86646_Auto_Edited.docx

WORD COUNT	11900	TIME SUBMITTED	28-AUG-2023 06:38PM
		PAPER ID	102310078

Effectiveness and safety of COVID-19 vaccines in patients with oncological diseases: State-of-art

Ivanov N *et al* COVID-19 vaccines in oncological patients

Abstract

Although the coronavirus disease 2019 (COVID-19) pandemic was declared to be no longer "a public health emergency of international concern" with its wide range of clinical manifestations and late complications, severe acute respiratory syndrome coronavirus 2 infection proved to be a serious threat, especially to the elderly and patients with comorbidities. Patients with oncologic diseases are vulnerable to severe infection and death. Indeed, patients with oncohematological diseases have a higher risk of severe COVID-19 and impaired post-vaccination immunity. Unfortunately, cancer patients are usually excluded from vaccine trials and investigations of post-vaccinal immune responses and the effectiveness of the vaccines. We aimed to elucidate to what extent patients with cancer are at increased risk of developing severe COVID-19 and what is their overall case fatality rate. We also present the current concept and evidence on the effectiveness and safety of COVID-19 vaccines, including boosters, in oncology patients. In conclusion, despite the considerably higher mortality in the cancer patients group than the general population, countries with high vaccination rates have demonstrated trends toward improved survival of cancer patients early and late in the pandemic.

Key Words: COVID-19; COVID-19 vaccines; RNA vaccines; Cancer; Oncological; Safety; efficacy; Immunogenicity

Ivanov N, Krastev B, Miteva DG, Batselova H, Alexandrova R, Velikova T. Effectiveness and safety of COVID-19 vaccines in patients with oncological diseases: State-of-art. *World J Clin Oncol* 2023; In press

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic had an enormous impact on the lives of cancer patients. Medical care for them has been challenging, given the competing risks of death from cancer and serious complications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Cancer patients are at high risk for severe complications from COVID-19 and mortality. Protective SARS-CoV-2 antibodies and cellular immune response are induced after infection or/and COVID-19 vaccination. Vaccines decrease the risk of hospitalization and death from COVID-19, including for cancer patients. There are evidence that the virus can persist in people with compromised immune system, which may lead to the rise of new variants. Therefore, vaccination of specific vulnerable groups, such as oncological patients, and all people in general, will slow the virus spread and save lives.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has considerably impacted cancer patients' lives. Medical care for them has been challenging because of the competing risks of death from cancer or serious complications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the likely higher lethality in immunocompromised hosts[1,2]. Furthermore, patients diagnosed with malignancies are at higher risk for developing severe COVID-19[3] and fatal outcomes due to the disease. Studies have demonstrated variable mortality rates among subjects with hematological cancers and solid tumors, with some reporting fatality cases of as much as 40% of the infected subjects[4]. Despite this considerably higher mortality than the one observed in the general population, trends towards improved survival during the evolution of the pandemic have already been demonstrated in Europe, and much of this could be a direct result of the rigorous COVID-19 vaccination in this region[5].

Since the beginning of the pandemic, hundreds of different therapeutic options have been studied: Well-known in the treatment of other diseases reoriented drugs. Amongst them are remdesivir, initially developed for hepatitis C treatment; tocilizumab-

rheumatoid arthritis, hydroxychloroquine-malaria, lupus, *etc.*), corticosteroids, plasma from donors who have recovered from COVID-19, monoclonal antibodies (casirivimab + imdevimab, bamlanivimab, sotrovimab, cilgavimab + tixagevimab, *etc.*), JAK inhibitors (baricitinib), even mesenchymal stem cells[6,7]. Targeting both the virus itself and the host's immune response with variable effectiveness during the different stages of the disease. However, prevention in the form of COVID vaccines remains the most desirable option for the general population both in long-term health-related and financial terms. Cancer patients are no exception in this regard. But exactly how effective are vaccines in cancer patients compared to the general population? This is the question we will try to answer.

In this review, we aimed to elucidate to what extent patients with cancer are at increased risk of developing severe COVID-19 and what is their overall case fatality rate. We also present the current concept and evidence on the effectiveness and safety of COVID-19 vaccines, including boosters, in oncology patients.

SEARCH STRATEGY

We performed a modified form of a biomedical narrative review according to recent recommendations for writing[8]. First, we thoroughly searched scientific bibliographic databases Medline (PubMed) and Scopus. We used relevant free-text and MeSH terms, as follows: ("COVID-19" OR "SARS-CoV-2") AND ("cancer patients" OR "oncological patients") AND ("COVID-19 vaccine" OR "mRNA vaccine"). We confined the search from January 1, 2020, to June 20, 2023. Secondly, we identified additional papers using the search engine Google Scholar. Information from advisory committee meetings was also added.

COVID-19 AND PATIENTS WITH ONCOLOGICAL DISEASES

Patients with oncologic diseases are affected by SARS-CoV-2 in many different ways. Like many other infections, COVID-19 poses an additional risk of a fatal outcome for cancer patients. However, it is challenging to say to what extent patients with

malignancies are threatened by complications of severe infections. As oncological diseases and treatment protocols are extremely diverse, it can be expected that the course of SARS-CoV2 infection would also be quite different[9-11].

The stage of the disease, the type of malignancy, and the sort and the phase of the applied treatment modalities (surgery, chemotherapy, radiation therapy, and immunotherapy) introduce even more variables, respectively-more superimposing confounding factors and make this group of patients even more heterogeneous and difficult for overall risk assessment. Studies show that cancer patients who have recently undergone surgery or chemotherapy (especially during the induction phase with high-dose intensive regimens) are at a dramatically increased risk of death from COVID[12,13]. Side effects of chemotherapy, such as secondary immunodeficiency due to severe leukopenia and specific tissue toxicity due to some chemo- and immunotherapeutics, can significantly alter the course of COVID-19 infection, from worsening the patient's overall condition and increasing the risk of complications and death to masking or mimicking the radiological pulmonary signs (*e.g.*, immune checkpoint related pneumonitis)[13]. Finally, another confounding factor is the various therapeutic regimens used to treat infection in hospitals and intensive care units worldwide. Cancer patients are treated as high-risk by default, which carries a risk (polypharmacy, drug interactions, adverse drug effects, acute kidney or liver failure, *etc.*)[14].

