Vaccination against cOvid In CancEr

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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 is recommended. However, phase III studies do 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 different time points by venipuncture 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 6 time points, and participants who receive a third vaccination will have 2 additional hospital visits. The vaccine will be administered two times according to the standard of care, with the option of a third vaccination for participants without an adequate response after 2 vaccinations. Blood will be drawn (~373 ml in total for participants receiving 2 vaccinations, and ~539 ml in participants receiving 3 vaccinations) prior to the vaccinations and at day 28 and 6 months, 11 months and 18 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. 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, 9,12, 15 and 18 months after the second 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. It will also explore immune response and safety of a third vaccination in participants without an adequate antibody response after the second vaccination. 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 second vaccination, and again after completion of measurements for 6 months and 28 days after third vaccination, and 11 months and 18 months after the second vaccination.

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 intramuscular 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. In several countries including Belgium and France, immunocompromised patients are now offered a third vaccination. An advice from the Dutch Health Council about additional vaccination of immunocompromised patients in the Netherlands is expected soon. 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.

1.6 First results VOICE trial

Between February 17th and March 12th, 2021, 791 participants were enrolled in the current trial. For the primary endpoint at 28 days after the second vaccination, 743 participants were evaluable (per-protocol population): 240 individuals without cancer and 131 patients receiving immunotherapy, 229 patients receiving chemotherapy, and 143 patients receiving chemo-immunotherapy. SARS-CoV-2-binding antibody response (>10 binding antibody units (BAU)/mL) was found in 100%, 99.3%, 97.4%, and 100% of the participants in cohorts A, B, C, and D, respectively.

Given the importance for clinical decisions, we defined, based on neutralizing capacity, a cut-off level at 300 BAU/mL to discriminate between suboptimal and adequate responders. Twenty eight days after the second vaccination, 99.6% (A), 93.1% (B), 83.8% (C), and 88.8% (D) had an adequate response. Spike-specific T cell responses were detected in almost half of the suboptimal and non-responders. No new safety signals were observed [36].

1.7 Third vaccination

Although most patients with solid tumors develop an adequate SARS-CoV-2-binding antibody response after vaccination, 6.9%, 16.2%, and 11.2% of patients treated with immunotherapy, chemotherapy, and chemo-immunotherapy, respectively, are still suboptimal or non-responders. As most of them show an increase in antibody concentration after the second vaccination, an additional third vaccination might turn them into adequate responders. In the extension of the VOICE trial, we will investigate whether non and suboptimal responders might benefit from a third vaccination. We will study whether an additional mRNA-1273 administration can improve the antibody response of participants in the VOICE trial who had a low antibody response on day 28 following two mRNA-1273 vaccinations. In addition safety, neutralizing antibodies and SARS-CoV-2 Spike-specific interferon-gamma T cell response will be studied.

1.8 Current vaccination strategy in the Netherlands

Since October 2021, all patients with cancer who received chemotherapy and/or immunotherapy during or within 3 months before their first vaccination received an invitation for a third vaccination with an mRNA vaccine as part of their primary vaccination. This applies to all patients in the VOICE trial who did not receive a third vaccination within the study. Furthermore, everyone is entitled to receive a booster vaccination with an mRNA vaccine at least 3 months after completion of the primary vaccination, whether that consisted

of 2 or 3 vaccinations. This means that the majority of the study participants will have had extra vaccinations at different time points by January 2022. Therefore, we will implement 2 cross sectional measurements at 11 and 18 months after the second vaccination (in February and September 2022) and record the date and type of those extra vaccinations retrospectively. This will provide insight in the immune status against COVID-19 of cancer patients in the Netherlands compared to a cohort without cancer in 2022.

