

# Six-Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors



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## ABSTRACT

We had previously reported short-term efficacy, immunogenicity, and safety of the BNT162b2 vaccine among cancer patients with solid tumors. We aimed to evaluate these outcomes at six months postvaccination. The study cohort comprised patients who were on treatment during vaccination and throughout six months postvaccination. Serologic tests were performed after second vaccination and six months afterward. An age-matched cohort of health care workers served as controls. Documentation of COVID-19 infection, blood tests, and imaging studies during the study period was reviewed. Participants included 154 patients and 135 controls. Six months postvaccination, 122 (79%) patients were seropositive compared with 114 (84%) controls ( $P = 0.32$ ). Serology titer dramatically decreased in a similar manner in both cohorts. No COVID-19 cases were documented in controls, and one case occurred in patient cohort. All previously reported adverse effects resolved. Taken together, the pattern of immunogenicity, efficacy, and safety of BNT162b2 in patients with cancer with solid tumors at six months postvaccination resembles that of the general population.

**SIGNIFICANCE:** Evidence regarding efficacy and safety of COVID-19 vaccines in patients with cancer indicate a favorable short-term profile. Immunomodulation due to anticancer treatments may affect immunity and immunogenicity of patients with cancer to the BNT162b2 vaccine over time. Our study sheds light on these long-term outcomes and portrays a trend that resembles the general population.

## INTRODUCTION

The COVID-19 pandemic, with more than 4 million deaths worldwide as of July 2021, has led to a global effort to develop SARS-CoV-2 vaccines (1–3). High efficacy of the

mRNA-based BNT162b2 vaccine against SARS-CoV-2 has been demonstrated in both a large clinical trial and real-life data in the general population (1, 4). However, patients with cancer were underrepresented in these prospective

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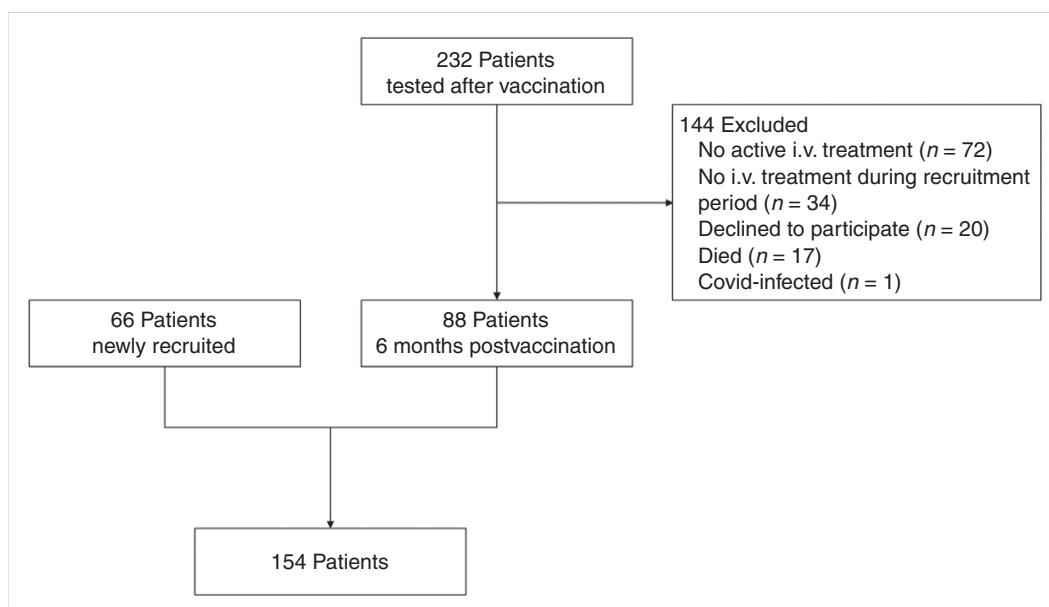
**Note:** Supplementary data for this article are available at Cancer Discovery Online (<http://cancerdiscovery.aacrjournals.org/>).