Below we present data from several studies that attempt to measure and objectify this risk. The first large-scale meta-analysis by 2020 done by Zhang *et al*[11] of 15 studies involving a total of 3019 patients from Europe, the United Kingdom, the United States, Canada, and Asia detects 22.4% circulating free RNAs (CFR) in cancer patients with COVID-19, compared to 5.9% in non-cancer patients. As in other patients, risk factors influencing the course and mortality are age over 65, male sex, and comorbidities (especially hypertension and diabetes). No significant difference in mortality was found between different continents. The study found that mortality in patients with lung

cancer and hematological malignancies was highest, although the incidence of complications did not differ[11].

A study by Yang *et al*[15] involving 1575 patients, of whom 52 with various cancers (lung, colorectal, breast, cervical, thyroid, *etc.*) showed that oncologic patients are at higher risk to present as severe/critical cases and are more likely to develop acute respiratory distress syndrome. Also, other life-threatening complications such as myocardial infarction and shock are significantly increased in frequency. Lower lymphocyte count, as well as higher concentrations of C-reactive protein, D-dimer, procalcitonin, IL-6, and lactate dehydrogenase, were reported to reach $P < 0.05$. It is also noted that cancer patients are more likely to have comorbidities, which, as it becomes clear in this study, contributes seriously to the overall higher CFR[15].

A meta-analysis of 122 papers and 9 studies, including a total of 805 patients by Afshar *et al*[16], demonstrated how heterogeneous the data on mortality in cancer patients are. They showed that cancer patients were more likely to be admitted to intensive care units, needed invasive ventilation, and were more likely to die. The published CFR in the analyzed studies ranged from 5.5% to 60.0%, with a pooled CFR of 21%. However, the authors warn that these data should be interpreted cautiously due to the high heterogeneity and the small number of patients in most studies[16].

Large-scale survival analysis by Li *et al*[9] based on data from UK Biobank followed 4606 cancer patients (288 positives) and 4606 non-cancer patients (275 positives) for 21 mo after the SARS-CoV2 test. The cumulative CFR of the positive cancer patients was six times higher than the negative ones. The hazard ratio was assessed for each specific malignancy in the study, and the results showed that hematological malignancies, melanoma, kidney, and uterine cancer had particularly high CFRs (up to 10 times higher than the non-cancer controls). The authors emphasize the importance of timely vaccination in these groups of patients[9].

In contrast to the data above, a study by Brar *et al*[17] included 585 patients, 117 with active malignancies. It showed no statistically significant difference in morbidity or mortality in cancer patients *vs* the general population. Furthermore, the authors argue

that the studies claiming the opposite did not consider confounding factors like age, sex, and comorbidities. According to this study, cytotoxic treatment within 90 d of admission is not associated with worse outcomes[17].

A team from London published a study in onco-hematology patients, where 40% (14 of 35) of patients hospitalized with COVID-19 had succumbed to the infection[18]. In general, COVID-19 appears to have an increased risk of complications and mortality in a large proportion of cancer patients. In addition, besides the virus itself, the pandemic and the restrictive measures were associated with disrupted access to medical care, hindered timely diagnosis and treatment, and the lack of follow-up of many patients and lower quality of life[19]. Studies show that since the beginning of the pandemic, the total number of newly diagnosed cancers has dropped substantially[20]. As many authors warned, this inevitably led to an increased frequency of advanced cancers at diagnosis. Delaying diagnosis and treatment resulted in lower chances of survival[21]. Yong *et al*[22] conducted a study in Canada using microsimulation models, which estimated that for colorectal cancers, only a suspension of primary screening for six months will increase cancer incidence by about 2200 cases, of which about 960 will be lethal over time. Consequences that otherwise would be prevented by the screening program and early detection.

Furthermore, there are many other indirect ways the COVID-19 pandemic affects cancer patients' quality of life and mortality[13]. At the same time, the standard of living, the structure and stability of the health care system, and even political factors in connection with dealing with the pandemic play a role that should not be underestimated[23]. Knowing risk factors for the severity and mortality of COVID-19, cancer patients have their unique risk factors. They may include active and progressing cancer, type of cancer, administration of cytotoxic chemotherapy; radiation therapy; impaired immune system due to leukocytopenia, low immunoglobulin levels, long-lasting immunosuppression, comorbidities, and others.

Malignancies reported as comorbidities in patients hospitalized with confirmed COVID-19 are in different countries: (1) Malignancies in 7.2% in a cohort study with 138

adults with confirmed COVID-19 pneumonia in Wuhan, China, in January 2020[24]; (2) malignancies in 8% at admission in a cohort study with 1591 patients with laboratory-confirmed COVID-19 in Lombardy, Italy, between February 20 and March 18, 2020[25]; and (3) malignancies reported in 5.6% at admission in a cohort study with 5700 patients with confirmed COVID-19 infection hospitalized in 12 New York City hospitals between March 1 and April 4, 2020[26].

In a cohort study of 928 adults with COVID-19 and current or past cancer diagnosis, were established solid tumors in 82%, including breast (21%), hematologic (22%), prostate (16%), gastrointestinal (12%), thoracic (10%), gynecologic (5%), and renal cell carcinoma (5%)[27,28]. The estimated overall mortality in the research was 13%: 20% for patients with multiple cancers, 18% for patients with hematological malignancies, and 12% for patients with solid tumors[27].

Zhang *et al*[11] showed the COVID-19 fatality rates in subgroup analysis: (1) By cancer type: 32.9% in patients with lung cancer; 34.2% in patients with hematologic cancer; 17.2% in patients with solid cancer; and (2) by cancer treatment: 25.6% in patients with chemotherapy, 27.6% in patients with surgery, 24.3% in patients with immunotherapy, 21.3% in patients with targeted therapy, and 20.5% in patients with radiation therapy[11].

Children with cancer and positive for COVID-19 are at more risk for severe illness than children without cancer. The cohort study found that about 20% of pediatric cancer patients with COVID-19 experienced a severe infection, compared to 1%-6% of children in the general population[29]. Among patients with hematologic malignancy and laboratory-confirmed COVID-19, mortality was reported in 34% of adults and 4% of children[4].

We can summarize that the main challenges in cancer patients regarding COVID-19 are the often immunocompromised state (*i.e.*, due to leukocytopenia, low immunoglobulin levels, long-lasting immunosuppression), the treatment (*i.e.*, severe chemotherapy, radiation therapy, *etc.*), progression of cancer, comorbidities, and others.

IMMUNE RESPONSE IN CANCER PATIENTS

Cancer cells induce an immune suppressive microenvironment and use various mechanisms to "escape" the body's immune response. As a systemic disease, cancer causes a wide range of functional and compositional changes in the immune system and can affect the body's defenses against various pathogens[30,31].