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

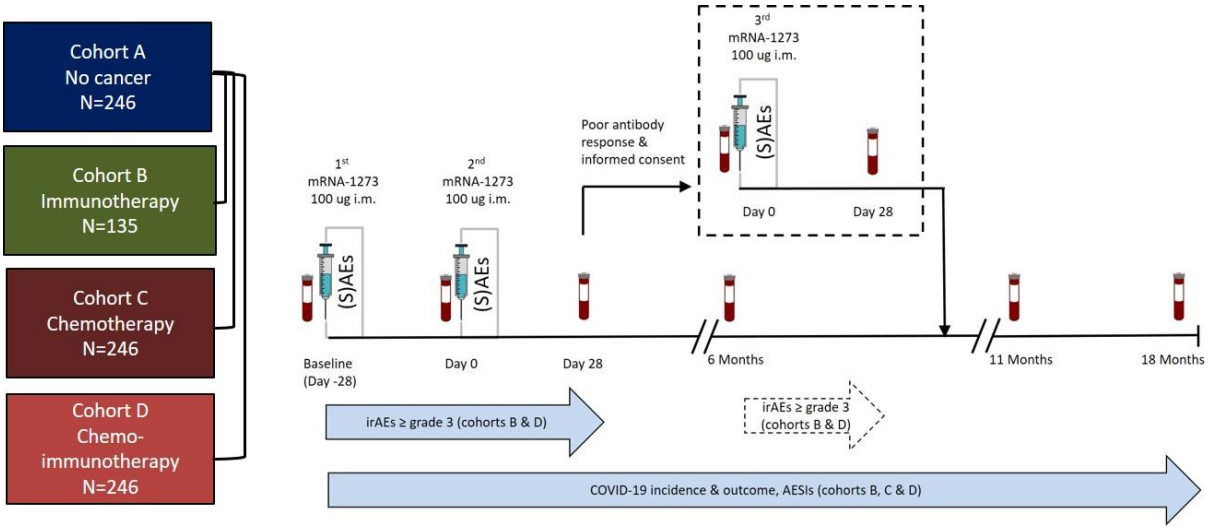
Exploratory Objectives:

- 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
- To analyze SARS-CoV-2-binding antibody concentration after a third vaccination in participants without an adequate antibody response after two vaccinations
- To analyze safety of a third vaccination

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 [37], 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. Participants with an inadequate antibody response will be offered a third vaccination. 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 (and if applicable the third) vaccination and at day 28 after the second and third vaccination and 6, 11 and 18 months after the second vaccination by venipuncture. To evaluate hematology, with or without liver and kidney function, additional blood samples will be collected at baseline, at the day of the second and third vaccination, and at day 28 after the second and third vaccination and 6, 11 and 18 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 and if applicable the third vaccination. irAEs are toxicities from immune checkpoint inhibitors and do not include infusion reactions [38]. 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 18 months after the second 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 18 months after the second 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 [38] 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 11 and 18 months after the second vaccination to measure longevity
- Measurement of SARS-CoV2 specific antibodies at day 28 after the third vaccination if applicable
- Assessment of SARS-CoV2 specific T cells response at 28 days after the second and third vaccination and at 6, 11 and 18 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 18 months after the second vaccination. To this end, questionnaires will be used. Information on positive corona tests during the study will also be collected from the RIVM.
- To analyze SARS-CoV-2-binding antibody concentration after a third vaccination in participants without an adequate antibody response after two vaccinations on day 28 after the third vaccination.
- To analyze safety of a third vaccination as indicated under 8.1.2
- To assess SARS-CoV2 specific T cell response at 28 days after the third vaccination

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 vacc 2[b] (± 3)	Day 90 (± 7)	Day 180 (± 7)	Vacc 3[m]	Day 28 vacc 3 (± 3)	Day 270 (±7)	Day 330 (± 14)	Day 540 (± 21)
Informed consent	x						x				
Inclusion/exclusion criteria	x										
Medical history	x										
Concomitant medication	x	x	x	x		x	x	x		x	x
Smoking history	x										
ECOG PS[b]	x										
Height/weight	x						x				
Vital signs[c]	x	x	x				x				
Blood tests[d]		x	x	x		x	x	x		x	x
Nasal MLF collection[e]		x		x							
Sollicited adverse events[f]	x	x	x	x			x				
SAEs[g]		x	x	x			x				
irAEs[h]	x	x	x	x			x	x			
AESIs[i]			Will be reported for the entire duration of the study								
Vaccine administration[j]		x	x				x				
COVID-19 questionnaire[k]	x				x	x	x		x	x	x
Survival status						x				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] ECOG performance status: see appendix 3.

[c] Vital signs: blood pressure, heart rate, temperature.

[d] See Table 2.

[e] MLF = mucosal lining fluid, will be collected using a synthetic absorptive matrix [39]

[f] 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.

[g] SAEs that occur within 7 days of each vaccination will be reported

[h] Newly developed irAEs [38] grade ≥ 3 need to be reported for cohort B and D up to 28 days after the second vaccination and from the third vaccination to 28 days thereafter.

