment with immunotherapy. We anticipated that in patients treated with immunotherapy, there is no suppressed immune system, and thus, in theory, an adequate immune response to the COVID-19 vaccine can be made. For those patients with cancer undergoing chemotherapy or chemotherapy in combination with immunotherapy, we expected a reduced immune response because the immune system is expected to be suppressed by the chemotherapy. Due to the lack of data on COVID-19 vaccine responses in patients with cancer treated with chemotherapy at the time of the trial design, we used data from the literature obtained in the context of influenza vaccinations given to patients with cancer treated with chemotherapy. Based on this limited influenza vaccination data, we anticipated a true response rate to COVID-19 vaccine of 60% in patients with cancer treated with chemotherapy.[6]

Assuming no true difference between the participants without cancer (cohort A) and the patients receiving immunotherapy (cohort B), (90% responders in both cohorts on day 28 after the second vaccination), 112 participants in cohorts A and B are required to ensure 80% certainty that the upper limit of a one-sided 95% confidence interval will exclude a difference in favour of cohort A of more than 10%. For the comparison between cohorts A and C/D, we also used the non-inferiority margin of 10%. A non-inferiority margin of 10% is used in the majority of vaccination studies and recommended by the FDA.[7,8] As we anticipated a true response rate of 90% in cohort A and 60% in cohorts C, and D, we assumed a true difference in favour of the control group of 30%. Adding the 10% non-inferiority margin to this anticipated true difference of 30% gives 40%.

With these assumptions, 205 participants were required in cohorts A, C, and D to ensure 80% certainty that the upper limit of a one-sided 95% confidence interval would exclude a difference in favour of the control group of more than 40%. To compensate for non-evaluable patients, e.g., due to SARS-CoV-2 specific antibodies at baseline, each cohort was enlarged by 20%.

Actual parameters used to test the primary endpoint

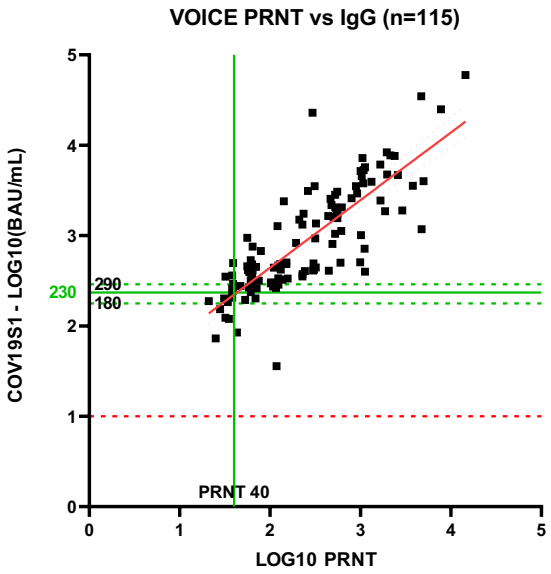
When analysing our data after the database lock, it became clear that our anticipated true response rates used in the power calculations considerably deviated from the observed true response rates. The anticipated true response rate in cohort A was 90%, but the observed true response rate was 100%. The anticipated true response rate for cohorts C and D was 60%, but the observed true response rates were 97·4% and 100%, respectively. Therefore, to test for non-inferiority, we decided that the anticipated true response rates in cohorts B, C, and D should all be equal to the observed true response rate in cohort A (i.e., 100%). For the primary endpoint, we kept the non-inferiority margin of 10% and alpha of 0·05. With these parameters, non-inferiority was demonstrated for each patient cohort in comparison to cohort A.

Selection method for neutralising antibody titre and T cell response measurements

Neutralising antibody titres were measured in all individuals with a SARS-CoV-2-binding antibody concentration >10 BAU/mL but ≤500 BAU/mL, and in an additional selection of 29 participants per cohort covering the concentration range >500 BAU/mL. Upfront it was initially thought to do an additional set of 15 samples per cohort which means that between these samples exist 14 intervals. Prior to the analyses, we decided to expand the number by selecting samples halfway each interval, meaning 14 new samples resulting in a total of 29 samples were selected in the end per cohort for the analyses. Participants with a SARS-CoV-2-binding antibody concentration >500 BAU/mL were ranked per cohort based on their SARS-CoV-2-binding antibody concentration for this additional selection. Subsequently, we selected per cohort participants at a regular rank-based interval. This rank-based interval was determined by dividing the total number of participants in a cohort - with SARS-CoV-2-binding antibody concentration >500 BAU/mL - by 28. For measurement of Spike-specific T cell responses, the same selection was used in addition to the samples from all non-responders (with a SARS-CoV-2-binding antibody concentration ≤10 on day 28 after the second vaccination).

1.3 Supplemental methods antibody threshold determination

The cut-off level of 300 BAU/mL was based on the quantitative relation between SARS-CoV-2-binding antibody concentration (in BAU/mL) and neutralising antibody titres by selecting a subset of sera from the VOICE study (n=115) that were seropositive (SARS-CoV-2-binding antibody concentration >10 BAU/mL) and positive in the plaque-reduction neutralisation assay, defined as a minimal reduction of virus infection of 50% ($PRNT_{50}$) at serum dilution 20. We considered a $PRNT_{50}$ titre ≥40 as minimally protective. We analysed which SARS-CoV-2-binding antibody concentration was consistent with a $PRNT_{50}$ titre ≥40 by linear regression of log^{10}-transformed SARS-CoV-2-binding antibody concentration and $PRNT_{50}$ data, which results in a SARS-CoV-2-binding antibody concentration of 230 BAU/mL at $PRNT_{50}$ 40, see figure below (IgG = SARS-CoV-2-binding antibody).



---The horizontal line in red reflects the cut-off level for seropositivity of the assay (10·08 BAU/mL).

The 95% confidence interval (CI) upper fit of this value, 290 BAU/mL (rounded to 300 BAU/mL), was chosen to minimize misclassification of patients who were SARS-CoV-2-binding antibody positive (>10 BAU/mL), but who were neutralisation negative ($PRNT_{50}$ <20). At the value of 300 BAU/mL, we determined how many patients, for which both SARS-CoV-2-binding antibody concentration and $PRNT_{50}$ data were available (n=140), were classified as SARS-CoV-2-binding antibody positive but with $PRNT_{50}$ <40, which was 4/140 (2·9%). See table below.

		$PRNT_{50}$ ≥40		
		Neg	Pos	
		n (%)	n (%)	Total
SARS-CoV-2-binding antibody concentration >300 BAU/mL	Neg	36 (25·7)	13 (9·3)	49
	Pos	4 (2·9)	87 (62·1)	91
	Total	40	100	140

% agreement = 87·9%

kappa = 0·721 (substantial agreement)

95% CI: 0·599 - 0·844

Section 2: Case description Stevens-Johnson syndrome

A 69-year-old female patient with metastatic melanoma received nivolumab 480 mg every 4 weeks. During the screening for the VOICE trial, she developed progressive disease, and anticancer treatment was switched to ipilimumab 3 mg/kg every three weeks. She received the first ipilimumab infusion nine days before the first vaccination. Because the last nivolumab administration was within three months of vaccination, she was eligible for cohort B. As concomitant medication, she used anastrozole for a previous diagnosis of breast cancer in 2016, and pantoprazole, both already for many months. On day nine after the first vaccination, the patient developed erythema multiforme of the vaccinated arm. Initially, this was thought to be a maculo-papular rash caused by ipilimumab and it was treated with topical steroids. The second vaccination was administered at an interval of 28 days. Thereafter, the skin manifestations spread over the body and progressed with desquamation. Her foot soles and hand palms were affected, and she had low-grade fever.

She was admitted to the hospital 16 days after the second vaccination because of a diagnosis of Stevens-Johnson syndrome (SJS). A biopsy showed interface dermatitis with vacuolisation at the dermo-epidermal junction, subepidermal oedema, and purpura. The patient was started on prednisone 2 mg/kg and quickly improved. Steroids we gradually tapered after complete remission of SJS manifestations. Upon tapering of the steroid dose, she had a flare-up of SJS, accompanied by high fever (39·2 °C), but no blistering or mucosal involvement. Increasing the steroid dose induced again a quick remission.

Section 3: Supplemental figures

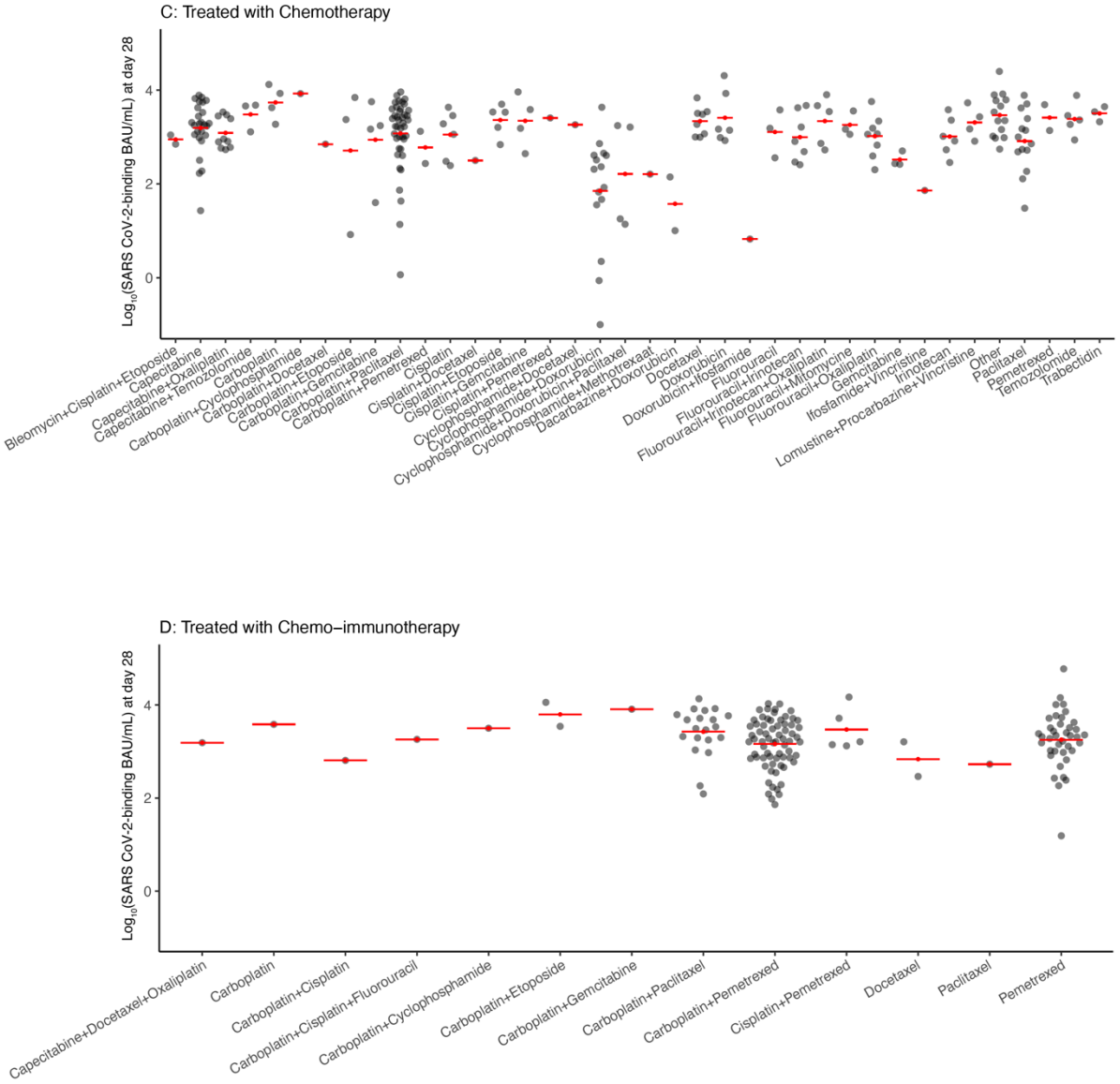


Figure S1. SARS-CoV-2-binding antibody concentration per chemotherapy regimen in cohorts C and D. Distributions of SARS-CoV-2-binding antibody concentrations in $\log_{10}$ transformed BAU/mL at day 28 after the second vaccination per chemotherapy regimen for cohort B (chemotherapy) and D (chemo-immunotherapy).