Dendritic cells (DCs) are antigen-presenting cells with an essential role in originating and directing cellular and humoral immune responses, converging innate and adaptive immunity. DCs have been recognized as the most potent professional antigen-presenting cells[32].

Tumors use different strategies to alter DC maturation and function, such as: (1) The ability to influence the capacity of hematopoietic progenitor cells to differentiate into functional DCs[33,34]; (2) production of various immunosuppressive factors that block the maturation of CD34+ stem cells into DCs[35]; and (3) spontaneous apoptosis of DCs in peripheral blood of patients with breast cancer has been reported[36]. Quantitative and functional DCs deficiencies have been widely observed in patients with several types of cancer, including breast cancer[37,38], prostate cancer[38], non-small cell lung cancer[39,40], colon cancer[41], and melanoma[42], *etc*.

Data reveal that tumors disrupt normal hematopoiesis, leading to extramedullary hematopoiesis and myeloid skewing. The three branches of terminally differentiated myeloid cells (macrophages, dendritic cells and granulocytes) are essential for normal innate and adaptive immune response functioning. The tumor microenvironment alters myeloid cells and can convert them into potent immunosuppressive cells[43,44]. Lymphopenia caused by disease or treatment is frequent in oncology patients and affects their prognosis[45,46].

T cells, one of the primary arms of the adaptive immune response, are also affected in oncology patients. Cancer cells express various membrane and soluble T-cell inhibitory signals. For example, programmed cell death protein-ligand 1 linking to programmed cell death protein 1 on T cells results in decreased activation, proliferation, survival and cytotoxicity[47]. The last discovery led to the development of checkpoint inhibitors, a breakthrough in immune-oncology and won the 2018 Nobel Prize for Physiology or

Medicine. Indoleamine 2,3-dioxygenase, a soluble enzyme physiologically expressed in many tissues, is overproduced in some cancers leading to tryptophan depletion in the tumor microenvironment. T cells, being highly sensitive to tryptophan deprivation, suffer a significant functional impairment, promoting tumor growth[48]. An increased rate of CD4+CD25+ regulatory T cells with potent immunosuppressive properties in the peripheral blood of individuals with cancer diseases has been reported[49,50].

Additionally, regulatory B cells (Bregs) are a newly designated subset of B cells that have been found to play a central role in regulating immune responses associated with inflammation, autoimmunity, and cancer. Increased Bregs have been reported to express immunosuppressive properties in gastric cancer through the secretion of anti-inflammatory molecules, such as IL-10, and facilitating the conversion of T cells to regulatory T cells[44,51,52]. Additionally, tumor progression is associated with the dysfunction of NK cells due to the combined action of tissue-specific and systemic factors[53]. All these immune alterations in cancer patients contribute to the differences in the immune response after vaccination, including after COVID-19 vaccine administration. Before the COVID-19 pandemic, we had an experience with influenza vaccine administration in patients with oncological diseases. Infectious complications resulting from bacterial, fungal, and viral (often due to reactivation of latent disease, primarily in patients with hematological malignancies) diseases are a severe cause of morbidity and mortality in cancer patients[54]. Oncology patients receiving chemotherapy are at increased risk for influenza virus infection and serious post-influenza complications. Cancer patients are eligible for influenza vaccination, although their response may be suboptimal due to immunosuppression associated with cancer itself and/or its treatment[55,56]. Data shows that cancer patients receiving chemotherapy can respond to influenza vaccination[57].

Breast cancer patients receiving influenza vaccination during FEC (5-fluorouracil, epirubicin, and cyclophosphamide)-containing treatment regimens have exhibited significantly lower responses to influenza virus vaccination than healthy controls. Vaccination early during the chemotherapy cycle (day 4) induces better responses than

vaccination on day 16[58]. The summary of the available evidence reveals that immunization of individuals with malignancies is critical to their care and may protect them from significant morbidity and mortality associated with vaccine-preventable diseases[59].

COVID-19 VACCINES FOR PATIENTS WITH ONCOLOGICAL DISEASES-DATA ON OUTCOMES AND EFFECTIVENESS

Several available COVID-19 vaccines are now in use all over the world. Moderate or severely immunocompromised people should receive a vaccination to protect them from severe COVID-19 disease[60,61].

The efficacy of COVID-19 vaccines in cancer patients is a question of continuous research, with most studies using immunological parameters as surrogate endpoints for clinical outcomes. Clinical trials investigating immune response after COVID-19 vaccination often use seroconversion to SARS-CoV-2 spike (S) protein as an endpoint for vaccine efficacy. Other parameters like anti-Spike antibody titers, detection of neutralizing antibodies, and cellular immune response are usually explored as secondary endpoints[62]. Some authors, however, underscore the role of neutralizing antibodies as the immunological parameter, which probably best correlates with the level of protection after COVID-19 vaccination[63-65].

Both humoral and cellular immune responses to COVID-19 vaccines differ in patients with malignancies compared to non-cancer patients, and this is being attributed not only to the immunosuppressive nature of the oncologic disease but to the anti-tumor therapy itself and its direct impact on immune cells. While patients with solid tumors have seroconversion rates similar to the general population, the most significant concern regarding post-vaccination and post-infectious COVID-19 immunity lies with hematological malignancies, especially those where lymphocyte-depletion therapy is used. In support of this is the research of Monin *et al*[66], who presented interim results of a prospective observational study that explores the immunogenicity of one compared to receiving two doses of the COVID-19 vaccine in patients with cancer by assessing the

humoral immune response between 151 patients (95 with solid tumors and 56 with hematological malignancies) and 54 healthy controls. Authors reported efficacy after the first dose in 94%, 38%, and 18% of control subjects, patients with solid tumors and hematological cancer, respectively. After the second dose, the response increased to 100% in controls, 95% in patients with solid cancers, and only 60% in the group with hematological malignancies[66].

When considering post-vaccination immunity in patients with cancer, we should consider that those with hematological malignancies are expected to show different levels of antibody response to COVID-19 vaccines compared to patients with solid tumors. One of the most substantial pieces of evidence in corroboration came from the CAPTURE trial[67]. This prospective clinical study assessed the humoral response after COVID-19 vaccination in more than 700 subjects with solid tumors or hematologic neoplasms, 585 of whom did not have previous SARS-CoV-2 infection. The trial demonstrated 85% and 54% seroconversion rates for anti-Spike antibodies after the second dose in patients with solid tumors and hematological, respectively. However, the response observed among participants was not the same for all SARS-CoV-2 variants[68].

