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Clinical Trial

Efficacy and safety of BNT162b2 vaccination in patients with solid cancer receiving anticancer therapy — a single centre prospective study

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COVID19; Cancer; Oncology; SARS-CoV-2; Vaccine; Seropositivity; Seronegativity; Co-morbidities; Immunoglobulin; IgG

Abstract  Aim: Patients with cancer are at an increased risk for severe coronavirus disease of 2019, thus data on the safety and efficacy of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines are essential. We conducted this prospective study of patients with cancer vaccinated with BNT162b2 and monitored for antibody response and safety. The aim was to evaluate the rate of seropositivity and define predictors for non-reactive immune response. Furthermore, we evaluated the frequency and the severity of adverse events.

Methods: The study included patients with solid tumours undergoing anticancer treatment and immunocompetent health-care workers serving as controls. Serum titres of the receptor-binding domain (RBD) immunoglobulin G (IgG) and neutralising antibodies were measured 2–4 weeks after each vaccine dose.

Results: The analysis included 129 patients, of which 70.5% patients were metastatic. Patients were treated with chemotherapy (55%), immunotherapy (31.4%), biological agents (24.8%), hormonal treatment (8.5%) and radiotherapy (4.6%), that were given either alone or in combinations. The seropositivity rate among patients with cancer and controls was 32.4% versus 59.8% (p < 0.0001) after the first dose and 84.1% versus 98.9% (p < 0.0001) after the second
dose, respectively. Median RBD-IgG titre was lower among patients than controls (p < 0.0001). Patients who were seronegative after the second dose had significantly more comorbidities than that with patients with seropositivity (77.8% vs 41.1%, respectively, p = 0.0042).

**Conclusion:** Adequate antibody response after BNT162b2 vaccination was achieved after two doses but not after one dose, in patients with cancer vaccinated during anticancer therapy.

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**1. Introduction**

Patients with cancer are at a significantly increased risk of severe morbidity and mortality from coronavirus disease of 2019 (COVID-19) [1–9], posing a challenge for clinicians in managing these patients. During the early days of the pandemic, the uncertainties concerning severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease were substantial, causing rapid changes and updates of medical guidelines. International oncological organisations such as the American Society of Clinical Oncology and the European Society of Medical Oncology published modified guidelines regarding cancer screening, as well as medical, radiation and surgical oncology [10,11]. Concerns were raised regarding repercussions of such modifications, which might result in delayed treatments and detections of primary or recurrent cancer.

The current efficacy data for COVID-19 mRNA vaccines are >90% with a favourable safety profile as demonstrated in pivotal trials [12, 13]. However, these studies excluded patients who were immune-compromised or affected by cancer. [14]. Data regarding safety and efficacy of mRNA COVID-19 vaccines in patients who were immune-compromised [15–18] and oncology patients [19–23] are now beginning to emerge.

In December 2020, the Israeli Government approved the mRNA COVID-19 vaccine, and the Israeli Ministry of Health launched a nationwide Pfizer BNT162b2 vaccination campaign. The primary goal was to rapidly vaccinate all medical staff and high-risk individuals. Considering the high risk of patients with cancer for severe COVID-19 disease and the available knowledge regarding safety and efficacy of other routinely used vaccines, for example, the influenza vaccine [24], the benefits of vaccination were assumed to outweigh the potential harms. Hence, the Israeli Ministry of Health prioritised vaccination of all high-risk individuals, including patients with cancer.

Here, we describe the efficacy and safety of BNT162b2 vaccination of actively treated patients with cancer. Our aim was to evaluate the rate of seropositivity after the first and second vaccine dose and to define clinical characteristics associated with seronegativity.

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**2. Methods**

**2.1. Study design and participants**

BNT162b2 mRNA vaccinations were offered to all patients with cancer who were actively treated in our institution, regardless of treatment type, disease stage, performance status or life expectancy. Patients previously infected with SARS-CoV-2 were excluded. Two doses of the BNT162b2 vaccine (Pfizer, New York, USA and BioNTech, Mainz, Germany) were administered, 21 days apart. Patients were actively screened for the vaccine-induced antibody response 2–4 weeks after each vaccine dose. Controls were immunocompetent healthcare workers tested for antibody response 2–4 weeks after each vaccine dose. Written informed consent form (ICF) was obtained from all participants. The institutional review board approved the study protocol and ICF.