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**Figure 1.** Study flow chart of patient cohort.

clinical trials. Furthermore, patients who received systemic cytotoxic therapy or immune-modifying agents prior to screening were excluded, reflecting the need to study the effect of SARS-CoV-2 vaccination in patients with cancer. Patients with cancer represent a unique population that was initially considered as a high-risk group to present higher morbidity and mortality rates due to COVID-19 infections. Nevertheless, it had been shown throughout the pandemic that this population is heterogeneous, and subsequently clinical outcomes and manifestations differ across types of malignancies and treatments, while patients with hematologic malignancies and lung cancer experienced excessively high mortality (5). Moreover, it was reported that the COVID-19 pandemic had a great impact on the delivery of cancer care, decreasing patients' visits and delaying treatments, which encouraged their early vaccination in mass immunization operations (6). Recent follow-up studies on SARS-CoV-2 vaccine efficacy in patients with cancer have demonstrated 80% to 95% seroconversion rates following the second vaccination (7–9). Toxicity profile was similar to the general population. Efficacy of the BNT162b2 vaccine after six months in the general population was high in preventing COVID-19 infections, despite gradual decline over time (10). Antibodies elicited by the vaccines persisted through six months after the second dose with a steady decay rate over time (11, 12). There is a paucity of data regarding the late-term efficacy in patients with cancer. In our previous work (13), we indicated that patients with solid tumors who are on active anticancer treatments display short-term efficacy, immunogenicity, and safety of the BNT162b2 vaccine similar to that found in age-matched vaccinated health care workers who served as controls. This study prospectively evaluated these outcomes at six months postvaccination.

## RESULTS

### Participants

The original study cohort (13) consisted of 232 patients with solid tumors. This study included 154 patients with solid tumors who were receiving active intravenous treatments at the Rambam Health Care Campus (RHCC) Oncology Center (Haifa, Israel) and a cohort of 135 age-matched health care workers from RHCC who served as controls. From the entire patient cohort ( $n = 154$ ), 88 patients were enrolled in the initial study (January 2021) and 64 patients who met inclusion criteria were added at the later time point (for whom all data are available except for serology status shortly after vaccination). Reasons for dropout from the initial study cohort are elaborated in Fig. 1. The patient group comprised 84 (55%) men and 70 (45%) women (median age, 66 years; range, 32–87); the control group comprised 75 (56%) women and 60 (44%) men (median age, 63 years; range, 50–87). The patients were tested  $166 \pm 29$  days after second vaccination dose (187 days from the first dose). Patient characteristics are reported in Table 1. The majority of patients (84%,  $n = 129$ ) had metastatic disease. The most common cancers were gastrointestinal (36%,  $n = 56$ ), lung (23%,  $n = 36$ ), breast (17%,  $n = 26$ ), and genitourinary (11%,  $n = 18$ ). Treatment protocols consisted of chemotherapy (62%), biological agents (36%), and immunotherapy (30%), and some patients received more than one treatment class. In patients with cancer with active intravenous treatment, 79% ( $n = 122$ ) of the patients had positive serologic test results, compared with 84% ( $n = 114$ ) in the control group ( $P = 0.32$ ). Analysis by age, sex, or disease stage yielded no significant differences within the patient cohort, as depicted in Table 2. Within the patient group, chemotherapy treatment was associated with seronegative serologic status compared with other treatment modalities

**Table 1. Patient characteristics**

Characteristics	N (%)
Total	154 (100)
Age, median (range), y	67 (32-87)
Sex	
Female	70 (45)
Male	84 (55)
Type of cancer	
Gastrointestinal	56 (36)
Lung	36 (23)
Breast	26 (17)
Genitourinary	18 (12)
Head and neck	5 (3)
Gynecologic	5 (3)
Neurologic	3 (2)
Melanoma	2 (1)
Sarcoma	2 (1)
Unknown primary	1 (1)
Stage	
Local	25 (16)
Metastatic	129 (84)
Treatment	
Chemotherapy	96 (62)
Biological agent	55 (36)
Immunotherapy	47 (30)

(27% vs. 10%; OR = 0.31;  $P = 0.02$ ), as previously reported (13). OR was adjusted as described above. Among the seropositive individuals, there was female predominance in the control cohort (93% vs. 75% in the patient group, OR = 0.21,  $P = 0.004$ ). There was no significant difference in the median absolute serology titer between the seropositive individuals within the two cohorts (patients vs. controls). Furthermore, both cohorts depicted a drastic decline over time (February 2021–August 2021) in serology titer but remained above threshold value. For patients with known serologic status shortly after second vaccination dose (initial cohort), 15% of the seropositive patients became seronegative after six months, comparable to the control group (Supplementary Table S1). All seronegative patients at the former short-term time point (February 2021) remained negative in both groups throughout the study period (Fig. 2).