The authors announced substantial differences in neutralizing antibodies concerning viral genotypes from the CAPTURE trial: 83% of patients developed detectable levels of the original SARS-CoV-2 and only 54% of the delta variant. And while nearly two-thirds (62%) of patients with solid tumors elicit humoral response against delta variant, only 31% of those with hematologic malignancies did so[67]. The prospective cohort study of immune response to COVID-19 vaccination in cancer patients CAPTURE (NCT03226886) also showed that among 585 patients, the antibody rates after two doses of BNT162b2 or AZD1222 vaccines given over 12 wk were assessed. The results showed that seroconversion was 85% and 59% after two doses in patients with solid and hematological malignancies, respectively. Neutralizing antibodies against SARS-CoV-2 VOCs were detected in a small proportion of patients, mainly with solid cancers.

Vaccine-induced T-cell responses were found in 80% of patients regardless of the vaccine or type of cancer[67].

In an attempt to overcome this relatively low rate of seroconversion in patients with blood cancers, Greenberger *et al*[69] conducted a large prospective cohort trial on nearly 700 patients vaccinated with three doses of the COVID-19 vaccine. It was estimated that antibody response indeed increased with the 3rd (booster) dose, so 43% of those without detectable antibodies after the 2nd dose demonstrated humoral response after the booster. However, about 20% of all hematological patients still failed to achieve a response even with 3 doses of vaccine[69]. In contrast to the plethora of research on humoral immunity after COVID-19 vaccination in cancer patients, the cellular immune response in this setting is considerably less studied. In a review article by Rüthrich *et al*[70], the authors tried to summarize what is currently known about the issue in patients with solid tumors and hematological malignancies, comparing data from COVID-19 vaccines and other "classical" vaccines. Although the assessment of T-cell immune response in the reviewed studies varied, most research used methods based on quantifying and characterizing pathogen-specific T-cells and/or estimating the T-cell function by cytokine measurement[70].

Observations on immune response in patients with hematological malignancies revealed that although this population may lack adequate levels of neutralizing viral antibodies, especially after treatment with B-cell depleting agents such as anti-CD20 monoclonal antibodies, COVID-19 vaccines are still able to produce protective cellular immunity. One of the best evidence for the sufficient efficacy of T-cell response comes from a trial in patients with agammaglobulinemia who demonstrated improved COVID-19 infection outcomes after vaccination. However, cellular immunity could also be impaired in this specific patient population, and some of the significant factors for this are age, disease activity, immunosuppressive treatment, and low lymphocyte counts in circulation[70].

This discordance between humoral and cellular immune response could also be seen In patients with solid tumors. In this population, T-cell response varies among different

cancer subtypes and is determined mainly by the type of systemic anti-tumor treatment. Various studies demonstrate wide ranges in terms of cellular immunity achieved after COVID-19 vaccination ranging from about half to nearly 90% of the vaccinated cases[71,72].

However, despite being generally higher than those observed in blood cancer patients, T-cell response in those with solid tumors remains significantly lower than in healthy controls. One of the most extensive trials reporting data on immune response in patients with solid tumors receiving systemic anti-cancer treatment is the VOICE study[73]. After recruiting nearly 800 subjects (240 without cancer), the authors assessed cellular immunity by measuring SARS-CoV-2 spike-specific IFNy T-cell response after two vaccine doses. They reported cellular response in 67%, 66%, and 53% of patients treated with chemotherapy, immunotherapy, or chemoimmunotherapy, respectively. Another interesting trial finding was that more than 40% of patients who did not elicit a humoral immune response could develop a T-cell response, highlighting the vaccine's 'double-edge sword' efficacy in this specific population. Similar to the model observed with the humoral response, whether the cellular response is affected by booster dose is still an open question since there exist conflicting data on this. Some studies report significant enhancement of T-cell response after 3rd dose, while others refute such assertions[73].

So far, most trials reporting COVID-19 vaccine efficacy in cancer rely on immunological endpoints and not so much on clinical outcomes. However, a recent study on infection rate and outcomes in vaccinated patients with solid tumors and hematologic malignancies raised concern that despite vaccination, these patients remain at risk of worse outcomes compared to the general population[74]. Among fully vaccinated cancer patients, who experienced breakthrough SARS-CoV-2 infection, the hospitalization rate, intensive care unit admission (or required mechanical vaccination), and death rate are 65%, 19%, and 13%, respectively. This is mainly attributed to patients' comorbidities and the much worse COVID-19 prognosis in those with hematological malignancies.

In a prospective study conducted by Goshen-Lago *et al*[75], it was shown that patients with solid tumors demonstrated short-term efficacy and safety of the BNT162b2 vaccine. A follow-up study aimed to evaluate these outcomes six months after vaccination[76]. Participants were 154 patients with solid tumors and 135 controls (health workers). Six months after vaccination, 122 patients were seropositive compared with 114 controls, and the serologic titers dramatically decreased almost equally in both cohorts. Efficacy and safety evidence of BNT162b2 vaccines shows that the serological profile in cancer patients after six months resembles that of the general population[76].

A similar study was conducted by Barrière *et al*[77], who evaluated the immunogenicity of the BNT162b2 vaccine in patients with solid tumors. Serological analyses were performed during the first vaccination, during the booster dose (w3-w4), and 3-4 wk after the booster dose (w6-w8). The study reported the results for 122 of 194 evaluable patients with solid tumors who had at least two doses from January 2021 to March 2021. In the first analysis (w3-w4), 58 patients had neutralizing antibodies, although the median levels were significantly lower than in the control group. In the following analysis (w6-w8), the data showed the same anti-S seroconversion rate, demonstrating impaired immunogenicity of the BNT162b2 vaccine in cancer patients[77].

Shroff *et al*[78] also compared anti-S seroconversion to the BNT162b2 mRNA vaccine in patients with solid tumors on active cytotoxic anti-cancer therapy with healthy control participants. Neutralizing antibodies were found in 67% of cancer patients after the first immunization, and a follow-up analysis found a threefold increase in titers after the second or third doses. A study with EudraCT Number 2021-000291-11 was conducted in patients with solid cancers, multiple myeloma, and inflammatory bowel disease[79]. The study is a prospective, open-label, phase four trial to monitor vaccine-specific antibody and cellular responses after booster vaccination with mRNA-1273 or BNT162b2. The data show that booster vaccination against SARS-CoV-2 reverses the lack of response and early antibody weakening in immunocompromised patients.