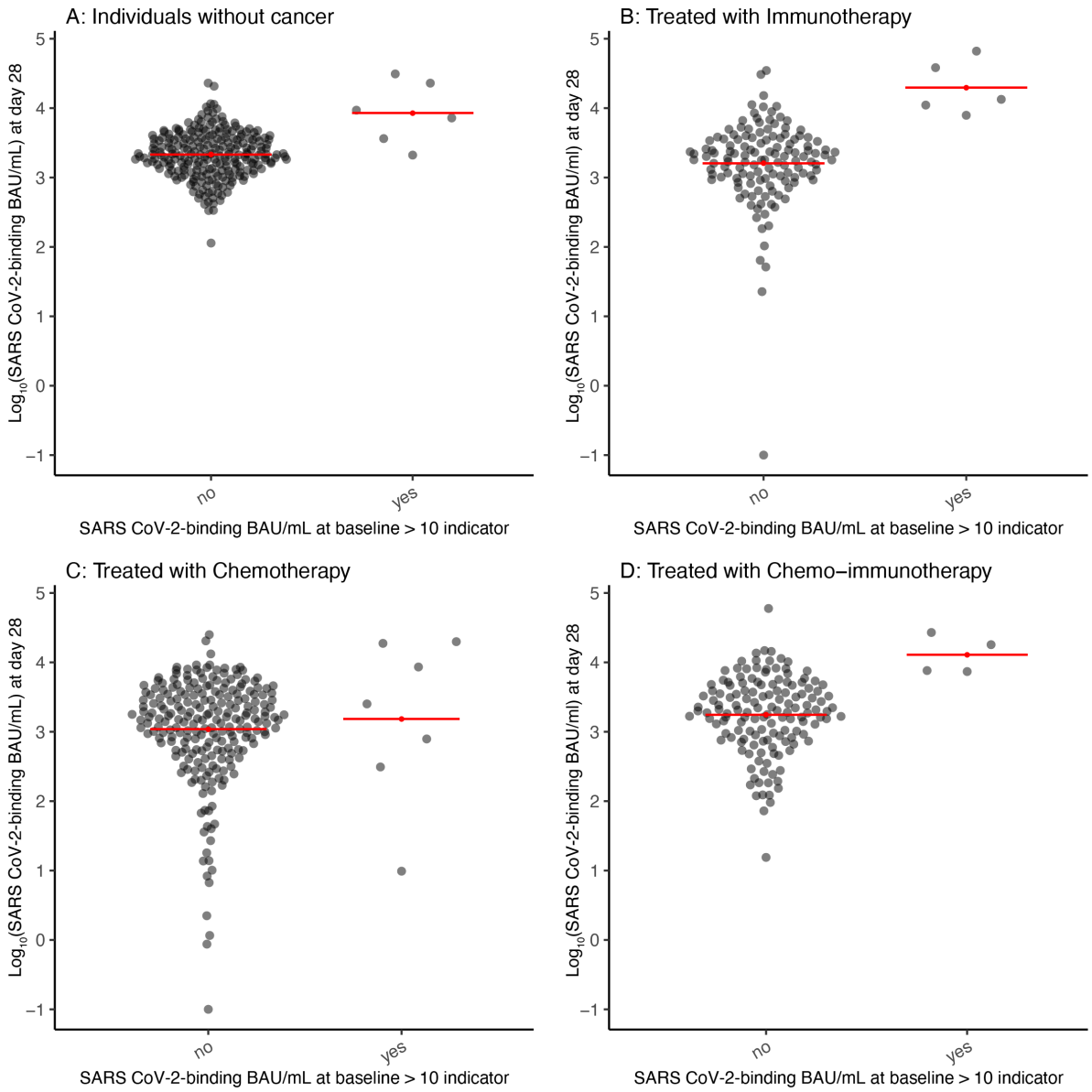


Figure S2. SARS-CoV-2-binding antibody concentration on day 28 after the second vaccination in participants with SARS-CoV-2-binding antibody concentration >10 BAU/mL at baseline.
These participants (n=22) were not included in the per protocol population for the primary endpoint analysis since this antibody response indicates an earlier unrecognised SARS-CoV-2 infection in cohort A (participants without cancer), B (immunotherapy cohort), C (chemotherapy cohort) and D (chemo-immunotherapy cohort). Red line indicates the geometric mean.

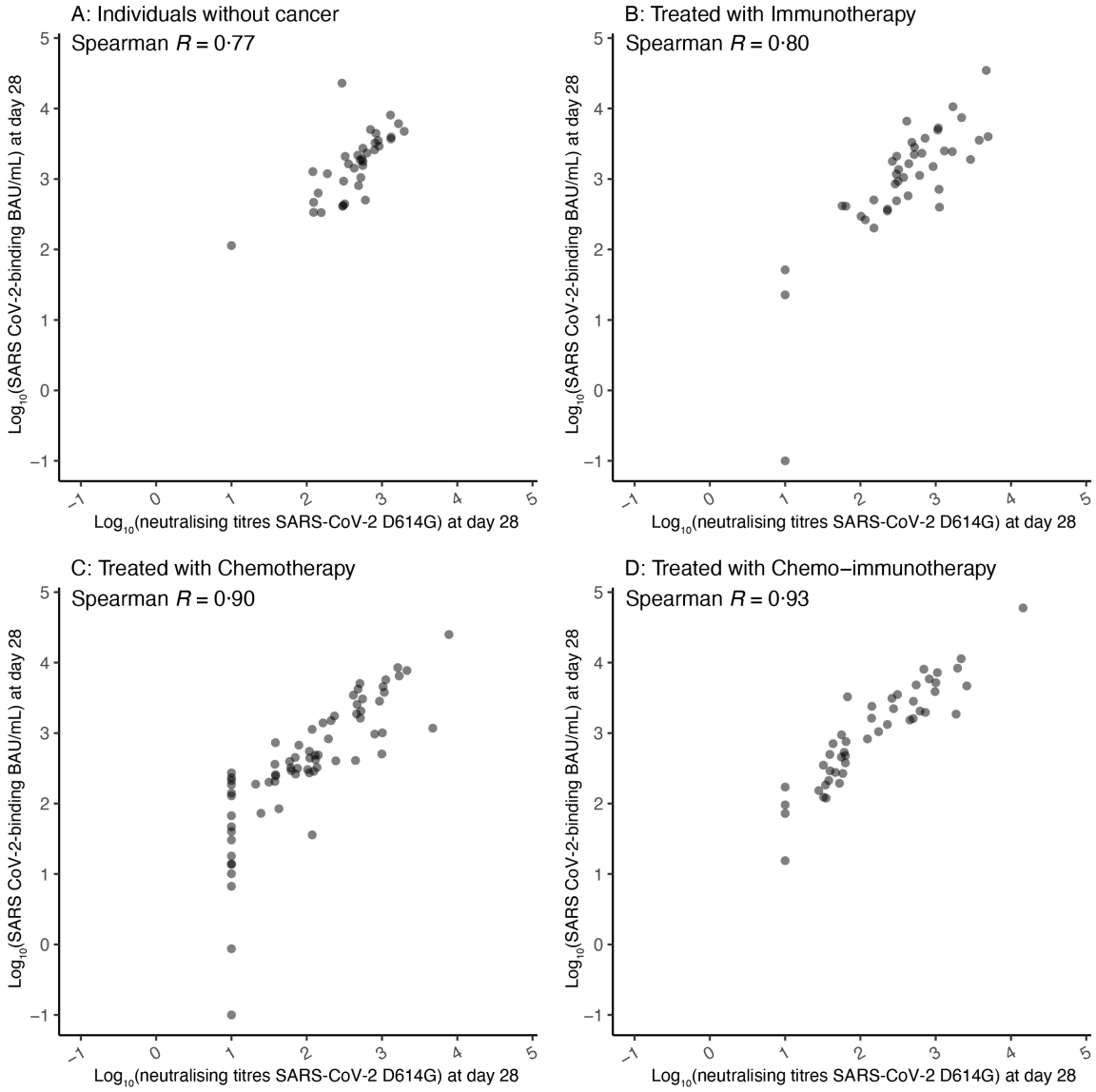


Figure S3. SARS-CoV-2 neutralising antibody titres versus SARS-CoV-2-binding antibody concentrations
Scatterplot of SARS-CoV-2-binding antibody concentrations in log10 transformed BAU/mL at day 28 after second vaccination versus neutralising log10 transformed titres for SARS-Cov-2 D614G at day 28 after second vaccination in the different cohorts. BAU=binding antibody units.

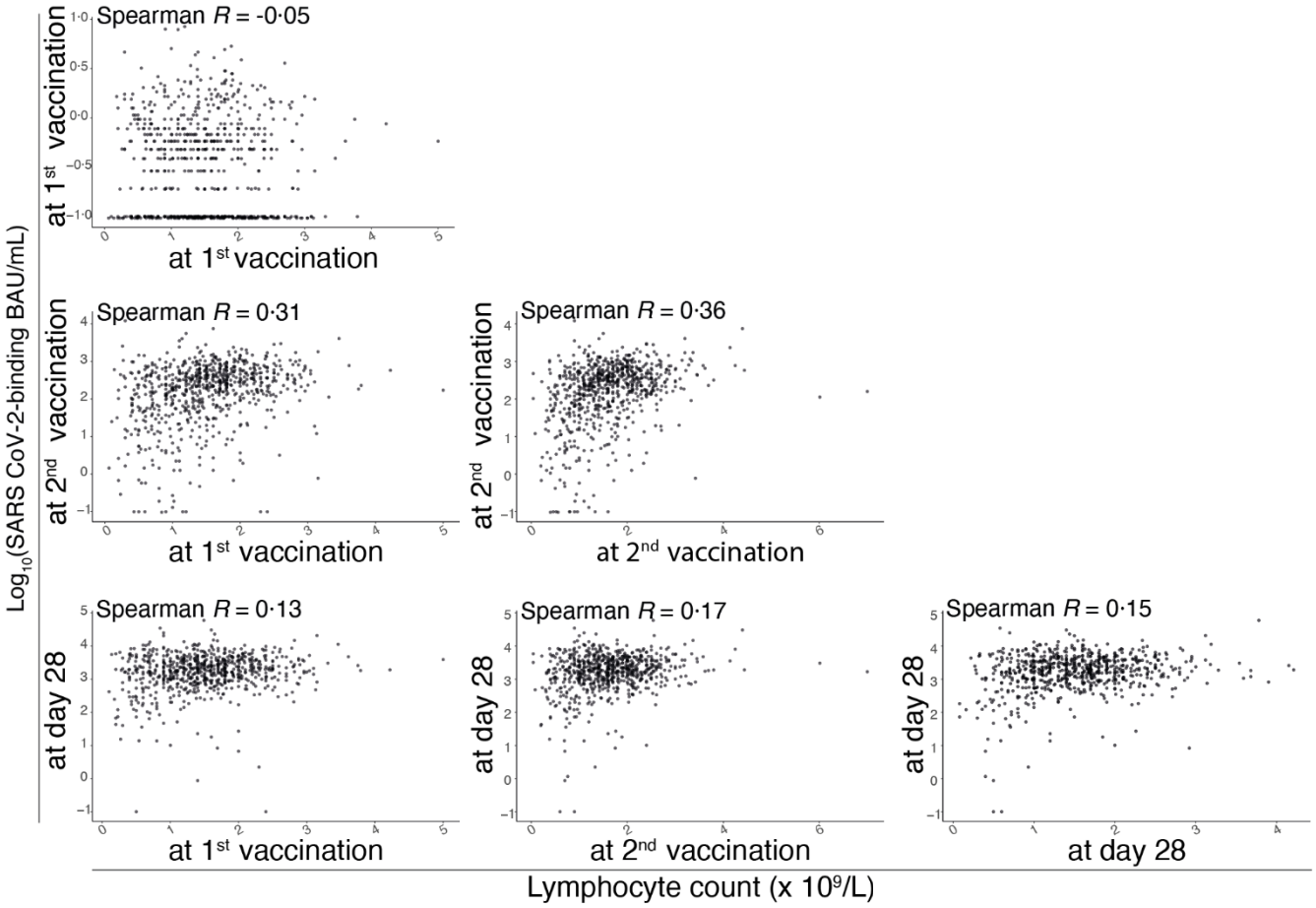


Figure S4. Association between lymphocyte count and SARS-CoV-2 binding antibody concentration.
Scatterplots of SARS-CoV-2-binding antibody concentrations in $\log_{10}$ transformed BAU/mL versus absolute lymphocyte count (x 10^9/L). Scatterplots are shown for measurements obtained at first and second vaccination day and at day 28 after second vaccination.

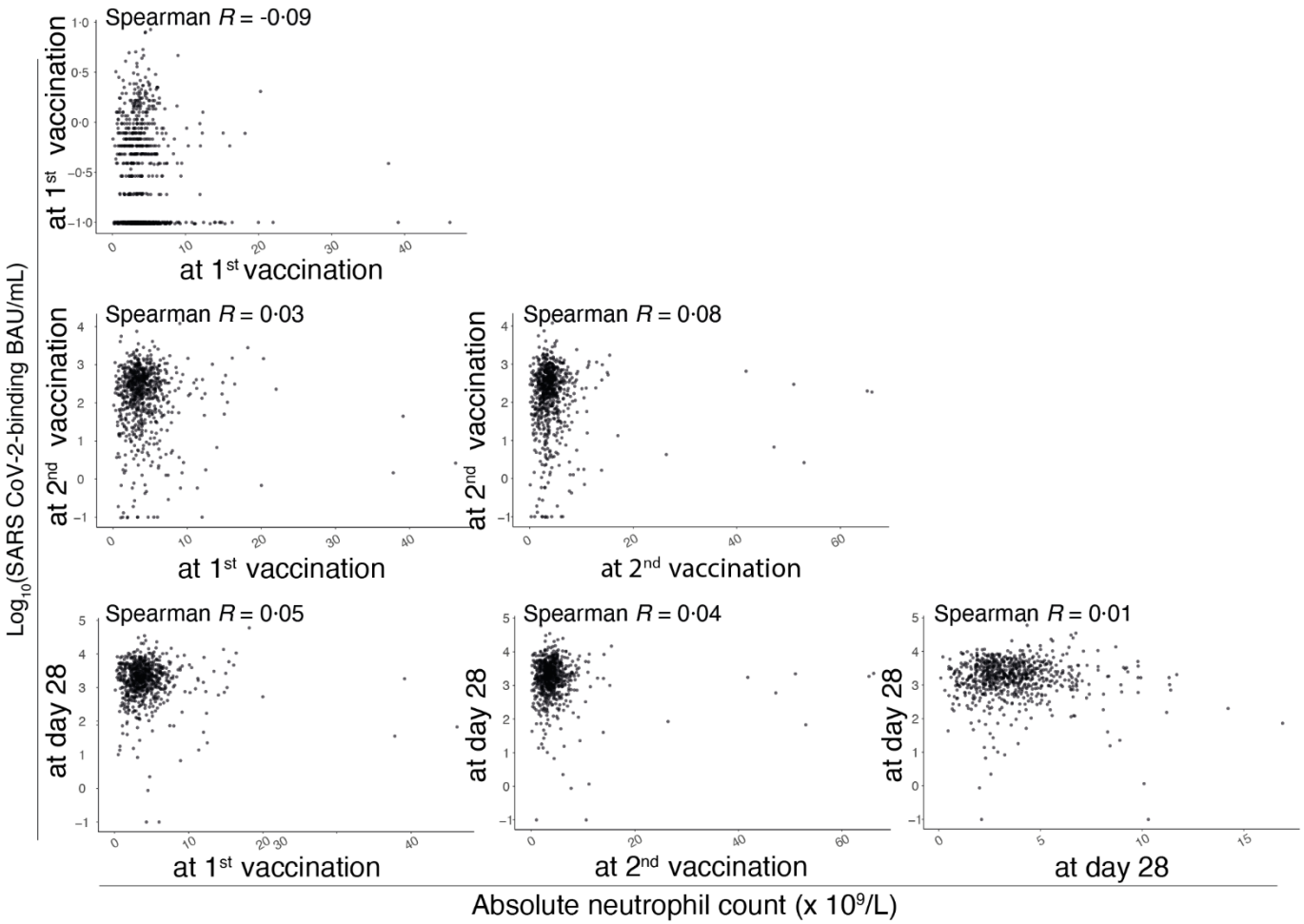


Figure S5. Association between neutrophil count and SARS-CoV-2-binding antibody concentration.
Scatterplots of SARS-CoV-2-binding antibody concentrations in $\log_{10}$ transformed BAU/mL versus absolute neutrophil count (x 10^9/L). Scatterplots are shown for measurements obtained at first and second vaccination day and at day 28 after second vaccination.