Review of the electronic medical records (EMR) noted that only one case of COVID-19 infection was documented after the second dose in the patient cohort (severe illness that required hospitalization). Otherwise, there were no documented cases of COVID-19 in either cohort throughout the study period. Note that every PCR for COVID-19 (positive or negative) is strictly documented routinely in the EMR countrywide.

### Systemic Reactions and Treatment Delays

As reported previously (13), elevation of liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and  $\gamma$ -glutamyltransferase) was documented in 10% of the patients up to six weeks after the first vaccine dose. Newly documented regional lymphadenopathy

(cervical or axillary) was noted in 5% of CT or PET scans (performed as routine cancer care). These adverse reactions were resolved during the study period in all patients. Delay of anticancer treatment two weeks after vaccination occurred in nine (6%) patients, all of them under chemotherapy treatment. Treatment delay was due to neutropenia ( $n = 7$ ), mild thrombocytopenia ( $n = 1$ ), and neutropenia with herpes labialis ( $n = 1$ ). All neutropenic patients had gradual decline before vaccination or neutropenia in other cycles. Treatment was renewed within a week in all patients. This delay was a single treatment delay episode in the timeline of these patients.

### DISCUSSION

Several studies have indicated the short-term efficacy and safety of the COVID-19 vaccines in the general population as well as unique groups such as patients with cancer. However, the long-term outcomes of the vaccines remain to be elucidated. Evidence is mounting regarding extended efficacy at three to six months postvaccination in healthy individuals such as health care workers (14, 15), yet there are no reports regarding these outcomes in patients with cancer. We have previously prospectively determined the immunogenicity, efficacy, and safety of the BNT162b2 vaccine in a cohort of patients with solid cancers who were receiving systemic intravenous antineoplastic treatments and demonstrated favorable profile following the second vaccination. Despite these corresponding rates of immunogenicity and efficacy comparable to those of healthy controls, patients with cancer demonstrated a gradual slower immunogenicity compared with the general population, manifested by significantly seronegative rates after the first vaccination that have risen to comparable rates following the second vaccination. Seroconversion rates after the second vaccination that resembled the general population were reported in other studies (8, 9). In our former study, we documented an increase in liver transaminases in 10% of the patients, and regional lymphadenopathy (cervical or axillary) was depicted in 5% of CT or PET scans that had not been documented in prior exams. This is in concordance with subsequent studies indicating similar rates of regional adenopathy in routine imaging studies (16, 17).

Our current study represents a longitudinal follow-up of patients with cancer with solid tumors who had been on active intravenous treatment at time of vaccination, and remained on treatment throughout the six-month study period and at current time point of evaluation. There were no differences in the pattern of immunogenicity, efficacy, and safety between patient and control cohorts. Both groups demonstrated a similar pattern of decline in antibody titer at six months post-second vaccination, although the vast majority of patients remained seropositive. Among the seronegative individuals, there was female predominance in both cohorts that was more pronounced in the control group. The subgroup of patients who received chemotherapy throughout the study period was in positive correlation to negative serology status. In our longitudinal follow-up, the observed phenomenon of elevated liver enzymes appeared transient and normalized in all affected patients. Moreover, lymphadenopathy that was observed shortly after vaccination in 5% of