[i] AESIs (see Appendix 2) will be reported by the treating physicians up to 18 months after vaccination for cohorts B-D.
[j] The name of the vaccine, batch number and date and time of administration will be recorded.
[k] Participants will complete a questionnaire for diagnosis of SARS-CoV-2 infection, severity and outcome of COVID-19.
[l] Only participants with an inadequate antibody response (≤300 BAU/mL) on day 28 after the second vaccination.

Table 2: Blood tests

	Vacc1[a]	Vacc2[a]	Day 28 Vacc2	Day 180	Vacc3[ad]	Day 28 vacc3	Day 330	Day 540
SARS-Cov-2 antibodies	x	x	x	x	x	x	x	x
PBMC isolation for in depth cellular immune response	x		x	x	x	x	x	x
Routine hematology[b]	x	x	x	x	x	x	x	x
Routine chemistry[c]	x	x	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] Only participants with an inadequate antibody response (≤300BAU/mL) on day 28 after the second vaccination.

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 each vaccination for cohorts A and C and up to day 28 after the last 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 [38]. For patients in cohorts B and D treated with immunotherapy, all irAEs [38] that occur between the first vaccination and 28 days after the last 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 [40]. 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 [41]; in individuals without measurable anti-S antibodies at baseline. Concentrations have been 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).The value of 1.04 AU/mL corresponds to 10 BAU/mL. 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 [42].

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, second and third 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, 11 and 18months 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, 11 and 18 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 after the second and third vaccination, and 6, 11 and 18 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 , 11 and 18 months after the second vaccination. 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 18 months after the second 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.
- Levels of SARS-CoV-2 S-specific IgG antibodies before the third vaccination, and at day 28 after the third vaccination will be measured to assess antibody response in participants with an inadequate response to two mRNA-1273 vaccinations.
- Safety of a third mRNA-1273 vaccination in participants with an inadequate response to two mRNA-1273 vaccinations as mentioned under 10.2.

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. Participants without an adequate antibody response after two vaccinations will be informed about the option to receive a third vaccination, a separate IC must be obtained. 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.

Participants without an adequate antibody response will be offered a third vaccination. Most participants in the VOICE study showed an increase in SARS-CoV-2-binding antibody concentration following a second vaccination, a third vaccination will therefore likely further increase the antibody response. Patients with cancer could therefore benefit from better protection induced by a third vaccination. A third vaccination with another mRNA vaccine (BNT162b2, Pfizer-BioNTech) in 101 solid organ transplant recipients showed that from the 59 patients who did not have SARS-CoV-2 specific antibodies before the 3rd vaccination, 44% was seropositive 28 days after the third vaccination. Patients who were already seropositive before the third vaccination showed a significant increase in antibody concentration. No serious adverse events were reported after the administration of the third dose, and no acute rejection episodes occurred [43]. The FDA

on August 12th authorized additional mRNA-1273 and BNT162b2 vaccine doses for immunocompromised individuals, administered at least 28 days after the two-dose regimen of the same vaccine [44]. Recently, Moderna requested a general FDA approval for a third dose of mRNA-1273, based on a study in 344 volunteers [45]. Currently both mRNA-1273 and BNT162b2 are used for third vaccinations in immunocompromised patients and for boosters in the Netherlands.

Participation in this study requires 6 hospital visits at which blood will be drawn by venipuncture and 2 non-invasive collections of nasal mucosal lining fluid are performed. Maximum 3 additional hospital visits are required for participants who will receive a third vaccination. Participants have to fill in a questionnaire at baseline, and at 3, 6, 9, 12, 15 and 18 months after the last 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, 11 and 18 months after the second vaccination. Participants who receive 3 vaccinations will also receive their antibody concentration on day 28 after the third vaccination. Potentially eligible subjects who decide not to participate in the study will have access to the general Dutch vaccination program, which now includes a third vaccination as part of the primary vaccination in immunocompromised patients and a booster for everybody at a minimum of 3 months after completion of the primary vaccination.

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 18 months after the second 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 is registered in a public trial registry (ClinicalTrials.gov), identifier NCT04715438.

The results of the study will be disclosed unreservedly and are submitted to a peer reviewed scientific journal. Data will be presented at the European Society for Medical Oncoloy (ESMO) annual conference presidential symposium on September 20th, 2021.

13. STRUCTURED RISK ANALYSIS

Patients will be vaccinated against COVID-19 according to the standard of care in the Netherlands. It is anticipated that a third vaccination will become standard of care for immunocompromized patients in the Netherlands by Autumn 2021, as is already the case in several other countries. 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: Summary of product characteristics

https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf