Immunogenicity and Safety of the BNT162b2 mRNA COVID-19 Vaccine Among Actively Treated Cancer Patients

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ABBREVIATIONS

COVID-19, coronavirus disease 2019.

ASCO, American Society for Clinical Oncology

ESMO, European Society for Medical Oncology

MOH, Ministry of Health

ICI, Immune checkpoint inhibitors

CLL, chronic lymphocytic leukemia

TASMC, Tel Aviv Sourasky Medical Center

mRNA, messenger ribonucleic acid

RBD, Receptor Binding Domain

Ab, antibody

Abs, antibodies

CMIA, chemiluminescent microparticle immunoassay
Abstract

Background: Activity and safety of the SARS-CoV2 BNT162b2 vaccine in actively treated patients with solid tumors is currently unknown.

Methods: We conducted a retrospective study of 326 patients with solid tumors treated with anti-cancer medications to determine the proportion of cancer patients with immunogenicity against SARS-CoV2, following two doses of the BNT162b2 vaccine. Control group was comprised of 164 vaccinated healthy adults. Anti-SARS-CoV-2 S IgG (Immunoglobulin G) antibodies (Abs) were measured, using level>50 AU/ml as cutoff for seropositivity. Adverse effects were collected using a questionnaire. All statistical tests were 2-sided.

Results: Most patients (205, 62.9%) were treated with chemotherapy, either alone or with additional therapy, 55 (16.9%) were treated with immune checkpoint inhibitors (ICI) and 38 (11.7%) with targeted therapy alone, 28 (8.6%) received other combinations. The vaccine was well tolerated and no severe side effects were reported. Among patients with cancer 39 (11.9%) were seronegative, compared to 5 (3.0%) of the control group ($P=0.001$). Median IgG titers were statistically significant lower among patients with cancer compared to control (931 AU/ml vs. 2817 AU/ml, $P=0.003$). Seronegativity proportions were higher in the chemotherapy treated group (19, 18.8%) compared to the ICI-treated patients (5, 9.1%) and to those treated with targeted therapy (1, 2.6%) ($P=0.02$). Titers were also statistically significant different among treatment types ($P=0.002$).

Conclusion: The BNT162b2 vaccine is safe and effective in actively treated patients with cancer. The relatively lower antibody titers and lower proportion of seropositive patients, especially among chemotherapy treated patients, call for continuing the use of personal protective measures in these patients, even following vaccination.
Patients with cancer are at increased risk for morbidity and mortality from coronavirus disease 2019 (COVID-19)\(^1\), and active treatment may further increase these risks\(^2\). Yet, patients with cancer were excluded from the pivotal trials of the COVID-19 vaccines \(^3\text{-}^5\) and the safety and efficacy of the vaccine in this large and vulnerable population are currently unknown. Despite lack of data, current guidelines of both the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) strongly support vaccination of patients with cancer treated with systemic anticancer therapy\(^6\text{-}^7\).

On December 19, 2020, the Israeli Ministry of Health (MOH) launched a national mass vaccination campaign, aiming at rapid vaccination of the entire adult Israeli population. All Israeli citizens at the age 16 or above who were not previously infected with SARS-CoV-2, were eligible for the messenger ribonucleic acid (mRNA) BNT162b2 vaccine. Vaccines were readily available and free of charge and administered, as recommended by the manufacturer at 21 days interval. The second dose was omitted if the patient contracted SARS-CoV-2 infection following the first dose. By April 30, 2021, 5,048,333 Israelis (55.8\% of the Israeli population) were already fully vaccinated. Despite lack of data, the Israeli MOH not only recommended on vaccination of all patients with cancer, but also prioritized them to be vaccinated at the early stages of the campaign, regardless of disease stage, performance status or life expectancy.

Accumulating data indicate that the BNT162b2 vaccine is indeed safe in actively-treated cancer patients. We have recently reported on the short-term safety of two doses of the BNT162b2 vaccine in 134 patients with a variety of solid cancers treated with immune checkpoint inhibitors (ICI)\(^8\), and Monin et al reported on the safety of the vaccine in a cohort of 151 patients, of whom 95 had solid cancers and 25 received two doses\(^9\). No unexpected or severe side effects were noted in both studies. Similarly, the vaccine was also found to be
safe among patients with chronic lymphocytic leukemia (CLL)\textsuperscript{10}. While data regarding safety are accumulating and reassuring, data regarding activity of the BNT162b2 vaccine are lacking. Direct assessment of the ability BNT162b2 vaccine to reduce morbidity and mortality among patients with cancer is limited due to the small number of cancer patients relatively to the general population and also due to the presence of major confounding factors, including social distancing and the low prevalence of SARS-CoV-2 infection in the general population following mass vaccination. Indeed, a cohort of nearly 600,000 individuals was required in order to determine the efficacy of the BNT162b2 vaccine at the national level\textsuperscript{11}. In order to overcome this obstacle, several surrogate markers for the activity of the vaccine are being used, with the most common is a direct measurement of anti-SARS-CoV-2 spike (S) antibody titers in the serum. Recent studies used this test and reported on antigenicity and seroconversion in patients with malignant diseases. A recent study from our institution noted an antibody response in only 40\% of 167 CLL patients receiving two doses of the BNT162b2 vaccine\textsuperscript{10} and low responses were also noted in a cohort of 29 multiple myeloma patients\textsuperscript{12}. Response to this vaccine in patients with solid cancers was evaluated in two small cohorts\textsuperscript{9,13}. While both reported on ~95\% immunogenicity following second vaccine dose, no association with either tumor or treatment type could be determined in either of these studies due to small number of patients. We describe here safety and antibody response following administration of the 2\textsuperscript{nd} dose of BNT162b2 vaccine, in a cohort of 326 actively-treated patients with solid tumors.

\textbf{Methods}

\textbf{Study design}

This was a retrospective cohort study, designed to evaluate the safety and efficacy of the of the BNT162b2 vaccine in actively-treated patients with solid cancers. The study was
conducted at the Oncology Division of Tel Aviv Sourasky Medical Center (TASMC), a tertiary referral center with over 4,000 new cancer patients a year. The study was approved by the institutional review board.

**Patient population**

The national vaccination campaign was initiated on 20 December 2020 and administration of the 2nd dose started on January 10th 2021. The antibody response to the BNT162b and mRNA-1273 vaccine shows a steep rise up to ~40 days following full vaccination, followed by a steady state afterwards\[^{14,15}\]. In order to avoid a bias associated with this period of antibody response upregulation, we aimed to evaluate the efficacy of the vaccine two months following the 2nd dose. Thus, blood collection was initiated on March 15, 2021 and last patient recruited by April 30, 2021. During this period, all patients with solid tumors, actively-treated at the day-care center of the oncology division at this time, were approached and offered to participate in the study. Active treatment was defined as any IV anti-cancer medication, administered during a period starting at two weeks before the 1st vaccine dose, and ending two weeks after the 2nd vaccine dose.

The control group consisted of fully vaccinated healthy adults with no personal history of cancer or active immune suppressive medications, who were either health care workers at the oncology division of TASMC offered to be tested for anti-SARS-CoV-2S IgG antibodies or individuals opted to test immunogenicity at the Integrated Cancer Prevention Center at TASMC. The control group was recruited at the same period of time for the purpose of this study.

Following signing an informed consent form, participants filled a detailed questionnaire regarding side effects of the vaccines and blood was captured for
immunogenicity analysis. Clinical data was retrieved from the hospital electronic medical records.

**Immunogenicity analysis**

Humoral response was evaluated by testing anti-SARS-CoV-2 Spike (S) Receptor Binding Domain (RBD) Immunoglobulin G (IgG) antibody (Ab) titer. The presence of anti-SARS-CoV-2S IgG antibodies was evaluated by using SARS-CoV-2 IgG assay chemiluminescent microparticle immunoassay (CMIA) intended for the quantitative detection of RBD IgG antibody levels to SARS-CoV-2 (SARS-CoV-2 IgG II Quant, Abbott, Ireland). Results were provided in arbitrary units (AU/ml) ranging between 0-40,000 for anti-S antibodies (level>50 AU/mL considered positive according to the manufacturer’s instructions).

**Outcomes**

The primary endpoint was proportion of cancer patients with immunogenicity against SARS-CoV-2, defined as antibody titer level>50AU/mL, following two doses of the BNT162b2 vaccine, compared to the healthy individuals. The secondary endpoints were antibody titer levels in cancer patients compared to the control group, association between seropositivity and cancer treatment and safety.

**Statistical Analysis**

All variables were characterized by appropriate descriptive measures. Clinical characteristics, anti-SARS-CoV-2S IgG antibodies and proportion of immunogenicity (seronegativity/positivity) comparisons were done using the Mann-Whitney U-test (numerical variables) and the chi-square test (categorical variables). Kruskal-Wallis test was used to evaluate differences in numerical variables (eg. age and 'SARS-CoV-2S AU IgG titer) among
different cancer types and treatment types (eg. Chemotherapy vs. Immunotherapy vs. Targeted therapy). Multiple comparisons of numerical variables were performed using Mann-Whitney test with Bonferroni correction.

A multivariable logistic regression model was used to evaluate the association between being a cancer patient and anti-SARS-CoV-2S IgG antibodies adjusted for age and gender, and to evaluate the effect of age, metastatic disease, time from 2\textsuperscript{nd} vaccination to IgG test, treatment type (chemotherapy Vs. no chemotherapy), and cancer type on seronegativity/positivity. All statistical tests were two-sided, and a P value less than 0.05 was considered statistically significant. Statistical analysis was done by the SPSS software. Transforming data to logs and plots formation were performed using GraphPad Prism version 9.0.1 for windows.

\section*{Results}

\subsection*{Patient characteristics}

Between March 15 and April 30, 2021, 326 out of 1383 (23.6\%) actively-treated patients with cancer agreed to participate in the study. Their characteristics are presented in Table 1. Median age was 66, most (n = 203, 62.3\%) were women and the most common tumor types were gastrointestinal cancers (n = 84, 25.8\%) followed by breast (n = 82, 25.2\%) and lung cancer (n = 45, 13.8\%). Most (n = 205, 62.9\%) were treated with chemotherapy, either alone (n = 101 patients) or in combination with additional therapy (ICI, targeted therapy, radiation and hormonal therapy, 104 patients), 55 (16.9\%) were treated with immune-check point inhibitors (ICI) and 38 (11.6\%) with targeted therapy alone, 28 (8.6\%) received other treatments (e.g. radiation alone or in combination with ICI or targeted therapy). Most patients (n = 230, 70.6\%) had metastatic disease. As expected from study design, median time from 2\textsuperscript{nd} vaccine dose to antibody testing was 78 days (range = 21-115 days).
The control group included 164 individuals. Their median age was statistically significantly younger from the cancer patients cohort (54 vs 64 years respectively, \( P<0.001 \), Table 1). Time from 2nd vaccine dose to antibody testing in the control group was 72 days (range = 21-115 years, \( P=0.08 \) compared to the cancer patients).

**Adverse Events**

Adverse effects were collected using a detailed questionnaire. The vaccine was well tolerated with local pain (\( n = 64, 19.6\% \)), weakness (\( n = 57, 17.5\% \)), myalgia (\( n = 41, 12.6\% \)) and headache (\( n = 21, 6.4\% \)) being the most prevalent (Figure 1). Importantly, no severe side effects, either life threatening or requiring hospitalization, were reported.

**Immunogenicity following vaccination**

Immunogenicity was assessed by measuring anti-SARS-CoV-2S IgG antibodies titer. According to the manufacturer's instructions\(^6\) and based on previous reports, a titer of \( >50 \) AU/ml was considered as seropositive\(^7, 18\). Using this cut point, 39 (11.9\%) cancer patients compared to 5 (3.0\%) of the control group were found to be seronegative (Table 2, \( P=0.001 \)). Moreover, median IgG titer were statistically significant lower the patients group compared to the healthy controls (931 AU/ml vs 2817 AU/ml, \( P=0.003 \); Table 2) with an odds ratio of 4.33 (95\% CI = 1.66 to 11.23). The distribution of antibody titers is presented in Figure 2. A multivariable logistic regression model indicated no statistically significant interaction between either age (\( P = 0.15 \)) or gender (\( P = 0.11 \)) and antibody titer levels.

In order to identify additional factors contributing for reduced response to the BNT162b2 vaccine, we also compared characteristics of the 39 patients with negative antibody titer (<50 AU/ml) to the 287 patients with positive antibody titers (Table 3). While no statistically significant differences were found between the two groups in age, gender,
metastatic disease status, time to IgG test or treatment type (chemotherapy vs no chemotherapy based treatment), the analysis is considered exploratory due to the relatively small number of patients who remained seronegative. Moreover, there was no statistically significant association between cancer type and immunogenicity status (\(P=0.21\), Table 3). However, statistically significant differences were found in the distribution of antibody titers among the different cancer type (\(P=0.02\)). Multicomparsions analysis between specific cancer types revealed statistically significant difference between gynecological cancers and GI cancers (\(P=0.02\)), as for gynecological cancer the distribution of the number of antibodies tends to be higher than for GI cancer. All other comparisons were not statistically significant (Figure 3).

Similarly, multivariable logistic regression models (generated separately for men and women as they differ by distinct cancer diagnosis) did not show any statistically significant association between seropositivity in patients with cancer and age, sex or cancer type variables (data not shown).

Finally, we analyzed the association between either antibody titers or immunogenicity and treatment administered (Table 4). Due to the heterogeneity of chemotherapy-based combinations the analysis was restricted to patients receiving only single type of systemic therapy: chemotherapy alone (\(n=101\)), ICI alone (\(n=55\)) or targeted therapy alone (\(n=38\)). Seronegativity proportions were higher in the chemotherapy treated group (18.8%) compared to 9.1% in the ICI-treated patients and 2.6% in those treated with targeted therapy (\(P=0.02\) for the comparison between the groups; Table 4) Antibody titers differ statistically significant between treatments (\(P=0.002\)), and further examination of the differences between each pair of treatments revealed a statistically significant difference between chemotherapy and targeted therapy (\(P=0.001\), Figure 4)
As expected from routine clinical practice, the distribution of tumor types, and therefore also sex and age, were different according to treatment type. For example, no women with breast cancer were treated with ICI, while 20 (36.4%) of the ICI-treated group had non-small cell lung cancer (Table 4). None of the study participant, either patients with cancer or the healthy individuals reported on contracting COVID-19 following the 2\textsuperscript{nd} vaccine dose.

**Discussion**

We report here on the safety and efficacy of the COVID-19 vaccine BNT162b2 in a large unselected population of patients with solid tumors at the time of active anti-cancer treatment. Importantly, all patients received two doses of the vaccine at the recommended schedule of days 1 and 21. Moreover, immunogenicity was examined six weeks following the 2\textsuperscript{nd} dose, a time expected to represent the steady state of protective antibodies levels.

Our data indicate the vaccine to be highly effective in this population, with 88\% having protective levels of anti-SARS-CoV-2S antibodies, compared to 97\% in healthy controls. However, chemotherapy-treated patients had lower proportion of patients with protective antibody levels, 81\%. Similarly, lower response rates were also noted in cancer patients following influenza vaccine\textsuperscript{19}.

Two small studies reported on 95\% seropositivity in 18\textsuperscript{9} and 40\textsuperscript{13} patients with solid tumors receiving two doses of the BNT162b2 vaccine. In addition to sample size, major advantages of the current study were the inclusion of only actively treated patients on one hand, without any selection and regardless of clinical characteristics on the other hand. Thus, our finding may better represent the general population of actively treated patients with cancer.
Development of anti-S antibodies are indicative of an immune response to the vaccine but are not synonymous to protection from clinical infection\textsuperscript{20}. The cutoff for a positive response in the assay used by us is defined as 50 AU/ml in accordance to validation studies for this specific test\textsuperscript{16}. However, while seropositivity is generally considered to be protective\textsuperscript{20}, antibody levels above this cutoff may also be of importance\textsuperscript{21} as the correlation between titer levels following vaccination and vaccination efficacy is not well characterized in COVID-19.

Indeed, differences between patients with cancer and the healthy controls in antibody titers were highly statistically significant, with median titer of nearly 3-fold higher in the control group (Table 2). It is remain to be elucidated whether these differences will translate to higher chances of SARS-CoV-2 infection.

The immune response may also be evaluated by testing T-cell response following vaccination. However, T-cell response might be affected in patients with cancer due to effect of systemic therapy or disease itself. Nevertheless, it was also demonstrated that T-cell response correlates with antibody titers in healthy individuals and cancer patients, with 88\% of cancer patients showing T-cell response and 95\% showing seropositivity following 2\textsuperscript{nd} dose of the vaccine\textsuperscript{9,14}. As antibody titers strongly correlate with T-cell response but are much easier to evaluate, this is possibly the preferred method for screening large number of patients.

The relatively high rates of seropositivity observed in patients with solid cancer are in stark contrast to recent reports in patients with CLL\textsuperscript{10} or other immunodeficiency states, including hemodialysis\textsuperscript{17} and solid organ transplant recipients\textsuperscript{22}. This may reflect the relatively smaller immunosuppressive effects of solid tumors and their treatments, compared to hematologic malignancies.
As only 39 (11.9%) of the patients did not show response to the vaccine, no clear association between clinical characteristics and response could be identify. The differences in distribution of antibody titers across tumor types and treatment types may signal an association between these factors and lower response, but due to small number of patients, this study should be considered primarily hypothesis generating, and larger studies are required in order to substantiate these observations.

There are several limitations to this study: patient population was compared to healthy controls consisting substantially of younger healthcare workers, yet SARS-CoV-2S Ab levels were statistically significant lower in the patient population after adjusting to age and gender. Though anti-SARS-CoV-2S testing was offered to all patients, low (24%) participation rate of active patients in this study was noted. This may be due to lack of clinical relevance of this test for patients with cancer at the time of the study as the Israeli authorities stated the antibody levels have no clear clinical value. Analysis of SARS-CoV-2S Ab levels was based on a one-time blood collection. As it was reported Ab levels achieve a steady state at ~40 days following full vaccination, however one time sampling may not reflect a steady Ab levels and a serial testing over time is needed to define the optimal time point for Ab testing in this population and the course of serum Ab levels over time.

We aimed to evaluate SARS-CoV-2S Ab levels of patients with cancer receiving different types of systemic therapy, however due to small number of patients they were grouped to three major treatment types and an analysis of the specific effects of each drug and combinations could not be performed. There is a need to further dissect the effect of systemic chemotherapy by individual drugs or drug classes in order to better characterize which patients are at greater risk.

None of the patients with cancer participating in this study contracted symptomatic SARS-CoV-2 infection. This may be attributed not only to the vaccine but also to the low
prevalence of SARS-CoV-2 infection in Israel during the study period and possibly, to strict adherence of cancer patients to personal safety and social distancing. Longer follow up time and more SARS-CoV-2S Ab testing may help clarify these points.

As expected from previous reports\(^9,^{13,10}\), no severe side effects were noted. Importantly, despite the relatively longer period from the 2\(^{nd}\) vaccine dose, no new safety signals were observed, regardless of treatment type. This finding strengthen the current recommendations to vaccinate all patients with cancer regardless of treatment type.

In conclusion, our study indicates the BNT162b2 mRNA vaccine as safe and effective in actively treated patients with cancer. However, the relatively lower antibody titers and lower proportion of patients with seropositive response, especially among chemotherapy treated patients, call for continuing the use of personal protective measures in these patients, even following vaccination.

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Data Availability

The data underlying this article cannot be shared publicly due to ethical guidelines, aiming to protect the privacy of individuals that participated in the study. The data may be shared on reasonable request to the corresponding author, after permission from the institutional review board.

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# Tables

Table 1. clinical characteristics of study participants

| Characteristics                          | Cancer patients (N=326) | Healthy controls (N=164) | P     |
|------------------------------------------|-------------------------|--------------------------|-------|
| Median Age, years (range)                | 66 (29-89)              | 54 (24-90)               | <0.001<sup>a</sup> |
| Female, No. (%)                          | 203 (62.3)              | 100 (60.9)               | 0.78<sup>b</sup>  |
| Days from 2<sup>nd</sup> dose to COVID-19| 78 (21-115)             | 72 (21-115)              | 0.08<sup>a</sup>  |
| Ab test, Median (range)                  |                         |                          |       |
| Cancer type, No. (%)                     |                         |                          |       |
| Gastrointestinal                         | 84 (25.8)               | NA                       |       |
| Breast                                   | 82 (25.2)               | NA                       |       |
| NSCLC                                    | 45 (13.8)               | NA                       |       |
| Gynecological                            | 41 (12.6)               | NA                       |       |
| Genitourinary                            | 29 (8.9)                | NA                       |       |
| Skin cancers including melanoma          | 13 (4.0)                | NA                       |       |
| CNS                                      | 12 (3.7)                | NA                       |       |
| Sarcoma                                  | 10 (3.1)                | NA                       |       |
| Head and Neck                            | 7 (2.1)                 | NA                       |       |
| Other                                    | 3 (0.9)                 | NA                       |       |
| Cancer Stage, No. (%)                    |                         |                          |       |
| Local                                    | 96 (29.4)               | NA                       |       |
| Metastatic                               | 230 (70.6)              | NA                       |       |

<sup>a</sup>P values derived from the non-parametric Mann-Whitney U test, two-sided. NA = not applicable; NSCLC = non-small cell lung cancer; CNS = central nervous system; Ab = antibody; COVID-19 = coronavirus disease 2019.

<sup>b</sup>P values derived from the parametric chi-square, two-sided.
Table 2. Immunogenicity in patients with cancer compared to healthy controls.

| Variables                          | Cancer patients (N=326) | Healthy controls (N=164) | $P$  |
|------------------------------------|-------------------------|--------------------------|------|
| Median IgG Ab titer (range), AU/ml | 931 (0-40000)           | 2817 (0-40000)           | 0.003$^a$ |
| Seronegative (<50 AU/ml), No. (%)  | 39 (11.9)               | 5 (3.0)                  | 0.001$^b$ |
| IgG titer (AU/ml) by range, No. (%)|                         |                          |      |
| 50-100                             | 21 (6.4)                | 0 (0.0)                  | 0.001$^b$ |
| 100-1000                           | 114 (35.0)              | 31 (18.9)                |      |
| 1000-5000                          | 106 (32.5)              | 74 (45.1)                |      |
| 5000-10000                         | 24 (7.4)                | 33 (20.1)                |      |
| <10000                             | 22 (6.7)                | 21 (12.9)                |      |

$^a$P values derived from the non-parametric Mann-Whitney U test, two-sided. Comparison of median IgG Ab between cancer patients and control group was adjusted for age and sex using a logistic regression model including these variables. Ab = antibody.

$^b$P values derived from the parametric chi-square, two-sided.
Table 3. Comparison between cancer patients with either seropositive or seronegative response to the BNT162b2 vaccine.

| Variables                                      | SARS-CoV-2S IgG seropositive (n=287) | SARS-CoV-2S IgG seronegative (n=39) | P   |
|------------------------------------------------|--------------------------------------|-------------------------------------|-----|
| Median age (range), y                           | 66 (22-91)                           | 67 (35-89)                          | 0.25<sup>a</sup> |
| Female, No. (%)                                 | 174 (60.6)                           | 29 (74.4)                           | 0.10<sup>b</sup> |
| Metastatic disease, No. (%)                     | 205 (71.4)                           | 25 (64.1)                           | 0.74<sup>b</sup> |
| Median days from 2nd vaccination to COVID-19 Ab test | 76 (23-115)                         | 76 (2-99)                           | 0.47<sup>a</sup> |
| Chemotherapy-based treatment, No. (%)           | 176 (61.3)                           | 29 (74.4)                           | 0.12<sup>b</sup> |
| Cancer type, No. (%)                            |                                      |                                     | 0.21<sup>c</sup> |
| Gastrointestinal                                | 78 (27.2)                            | 6 (15.4)                            |     |
| Breast cancer                                   | 68 (23.7)                            | 14 (35.9)                           |     |
| NSCLC                                           | 40 (13.9)                            | 5 (12.8)                            |     |
| Gynecological                                   | 39 (13.6)                            | 2 (5.1)                             |     |
| Genitourinary                                   | 24 (8.4)                             | 5 (12.8)                            |     |
| Other                                           | 38 (13.2)                            | 7 (17.9)                            |     |
| COVID-19 infection, No.                         | 0                                    | 0                                   | >0.99 |

<sup>a</sup>P values derived from the non-parametric Mann-Whitney U test, two-sided. COVID-19 = Coronavirus disease 2019; Ab = Antibody; NSCLC = non-small cell lung cancer

<sup>b</sup>P values derived from the parametric chi-square, two-sided.

<sup>c</sup>P-value derived from chi-square test, two-sided.
Table 4. Immunogenicity of BNT162b2 vaccine by treatment type.

| Variables                        | Chemotherapy (n=101) | ICI (n=55) | Targeted therapy (n=38) | P       |
|----------------------------------|----------------------|------------|-------------------------|---------|
| Median age (range), y            | 67 (22-84)           | 69 (27-91) | 63 (33-85)              | 0.01<sup>a</sup> |
| Female, No. (%)                  | 67 (66.3)            | 21 (38.2)  | 29 (76.3)               | <0.001<sup>b</sup> |
| Metastatic disease, No. (%)      | 63 (62.4)            | 39 (70.9)  | 26 (68.4)               | 0.52<sup>b</sup> |
| Cancer diagnosis, No. (%)        |                      |            |                         | 0.002<sup>b</sup> |
| Gastrointestinal                 | 36 (35.6)            | 7 (12.7)   | 3 (7.9)                 |         |
| Breast cancer                    | 27 (26.7)            | 0 (0.0)    | 13 (34.2)               |         |
| NSCLC                            | 5 (5.0)              | 20 (36.4)  | 2 (5.3)                 |         |
| Other                            | 33 (32.7)            | 28 (50.9)  | 20 (52.6)               |         |
| Median IgG titer (range), AU/ml  | 578 (0-28229)        | 793 (2-12658) | 1895 (46-40000)     | 0.002<sup>a</sup> |
| Seronegative <50 IU, No. (%)     | 19 (18.8)            | 5 (9.1)    | 1 (2.6)                 | 0.02<sup>b</sup> |

<sup>a</sup>P values derived from the non-parametric Kruskal-Wallis test, two-sided. ICI = immune checkpoint inhibitors; Ab = antibody; NSCLC = non-small cell lung cancer

<sup>b</sup>P values derived from the parametric chi-square, two-sided.
Figure Legends

Figure 1. Local and systemic side effects following BNT162b2 mRNA vaccination among actively treated cancer patients. Bars show the proportion of participants reporting on each side-effect. Only side effects reported by more than 1% of the patients are presented.

Figure 2. Lower SARS-Cov-2S IgG Ab among patients with solid cancers. SARS-Cov-2 S IgG Ab values in serum samples of actively treated patients with cancer (N=326 patients) and healthy control (N=164). Box plots represent serum SARS-Cov-2 S IgG Ab values. Ends of the boxes are the upper and lower quartiles and medians are marked by horizontal lines inside the boxes. Every dot represents one participant’s level of antibodies. Error bars represent the range between minimal and maximal points. The y-axis (log_{10} scale) represents SARS-Cov-2 S IgG Ab values transformed to log_{10} scale. The statistical significance of the differences was determined using 2-sided Mann-Whitney test adjusted for age and sex. Dashed line represents cutoff level of seropositivity (50 AU/ml). Cancer patients had lower plasma levels of SARS-Cov-2 S IgG Ab compared to healthy control (P=0.003). Ab = antibody.

Figure 3. Differences in the distribution of SARS-Cov-2S IgG Ab across different cancer types.
SARS-Cov-2 S IgG Ab values in serum samples of actively-treated patients with cancer (N=326 patients) by cancer type. Box plots represent serum SARS-Cov-2 S IgG Ab values. Ends of the boxes are the upper and lower quartiles and medians are marked by horizontal lines inside the boxes. Every dot represents one participant’s level of antibodies. Error bars represent the range between minimal and maximal points. The y-axis (log_{10} scale) represents...
SARS-CoV-2 S IgG Ab values transformed to $\log_{10}$ scale. Dashed line represents cutoff level of seropositivity (50 AU/ml). Statistical analyses were determined using the Kruskal–Wallis and the Mann-Whitney test with Bonferroni correction for multiple comparisons. Patients with gynecological cancers had higher SARS-CoV-2 S IgG Ab values compared to patients with gastrointestinal cancers ($P=0.02$, two-tailed). All other comparisons did not reach statistical significance. Ab = antibody; NSCLC = non-small cell lung cancer.

Figure 4. Differences in the distribution of SARS-CoV-2 S IgG Ab in patients receiving different anti-cancer treatments. SARS-CoV-2 S IgG Ab values in serum samples of cancer patients treated with chemotherapy (n=101), immunotherapy (n=55) and targeted therapy (n=38, green dots). Box plots represent serum SARS-CoV-2 S IgG Ab values. Ends of the boxes are the upper and lower quartiles and medians are marked by horizontal lines inside the boxes. Every dot represents one participant’s level of antibodies. Error bars represent the range between minimal and maximal points. The y-axis ($\log_{10}$ scale) represents SARS-CoV-2 S IgG Ab values transformed to $\log_{10}$ scale. Dashed line represents cutoff level of seropositivity (50 AU/ml). Statistically analyses were determined using the Kruskal–Wallis and the Mann-Whitney test with Bonferroni correction for multiple comparisons. Patients treated with targeted therapy had higher SARS-CoV-2 S IgG Ab values compared to patients treated with chemotherapy ($P=0.001$, two-tailed). All other comparisons did not reach statistical significance. Ab = antibody; ns = non-statistically significant.
Figure 1

![Bar chart showing prevalence of side effects]

**Local side effects**
- Local pain
- Local swelling
- Local rash
- Fatigue or weakness
- Myalgia or flu-like symptoms

**Systemic side effects**
- Headache
- Chills
- Fever
- Arthralgia

Prevalence of side effects (n=326)
Figure 2

SARS-CoV-2 S IgG Ab (log10)

Healthy control (N=164)  Cancer patients (N=326)

P=0.003

50 AU/ml
Figure 2

- Healthy control (N=164)
- Cancer patients (N=326)

SARS-CoV-2S IgG Ab (log_{10})

P = 0.003

50 AU/ml
Figure 3

- Gastrointestinal (n=84)
- Breast (n=81)
- NSCLC (n=44)
- Gynecological (n=41)
- Genitourinary (n=29)
- Other (n=45)

SARS-CoV-2S IgG Ab (log_{10})

- p=0.02

50 AU/ml
Figure 3

![Box plot showing SARS-CoV-2S IgG Ab (log10) with significance level p=0.02 for different cancer types: Gastrointestinal (n=84), Breast (n=81), NSCLC (n=44), Gynecological (n=41), Genitourinary (n=29), Other (n=45). The horizontal line at 50 AU/ml indicates the threshold for positive antibodies.](https://academic.oup.com/jnci/advance-article/doi/10.1093/jnci/djab174/6359210)
Figure 4

SARS-CoV-2S IgG Ab (log10)

Chemotherapy
(N=101)

Immunotherapy
(N=55)

Targeted therapy
(N=38)

50 AU/ml

p=0.001

ns

ns
Figure 4

The figure shows a box plot comparing SARS-CoV-2S IgG Ab (log10) levels across different treatment groups: Chemotherapy (N=101), Immunotherapy (N=55), and Targeted therapy (N=38).

- Chemotherapy: ns
- Immunotherapy: ns
- Targeted therapy: p=0.001

The 50 AU/ml threshold is indicated with a dotted line.