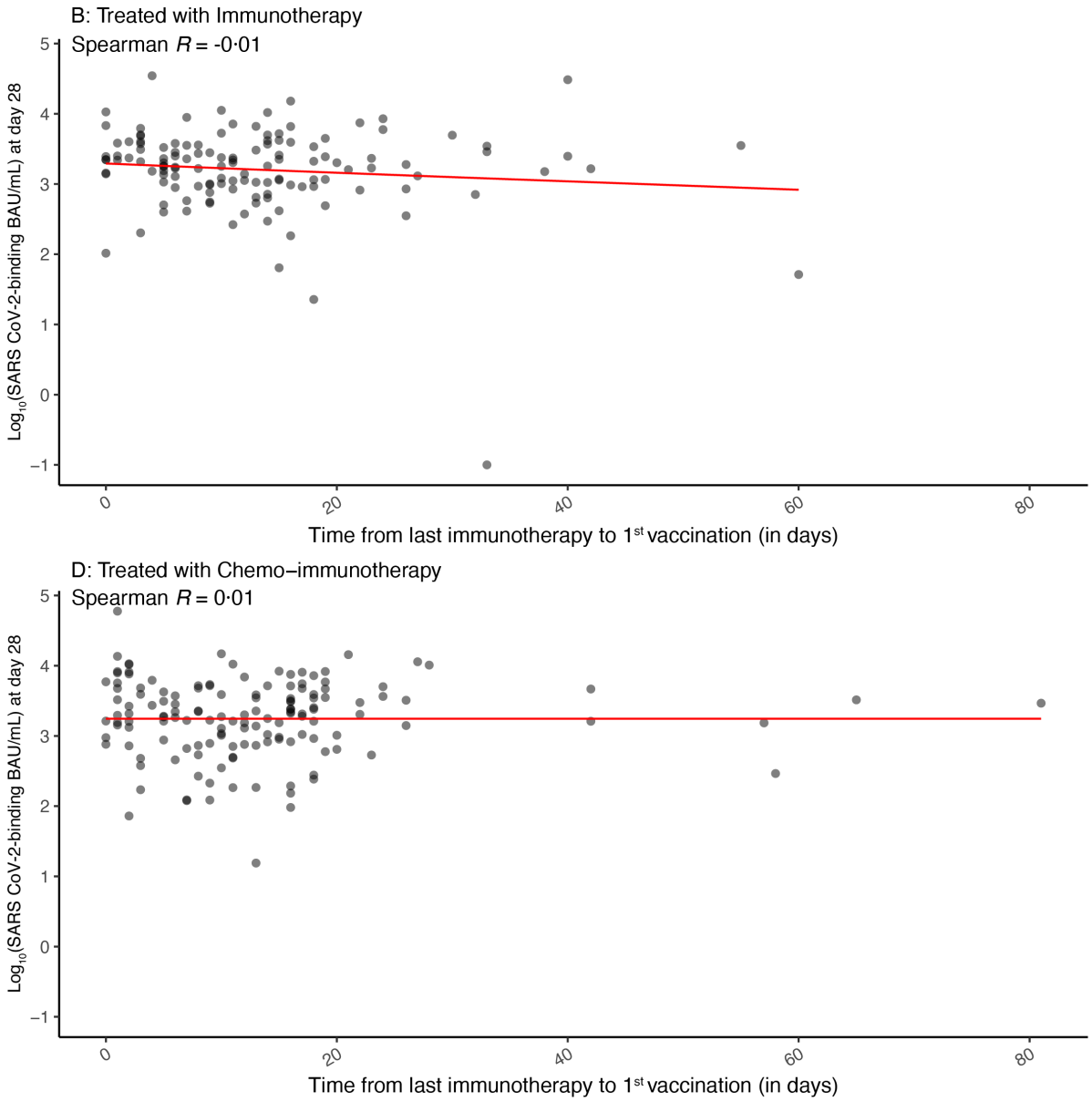


Figure S6A. Time between immunotherapy and first vaccination versus SARS-CoV-2-binding antibody concentration.
Scatterplot of SARS-CoV-2-binding antibody concentrations in $\log_{10}$ transformed BAU/mL at day 28 versus the interval between the most recent administration of immunotherapy prior to the first vaccination and day of first vaccination (in days) for cohorts B (immunotherapy) and D (chemo-immunotherapy).

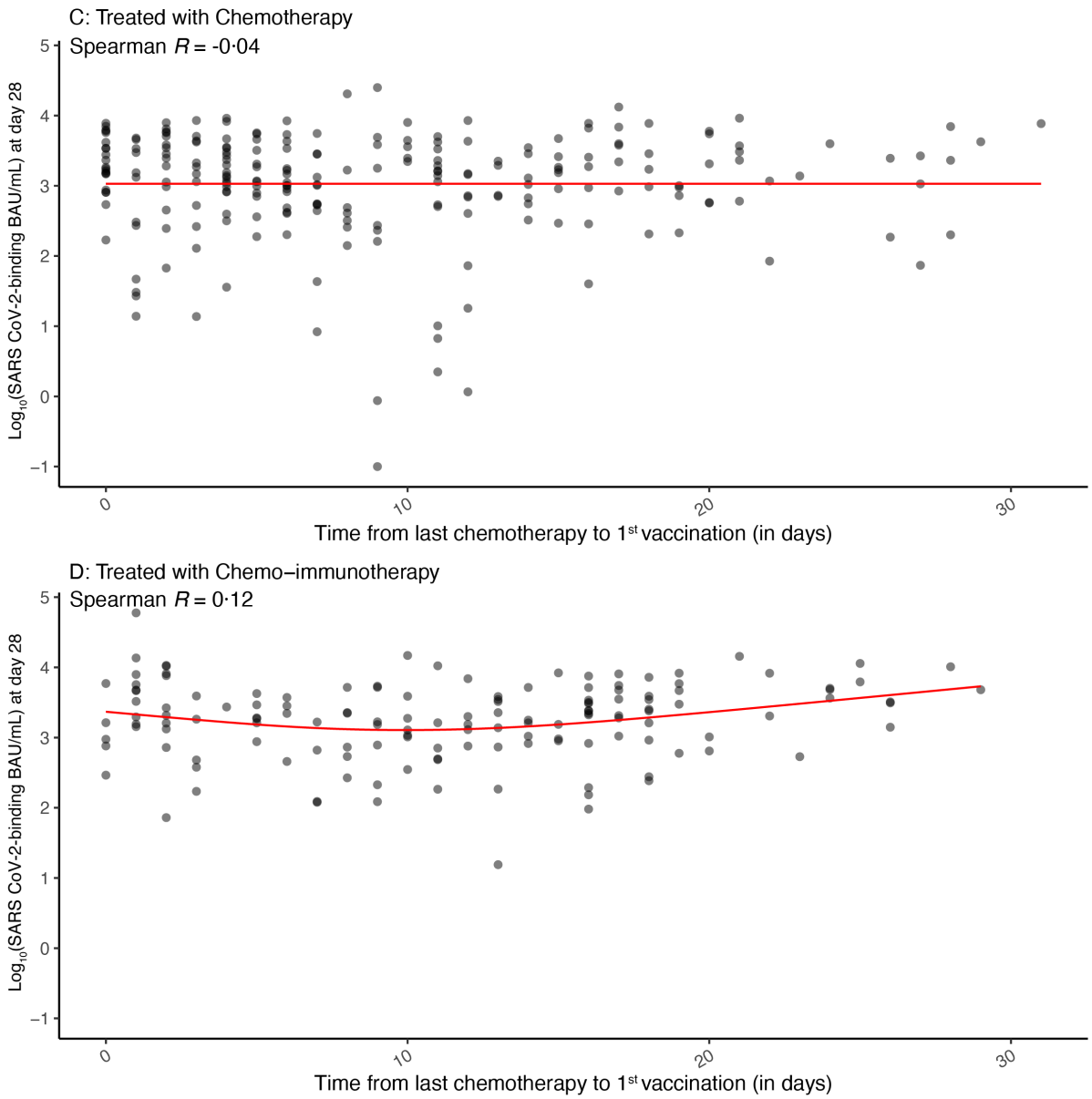


Figure S6B. Time between chemotherapy and first vaccination versus SARS-CoV-2-binding antibody concentration.
Scatterplot of SARS-CoV-2-binding antibody concentrations in $\log_{10}$ transformed BAU/mL at day 28 versus interval between the most recent administration of chemotherapy prior to the first vaccination and day of first vaccination (in days) for cohorts C (chemotherapy) and D (chemo-immunotherapy).

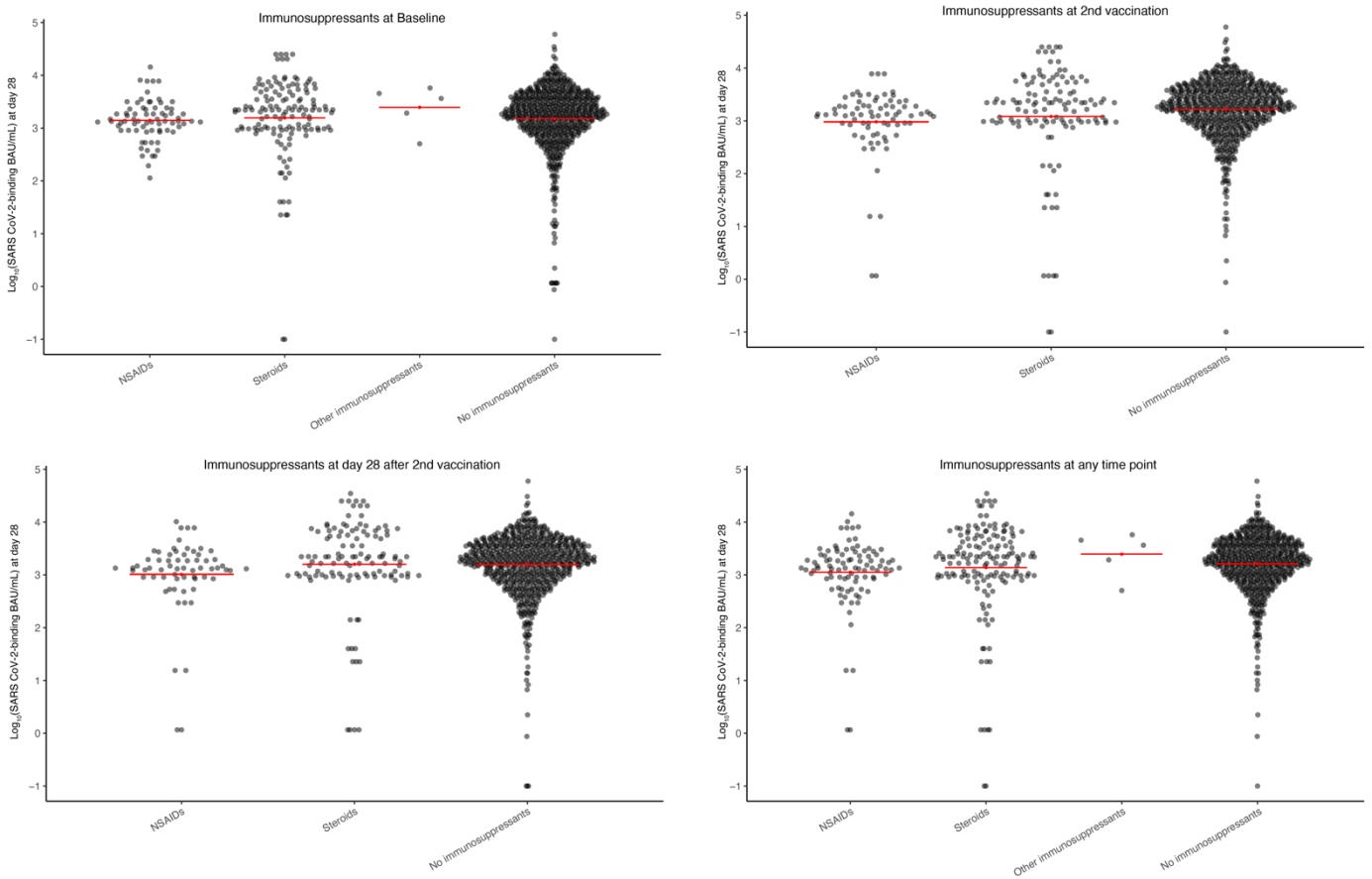


Figure S7. Use of immuno-suppressants versus SARS-CoV-2-binding antibody concentration.

Distributions of SARS-CoV-2-binding antibody concentrations in $\log_{10}$ transformed BAU/mL at day 28. Distributions are shown for participants who are using non-steroidal anti-inflammatory drugs (NSAIDs),* steroids, other immunosuppressants (mesalazine, tacrolimus, or pimecrolimus), or no immunosuppressants at the day of the first vaccination (baseline), at the day of the second vaccination, or at day 28 after the second vaccination.

** NSAIDs were included for analysis since NSAIDs may inhibit the inflammation reaction required for an adequate antibody response to vaccination and infections, including SARS-CoV-2 infection.*[9-11]

Section 4: Supplemental tables

Immunotherapy agents- no. (%)	
Atezolizumab	5 (3·8)
Avelumab	5 (3·8)
Cemiplimab	7 (5·3)
Durvalumab	2 (9·2)
Nivolumab	66 (50·4)
Pembrolizumab	36 (27·3)

Table S1. **Treatment Characteristics Immunotherapy Cohort (N=131).**

Treatment characteristic	
Radiochemotherapy - no. (%)	
Yes	39 (17·0)
No	190 (83·0)
Regimen – no. (%)	
Single agent chemotherapy	99 (43·2)
Doublet chemotherapy	115 (50·2)
Triplet chemotherapy	15 (6·6)
Chemotherapy regimens – no. (%)	
Bleomycin, Cisplatin, Etoposide	2 (0·9)
Cabazitaxel	5 (2·2)
Capecitabine	26 (11·4)
Capecitabine, Oxaliplatin	10 (4·4)
Capecitabine, Temozolomide	3 (1·3)
Carboplatin	4 (1·7)
Carboplatin, Cyclophosphamide	1 (0·4)
Carboplatin, Docetaxel	1 (0·4)
Carboplatin, Etoposide	3 (1·3)
Carboplatin, Gemcitabine	4 (1·7)
Carboplatin, Paclitaxel	41 (17·9)
Carboplatin, Pemetrexed	2 (0·9)
Cisplatin	6 (2·6)
Cisplatin, Docetaxel	1 (0·4)
Cisplatin, Etoposide	5 (2·2)
Cisplatin, Gemcitabine	4 (1·7)
Chloorambucil	1 (0·4)
Cisplatin, Pemetrexed	1 (0·4)
Cyclophosphamide, Docetaxel	1 (0·4)
Cyclophosphamide, Doxorubicin	15 (6·6)
Cyclophosphamide, Doxorubicin, Paclitaxel	4 (1·7)
Cyclophosphamide, Methotrexate	1 (0·4)
Dacarbazine, Doxorubicin	2 (0·9)
Docetaxel	8 (3·5)
Doxorubicin	6 (2·6)
Doxorubicin, Ifosfamide	1 (0·4)
Eribuline	1 (0·4)
Floxuridine	1 (0·4)
Fluorouracil	3 (1·3)
Fluorouracil, Irinotecan	7 (3·1)
Fluorouracil, Irinotecan, Oxaliplatin	5 (2·2)
Fluorouracil, Mitomycin	3 (1·3)
Fluorouracil, Oxaliplatin	8 (3·5)
Gemcitabine	3 (1·3)
Ifosfamide, Vincristine	1 (0·4)
Irinotecan	6 (2·6)
Lomustine, Procarbazine, Vincristine	4 (1·7)
Paclitaxel	13 (5·7)
Pemetrexed	2 (0·9)
Tegafur	2 (0·9)
Temozolomide	5 (2·2)
Trabectedin	3 (1·3)
Trastuzumab-emtansine	3 (1·3)
Vinblastine	1 (0·4)

Table S2. **Treatment characteristics chemotherapy cohort (N=229).**

Treatment characteristics	
Regimen– no. (%)	
Single-agent chemotherapy	43 (30·1)
Doublet chemotherapy	99 (69·2)
Triplet chemotherapy	1 (0·7)
Chemotherapy agents – no. (%)	
Capecitabine, Docetaxel, Oxaliplatin	1 (0·7)
Carboplatin	2 (1·4)
Carboplatin, Fluorouracil	1 (0·7)
Carboplatin, Cyclophosphamide	1 (0·7)
Carboplatin, Etoposide	2 (1·4)
Carboplatin, Gemcitabine	1 (0·7)
Carboplatin, Paclitaxel	20 (14·0)
Carboplatin, Pemetrexed	68 (47·6)
Cisplatin, Pemetrexed	5 (3·5)
Docetaxel	2 (1·4)
Pemetrexed	39 (27·3)
Immunotherapy agents – no. (%)	
Atezolizumab	11 (7·7)
Nivolumab	2 (1·4)
Pembrolizumab	130 (90·9)

Table S3. **Treatment characteristics chemo-immunotherapy cohort (N=143).**

Characteristic	Controls (N=247)	Immunotherapy (N=137)	Chemotherapy (N=244)	Chemo-immunotherapy (N=163)
Age, years (IQR)				
Median age	62 (55-69)	66 (58-74)	60 (50-67)	65 (58-70)
Sex – no. (%)				
Female	116 (47·0)	46 (33·6)	153 (62·7)	87 (53·4)
Male	131 (53·0)	91 (66·4)	91 (37·3)	76 (46·6)
Smoking – no. (%)				
Current	33 (13·4)	15 (10·9)	20 (8·2)	24 (14·7)
Former	91 (36·8)	73 (53·3)	106 (43·4)	123 (75·5)
Never	123 (49·8)	49 (35·8)	118 (48·4)	16 (9·8)
Mean body mass index (SD) †				
Mean	27·0 (4·0)	27·0 (4·5)	26·3 (4·6)	25·7 (5·2)
WHO performance status – no. (%)				
0	228 (92·3)	94 (68·6)	134 (54·9)	65 (39·9)
1	17 (6·9)	42 (30·7)	103 (42·2)	82 (50·3)
2	1 (0·4)	0	7 (2·9)	15 (9·2)
3	0	1 (0·7)	0	1 (0·6)
Unknown	1 (0·4)	0	0	0
Primary tumour localisation – no. (%)				
Bone or soft tissue		1 (0·7)	9 (3·7)	0
Breast		0	75 (30·7)	3 (1·8)
Central nervous system		0	10 (4·1)	0
Digestive tract		4 (2·9)	67 (27·5)	2 (1·2)
Endocrine glands		0	3 (1·2)	0
Female genital organs		0	24 (9·8)	0
Head and neck		2 (1·5)	6 (2·5)	1 (0·6)
Male genital organs		0	20 (8·2)	0
Respiratory tract		29 (21·2)	20 (8·2)	157 (96·3)
Skin		68 (49·6)	0	0
Urinary tract		32 (23·4)	10 (4·1)	0
Other/unspecified		1 (0·7)	0	0
Tumour stage – no. (%)				
I		2 (1·5)	16 (6·6)	0
II		2 (1·5)	38 (15·6)	0
III		34 (24·8)	52 (21·3)	10 (6·1)
IV		99 (72·3)	136 (55·7)	153 (93·9)
Unknown		0	1 (0.4)	0
Treatment intent – no. (%)				
Curative		45 (32·8)	121 (49·6)	19 (11·7)
Non-curative		92 (67·2)	123 (50·4)	144 (88·3)

* Percentages may not total 100 because of rounding
† The body-mass index is the weight in kilograms divided by the square of the height in meters
IQR, interquartile range; SD, standard deviation

Table S4. **Demographic and clinical characteristics of all participants included in the study at baseline.***

Adverse Event*	Controls (N=247)		Immunotherapy (N=137)		Chemotherapy (N=244)		Chemo-immunotherapy (N=163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Urinary tract infection	0	0	2 (1·5)	2 (1·5)	1 (0·4)	1 (0·4)	0	0
Fever	0	0	0	0	1 (0·4)	0	2 (1·2)	0
Sepsis	0	0	1 (0·7)	1 (0·7)	0	0	1 (0·6)	1 (0·6)
Diarrhoea	0	0	0	0	0	0	1 (0·6)	0
Febrile neutropenia	0	0	0	0	1 (0·4)	1 (0·4)	0	0
Ischemia cerebrovascular	0	0	0	0	0	0	1 (0·6)	0
Lung infection	0	0	1 (0·7)	0	0	0	0	0
Mucositis oral	0	0	0	0	1 (0·4)	1 (0·4)	0	0
Peripheral ischaemia	0	0	0	0	1 (0·4)	1 (0·4)	0	0
Skin infection	0	0	0	0	1 (0·4)	1 (0·4)	0	0
Vomiting	0	0	0	0	1 (0·4)	1 (0·4)	0	0

* Serious adverse events (SAEs) that occurred within 7 days after each vaccination were collected. Grading was done according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5·0.[12] SAEs considered related to vaccination: fever (2), diarrhoea (1), and febrile neutropenia (1).

Table S5. **Serious adverse events.**

Adverse Event	Immunotherapy (N=137)		Chemotherapy (N=244)		Chemo-immunotherapy (N=163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AESI †	4 (2·9)	3 (2·2)	7 (2·9)	7 (2·9)	8 (4·9)	8 (4·9)
Death (any cause)	1 (0·7)	1 (0·7)	3 (1·2)	3 (1·2)	6 (3·7)	6 (3·7)
Erythema multiforme / Stevens-Johnson syndrome	1 (0·7)	1 (0·7)	0	0	0	0
Other						
Thromboembolic event	1 (0·7)	0	1 (0·4)	1 (0·4)	2 (1·2)	2 (1·2)
Thromboembolic event and decreased platelet count	0	0	1 (0·4)	1 (0·4)	0	0
Myocardial infarction	1 (0·7)	1 (0·7)	1 (0·4)	1 (0·4)	0	0
Acute myeloid leukaemia	1 (0·7)	1 (0·7)	0	0	0	0
Convulsion	0	0	1 (0·4)	1 (0·4)	0	0

* Adverse events of special interest (AESIs) were collected for the patient cohorts. AESIs were defined in the protocol and included death from any cause, but also undefined AESIs could be reported. Grading was done according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5·0.[12] Eight patients died from progressive disease, one from pneumonitis, and one from acute myeloid leukaemia as secondary malignancy. AESIs considered related to vaccination were 2 thromboembolic events and erythema multiforme that progressed to Stevens-Johnson syndrome (SJS). The combination of low platelet count and thromboembolic event was considered not related: thrombocytopenia was chemotherapy-related, and thrombosis was preceded by thrombophlebitis at the site of an intravenous catheter.

† Numbers may not add up because some patients had more than one AESI.

Table S6. **Adverse events of special interest.***

Adverse Event*	Immunotherapy (N=137)		Chemo-immunotherapy (N=163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any irAE †	6 (4·4)	2 (1·5)	7 (4·3)	1 (0·6)
Pruritus	1 (0·7)	0	3 (1·8)	0
Arthritis	1 (0·7)	0	1 (0·6)	0
Rash maculo-papular	0	0	2 (1·2)	0
Adrenal insufficiency	1 (0·7)	1 (0·7)	0	0
Arthralgia	1 (0·7)	0	0	0
Hepatitis	1 (0·7)	0	0	0
Hypothyroidism	1 (0·7)	0	0	0
Platelet count decreased	1 (0·7)	1 (0·7)	0	0
Pneumonitis	0	0	1 (0·6)	1 (0·6)

* Newly occurring immune-related adverse events (irAEs) up to 28 days after the second vaccination were collected in patients receiving immunotherapy (cohort B) and chemo-immunotherapy (cohort D). Grading was done according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5·0.[12] One patient died from pneumonitis.
† Numbers may not add up because some patients had more than one irAE.

Table S7*. Immune related adverse events.

Section 5: Supplemental references

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12. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, National Cancer Institute, November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Section 6: Recruitment in participating institutes

Institute	Principal investigator	Number of included participants
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University Medical Centre Groningen, Groningen, the Netherlands	Sjoukje Oosting MD, PhD	263
Erasmus Medical Centre, Rotterdam, the Netherlands	Astrid AM van der Veldt MD, PhD	260

Section 1: Study protocol

Vaccination against cOvid In CancEr

(March 2021)

PROTOCOL TITLE: **VOICE Vaccination against cOvid In CancEr**

Protocol ID	Will be submitted to ClinicalTrials.gov.
Short title	VOICE
Version	4.1
Date	14 March 2021
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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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Project leader: E.G.E. de Vries, MD, PhD		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AESI	**Adverse Event of Special Interest**
ALAT	**Alanine aminotransferase**
ASAT	**Aspartate aminotransferase**
CBG	**College ter Beoordeling van Geneesmiddelen**
CBS	**Centraal Bureau voor de Statistiek**
CI	**Confidence Interval**
COVID-19	**Coronavirus Disease 2019**
CRP	**C-reactive protein**
CTCAE	**Common Terminology Criteria for Adverse Events**
DSMB	**Data Safety Monitoring Board**
ECOG PS	**Eastern Cooperative Oncology Group Performance Status**
EMA	**European Medicines Agency**
EU	**European Union**
GBA	**Gemeentelijke Basis Administratie**
GCP	**Good Clinical Practice**
GMC	**Geometric Mean Concentration**
IC	**Informed Consent**
ICI	**Immune Checkpoint Inhibitor**
IKNL	**Integraal Kankercentrum Nederland**
IFN-ɣ	**Interferon-gamma**
irAE	**immune related Adverse Event**
IST	**Investigator Sponsored Trial**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MIA	**Multiplex Immunoassay**
NIBSC	**National Institute for Biological Standards and Control**
PBMC	**Peripheral Blood Mononuclear Cells**
PD1	**Programmed Death 1 (immune checkpoint)**
PD-L1	**Programmed Death-ligand 1 (immune checkpoint)**
PIF	**Participant Information Form**
(S)AE	**(Serious) Adverse Event**
SARS-CoV-2	**Severe Acute Respiratory Syndrome Coronavirus 2**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie**

	IB1-tekst
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WHO	**World Health Organization**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Patients with cancer have an increased risk of adverse outcome of COVID-19, which is determined by their underlying disease and/or cancer treatment. Therefore, vaccination of cancer patients against COVID-19 needs to be prioritized. However, (ongoing) phase III studies, that will be the basis of vaccine registrations, will not provide robust information on efficacy and safety in this vulnerable population. In patients with cancer, the disease itself, but also immunotherapy and chemotherapy, may have a significant impact on the ability to develop an effective immune response to COVID-19 vaccination, and could even increase the risk of adverse events.

Objective: To assess immune response and adverse events after administration of one approved vaccine against COVID-19 in patients with cancer treated with immunotherapy and/or chemotherapy.

Study design: This is a prospective multicenter, multicohort study.

Study population: Four cohorts will receive vaccination against COVID-19:
A. Individuals without cancer (N=246, i.e., partners of patients in cohort B, C, and D)
B. Patients with cancer treated with immunotherapy (N=135)
C. Patients with cancer treated with chemotherapy (N=246)
D. Patients with cancer treated with chemo-immunotherapy (N=246)
Main inclusion criteria:
- age of 18 years or older
- life expectancy > 12 months
- ability to provide informed consent
- last immunotherapy cycle within 3 months of vaccination (cohort B and D)
- last chemotherapy cycle within 4 weeks of vaccination (cohort C and D)
Main exclusion criteria:
- confirmed SARS-CoV-2 infection (current or previous)
- women who are pregnant or breastfeeding
- active hematologic malignancy
- immune deficiency not related to cancer or cancer treatment
- systemic treatment with immune suppressive medication, including chronic steroid use of >10 mg prednisone or equivalent

Intervention: Participants will be vaccinated against COVID-19 with an approved vaccine. Blood will be drawn at 4 different time points by venipuncture and at 1 time point by a finger prick and mucosal lining fluid will be collected at 2 time points.

Main study parameters/endpoints: The primary endpoint is the antibody based immune response on day 28 after the second vaccination. Participants will be classified as responders or non-responders. The definition of response is seroconversion defined as presence of SARS-CoV-2 spike S1-specific IgG antibodies in individuals without measurable anti-S antibodies at baseline. Participants who are seropositive at baseline will not be included in the analysis of the primary endpoint. The percentage of responders of each patient cohort will be compared with the percentage responders in the control group. Safety is a secondary endpoint which will be reported in terms of percentage of solicited local and systemic adverse events (AEs) graded according to severity. Other secondary endpoints include longevity at 6 months and levels of SARS-CoV-2 specific T cell responses.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will have to visit the hospital at 4 time points. The vaccine will be administered two times according to the standard of care. Blood will be drawn (~235 ml in total) prior to both vaccinations and at day 28 and 6 months after the second vaccination. Nasal mucosal lining fluid samples will be collected at baseline and day 28 after the second vaccination in a subgroup of patients. Twelve months after vaccination participants will receive a finger prick set with instructions for self-collection of a blood sample. Blood sampling will give minor discomfort, mucosal lining fluid collection is a non-invasive procedure. Vaccination can cause AEs including fatigue, chills, headache, myalgia, and pain at the injection site. For seven days after each vaccination, participants will be asked to record local and systemic reactions using a questionnaire. At baseline and at 3, 6, 9 and 12 months after vaccination, patients will be asked to complete questionnaires about potential subsequent testing for SARS-CoV-2, diagnosis of COVID-19, and severity of COVID-19.

This study will collect information on immune response and adverse events after vaccination against COVID-19 in a vulnerable patient cohort. Understanding the ability or disability to mount a protective immune response after vaccination will help to counsel patients during the pandemic and support decisions on whom to vaccinate and to identify patients who require other measures to protect them from COVID-19. Participants will be informed about their antibody titer in a letter that includes an explanation about what this means to them. This will

be done after antibody measurements have been completed for day 28 after vaccination, and again after 6 months and after 12 months.

1. INTRODUCTION AND RATIONALE

1.1 Impact of COVID-19 pandemic on oncological care

The SARS-CoV-2 pandemic is having a huge impact on societies all around the globe. As of December 8, 2020, over 65 million people have been diagnosed with Coronavirus induced disease (COVID-19), resulting in over 1,5 million deaths with numbers still increasing [1,2]. Over the past 6 months, regular health care, including cancer care [3,4], has been scaled down because hospitals were flooded with patients with COVID-19. In addition, hospital visits for anticancer therapies may put patients at even more risk of getting infected with SARS-CoV-2 [5,6]. As the COVID-19 pandemic overwhelmed healthcare systems worldwide, non-evidence-based decisions had to be made about the treatment of patients with cancer. Consequently, oncological treatment was frequently adjusted during the COVID-19 pandemic, even in regions with relatively low COVID-19 incidence [3]. These treatment adjustments were made according to COVID-19 guidelines of (inter)national oncological societies, which were primarily based on expert opinions [7-10]. The limited capacity to deliver cancer care, the lockdown isolating patients at home, and their fear of entering hospitals, has led to suboptimal cancer care. In addition, there was a 30% underdiagnosis and delayed diagnosis of cancer in the Netherlands [11,12]. This most likely will result in higher cancer-specific mortality rates in the years to come.

1.2 Outcome of COVID-19 in patients with cancer

Patients with cancer have a higher risk for a dismal outcome of COVID-19 [13-15]. Therefore, international registries have been initiated to identify the clinical characteristics of cancer patients with severe COVID-19 [5,6, 16-25]. The worse outcome of COVID-19 in patients with cancer is determined by their underlying disease and/or cancer treatment. In particular, lung cancer and hematological malignancies are independent risk factors for a fatal outcome of COVID-19 [4]. In addition, chemotherapy and chemo-immunotherapy have been identified as risk factors for mortality of COVID-19 in patients with cancer [26,27].

1.3 COVID-19 vaccination

Several vaccines are currently in development and the RNA vaccines by BioNTech/Pfizer and Moderna [28-31], were granted conditional marketing authorization by EMA. Vaccination of the Dutch population has started in January 2021. For the VOICE study the mRNA-1273 SARS-CoV-2 vaccine from Moderna will be used. In the randomized phase III study with

mRNA-1273, 30,420 volunteers received two intramusluclar injections of the vaccine (100 ug) or placebo 28 days apart [32]. None of the participants was treated with chemotherapy and/or immunotherapy for cancer at the time of vaccination. In the placebo group 185 participants developed symptomatic COVID-19 versus 11 participants who received the vaccine, resulting in 94.1% vaccine efficacy (95% CI, 89.3 to 96.8%; P<0.001). Severe COVID-19 only occurred in the placebo group: in 30 participants including one fatality. Solicited AEs at the injection site were common in the vaccine group (84.2% after the first injection and 88.6% after the second injection) but mainly low grade and of short duration. Solicited systemic AEs in this group were reported by 54.9% of the participants after the first dose and by 79.4% after the second dose, and mainly consisted of headache, fatigue, myalgia and chills. The rate of unsolicited AEs and SAEs up to 28 days after vaccination was similar in both arms. Hypersensitivity reactions occurred in 1.5% in the vaccine group and 1.1% in the placebo group.

1.4 COVID-19 vaccination in patients with cancer

Patients with cancer have an increased risk for an adverse outcome of COVID-19 [13-15]. As a consequence, many patients strictly adhere to self-isolation, resulting in loneliness and loss of quality of life. Therefore, vaccination needs to be prioritized for these vulnerable patients. In addition, effective COVID-19 vaccination is of extreme importance to protect patients with cancer to continue care and cure. An immune response to vaccination would not only protect them from life-threatening COVID-19 but also allow close contact with their loved ones. Therefore, patients and patient organizations have already claimed prioritization of vaccination against COVID-19 for patients with cancer.

For proper protection against COVID-19 by vaccination, specific immune responses need to be induced. SARS-CoV-2 specific immune cells are essential to combat the virus. B cells are important for antibody responses to neutralize the virus, while CD8 positive T cells can specifically recognize and eradicate virus-infected cells. In addition, CD4 positive T cells are required for providing necessary help to B cells and CD8 positive T cells. Cancer immunotherapy activates T cells against cancer cells by blocking the interaction between Programmed Death 1 (PD1) and its ligand (PD-L1) [33]. How this treatment impacts immune responses to vaccination is unknown. Chemotherapy causes bone marrow suppression and reduces the number of immune cells in the blood circulation, which may hamper the induction of protective immune responses after vaccination as suggested in studies on influenza vaccination [34]. However, it is striking how little information is available on safety and efficacy of vaccination in cancer patients. As compared to the healthy population, patients with cancer treated with immunotherapy and/or chemotherapy may be more prone to adverse events of vaccination. Immunotherapy could potentially result in an augmented immune response to vaccination resulting in fever, chills, and other immune-related adverse events. Chemotherapy is known for significant fatigue, which impacts performance status and increases vulnerability. As a result, immunotherapy and chemotherapy may have a significant impact on the effectiveness but also on the safety of COVID-19 vaccination. To protect patients with cancer from COVID-19, clinical trials are urgently needed to evaluate whether they develop an effective, safe, and durable immune response during immunotherapy and/or chemotherapy.

1.5 Current trial

The one central question is whether patients with cancer and especially those requiring systemic treatment, can develop protective immunity against COVID-19 upon vaccination. This question needs to be answered urgently and would help the medical oncology community to decide whether optimal cancer care can be delivered safely to vaccinated

patients with cancer. In the VOICE trial, this important question will be addressed in a longitudinal cohort in which patients with solid cancers requiring systemic therapy will be vaccinated with the available COVID-19 vaccine according to the Dutch vaccination program. Patients with hematologic malignancies are not included in this study because it is known from influenza vaccination studies that those patients are frequently not able to build an effective immune response [35]. This means that protection of patients with a hematologic malignancy may require a different protective strategy such as treatment with SARS-CoV-2 specific antibodies.

In the VOICE study, the ability to mount antibody responses, will be measured in three cohorts of patients treated with chemotherapy, immunotherapy, or chemo-immunotherapy. Their immune response to COVID-19 vaccination will be compared to the immune response of participants without cancer and vaccinated with the same vaccine. Next to measuring antibody responses and their kinetics over time, also an in-depth analysis of T cell immunity, side effects of vaccination, SARS-CoV-2 infection rate, and severity of COVID-19 will be assessed. The VOICE trial will address a high unmet medical need, i.e., vastly gathering information on vaccine safety and effectiveness in one of the most vulnerable populations and could serve as a model for studies in other fragile populations. Understanding the ability or disability to mount a protective immune response to a COVID-19 vaccine will help to counsel patients with cancer during this pandemic. Moreover, it will support decisions how to administer the best cancer care safely.

2. OBJECTIVES

Primary Objective:

- To assess the antibody based immune response after vaccination against COVID-19 in patients with cancer treated with immunotherapy and/or chemotherapy as compared to controls

Secondary Objectives:

- To assess adverse events (AEs) after vaccination against COVID-19 in patients with cancer treated with immunotherapy and/or chemotherapy
- To assess durability of the antibody response in patients with cancer treated with immunotherapy and/or chemotherapy
- To analyze the SARS-CoV-2 specific T cell response after vaccination in patients with cancer treated with immunotherapy and/or chemotherapy

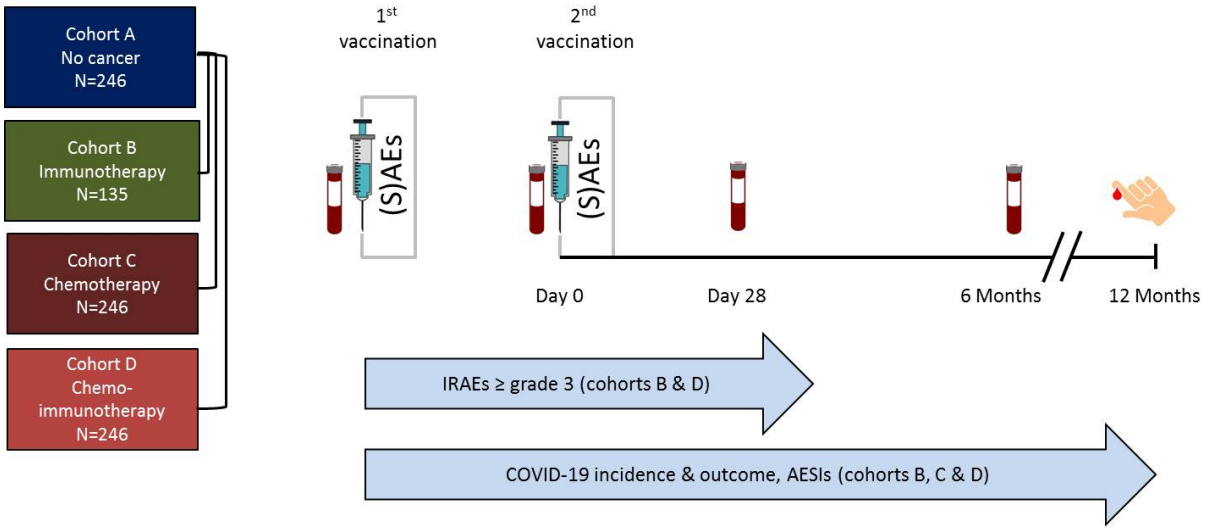
Exploratory Objectives:

- To perform in-depth analysis of cellular immune responses in patients with cancer treated with immunotherapy and/or chemotherapy
- To identify baseline (immune) parameters associated with vaccination response in patients with cancer treated with immunotherapy and/or chemotherapy
- To assess the neutralizing capacity of antibodies against SARS-CoV-2 after vaccination in patients with cancer treated with immunotherapy and/or chemotherapy
- To analyze induction of mucosal antibodies against SARS-CoV-2 in mucosal lining fluid samples. To describe the incidence of SARS-CoV-2 infection, outcome of COVID-19 during 12 months after vaccination in patients with cancer treated with immunotherapy and/or chemotherapy

3. STUDY DESIGN

This is a prospective multicenter cohort study, designed to evaluate the immune response and safety after vaccination against COVID-19 in three cohorts with cancer patients and one cohort of participants without cancer (see Fig.1). The patient cohorts are defined by type of cancer treatment. Immunotherapy, chemotherapy and chemo-immunotherapy were chosen because these treatment regimens may affect the efficacy and safety of vaccination against COVID-19 in different ways.

Figure 1. Trial design



To reflect the real-world population of patients with cancer treated with immunotherapy and/or chemotherapy, this trial is designed as inclusive as possible. Exclusion criteria are minimal and serve to exclude patients who are not evaluable, or in whom vaccination is considered not safe or not effective. A cohort of volunteers without a cancer diagnosis is included for comparison. Because age is an important predictor of the ability to mount an effective immune response to vaccination [36], partners of patients are enrolled in cohort A. We will take care that from all patient cohorts partners are approached, until cohort A is complete. We anticipate that accrual of cohort A will be completed earlier than the patient cohorts.

All participants will receive two vaccinations against COVID-19 according to standard of care. To assess immune responses after vaccination, blood samples will be collected at baseline (i.e. prior to first vaccination), at the day of the second vaccination and at day 28 and 6 months after the second vaccination by venipuncture, and at 12 months after vaccination by finger prick. To evaluate hematology, liver and kidney function, additional blood samples will

be collected at baseline, at the day of the second vaccination, and at day 28 and 6 months after the second vaccination. Nasal mucosal lining fluid will be collected at baseline and at day 28 after the second vaccination according to a non-invasive sampling method.

To evaluate vaccination related AEs, patients will be asked to collect solicited local and systemic AEs for 7 days after each vaccination using a questionnaire. Similarly serious AEs (SAEs) will be collected for 7 days after each vaccination. Most patients who receive systemic cancer treatment experience multiple AEs that are cancer treatment related, or disease related. As vaccination related AEs are mainly expected within the first week after vaccination, it is not useful to collect all AEs for a prolonged period. Instead, all newly occurring immune related AEs (irAEs) are collected for the immunotherapy and chemo-immunotherapy cohorts (B and D) up to 28 days after the second vaccination. irAEs are toxicities from immune checkpoint inhibitors and do not include infusion reactions [37]. Furthermore, adverse events of special interest (AESIs) will be collected for the duration of the study in the patient cohorts.
Information on incidence of SARS-CoV-2 infection, outcome of COVID-19 during 12 months after vaccination will be collected using questionnaires. For the study participants who give separate consent, information on positive corona tests during the study will also be collected from the RIVM.
Although this study is not powered to detect differences in protection against COVID-19 between patients and controls, information on incidence of SARS-CoV-2 infection, outcome of COVID-19 will be collected up to 12 months after vaccination for descriptive purposes.

4. STUDY POPULATION

4.1 Population (base)

4.2 Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Age of 18 years or older
- Life expectancy > 12 months
- Ability to provide informed consent

Additional criteria for cohort A:

- Partner of a participating patient

Additional criteria for cohort B:

- Histological diagnosis of a solid malignancy
- Treatment with monotherapy immune checkpoint inhibitor (ICI) against Programmed Death 1 (PD1) or its ligand PD-L1 (in curative or non-curative setting)
- Last ICI administration within 3 months of vaccination

Additional criteria for cohort C:

- Histological diagnosis of a solid malignancy
- Treatment with cytotoxic chemotherapy (monotherapy and combination chemotherapy is allowed, as well as a combination with radiotherapy, in curative or non-curative setting)
- Last chemotherapy administration within 4 weeks of vaccination

Additional criteria for cohort D:

- Histological diagnosis of a solid malignancy
- Treatment with a PD1 or PD-L1 antibody in combination with cytotoxic chemotherapy (in curative or non-curative setting)
- Last chemotherapy administration within 4 weeks of vaccination
- Last ICI administration within 3 months of vaccination

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Confirmed SARS-CoV-2 infection (current or previous)
- Women who are pregnant or breastfeeding
- Active hematologic malignancy

- Any immune deficiency not related to cancer or cancer treatment (e.g. inherited immune deficiency or known infection with Human Immunodeficiency Virus)
- Systemic treatment with corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of vaccination. Inhaled or topical steroids, and adrenal replacement steroids (> 10 mg daily prednisone equivalent) are permitted. In addition, standard of care with short course steroids to prevent nausea and allergic reactions from chemotherapy or iodinated CT contrast is allowed.

Additional criteria for cohort A:

- Current or previous diagnosis of a solid malignancy, unless treated with curative intent >5 years before enrolment and without signs of recurrence during proper follow-up
- Previous history of a hematologic malignancy

Additional criteria for cohort B:

- Treatment with cytotoxic chemotherapy within 4 weeks of vaccination

Additional criteria for cohort C:

- Treatment with an ICI within 3 months of vaccination

4.4 Sample size calculation

The primary endpoint is the antibody based immune response on day 28 after the second vaccination in patients receiving cancer treatment as compared to individuals without cancer. Participants are classified as responders or non-responders to vaccination against COVID-19. In patients treated with immunotherapy, we assume that the immune response rate is similar to that in individuals without cancer. In patients treated with chemotherapy or chemo-immunotherapy, we expect a lower immune response rate. As the percentage of responders is still unknown for vaccination against COVID-19, especially when a lower rate of immune response is expected, a power calculation for different scenarios has been performed, thereby comparing cohorts B, C, and D separately with cohort A.

Patients receiving immunotherapy (cohort B) *vs.* individuals without cancer (cohort A)

We assume that 90% of the individuals without cancer will be responders and that this will be similar in patients receiving immunotherapy. If there is truly no difference (90% responders in both groups), then 112 individuals without cancer and 112 patients are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the individuals without cancer of more than 10%.

Patients receiving chemotherapy (cohort C) or chemo-immunotherapy (cohort D) *vs.* individuals without cancer (cohort A)

For patients receiving chemotherapy or chemo-immunotherapy, we expect a lower percentage of responders compared to the group without cancer based on influenza vaccination trials [29]. However, the percentage of responders is still unknown for vaccination against COVID-19. Therefore, we performed a power calculation for two different scenarios, 1) anticipated true response rate in the groups receiving chemotherapy and chemo-immunotherapy of 60% and 2) anticipated true response rate in the groups receiving chemotherapy and chemo-immunotherapy of 40%.

Scenario 1: If there is a true difference in favor of the group without cancer of 30% (90% *vs.* 60%), then 205 individuals without cancer and 205 patients in cohort C and D are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the group without cancer of more than 40%.

Scenario 2: If there is a true difference in favor of the group without cancer of 50% (90% *vs.* 40%), then 205 individuals without cancer and 205 patients in cohort C and D are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the group without cancer of more than 50%.

In summary, these power calculations indicate that for the cohort C *vs.* cohort A comparison and for the cohort D *vs.* A comparison we need a total of 205 individuals without cancer , 205 patients treated with chemotherapy and 205 patients treated with chemo-immunotherapy. With these numbers we have enough power to assess non-inferiority in both scenarios with an alpha of 0.05 and 80% power.

Correction for drop-out

We expect that a proportion of the participants will already have SARS-CoV-2 antibodies at baseline and will not be evaluable for the primary endpoint. In addition, we anticipate that there will be a drop-out of participants at later time points. Reasons for drop-out may include death or poor performance status as a result of progressive malignancy and/or cancer treatment related AEs. Therefore, we will correct for non-evaluable patients by increasing each cohort with 20%. This means that 246 participants will be recruited in cohorts A, C and D, and 135 participants will be enrolled in cohort B. In total, 873 participants (627 patients and 246 individuals without cancer) will be included.

5. TREATMENT OF SUBJECTS

Vaccination will be performed according to the standard of care. The name of the vaccine, batch number and date and time of administration will be recorded. This study investigates the immune response and AEs in a vulnerable population of patients who receive cancer treatment. If subjects had not participated in this study, they would have received the same vaccine or another registered vaccine against COVID-19 according to standard of care via their general practitioner without additional testing.

6. INVESTIGATIONAL PRODUCT

The product information of the approved mRNA-1273 SARS-CoV-2 vaccine administered to participants in this study is provided in Appendix 4.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint is the antibody based immune response to vaccination against COVID-19 on day 28 after the second vaccination in patients receiving cancer treatment as compared to individuals without cancer . Participants will be classified as responders or non-responders. The definition of response is seroconversion defined as presence of SARS-CoV-2 spike S1-specific IgG antibodies in individuals without measurable anti-S antibodies at baseline. Participants who are seropositive at baseline will not be included in the analysis of the primary endpoint (see paragraph 10.1). The percentage of responders of each patient cohort will be compared with the percentage responders in the group without cancer.

8.1.2 Secondary study parameters/endpoints

- Safety assessment through:
    - Incidence and severity of solicited AEs during 7 days after each vaccination (see Appendix 1)
    - Incidence and nature of SAEs during 7 days after each vaccination
    - Incidence and nature of newly occurring irAEs [37] grade ≥ 3 in cohort B and D up to 28 days after the last vaccination graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAEv5.0)
    - Incidence, nature and severity of AESIs (see Appendix 2) graded according to CTCAEv5.0
- In depth assessment of immune response through:
    - Measurement of SARS-CoV2 specific antibodies before the second vaccination to analyze initial response, and at 6 and 12 months after the second vaccination to measure longevity
    - Assessment of SARS-CoV2 specific T cells response at 28 days and 6 months after the second vaccination using a high throughput Interferon ɣ ELIspot

8.1.3 Exploratory study parameters

- In-depth flow-cytometric analyses for functional and phenotypical characterization of SARS-CoV-2 specific cellular immune responses will be performed followed by

assessment of proliferative capacity, cytokine production and phenotypical markers in a subset of patients

- To determine baseline (immune) parameters associated with immune response to COVID-19 vaccination
- To assess the induction of SARS-CoV-2-specific antibodies in mucosal lining fluid
- Neutralizing capacity of antibodies to test functionality. Information on incidence of SARS-CoV-2 infection, outcome of COVID-19 will be collected and reported during 12 months after vaccination. To this end, questionnaires will be used. Information on positive corona tests during the study will also be collected from the RIVM.

8.2 Randomization, blinding and treatment allocation

Not applicable.

8.3 Study procedures

This study is executed as a low-risk intervention trial, for which no labeling is required according to Annex 13. However, the vaccine release and drug accountability will be done according to GCP.

Table 1: Flow chart/time and events schedule

Procedure	Screening[a] (within 28 days)	Vacc 1	Vacc 2	Day 28[b] (± 3)	Day 90[b] (± 7)	Day 180[b] (± 7)	Day 270[b] (±7)	Day 360[b] (± 7)
Informed consent	x							
Inclusion/exclusion criteria	x							
Medical history	x							
Concomitant medication	x	x	x	x		x		
Smoking history	x							
ECOG PS[c]	x							
Height/weight	x							
Vital signs[d]	x	x	x					
Blood tests[e]		x	x	x		x		x
Nasal MLF collection[f]		x		x				
Sollicited adverse events[g]	x	x	x					
SAEs[h]		x	x					

irAEs[i]	x	x	x	x				
AESIs[j]		Will be reported for the entire duration of the study						
Vaccine administration[k]		x	x					
COVID-19 questionnaire[l]	x				x	x	x	x
Survival status						x		x

[a] Screening should be performed within 28 days prior to the first vaccination but can be done on the same day as the first vaccination.
[b] Day numbers are relative to the second vaccination. The time window allowed for Day 28 is + or – 3 days and for the other Days: + or – 7 days.
[c] ECOG performance status: see appendix 3.
[d] Vital signs: blood pressure, heart rate, temperature.
[e] See Table 2.
[f] MLF = mucosal lining fluid, will be collected using a synthetic absorptive matrix [38]
[g] Participants will complete a questionnaire for solicited systemic and local AEs on a daily basis from each vaccination until 7 days after each vaccination, see Appendix 1.
[h] SAEs that occur within 7 days of each vaccination will be reported
[i] Newly developed irAEs [37] grade ≥ 3 need to be reported for cohort B and D up to 28 days after the second vaccination.
[j] AESIs (see Appendix 2) will be reported by the treating physicians up to 12 months after vaccination for cohorts B-D.
[k] The name of the vaccine, batch number and date and time of administration will be recorded.
[l] Participants will complete a questionnaire for diagnosis of SARS-CoV-2 infection, severity and outcome of COVID-19.