**2.2. Clinical data extraction**

Relevant clinical data were retrieved from electronic medical records of patients with cancer and included age, gender, body mass index (BMI), cancer type, diagnosis date and cancer stage (i.e. local or metastatic). Comorbidities included hypertension, diabetes mellitus, cardiac disease, lung disease and autoimmune disease. Anticancer therapies were classified as chemotherapy, immunotherapy, biological-targeted therapy, hormonal therapy and radiation, given either alone or in combinations.

**2.3. Serology assays**

Samples were evaluated with an enzyme-linked immunosorbent assay (ELISA) that detects IgG (immunoglobulin G) antibodies against the RBD (receptor-binding domain) of SARS-CoV-2 [25]. The ELISA index value below 0.9 was considered negative, between 0.9 and 1.1 equivocal and equal to or above 1.1 positive. Samples that were positive for RBD-IgG were tested for neutralising antibodies (NAs). A SARS-CoV-2 pseudovirus neutralisation assay was performed using a propagation-competent VSV (vesicular stomatitis virus).
spike similar to that previously published [26] (kindly provided by Gert Zimmer, University of Bern, Switzerland). Sera not capable of reducing viral replication by 50% at a 1:8 dilution or below were considered non-neutralising. Negative RBD-IgG samples were not tested for NAs, because these have previously been shown to yield negative NA tests.

2.4. Safety

Adverse events (AEs) were obtained once, after completion of two vaccine doses, using specific yes/no questions regarding local reactions (i.e. pain at the injection site, redness and swelling) and systemic reactions (i.e. fever >38 °C, fatigue, headache, myalgia, chills, nausea and vomiting, paraesthesia and use of palliative drugs).

2.5. Statistical methods

Continuous variables are presented as mean and standard deviation or as geometric mean (GMT) and 95% confidence interval (CI). Categorical variables are presented as percentages. For GMT calculation, negative NA (=0), missing NA or negative RBD-IgG tests were counted as titres of 2. Multivariable logistic regression analysis was used to identify factors associated with vaccine-induced antibody response among the entire cohort (patients with cancer and healthy control). Results are presented as odds ratio (OR), 95% CI and P-value.

A scatter plot of log-transformed IgG and NAs was obtained using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). The correlation between IgG and log-transformed NAs was analysed using Spearman’s correlation by two-tailed parametric t-test means with 95% CIs.

Univariate analyses were used to determine the influence of various parameters on seropositivity after the second vaccine dose among patients with cancer, by the chi-square test for categorical variables and Student’s t-test for continuous variables. These parameters included age, gender, BMI, comorbidities, AEs, cancer type and stage, years since primary diagnosis and metastases, anticancer treatment type and timing before and after the second vaccination.

Table 1
Demographic and clinical characteristics of patients with cancer and controls.

| Gender          | Patients with cancer (N = 129) | Controls first dose (N = 348) | P         | Controls second dose (N = 261) | P-value |
|-----------------|---------------------------------|------------------------------|-----------|-------------------------------|---------|
| Female N (%)    | 67 (51.9)                       | 272 (78.2)                  | <0.001    | 195 (74.7)                    | <0.0001 |
| Male N (%)      | 62 (48.1)                       | 76 (21.8)                   |           | 66 (25.3)                     |         |
| Age mean ± SD   | 62.40 ± 12.81                   | 47.28 ± 12.33               | <0.0001   | 55.84 ± 14.34                 | <0.0001 |
| BMI mean ± SD   | 25.59 ± 4.92                    | 25.19 ± 4.89                | 0.4265    | 25.61 ± 4.44                  | 0.9626  |
| Comorbidities N (%) | 63 (48.8)                    | 66 (19.0)                   | <0.0001   | 79 (30.3)                     | 0.0003  |
| Hypertension N (%) | 36 (27.9)                     | 40 (11.5)                   | <0.0001   | 59 (25.0)                     | 0.5     |
| Diabetes N (%)  | 25 (19.4)                       | 19 (5.5)                    | <0.0001   | 23 (9.7)                      | 0.009   |
| Cardiac disease N (%) | 20 (15.5)                     | 10 (2.9)                    | <0.0001   | 13 (5.5)                      | 0.0015  |
| Lung disease N (%) | 11 (8.5)                      | 14 (4.0)                    | 0.05      | 8 (3.4)                       | 0.0347  |
| Autoimmune N (%) | 6 (4.7)                        | 0 (0)                       | NA        | 0 (0)                         | NA      |

BMI, body mass index; SD, standard deviation.

Table 2
Cancer diagnosis and treatment characteristics.

| Cancer type N (%) | Patients with cancer (N = 129) |
|------------------|--------------------------------|
| Gastrointestinal | 55 (42.6)                      |
| Breast           | 26 (20.2)                      |
| Lung             | 19 (14.7)                      |
| Melanoma         | 14 (10.9)                      |
| Genitourinary    | 10 (7.8)                       |
| Othera           | 5 (3.9)                        |

Cancer stage N (%)

| Locoregional | 38 (29.5) |
| Metastatic   | 91 (70.5) |

Cancer treatment N (%)

| Chemotherapyb | 41 (31.8) |
| Biological-targeted agentc | 16 (12.4) |
| Hormonal therapyd | 5 (3.9) |
| Immunotherapye | 26 (20.2) |
| Chemo + immunotherapy | 9 (7.0) |
| Chemo + biological agent | 21 (16.3) |
| Hormonal + biological agent | 5 (3.9) |
| Radiotherapy | 5 (3.9) |
| Radiotherapy + chemotherapy | 1 (0.8) |

a Other: brain, thymoma, endometrial, skin and neuroendocrine.

b Chemotherapy: Adriamycin, AC-T, AC-TPH, CMF, pemetrexed, cisplatin, carboplatin, capécitabine, paclitaxel, nab-paclitaxel, TDM-1, FOLFOX, FOLFIRI, FOLFIRINOX, gemcétabine and vinorelbine.

c Biological targeted agents: bevacizumab, panitumumab, cetuximab, palbociclib, entrectinib, abemaciclib, trastuzumab, lenvatinib, neratinib, rucaparib, osimertinib and dabrafenib.

d Hormonal therapy: letrozole, anastrazole, goserlin, megestrol and octreotide.

e Immunotherapy: pembrolizumab, nivolumab, atezolizumab, cemiplimab, ipilimumab and durvalumab.
### 3. Results

Between 27th December 2020 and 24th March 2021, 129 actively treated patients with solid cancer, who were vaccinated while on treatment, were included in this study. Serum tests were performed in 16 (12.4%) patients after the first vaccine dose only, in 58 (45%) patients after the second vaccine dose only and in 55 (42.6%) patients after both the first and second vaccine doses.

Immunocompetent health-care workers with no medical history of cancer, other immune compromising disease or autoimmune disease served as controls. A total of 645 serum tests were performed, 384 (59.5%) samples after the first vaccine dose and 261 (40.5%) samples after the second dose.

#### 3.1. Patient characteristics

Demographic and clinical characteristics of patients with cancer and controls are shown in Table 1. For patients with cancer, the median age was 62.4 ± 12.8 years (range, 32–88), 62 (48.1%) were men. Sixty-three (48.8%) patients had concomitant comorbidities: hypertension (27.9%); diabetes (19.4%); cardiac disease (15.5%); lung disease (8.5%); and autoimmune disease (4.7%). The mean BMI was 25.6 ± 4.9 (range 15.2–41.1). Subjects in the control group included more women, were younger in age and had less comorbidities than patients with cancer, all statistically significant.

Cancer diagnosis and treatments are detailed in Table 2. Cancer diagnosis included gastrointestinal...
malignancies in 55 (42.6%) patients, breast cancer in 26 (20.2%) patients, lung cancer in 19 (14.7%) patients, melanoma in 14 (10.9%) patients, genitourinary malignancies in 10 (7.8%) patients and 5 (3.9%) had other tumours (i.e. brain, thymoma, endometrial, skin and neuroendocrine). The disease stage was local in 29.5% of patients and metastatic in 70.5% of patients.

Oncological treatments included chemotherapy in 71 (55%) patients either with or without other agents. Forty-four (34.1%) patients were treated with immune checkpoint inhibitors, 32 (24.8%) patients were treated with biological-targeted agents, 11 (8.5%) patients received hormonal treatment, and 6 (4.6%) patients were treated with radiotherapy (Table 2).

### 3.2. Immunogenicity after BNT162b2 vaccination

At a mean time of 16 days after the first vaccination, 23/71 (32.4%) patients with cancer developed RBD-IgG compared with 208/348 (59.8%) controls, p < 0.0001. At a mean time of 20 days after the second vaccination, 95/113 (84.1%) patients with cancer developed RBD-IgG compared with 258/261 (98.9%) controls, P < 0.0001 (Table 3). The GMT RBD-IgG was lower among patients than that of controls, 3.25 (95%CI 2.7–3.9) versus 6.1 (95%CI 5.8–6.4), respectively, p < 0.001. The GMT of neutralising antibodies was lower in patients with cancer versus controls 221.1 (95% CI 160.0–305.7) versus 482.8 (95% CI 410.8–567.5), respectively, p < 0.001 (Fig. 1). A high correlation 

(r = 0.87, 95%CI 0.81–0.91, p < 0.0001) was found between RBD-binding IgG and NAs (Fig. 2).

In a multivariate logistic regression model adjusted for age, gender, comorbidity and days after the second

![Fig. 1. Quantification of IgG after the second dose of the BNT162b2 vaccine in patients with cancer and controls. (a) RBD-IgG levels, GMT; (b) Neutralising antibodies above the cutoff. The dotted black line indicates the limit level of positive antibodies. The short black line indicates GMT and 95%CI. RBD, receptor-binding domain, GMT, geometric mean titres, S/CO, sample/cutoff ratio; IgG, immunoglobulin G; CI, confidence interval.](image1)

![Fig. 2. Spearman correlation between RBD-IgG and log-transformed neutralising antibodies. 2–4 weeks after the second vaccine dose. IgG, immunoglobulin G, RBD receptor-binding domain, S/CO, sample/cutoff ratio.](image2)
vaccine dose, only comorbidity was significantly associated with decreased seropositivity with an OR (odds ratio) of 0.22 (95%CI 0.07−0.72, p < 0.0119). The estimated OR for a positive humoral response was significantly reduced in patients with cancer compared with controls (OR = 0.07, 95%CI 0.02−0.27, p < 0.0001).

Eighteen patients (9 men, 9 women) did not show a positive seroreactive level of IgG anti-RBD antibodies after the second vaccine dose (Table 4). In a univariate analysis, only comorbidities were more common among non-responders versus responders (77.8% vs 41.1%, respectively, p = 0.0042), specifically diabetes (38.9% and 16.8%, respectively, p = 0.033) and autoimmune disease (16.7% and 1.1%, respectively, p = 0.001) (Table 5).

Vaccine-related serious AEs or allergic reactions were not observed among vaccinated patients with cancer. Seventy-one per cent of patients reported at least one AE after the vaccination (Table 6): 39% after the first dose and 58% after the second dose. The most common AEs were local, reported by 34.9% of patients (26.4% and 20.2% after the first and second dose, respectively). Systemic AEs were reported by 35.7% of patients, including fatigue, fever, chills, headache and myalgia, and were more common after the second vaccine dose than that with the first dose (33.3% vs 7%, respectively). Most systemic events were mild to moderate.

### 4. Discussion

This is a prospective study evaluating serological responsiveness and NA levels in response to mRNA SARS-CoV-2 vaccines among patients with solid cancer receiving active treatment. We found that 32% of patients were seropositive after the first vaccine dose, and 84% of patients were seropositive after the second vaccine dose. This is in line with previous published data in patients with cancer [19–21,27]. Patients who were seronegative after the second dose had significantly more comorbidities than patients who are seropositive (78% vs 41%).

Serum RBD-IgG and NA levels after each vaccine dose were significantly lower in patients with cancer versus controls. Data regarding the serum antibody response to vaccination during treatment among patients with cancer are scarce. A small trial assessing immune response in patients with breast cancer receiving influenza vaccination during 5-fluorouracil, epirubicin and cyclophosphamide immunotherapy

| Table 5 |
| --- |

Univariate analysis of seropositivity after the second vaccine dose among patients with cancer.

|                         | Seronegative (N = 18) | Seropositive (N = 95) | p-value |
|-------------------------|-----------------------|-----------------------|---------|
| Metastatic stage N (%)  |                       |                       |         |
| Gastrointestinal        | 8 (44.4)              | 37 (38.9)             | 0.7491  |
| Breast                  | 2 (11.1)              | 21 (22.1)             | 0.1924  |
| Lung                    | 3 (16.7)              | 13 (13.7)             |         |
| Melanoma                | 0 (0.0)               | 14 (14.7)             |         |
| Genitourinary           | 3 (16.7)              | 7 (7.4)               |         |
| Other a                 | 2 (11.1)              | 3 (3.2)               |         |
| Days from treatment to second vaccine dose mean ± SD | 33.47 ±95.39 | 14.91 ±32.39 | 0.9357 |
| Days from second vaccine dose to treatment mean ± SD | 8.29 ±7.81 | 7.55 ±7.49 | 0.7388 |
| Years since cancer diagnosis mean ± SD | 3.30 ±4.54 | 3.33 ±4.37 | 0.9846 |
| Years since metastasis mean ± SD | 2.74 ±2.08 | 2.59 ±2.12 | 0.8101 |
| Treatment type N (%)    |                       |                       |         |
| Chemotherapy            | 8 (44.4)              | 51 (53.7)             | 0.4718  |
| Biological-targeted agent | 3 (16.7)              | 22 (23.2)             | 0.5430  |
| Hormonal therapy        | 1 (5.6)               | 10 (10.5)             | 0.5142  |
| Immunotherapy           | 5 (27.8)              | 37 (38.9)             | 0.3686  |
| Radiation               | 3 (16.7)              | 2 (2.1)               | 0.0059  |
| Comorbidities any N (%) | 14 (77.8)             | 39 (41.1)             | 0.0042  |
| Hypertension            | 6 (33.3)              | 27 (28.4)             | 0.6743  |
| Diabetes                | 7 (38.9)              | 16 (16.8)             | 0.0332  |
| Cardiac disease         | 4 (22.2)              | 14 (14.7)             | 0.4262  |
| Lung disease            | 2 (11.1)              | 7 (7.4)               | 0.5907  |
| Autoimmune disease      | 3 (16.7)              | 1 (1.1)               | 0.0010  |
| Adverse events N (%)    |                       |                       |         |
| Any                     | 9 (50.0)              | 52 (54.7)             | 0.7116  |
| Local                   | 5 (27.8)              | 32 (33.7)             | 0.6244  |
| Systemic                | 6 (33.3)              | 35 (36.8)             | 0.7765  |
| Any, after the first dose | 4 (22.2)              | 28 (29.5)             | 0.5312  |
| Any, after the second dose | 8 (44.4)              | 44 (46.3)             | 0.8839  |

SD, standard deviation.

* Other: brain, thymoma, endometrial, skin and neuroendocrine.
found a significantly lower response to influenza vaccination than that with healthy controls [28]. Another study found that patients with breast cancer had lower levels of total IgG, IgG1 and NAs after vaccinia vaccination [29]. The lower immunogenicity might be attributed to the immunosuppressive effect of cancer itself or to the anticancer treatment used.

The higher antibody titre found among the control immunocompetent group in this study could be attributed to differences in characteristics, mainly less comorbidities. Coexisting comorbidities have previously been shown to be associated with lower immunogenicity even in persons who are immunocompetent [30]. In our study, diabetes and autoimmune disease negatively impacted immune response to BNT162b2 vaccination in patients with cancer. Hyperglycaemia in patients with diabetes is known to cause dysfunction of the immune response and increases susceptibility to infections [31].

Compared with previously published data on the seropositivity rate after vaccination of other immunosuppressed populations, such as patients who received heart or renal transplantation, the seropositivity rate of patients with cancer in our study was higher (18–37.5% vs 84%, respectively) [15–18].

We did not find any correlation between seronegativity and either cancer type and stage, treatment type, time from diagnosis and time from treatment to vaccination or vice versa. It should be emphasised that the per cent of patients with metastasis among the seronegative group was not significantly different from that of the seropositive group (72.2% vs. 68.4%, respectively, p = 0.7491).

Symptoms of cancer itself or chemotherapy-induced AEs (e.g. fatigue, fever, and so on) could possibly be mistaken for vaccine-related systemic side-effects. However, we found that the vaccine was safe, without any severe side-effects, among patients with cancer.

This study had several limitations. First, prevaccination SARS-CoV-2 antibody titres and/or polymerase chain reaction were not evaluated, and hence previous infection status is uncertain. Second, we used humoral response as a surrogate for vaccine efficacy, yet we neither checked T cell activity against the virus nor showed clinical outcomes. Other limitations include small sample size, lack of clinical correlation with the SARS-CoV-2 positivity rate among patients who are seronegative after vaccinations and data regarding long-term serum antibody titres.

5. Conclusions

This study demonstrated that completing two doses of BNT162b2 mRNA COVID-19 vaccine while on active cancer treatment yields satisfactory immunogenic effect among patients with solid cancer. Comorbidities negatively affected seropositivity, specifically in patients with cancer, diabetes and autoimmune disease. The durability and long-term effects remain unknown and must be addressed in future research.

Author contributions

Conceptualisation: ESS, AI, RB, IL, GRY and GR.
Data curation: ESS, AI, OM, RB, IL, GRY and GR.
Project administration: ESS. Roles/Writing — original draft: ESS, AI. Writing — review and editing: ESS, AI, OM and GR. Validation: OM and GR. Software: OM.
Investigation: SH, MJ and YL. Resources: SH, MJ and EGL. Formal analysis: EGL and LO. Methodology: EGL, LO and GR. Visualisation: YL. Supervision: GR.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.007.

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