Another study on the efficacy and safety of heterologous booster vaccination with Ad26.COV2.S after BNT162b2 mRNA vaccine in cancer patients without antibody

response was conducted in 2022[80]. The assessment was done directly before vaccination and four weeks after. Ad26.COV2.S booster vaccination resulted in a serological response in 31% of non-responders after a double dose of BNT162b2. Clinical trials with the number NCT04368728 reported results from individuals with a history of past or active neoplasms and up to 6 mo of follow-up after dose 2 of a placebo-controlled, observer-blinded trial of the BNT162b2 vaccine[81]. In participants with past or active neoplasms, two doses of the BNT162b2 vaccine improved efficacy and safety profile as in the overall trial population. No vaccine-related deaths were reported.

One of the first evaluations of the effectiveness of vaccination against breakthrough SARS-CoV-2 infections in cancer patients at a population level was done by Lee *et al*[82]. Analysis was performed in the cancer cohort by vaccine type (BNT162b2, ChAdOx1 nCov-19, or mixed and other), cancer type and subtype, stage, date of cancer diagnosis, and anti-cancer treatment or radiotherapy. Data show that vaccination with different COVID-19 vaccines is effective in people with cancer, providing varying levels of protection against SARS-CoV-2 infection. However, it is lower in cancer patients than in the general population[82].

A single-arm prospective clinical trial was conducted with 106 cancer patients by Thakkar *et al*[83]. They received two doses of mRNA followed by one dose of AD26.CoV2.S vaccine or a third dose of mRNA vaccine. The results showed that a third dose induced immunity in cancer patients. Seroconversion was also assessed in 57% of patients who did not respond to primary vaccination. A fourth dose boosted the immune response by two-thirds. Some patients have neutralizing activity against the Omicron variant[83].

In conclusion, all these studies confirm that people with cancer are at increased risk of severe COVID-19 disease, hospitalization, and death after SARS-CoV-2 infection compared to the general population. The above data show that cancer patients have impaired overall vaccine effectiveness to the approved COVID-19 vaccines. Seroconversion in them decreases faster than in the control population. Although

vaccination provides different levels of protection, there should be a global prioritization of the programs to boost vaccination for cancer people, considering the impact of other treatments.

There is still a lack of data on vaccine efficacy in cancer patients concerning novel virus variants like Omicron[68]. Table 1 presents the studies on the effectiveness and safety of COVID-19 vaccination with different approved COVID-19 vaccines in oncological patients with solid tumors[5,63,66,67,69-71,73,75-84,84].

COVID-19 VACCINES AND CHEMOTHERAPY INTERACTIONS

People with cancer often have an increased susceptibility to infections due to various factors, including cancer itself and/or, in some cases, the applied therapy, poor nutrition, and damaged physiological barriers. In addition, the incidence of neoplasia is highest in individuals aged 65 and over. When the immune system's effectiveness is weakened, the elderly often have concomitant diseases for which they can also take medications[54,85].

Regarding cancer chemotherapy, conventional antitumor chemotherapeutic agents kill actively proliferating cells, including bone marrow cells, and myelosuppression is one of clinical oncology's most common side effects[86]. Chemotherapy-induced neutropenia is a significant cause of hematological and dose-limiting toxicities of chemotherapy[87]. Some currently available anti-cancer drugs, such as methotrexate and cyclophosphamide, express immunosuppressive effects and impair peripheral T cells' proliferative and/or effector functions. Methotrexate is an antimetabolite of the antifolate type developed in 1947 and is included in the World Health Organization's List of Essential Medicines. Nowadays, it is widely used not only in clinical oncology (in the treatment of acute lymphoblastic leukemia, acute myeloid leukemia, meningeal leukemia and lymphoma, osteosarcomas, non-Hodgkin's lymphoma, breast and bladder cancer, *etc.*) but also as a first-line treatment in autoimmune, inflammatory diseases such as rheumatoid arthritis, psoriasis and Crone's disease[88-90]. Methotrexate has been found to disturb antibody response after pneumococcal vaccination[91,92]; the

drug reduces circulating Th17 cells and impairs plasmablast and memory B cell expansions following pneumococcal conjugate immunization in patients with rheumatoid arthritis[93].

Cyclophosphamide is an alkylating agent synthesized in 1958 and used for decades in clinical practice in the therapy regimens of neoplasms (malignant lymphomas, multiple myeloma, sarcoma, breast cancer, disseminated neuroblastomas, retinoblastoma, ovarian adenocarcinoma, *etc.*) and as an immunosuppressive agent for the treatment of autoimmune and immune-mediated diseases such as multiple sclerosis. Cyclophosphamide shows selectivity for T cells and is an immunosuppressant to prevent transplant rejection and graft-vs-host complications[94]. Cyclophosphamide has been associated with suppressing helper Th1 activity and enhancing helper Th2 responses[95]. This drug inhibits Th1/Th17 responses and increases the cells secreting anti-inflammatory cytokines such as interleukin (IL) IL-4, IL-10, and TGF-b[96]. A single administration of low-dose cyclophosphamide selectively suppresses regulatory T cells (Tregs). The low-dose cyclophosphamide promotes anti-tumour immunity by selectively depleting regulatory T cells and enhancing effector T cell function. However, cyclophosphamide can also increase the number of myeloid-derived suppressor cells[97,98].

Treatment with tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib applied in the treatment of chronic myeloid leukemia is associated with loss of memory B-cell subsets and impaired humoral immune responses to 23-valent polysaccharide pneumococcal vaccine, likely due to the off-target kinase inhibitory activity of these drugs[99].

CONCLUSION

Data so far show that patients with cancer are at increased risk of severe COVID-19 and developing various complications mainly due to their immunocompromised state, type of treatment and comorbidities. Although cancer patients were excluded from vaccine trials, the investigations of post-vaccinal immune responses and the effectiveness of the

vaccines showed that both humoral and cellular immune responses to COVID-19 vaccines differ in patients with malignancies compared to non-cancer patients, and this is being attributed not only to the immunosuppressive nature of the oncologic disease but to the anti-tumor therapy itself and its direct impact on immune cells.

The evidence indicates that the efficacy of vaccinations could be impaired in cancer patients in line with a reduced rate of seroconversion and shorter duration compared to healthy controls. Despite these data, when focusing on the clinical outcomes instead of immunological endpoints regarding vaccine efficacy, COVID-19 vaccines demonstrated high effectiveness in preventing severe COVID-19 and infection-related death, and safety profile with comparable to healthy controls adverse effects in patients with solid tumors and hematological malignancies.