**Table 2. Patient characteristics six months postvaccination**

Characteristics	Patients			Controls		
	Seropositive	Seronegative	All	Seropositive	Seronegative	All
Total	122 (79)	32 (21)	154 (100)	114 (84)	21 (16)	135 (100)
Median day from second vaccine dose	176	171		180	180	
Sex						
Female	53 (43)	17 (53)	70 (45)	70 (61)	5 (24)	75 (56)
Male	69 (57)	15 (47)	84 (55)	44 (35)	16 (76)	60 (44)
Age, median (range), y	66 (32-86)	69 (32-87)		63 (50-82)	64 (53-87)	63 (50-87)
Type of cancer						
Gastrointestinal	45 (37)	11 (34)	56 (36)			
Lung	29 (24)	6 (19)	36 (23)			
Breast	19 (16)	7 (22)	26 (17)			
Genitourinary	16 (13)	2 (6)	18 (12)			
Head and neck	4 (3)	1 (3)	5 (3)			
Gynecologic	4 (3)	1 (3)	5 (3)			
Neurologic	2 (2)	1 (3)	3 (2)			
Melanoma	2 (2)	0 (0)	2 (1)			
Sarcoma	2 (2)	0 (0)	2 (1)			
Unknown primary	1 (1)	0 (0)	1 (1)			
Stage						
Local	18 (15)	7 (22)	25 (16)			
Metastatic	104 (85)	25 (78)	129 (84)			
Treatment						
Chemotherapy	70 (57)	26 (81)	96 (62)			
Biological agent	44 (36)	11 (34)	55 (36)			
Immunotherapy	41 (34)	6 (19)	47 (31)			

the patients disappeared on later imaging studies. It is notable that former evidence regarding immunocompromised patients with hematologic malignancies or organ transplants depicted a differential pattern, manifested by an initial lower seroconversion rate shortly postvaccination (8, 18–21). Note that geographic variant differences might affect the efficacy of COVID-19 vaccination. In Israel, the most common variant was Alpha until June 2021 (70%–90%), when the Delta variant became predominant (>90%; ref. 22).

There are several limitations to our study. First, this study cohort was comprised of patients who were on active anticancer treatment at the time of the two doses of vaccination and throughout the study period (six months). Patients who either had completed their treatment or are currently without systemic treatment or who had been diagnosed/commenced their treatment after vaccination were excluded from the study. We were therefore able to analyze only a part of the initial study cohort (subtracting the ones who concluded treatment) and added individuals who met inclusion criteria and who were not included at the initial time of vaccination. Nevertheless, the trends demonstrated in the large cohort were also significant in the smaller longitudinal cohort, affirming the implication of the results. Second, there is still an ongoing debate regarding the correlation of positive serology to effective immunity, or negative serology to lack of immunity.

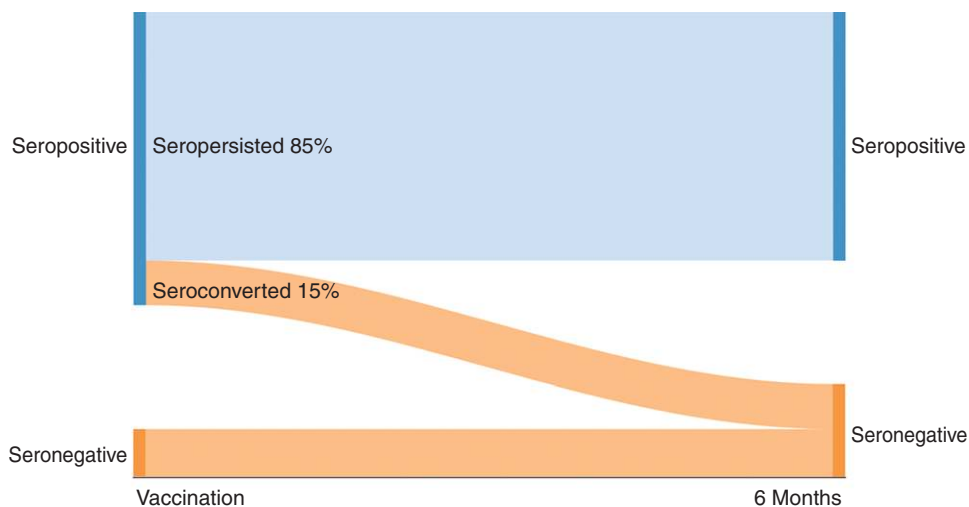
Because there were no documented cases of COVID-19 also in the seronegative individuals, clear correlation of serology status to effective immunity cannot be determined.

In conclusion, our study indicates that the pattern of immunogenicity and efficacy of the BNT162b2 vaccine in patients with solid tumors on active intravenous anticancer treatment six months postvaccination resembles the pattern of the general population. Former subtle differences that were evident between the two cohorts shortly after vaccination disappeared over time. Nonetheless, due to uncertainty of the extended efficacy of the vaccine in the general population and recent reports on rising infection rates among vaccinated individuals, adherence to health care risk reduction recommendations is cardinal.

## METHODS

### Participants and Design

The study population was comprised of patients with solid tumors receiving intravenous treatment administered at the infusion ambulatory unit of the oncology center within the RHCC, Haifa, Israel. As previously described (13), this is a prospective follow-up report of the primary study. Initially, following mass vaccination of high-risk populations that was launched in Israel on December 20, 2021, patients with cancer without prior COVID-19 documented infection, who were vaccinated (first and second dose),



**Figure 2.** Alluvial diagram of seroconversion rate. Schematic representation of seroconversion and seropersistence in patients with cancer six months postvaccination.

were enrolled during their routine visit to the oncology center. Primary study time points were after the first vaccination and approximately 14 days after the second dose. Participants were followed for six months. The study flowchart is depicted in Fig. 1. The current study population consisted of patients who were on active intravenous anticancer treatment at the time of the two doses of vaccination and throughout the entire study period. To expand the study cohort, patients who met inclusion criteria and were not part of the original cohort (i.e., were on active intravenous anticancer treatment at the time of vaccination and throughout the six-month period afterward) were enrolled into the current phase of the study between July 14, 2021, and August 1, 2021, during their routine treatment visit to the oncology center. Patients who either had completed their treatment or are currently without systemic treatment or who had been diagnosed/commenced their treatment after vaccination were excluded from the study. The control group consisted of healthy health care workers who were tested for serology at the same time points. Once the accrual of patients into this study was completed and cohort profile was established, an age-matched cohort was randomly cropped (computer generated) from the large general workers' cohort, to match the same age range of the patients and to avoid selection bias. All participants consented to the study and signed an informed consent form. The study protocol was approved by the Institutional Ethics Committee of RHCC (RMB 0209–20). The study was conducted in accordance with the Declaration of Helsinki. Electronic health records of RHCC were accessed by the study investigators to review patients' clinical characteristics as well as laboratory tests (complete blood count, liver enzymes, creatinine) and imaging assays (PET and CT scan) performed as part of routine cancer care (January 15, 2021–August 1, 2021) as well as documented COVID-19 infection (by RT-PCR assay) throughout the study period.

### SARS-CoV-2 Serology

Serum samples were analyzed at all measurement times for the detection of anti-SARS-CoV-2 antibodies. For IgG expression, we used SARS-CoV-2 anti-spike (S) S1/S2 IgG assay (Liaison; DiaSorin) to detect S1/S2 IgG antibodies. Cutoff values for positive serologic findings were 15 arbitrary U/mL, as established previously (23). All serologic tests were conducted at the RHCC Virology Diagnostic laboratory.

### Statistical Analysis

Negative and positive serologic samples among patients with cancer and controls were compared using the  $\chi^2$  test or Fisher exact test for categorical variables and a two-tailed unpaired *t* test or Mann-Whitney test for continuous variables. Adjusted ORs were calculated using multivariate logistic regression with a stepwise model-reduction procedure, including the covariates of age, gender, type of treatment, disease stage, laboratory tests, and imaging assays. Statistical analysis was conducted using R, version 4.1.0 (R Foundation for Statistical Computing). The significance threshold was set at  $P < 0.05$  for the two-sided unpaired tests.

### Data Availability Statement

The data generated in this study are available within the article.

### Authors' Disclosures

A. Peer reports other support from MSD, BMS, Pfizer, Janssen, Eisai, Bayer, Astellas, Ferring, and other support from AstraZeneca outside the submitted work. No disclosures were reported by the other authors.

### Authors' Contributions

**I. Waldhorn:** Conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. **R. Holland:** Data curation, validation. **T. Goshen-Lago:** Conceptualization, data curation, validation, investigation, methodology. **Y. Shirman:** Data curation, validation. **M. Szwarcwort-Cohen:** Resources, data curation, project administration. **A. Reiner-Benaim:** Formal analysis, validation, visualization. **Y. Shachor-Meyouhas:** Data curation, validation. **K. Hussein:** Data curation, validation, project administration. **L. Fahoum:** Data curation, validation. **A. Peer:** Data curation, visualization. **R. Almog:** Formal analysis, validation. **Y. Shaked:** Data curation, validation. **M. Halberthal:** Conceptualization, supervision, validation. **I. Ben-Aharon:** Conceptualization, supervision, validation, methodology, writing—original draft.

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