Table 2: Blood tests

	Vacc1[a]	Vacc2[a]	Day 28	Day 180	Day 360
SARS-Cov-2 antibodies	x	x	x	x	x[d]
PBMC isolation for in depth cellular immune response	x		x	x	
Routine hematology[b]	x	x	x	x	
Routine chemistry[c]	x	x	x		

PBMC = peripheral blood mononuclear cells
[a] Blood has to be drawn before vaccination
[b] Hemoglobin, red blood cell count, platelet count, white blood cell count, white blood cell differential
[c] glucose, creatinine, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP).

[d] Obtained by finger prick

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Not applicable

8.6 Follow-up of subjects withdrawn from treatment

Participants who receive at least one dose of the vaccine will be monitored for AEs, SAEs, AESIs and irAEs according to the protocol (up to day 7 after both vaccinations for cohorts A and C and up to day 28 after the second vaccination for cohorts B and D). If the subject does not withdraw consent, also blood samples will be drawn according to the protocol.

8.7 Premature termination of the study

Not applicable since vaccination is standard of care.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, AESIs and SUSARs

9.2.1 Adverse events (AEs)

AEs are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to COVID-19 vaccination. In this study, solicited AEs will be reported by all participants on a daily basis for 7 days after each vaccination.

9.2.2 Serious Adverse events (AEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs that occur within 7 days of administration of the vaccine to the PI without undue delay after obtaining knowledge of the events.

The coordinating investigator, the PI or delegated trial personnel will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) and serious adverse events (SAEs) frequently occur in patients with cancer who receive systemic therapy as a result of the cancer treatment or the underlying disease. Therefore, AESIs will be collected in this study (see Appendix 2). Treating physicians from patients in cohorts B, C and D will report AESIs to the PI. The coordinating investigator, the PI or delegated trial personnel will report the AESIs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after first knowledge of the AESIs.

Since the vaccine is a registered agent, and the number of controls in this study is very small compared to the registration trials, AESIs from the control group will not meaningfully add to the existing safety data. Therefore, subjects in the control group will be asked to report potential side effects of vaccination according to the national guidelines for the general population to the Dutch pharmacovigilance center Lareb.

Death of any cause is considered an AESI, because life expectancy of at least 12 months is required for inclusion. We will report deaths and collect information on cause of death. In order to be as complete as possible, informed consent is asked for coupling of data with the Gemeentelijke Basis Administratie (GBA) and Centraal bureaus voor Statistiek (CBS), also from individuals without cancer. However, this is optional and participants who do not consent to coupling of data with CBS and GBA can participate in the study.

9.2.4 Immune related adverse events (irAEs)

irAEs are toxicities from immune checkpoint inhibitors and do not include infusion reactions [37]. For patients in cohorts B and D treated with immunotherapy, all irAEs [37] that occur between the first vaccination and 28 days after the second vaccination will be collected and graded according to CTCAEv5.0. irAEs of grade ≥3 are required to be reported to the PI immediately (i.e. no more than 24 hours after learning of the

event). The coordinating investigator, the PI or delegated trial personnel will report grade ≥3 irAEs through the web portal ToetsingOnline to the accredited METc that approved the protocol, within 15 days of first knowledge of the irAEs that result in death or are life-threatening. All other irAEs will be reported within a period of maximum 15 days.

9.2.5 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious:
   - results in death;
   - is life-threatening (at the time of the event);
   - requires hospitalization or prolongation of existing inpatients' hospitalization;
   - results in persistent or significant disability or incapacity;
   - is a congenital anomaly or birth defect; or
   - any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Summary of Product Characteristics (SPC).

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the vaccine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC and competent authority.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of AEs

All solicited AEs, SAEs, AESIs and irAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

10. STATISTICAL ANALYSIS

A description of the participant population will be included in a statistical output report, including subgroups of gender, tumor type, treatment, and treatment intent (curative versus non-curative).

Participants who are seropositive to SARS-CoV-2 at baseline and participants who have not received at least one dose of the vaccine will be excluded from the immune response analyses, including the primary analysis. All subjects who received at least one administration of the vaccine will be included in the analyses of AEs, SAEs and AESIs, as well as irAEs for cohorts B and D.

For description of the results of this study, appropriate descriptive statistics will be used, including estimates of variance. For comparisons between patient cohorts and controls, the most robust appropriate statistical tests will be applied, after checking that all assumptions for a specific test are met. We will be fully transparent about the analyses (including scripts for analyses) and will report the testing results of the assumptions. In addition, we will present all individual data points of the primary and secondary study parameters.

10.1 Primary study parameter

The primary study parameter is the antibody based immune response to vaccination against COVID-19 on day 28 after the second vaccination in cancer patients as compared to individuals without cancer. SARS-CoV-2 S-specific serum IgG antibody concentrations will be measured at the RIVM using a validated fluorescent bead-based multiplex-immunoassay [39].. Geometric mean concentrations (GMCs) and 95% confidence intervals (CIs) will be calculated for the SARS-CoV-2 S-protein-specific IgG antibodies at baseline and day 28 after vaccination for each cohort. Participants will be classified as responders or non-responders. The definition of response is seroconversion defined as presence of SARS-CoV-2 spike S1-specific IgG antibodies with a threshold for seropositivity based on Receiver Operator Curve (ROC) analysis and set at 1,04 AU/mL [40]; in individuals without measurable anti-S antibodies at baseline. Participants who are seropositive at baseline will not be included in the analysis of the primary endpoint. The percentage of responders and corresponding 95% CI for each cohort will be calculated. The percentage of responders of each patient cohort will be compared with the percentage responders in the group without cancer, using a modified standard fixed-delta test [41].

10.2 Secondary study parameters

- Incidence and severity of solicited AEs during 7 days after each vaccination is a key secondary endpoint (see Appendix 1). Frequencies and absolute numbers of mild, moderate and severe solicited AEs per cohort will be listed for the first and second vaccination separately.
- The numbers, nature and severity of SAEs graded according CTCAEv5.0 will be listed per cohort.
- Incidence and nature of newly occurring irAEs grade ≥ 3 in cohorts B and D up to 28 days after the second vaccination is the second safety endpoint. irAEs will be graded according CTCAEv5.0. Frequencies and absolute numbers of all newly occurring irAEs grade ≥ 3 that occur between the first vaccination and 28 days after the second vaccination in cohorts B and D will be listed.
- Incidence, nature and severity of AESIs comprise the third safety endpoint. AESIs will be graded according CTCAEv5.0. Absolute numbers and frequencies of all AESIs will be listed per cohort and subdivided by severity.
- Levels of SARS-CoV-2 S-specific IgG antibodies at 28 days after the second vaccination will be compared between each patient cohort and the non-cancer cohort using ANOVA or Kruskal–Wallis one-way analysis of variance, and Welch t-tests or Mann-Whitney U tests, depending on the distribution of the data.
- Levels of SARS-CoV-2 S-specific IgG antibodies before the second vaccination and at 6 and 12 months after the second vaccination will be measured to assess early antibody response and longevity. GMCs and 95% CIs will be calculated. The absolute numbers and percentages of responders will be reported for each cohort for each time point. Antibody levels before the second vaccination and at 6 and 12 months will be compared between each patient cohort and the non-cancer cohort using ANOVA or Kruskal–Wallis one-way analysis of variance, and Welch t-tests or Mann-Whitney U tests, depending on the distribution of the data.
- SARS-CoV-2 specific T cell response will be measured at baseline, and at 28 days, and 6 months after the second vaccination and expressed as the number of IFN-ɣ producing SARS-CoV2 specific T cells/million PBMC. To assess the contribution of CD8+ T cells in this response, we will assess the number of IFN-ɣ producing T cells after blocking with an MHC class I antibody. This will be expressed as the number of IFN-ɣ producing CD4+ T cells/ million PBMCs. Subtraction of the number of responding CD4+ T cells from the total number of responding T cells will lead to the number of IFN-γ producing CD8+ T cells/ million PBMCs. Results will be compared between each patient cohort and the cohort of

individuals without cancer using ANOVA or Kruskal–Wallis one-way analysis of variance, and Welch t-tests or Mann-Whitney U tests, depending on the distribution of the data.

10.3 Other study parameters

- Dynamics of SARS-CoV-2 specific antibody concentrations will be analyzed, e.g. by calculating geometric mean fold-rise between baseline and post-baseline time points and antibody decay after day 28.
- In-depth flow-cytometric analyses for functional and phenotypical characterization of SARS-CoV-2 specific cellular responses will be performed by assigning proliferative capacity, cytokine production and phenotypical markers (>25 markers in parallel) in a subset of patients. These descriptive study parameters will not be statistically compared between cohorts.
- Baseline (immune) parameters will be related to vaccination response using univariate analysis.
- As a functional readout, the neutralizing capacity SARS-CoV-2 antibodies will be measured at baseline, 28 days and 6 months. Titers will be expressed as GMCs with 95% CIs for each cohort, for each time point.
- To assess induction of a mucosal antibody response, mucosal lining fluid samples will be collected for measurement of SARS-CoV-2-specific antibody concentrations with multiplex immunoassay at baseline and at 28 days after the second vaccination. Additional analyses e.g. neutralizing capacity of mucosal antibodies can be performed.
- Mucosal SARS-CoV-2-specific antibody response will be correlated with serum SARS-CoV-2-specific antibody response.
- Information on incidence of SARS-CoV-2 infection, outcome of COVID-19 during 12 months after vaccination will be collected. The number of participants tested, the number of SARS-CoV-2 tests and test results will be reported. For participants with a positive test, information about severity will be presented including hospital admissions, use of oxygen, intensive care admission and mechanical ventilation.

10.4 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinicalpractice_en.pdf). The study will be in agreement with the principles of the Declaration of Helsinki (64, October 2013, Fortaleza, Brazil, available on the World Medical Association web site (http://www.wma.net) and with Dutch law, in accordance with the Medical Research Involving Human Subjects Act (WMO, available at https://wetten.overheid.nl/BWBR0009408/2020-01-01).

11.2 Recruitment and consent

Vaccination of elderly has started in Q1 2021 in the Netherlands. In order to be able to launch this study at the time the vaccine is available, potential participants will be identified early at oncology clinics in the participating institutes and informed about:

- the aims of the study
- the potential risks of participation
- the procedures and the possible hazards to which participants will be exposed
- the obligation to register date of vaccination and type of vaccine in a national database
- otherwise strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

A pre-screening Participant Information Form (PIF) will be offered. After signing pre-screening informed consent (IC), baseline information will be collected and eligibility for the study will be estimated. A list of potentially eligible individuals will be created who can be contacted immediately when the vaccine is available. Potential participants will then receive the study PIF. Both the pre-screening PIF and the study PIF will be submitted to the METC along with the study protocol, there are separate versions for cancer patients (cohort B-D) and individuals without cancer (cohort A). A statement of approval should be provided before commencement of the study. Potential participants will be asked for IC by one of the investigators (a medical doctor or specialized nurse). Each subject will be given the opportunity to ask questions and will be informed about the right to withdraw from the study at any time without prejudice. The formal written IC for this trial must be obtained before initiation of any study-specific procedures. Subjects must be given adequate opportunity to read the information and enquire about details of the study before consent

is given. The IC procedure is done according to the ICH guidelines on Good Clinical Practice. This implies that the written informed consent form will be signed and personally dated by the participant. The informed consent statement will be signed and dated by the investigator afterwards and the subject will receive a copy. Subjects are free to decide whether or not to participate in this trial. Non-participation will not have any consequences concerning their treatment. If the patient does not want to participate in the trial, it will be enough if he/she informs one of the investigators about the decision. The decision will be documented in the (electronic) patient dossier.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Patients with cancer are hit harder by the COVID-19 pandemic than healthy individuals. As they have a higher risk of adverse outcome of COVID-19, many patients strictly adhere to self-isolation, resulting in loneliness and loss of quality of life. An immune response to vaccination would not only protect them from life-threatening COVID-19 but also allow close contact with their loved ones. Participation in this study gives early access to vaccination against COVID-19. For the control group, participation in the trial helps to protect their partners with cancer from getting COVID-19, and gives them early access to the vaccine. This study will generate highly valuable information on the ability to mount an effective immune response during cancer treatment that can guide management of cancer patients during the pandemic worldwide.

Participation in this study requires 4 hospital visits at which blood will be drawn by venipuncture and 2 non-invasive collections of nasal mucosal lining fluid are performed, and a finger prick. Participants have to fill in a questionnaire at baseline, and at 3, 6, 9, and 12 months after the second vaccination. Participants will be informed about their antibody titer in a letter that includes an explanation about what this means to them. This will be done after antibody measurements have been completed for day 28 after vaccination, and again after 6 months and after 12 months. Potentially eligible subjects who decide not to participate in the study will have access to the general Dutch vaccination program.

11.5 Incentives (if applicable)

For each day of subject related study procedures, the subjects will receive compensation for travelling expenses (€ 0.19/km) and parking.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Study subjects will receive a code. The key to the code (number linked to patient) is safeguarded by the investigator. The study code assigned to the patients will be used in the collection of all the study results by IKNL (Integraal Kankercentrum Nederland).

An overview of all data and data-analysis is made according to this code, so that the final results cannot be traced back to the patients by another person than the investigators involved in the study (in compliance with the Dutch Personal Data Protection Act). For the study participants who give separate consent, information on positive COVID-19 tests during the study will also be collected from the RIVM. Data will be stored for a maximum period of 15 years after the study is finished.

12.2 Monitoring and Quality Assurance

On-site and centralized monitoring will take place according to the NFU (Nederlandse Federatie van Universitaire Medisch Centra)-guideline “Kwaliteitsborging van mensgebonden onderzoek 2019” by the appointed monitor. This study is classified as negligible risk because vaccination is standard of care. Monitoring will take place to assure the quality and validity of the research data. The monitor will perform source data verification on the research data by comparing the data entered into the CRF with the available source documentation and other available documents. Source documents are defined as the patient’s hospital medical records, clinician notes, laboratory print outs, digital and hard copies of imaging, memos, electronic data etc.