Despite the considerably higher mortality in the cancer patients group from COVID-19 than the general population, countries with high vaccination rates have demonstrated trends toward improved survival of cancer patients early and late in the pandemic. Nevertheless, vaccination of these patients and overall vaccination of the population has proven to significantly reduce the risk of complications and mortality of COVID-19 and should be promoted worldwide.

REFERENCES

1 **Yu J**, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol* 2020; **6**: 1108-1110 [PMID: 32211820 DOI: 10.1001/jamaoncol.2020.0980]

2 **Lewis MA**. Between Scylla and Charybdis-Oncologic Decision Making in the Time of Covid-19. *N Engl J Med* 2020; **382**: 2285-2287 [PMID: 32267650 DOI: 10.1056/NEJMp2006588]

3 **ElGohary GM**, Hashmi S, Styczynski J, Kharfan-Dabaja MA, Alblooshi RM, de la Cámara R, Mohmed S, Alshaibani A, Cesaro S, Abd El-Aziz N, Almaghrabi R, Gergis U, Majhail NS, El-Gohary Y, Chemaly RF, Aljurf M, El Fakih R. The Risk and Prognosis of COVID-19 Infection in Cancer Patients: A Systematic Review and Meta-Analysis.

Hematol Oncol Stem Cell Ther 2022; **15**: 45-53 [PMID: 32745466 DOI: 10.1016/j.hemonc.2020.07.005]

4 **Vijenthira A**, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, Martín-Moro F, Razanamahery J, Riches JC, Zwicker J, Patell R, Vekemans MC, Scarfò L, Chatzikonstantinou T, Yildiz H, Lattenist R, Mantzaris I, Wood WA, Hicks LK. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 2020; **136**: 2881-2892 [PMID: 33113551 DOI: 10.1182/blood.2020008824]

5 **OnCovid Study Group**, Pinato DJ, Patel M, Scotti L, Colomba E, Dolly S, Loizidou A, Chester J, Mukherjee U, Zambelli A, Dalla Pria A, Aguilar-Company J, Bower M, Salazar R, Bertuzzi A, Brunet J, Lambertini M, Tagliamento M, Pous A, Sita-Lumsden A, Srikandarajah K, Colomba J, Pommeret F, Seguí E, Generali D, Grisanti S, Pedrazzoli P, Rizzo G, Libertini M, Moss C, Evans JS, Russell B, Harbeck N, Vincenzi B, Biello F, Bertulli R, Ottaviani D, Liñan R, Rossi S, Carmona-García MC, Tondini C, Fox L, Baggi A, Fotia V, Parisi A, Porzio G, Queirolo P, Cruz CA, Saoudi-Gonzalez N, Felip E, Roqué Lloveras A, Newsom-Davis T, Sharkey R, Roldán E, Reyes R, Zoratto F, Earnshaw I, Ferrante D, Marco-Hernández J, Ruiz-Camps I, Gaidano G, Patriarca A, Bruna R, Sureda A, Martinez-Vila C, Sanchez de Torre A, Berardi R, Giusti R, Mazzoni F, Guida A, Rimassa L, Chiudinelli L, Franchi M, Krengli M, Santoro A, Prat A, Tabernero J, Van Hemelrijck M, Diamantis N, Gennari A, Cortellini A. Time-Dependent COVID-19 Mortality in Patients With Cancer: An Updated Analysis of the OnCovid Registry. *JAMA Oncol* 2022; **8**: 114-122 [PMID: 34817562 DOI: 10.1001/jamaoncol.2021.6199]

6 **Chen L**, Qu J, Kalyani FS, Zhang Q, Fan L, Fang Y, Li Y, Xiang C. Mesenchymal stem cell-based treatments for COVID-19: status and future perspectives for clinical applications. *Cell Mol Life Sci* 2022; **79**: 142 [PMID: 35187617 DOI: 10.1007/s00018-021-04096-y]

7 **Yuan Y**, Jiao B, Qu L, Yang D, Liu R. The development of COVID-19 treatment. *Front Immunol* 2023; **14**: 1125246 [PMID: 36776881 DOI: 10.3389/fimmu.2023.1125246]

8 **Gasparyan AY**, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011; **31**: 1409-1417 [PMID: 21800117 DOI: 10.1007/s00296-011-1999-3]

9 **Li H**, Baldwin E, Zhang X, Kenost C, Luo W, Calhoun EA, An L, Bennett CL, Lussier YA. Comparison and impact of COVID-19 for patients with cancer: a survival analysis of fatality rate controlling for age, sex and cancer type. *BMJ Health Care Inform* 2021; **28** [PMID: 33980502 DOI: 10.1136/bmjhci-2021-100341]

10 **He W**, Chen L, Chen L, Yuan G, Fang Y, Chen W, Wu D, Liang B, Lu X, Ma Y, Li L, Wang H, Chen Z, Li Q, Gale RP. COVID-19 in persons with haematological cancers. *Leukemia* 2020; **34**: 1637-1645 [PMID: 32332856 DOI: 10.1038/s41375-020-0836-7]

11 **Zhang H**, Han H, He T, Labbe KE, Hernandez AV, Chen H, Velcheti V, Stebbing J, Wong KK. Clinical Characteristics and Outcomes of COVID-19-Infected Cancer Patients: A Systematic Review and Meta-Analysis. *J Natl Cancer Inst* 2021; **113**: 371-380 [PMID: 33136163 DOI: 10.1093/jnci/djaa168]

12 **Aries JA**, Davies JK, Auer RL, Hallam SL, Montoto S, Smith M, Sevillano B, Foggo V, Wrench B, Zegocki K, Agrawal S, Le Dieu R, Truelove E, Erblich T, Araf S, Okosun J, Oakervee H, Cavenagh JD, Gribben JG, Riches JC. Clinical outcome of coronavirus disease 2019 in haemato-oncology patients. *Br J Haematol* 2020; **190**: e64-e67 [PMID: 32420609 DOI: 10.1111/bjh.16852]

13 **Tsamakis K**, Gavriatopoulou M, Schizas D, Stravodimou A, Mougkou A, Tsiptsios D, Sioulas V, Spartalis E, Sioulas AD, Tsamakis C, Charalampakis N, Mueller C, Arya D, Zarogoulidis P, Spandidos DA, Dimopoulos MA, Papageorgiou C, Rizos E. Oncology during the COVID-19 pandemic: challenges, dilemmas and the psychosocial impact on cancer patients. *Oncol Lett* 2020; **20**: 441-447 [PMID: 32565968 DOI: 10.3892/ol.2020.11599]

14 **Iloanusi S**, Mgbere O, Essien EJ. Polypharmacy among COVID-19 patients: A systematic review. *J Am Pharm Assoc (2003)* 2021; **61**: e14-e25 [PMID: 34120855 DOI: 10.1016/j.japh.2021.05.006]

15 **Yang F**, Shi S, Zhu J, Shi J, Dai K, Chen X. Clinical characteristics and outcomes of cancer patients with COVID-19. *J Med Virol* 2020; **92**: 2067-2073 [PMID: 32369209 DOI: 10.1002/jmv.25972]

16 **Afshar ZM**, Dayani M, Naderi M, Ghanbarveisi F, Shiri S, Rajati F. Fatality rate of COVID-19 in patients with malignancies: a sytematic review and meta-analysis. *J Infect* 2020; **81**: e114-e116 [PMID: 32474042 DOI: 10.1016/j.jinf.2020.05.062]

17 **Brar G**, Pinheiro LC, Shusterman M, Swed B, Reshetnyak E, Soroka O, Chen F, Yamshon S, Vaughn J, Martin P, Paul D, Hidalgo M, Shah MA. COVID-19 Severity and Outcomes in Patients With Cancer: A Matched Cohort Study. *J Clin Oncol* 2020; **38**: 3914-3924 [PMID: 32986528 DOI: 10.1200/JCO.20.01580]

18 **Onder G**, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* 2020; **323**: 1775-1776 [PMID: 32203977 DOI: 10.1001/jama.2020.4683]

19 **Guven DC**, Aktas BY, Aksun MS, Ucgul E, Sahin TK, Yildirim HC, Guner G, Kertmen N, Dizdar O, Kilickap S, Aksoy S, Yalcin S, Turker A, Uckun FM, Arik Z. COVID-19 pandemic: changes in cancer admissions. *BMJ Support Palliat Care* 2020 [PMID: 32665259 DOI: 10.1136/bmjspcare-2020-002468]

20 **Skovlund CW**, Friis S, Christensen J, Nilbert MC, Mørch LS. Drop in cancer diagnosis during the COVID-19 pandemic in Denmark: assessment of impact during 2020. *Acta Oncol* 2022; **61**: 658-661 [PMID: 35020549 DOI: 10.1080/0284186X.2021.2024879]

21 **Vázquez Rosas T**, Cazap E, Delgado L, Ismael J, Bejarano S, Castro C, Castro H, Müller B, Gutiérrez-Delgado F, Santini LA, Vallejos Sologuren C. Social Distancing and Economic Crisis During COVID-19 Pandemic Reduced Cancer Control in Latin America and Will Result in Increased Late-Stage Diagnoses and Expense. *JCO Glob Oncol* 2021; **7**: 694-703 [PMID: 33999696 DOI: 10.1200/GO.21.00016]

22 **Yong JH**, Mainprize JG, Yaffe MJ, Ruan Y, Poirier AE, Coldman A, Nadeau C, Iragorri N, Hilsden RJ, Brenner DR. The impact of episodic screening interruption:

COVID-19 and population-based cancer screening in Canada. *J Med Screen* 2021; **28**: 100-107 [PMID: 33241760 DOI: 10.1177/0969141320974711]

23 **Salunke AA**, Nandy K, Pathak SK, Shah J, Kamani M, Kottakota V, Thivari P, Pandey A, Patel K, Rathod P, Bhatt S, Dave P, Pandya S. Impact of COVID -19 in cancer patients on severity of disease and fatal outcomes: A systematic review and meta-analysis. *Diabetes Metab Syndr* 2020; **14**: 1431-1437 [PMID: 32755847 DOI: 10.1016/j.dsx.2020.07.037]

24 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

25 **Grasselli G**, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574-1581 [PMID: 32250385 DOI: 10.1001/jama.2020.5394]

26 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

27 **Kuderer NM**, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Hsu CY, Desai A, de Lima Lopes G Jr, Grivas P, Painter CA, Peters S, Thompson MA, Bakouny Z, Batist G, Bekaii-Saab T, Bilen MA, Bouganim N, Larroya MB, Castellano D, Del Prete SA, Doroshow DB, Egan PC, Elkrief A, Farmakiotis D, Flora D, Galsky MD,

Glover MJ, Griffiths EA, Gulati AP, Gupta S, Hafez N, Halfdanarson TR, Hawley JE, Hsu E, Kasi A, Khaki AR, Lemmon CA, Lewis C, Logan B, Masters T, McKay RR, Mesa RA, Morgans AK, Mulcahy MF, Panagiotou OA, Peddi P, Pennell NA, Reynolds K, Rosen LR, Rosovsky R, Salazar M, Schmidt A, Shah SA, Shaya JA, Steinharter J, Stockerl-Goldstein KE, Subbiah S, Vinh DC, Wehbe FH, Weissmann LB, Wu JT, Wulff-Burchfield E, Xie Z, Yeh A, Yu PP, Zhou AY, Zubiri L, Mishra S, Lyman GH, Rini BI, Warner JL; COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020; **395**: 1907-1918 [PMID: 32473681 DOI: 10.1016/S0140-6736(20)31187-9]

28 **Jee J**, Foote MB, Lumish M, Stonestrom AJ, Wills B, Narendra V, Avutu V, Murciano-Goroff YR, Chan JE, Derkach A, Philip J, Belenkaya R, Kerpelev M, Maloy M, Watson A, Fong C, Janjigian Y, Diaz LA Jr, Bolton KL, Pessin MS. Chemotherapy and COVID-19 Outcomes in Patients With Cancer. *J Clin Oncol* 2020; **38**: 3538-3546 [PMID: 32795225 DOI: 10.1200/JCO.20.01307]

29 **Mukkada S**, Bhakta N, Chantada GL, Chen Y, Vedaraju Y, Faughnan L, Homsi MR, Muniz-Talavera H, Ranadive R, Metzger M, Friedrich P, Agulnik A, Jeha S, Lam C, Dalvi R, Hessissen L, Moreira DC, Santana VM, Sullivan M, Bouffet E, Caniza MA, Devidas M, Pritchard-Jones K, Rodriguez-Galindo C; Global Registry of COVID-19 in Childhood Cancer. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. *Lancet Oncol* 2021; **22**: 1416-1426 [PMID: 34454651 DOI: 10.1016/S1470-2045(21)00454-X]