The monitor will verify the following items: Informed consent forms (presence, dates, signatures); Informed consent process, Investigator Files (presence of all documents), in-/exclusion criteria (using source documents); AESIs/irAEs/SAEs (number, missed, reporting procedures); study product (administration). After each control the monitor will send a written report to the sponsor (including a summary; quality assessment; summary of findings, deviations and shortcomings; possible solutions to warrant compliance with the protocol; final conclusion).

12.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;

- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, SAEs/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as 12 months after the last vaccination of the last patient.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

This study will be registered in a public trial registry (ClinicalTrials.gov) before the first patient is recruited.

The results of the study will be disclosed unreservedly and will be submitted to a peer reviewed scientific journal.

13. STRUCTURED RISK ANALYSIS

Patients will be vaccinated against COVID-19 according to the standard of care in the Netherlands. The vaccine is approved for use by EMA and CBG. A full synthesis of the risk of vaccination with mRNA-1273 SARS-CoV-2 vaccine can be found in the SPC. The burden for the subject is described in section 11.4.

Patients who receive cancer treatment might have a higher risk of AEs related to vaccination, therefore safety is a secondary endpoint and will be assessed by collection of solicited AEs, SAEs, AESIs and irAEs.

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Appendix 1: Toxicity grading scale for solicited systemic and local adverse events.

	Mild	Moderate	Severe
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Fever	38.0°C – 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
Nausea	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration
Size (diameter) of erythema/redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Size (diameter) of induration/swelling	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Pain (at injection site)	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity

Appendix 2: Adverse events of special interest

Body system/ Classification	**AESI**
Auto-immune diseases	Guillain-Barre Syndrome (GBS) Acute disseminated encephalomyelitis (ADEM) Narcolepsy Acute aseptic arthritis Type I Diabetes
Cardiovascular system	Acute cardiovascular injury including: Microangiopathy, Heart failure, Stress cardiomyopathy, Myocarditis
Circulatory system	Single Organ Cutaneous Vasculitis
Nerves and central nervous System	Generalized convulsion Meningoencephalitis Transverse myelitis
Respiratory system	Acute respiratory distress syndrome
Skin and mucous membrane, bone and joints system	Erythema multiforme
Other system	Anaphylaxis Death (any causes)
Other	Any AE that is considered of special interest in relation to vaccination by the treating physician

Appendix 3: ECOG performance status

ECOG performance status	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 4: Product information vaccine

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 Vaccine Moderna dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial which contains 10 doses of 0.5 mL.

One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection
White to off white dispersion (pH: 7.0 – 8.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COVID-19 Vaccine Moderna is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older
COVID-19 Vaccine Moderna is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose (see sections 4.4 and 5.1).

There are no data available on the interchangeability of COVID-19 Vaccine Moderna with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of COVID-19 Vaccine Moderna should receive the second dose of COVID-19 Vaccine Moderna to complete the vaccination course.

Paediatric population
The safety and efficacy of COVID-19 Vaccine Moderna in children and adolescents less than 18 years of age have not yet been established. No data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥65 years of age.

Method of administration

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Anaphylaxis has been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. The second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine Moderna.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine Moderna may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Individuals may not be fully protected until 14 days after their second dose. As with all vaccines, vaccination with COVID-19 Vaccine Moderna may not protect all vaccine recipients.

Excipients with known effect

Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per 0.5 mL dose, that is to say, essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Concomitant administration of COVID-19 Vaccine Moderna with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of COVID-19 Vaccine Moderna in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of COVID-19 Vaccine Moderna in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether COVID-19 Vaccine Moderna is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

COVID-19 Vaccine Moderna has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of COVID-19 Vaccine Moderna was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of COVID-19 Vaccine Moderna (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older.

The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Overall, there was a higher incidence of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above.
Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

Tabulated list of adverse reactions

The safety profile presented below is based on data generated in a placebo- controlled clinical study on 30,351 adults ≥ 18 years of age.

Adverse reactions reported are listed according to the following frequency convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Nervous system disorders	Very common	Headache
	Rare	Acute peripheral facial paralysis**
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling
	Common	Injection site erythema, Injection site urticaria, Injection site rash

	Uncommon	Injection site pruritus
	Rare	Facial swelling***

*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site.
**Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the COVID-19 Vaccine Moderna group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.
***There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination

The reactogenicity and safety profile in 343 subjects receiving COVID-19 Vaccine Moderna, that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

No case of overdose has been reported.
In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action
COVID-19 Vaccine Moderna contains mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into viral protein. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19.

Clinical efficacy
The randomised, placebo-controlled, observer-blind Phase 3 clinical study (NCT04470427) excluded individuals who were immunocompromised or had received immunosuppressants within 6 months, as well as participants who were pregnant, or with a known history of SARS-CoV-2 infection. Participants with stable HIV disease were not excluded. Influenza vaccines could be administered 14 days before or 14 days after any dose of COVID-19 Vaccine Moderna. Participants were also required to observe a minimum interval of 3 months after receipt of blood/plasma products or immunoglobulins prior to the study in order to receive either placebo or COVID-19 Vaccine Moderna.

A total of 30,351 subjects were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 subjects who received either COVID-19 Vaccine Moderna (n=14,134) or placebo (n=14,073) and had a negative baseline SARS-CoV-2 status. The PPS study population included 47.4% female, 52.6% male, 79.5% White, 9.7% African American, 4.6% Asian, and 6.2% other. 19.7% of participants identified as Hispanic or Latino. The median age of subjects was 53 years (range 18-94). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS. 98% of vaccine recipients received the second dose 25 days to 35 days after dose 1 (corresponding to -3 to +7 days around the interval of 28 days).

COVID-19 cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT PCR) and by a Clinical Adjudication Committee. Vaccine efficacy overall and by key age groups are presented in Table 2.

Table 2: Vaccine Efficacy Analysis: confirmed COVID-19# regardless of severity starting 14 days after the 2nd dose – Per-Protocol Set

Age Group (Years)	COVID-19 Vaccine Moderna			Placebo			
	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	% Vaccine Efficacy (95% CI)*
Overall (≥18)	14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)**
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2,953	4	5.586	2,864	22	31.744	82.4% (48.9, 93.9)
≥75	630	0	0	688	7	41.968	100% (NE, 100)

#COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*Vaccine efficacy and 95% confidence interval (CI) from the stratified Cox proportional hazard model
** CI not adjusted for multiplicity. Multiplicity adjusted statistical analyses were carried out in an interim analysis based on less COVID-19 cases, not reported here.

Among all subjects in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 of 185 (16%) cases reported in the placebo group. Of the 30 participants with severe disease, 9 were hospitalised, 2 of which were admitted to an intensive care unit. The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO2) criterion for severe disease (≤ 93% on room air).

The vaccine efficacy of COVID-19 Vaccine Moderna to prevent COVID-19, regardless of prior SARS-CoV-2 infection (determined by baseline serology and nasopharyngeal swab sample testing) from 14 days after Dose 2 was 93.6% (95% confidence interval 88.5, 96.4%).

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Elderly population

COVID-19 Vaccine Moderna was assessed in individuals 18 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of COVID-19 Vaccine Moderna was consistent between elderly (≥65 years) and younger adult subjects (18-64 years).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with the COVID-19 Vaccine Moderna in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

Conditional Approval
This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General Toxicity:
General toxicity studies were conducted in rats (intramuscularly receiving up to 4 doses exceeding the human dose once every 2 weeks). Transient and reversible injection site oedema and erythema and transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Results suggests the toxicity potential to humans is low.

Genotoxicity/Carcinogenicity:
In vitro and in vivo genotoxicity studies were conducted with the novel lipid component SM-102 of the vaccine. Results suggests the genotoxicity potential to humans is very low. Carcinogenicity studies were not performed.

Reproductive Toxicity:
In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of COVID-19 Vaccine Moderna was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of mRNA-1273 vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid SM-102
Cholesterol
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG)
Tromethamol
Tromethamol hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened vial:
7 months at -25°C to -15°C.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days.

Once thawed the vaccine should not be re-frozen.

The unopened vaccine may be stored at 8°C to 25°C up to 12 hours after removal from refrigerated conditions.

Punctured Vial:
Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 25°C after initial puncture. From a microbiological point of view, the product should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user

6.4 Special precautions for storage

Store frozen between -25°C to -15°C.
Store in the original carton to protect from light.
Do not store on dry ice or below -40°C.
For storage conditions after thawing and first opening see section 6.3.

6.5 Nature and contents of container

5 ml dispersion in a vial (type 1 or type 1 equivalent glass) with a stopper (chlorobutyl rubber) and a flip-off plastic cap with seal (aluminium seal).

Each vial contains 10 doses of 0.5mL.

Pack size: 10 multidose vials

6.6 Special precautions for disposal and other handling

The vaccine should be prepared and administered by a trained healthcare professional using aseptic techniques to ensure sterility of the dispersion.

The vaccine comes ready to use once thawed.

Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal.

COVID-19 Vaccine Moderna vials are multidose.

Ten (10) doses (of 0.5mL each) can be withdrawn from each vial.

An additional overfill is included in each vial to ensure that 10 doses of 0.5 mL can be delivered.

Frozen Storage

Thaw Each Vial Before Use

Vial images for illustrative purposes only

Let vial sit at room temperature for 15 minutes before administering

Instructions Once Thawed

Withdraw each 0.5 mL dose of vaccine from the vial using a new sterile needle and syringe for each injection to prevent transmission of infectious agents from one person to another. The dose in the syringe should be used immediately.

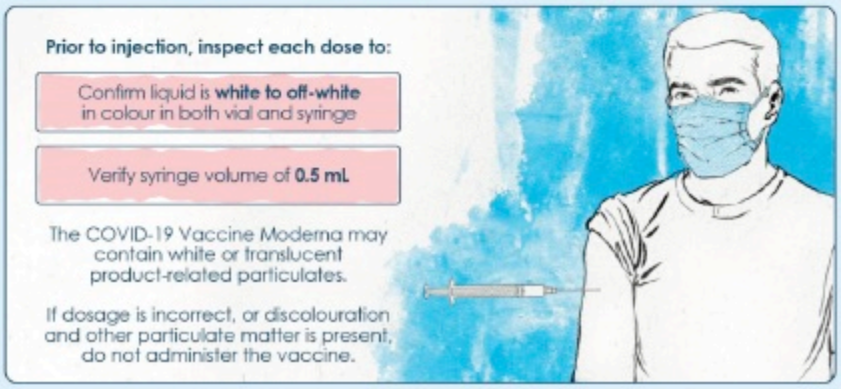
Once the vial has been punctured to withdraw the initial dose, the vaccine should be used immediately and be discarded after 6 hours.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

NEVER **refreeze thawed vaccine**

Administration

Swirl vial gently after thawing and before each withdrawal.
The vaccine comes ready to use once thawed. **Do not shake or dilute.**



7. MARKETING AUTHORISATION HOLDER

MODERNA BIOTECH SPAIN, S.L.
Calle Monte Esquinza 30
28010 Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1507/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

VOICE study substantial amendments

January 29, 2021

On the day of the second vaccination, 5 ml additional blood will be drawn to determine early antibody response.

In a subgroup of patients, nasal fluid will be collected non-invasively with an absorbent strip at baseline and 28 days after the second vaccination to determine the mucosal antibodies against SARS-CoV-2.

Collection of questionnaires will be done via CASTOR, a data-management system for studies in which the CRF is also built. This way, no third party is involved.

The estimated duration of the hospital visit has been increased to 60 minutes to allow time for registration of the vaccination and an observation period of 15 minutes,

The following has been clarified/adjusted in the participant information forms:

- It is explained that during the study, participants are asked to complete questionnaires via CASTOR.
- The estimated duration of the hospital visit is changed into 60 minutes.
- It has been added that nasal fluid is collected at baseline and 28 days after vaccination.
- For the vaccine's side effects, a reference is made to the appendix with a placeholder for the package leaflet because it is not yet clear which vaccine will be given. The Medical Ethical Committee will be informed once this information is available.
- The possible side effects of the blood draws and the collection of nasal fluid are added.
- In Appendix D, the consent form, it is indicated that with the signature, permission is also given for sending the questionnaires.
- For the contact details for sending the questionnaires, a separate attachment has been made.

Some small changes were made to the pre-screening form and the participant information form as requested by the Medical Ethical Committee.

A participant card has been added for the UMCG and a non-site-specific version with contact details of the study team.

February 16, 2021

At the request of the Central Committee on Research Involving Human Subjects, the study design is changed from an observational study into an interventional study.

It is decided that the Covid-19 vaccine mRNA-1273 will be used.

The study protocol, participant information, and ABR-form are changed accordingly, the summary of product characteristics is added to the protocol, and the package leaflet information is added to the participant information.

An EudraCT form and a study drug accountability form are created.

March 22, 2021

The primary endpoint with regards to the definition of antibody response is now exactly defined.

It was hoped that a threshold of an antibody concentration would be known in time that could serve as a correlate for protection against COVID-19, but unfortunately, that is not the case. That is why we fall back on the second option, namely seroconversion. However, we do not define this as a fourfold increase from the baseline because we assume that most participants have no antibodies against COVID-19 at inclusion in the study, unlike in influenza vaccination studies. We will therefore use a cut-off value for seropositivity that is based on previous studies done by RIVM.
A letter is added that will be sent to the participants to inform them that we intend to send them their personal result of the antibody concentration and what that means for them.