30 **Vinay DS**, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, Lichtor T, Decker WK, Whelan RL, Kumara HMCS, Signori E, Honoki K, Georgakilas AG, Amin A, Helferich WG, Boosani CS, Guha G, Ciriolo MR, Chen S, Mohammed SI, Azmi AS, Keith WN, Bilsland A, Bhakta D, Halicka D, Fujii H, Aquilano K, Ashraf SS, Nowsheen S, Yang X, Choi BK, Kwon BS. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol* 2015; **35** Suppl: S185-S198 [PMID: 25818339 DOI: 10.1016/j.semcancer.2015.03.004]

31 **Hiam-Galvez KJ**, Allen BM, Spitzer MH. Systemic immunity in cancer. *Nat Rev Cancer* 2021; **21**: 345-359 [PMID: 33837297 DOI: 10.1038/s41568-021-00347-z]

32 **Nesmiyanov PP**. Dendritic Cells. *Encyclop of Infect and Immun* 2022; **1**: 110-117 [DOI: 10.1016/B978-0-12-818731-9.00039-2]

33 **Gabrilovich DI**, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, Kavanaugh D, Carbone DP. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat Med* 1996; **2**: 1096-1103 [PMID: 8837607 DOI: 10.1038/nm1096-1096]

34 **Menetrier-Caux C**, Montmain G, Dieu MC, Bain C, Favrot MC, Caux C, Blay JY. Inhibition of the differentiation of dendritic cells from CD34(+) progenitors by tumor cells: role of interleukin-6 and macrophage colony-stimulating factor. *Blood* 1998; **92**: 4778-4791 [PMID: 9845545 DOI: 10.1182/blood.V92.12.4778]

35 **Kiertscher SM**, Luo J, Dubinett SM, Roth MD. Tumors promote altered maturation and early apoptosis of monocyte-derived dendritic cells. *J Immunol* 2000; **164**: 1269-1276 [PMID: 10640740 DOI: 10.4049/jimmunol.164.3.1269]

36 **Pinzon-Charry A**, Maxwell T, McGuckin MA, Schmidt C, Furnival C, López JA. Spontaneous apoptosis of blood dendritic cells in patients with breast cancer. *Breast Cancer Res* 2006; **8**: R5 [PMID: 16417648 DOI: 10.1186/bcr1361]

37 **Della Bella S**, Gennaro M, Vaccari M, Ferraris C, Nicola S, Riva A, Clerici M, Greco M, Villa ML. Altered maturation of peripheral blood dendritic cells in patients with breast cancer. *Br J Cancer* 2003; **89**: 1463-1472 [PMID: 14562018 DOI: 10.1038/sj.bjc.6601243]

38 **Mastelic-Gavillet B**, Sarivalasis A, Lozano LE, Wyss T, Inoges S, de Vries IJM, Dartiguenave F, Jichlinski P, Derrè L, Coukos G, Melero I, Harari A, Romero P, Viganó S, Kandalaft LE. Quantitative and qualitative impairments in dendritic cell subsets of patients with ovarian or prostate cancer. *Eur J Cancer* 2020; **135**: 173-182 [PMID: 32590296 DOI: 10.1016/j.ejca.2020.04.036]

39 **Tabarkiewicz J**, Rybojad P, Jablonka A, Rolinski J. CD1c+ and CD303+ dendritic cells in peripheral blood, lymph nodes and tumor tissue of patients with non-small cell lung cancer. *Oncol Rep* 2008; **19**: 237-243 [PMID: 18097601 DOI: 10.3892/or.19.1.237]

40 **Lu Y**, Xu W, Gu Y, Chang X, Wei G, Rong Z, Qin L, Chen X, Zhou F. Non-small Cell Lung Cancer Cells Modulate the Development of Human CD1c(+) Conventional Dendritic Cell Subsets Mediated by CD103 and CD205. *Front Immunol* 2019; **10**: 2829 [PMID: 31921114 DOI: 10.3389/fimmu.2019.02829]

41 **Legitimo A**, Consolini R, Failli A, Orsini G, Spisni R. Dendritic cell defects in the colorectal cancer. *Hum Vaccin Immunother* 2014; **10**: 3224-3235 [PMID: 25483675 DOI: 10.4161/hv.29857]

42 **Failli A**, Legitimo A, Orsini G, Romanini A, Consolini R. Numerical defect of circulating dendritic cell subsets and defective dendritic cell generation from monocytes of patients with advanced melanoma. *Cancer Lett* 2013; **337**: 184-192 [PMID: 23684927 DOI: 10.1016/j.canlet.2013.05.013]

43 **Gabrilovich DI**, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol* 2012; **12**: 253-268 [PMID: 22437938 DOI: 10.1038/nri3175]

44 **Wang WW**, Yuan XL, Chen H, Xie GH, Ma YH, Zheng YX, Zhou YL, Shen LS. CD19+CD24hiCD38hiBregs involved in downregulate helper T cells and upregulate regulatory T cells in gastric cancer. *Oncotarget* 2015; **6**: 33486-33499 [PMID: 26378021 DOI: 10.18632/oncotarget.5588]

45 **Ray-Coquard I**, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, Tredan O, Verweij J, Biron P, Labidi I, Guastalla JP, Bachelot T, Perol D, Chabaud S, Hogendoorn PC, Cassier P, Dufresne A, Blay JY; European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res* 2009; **69**: 5383-5391 [PMID: 19549917 DOI: 10.1158/0008-5472.CAN-08-3845]

46 **Wang JL**, Ma R, Kong W, Zhao R, Wang YY. Lymphopenia in Esophageal Cancer: What Have We Learned? *Front Oncol* 2021; **11**: 625963 [PMID: 33791213 DOI: 10.3389/fonc.2021.625963]

47 **Han Y**, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res* 2020; **10**: 727-742 [PMID: 32266087]

48 **Ye Q**, Wang C, Xian J, Zhang M, Cao Y, Cao Y. Expression of programmed cell death protein 1 (PD-1) and indoleamine 2,3-dioxygenase (IDO) in the tumor microenvironment and in tumor-draining lymph nodes of breast cancer. *Hum Pathol* 2018; **75**: 81-90 [PMID: 29447919 DOI: 10.1016/j.humpath.2018.02.004]

49 **Wolf AM**, Wolf D, Steurer M, Gastl G, Gunsilius E, Grubeck-Loebenstein B. Increase of regulatory T cells in the peripheral blood of cancer patients. *Clin Cancer Res* 2003; **9**: 606-612 [PMID: 12576425]

50 **Liu L**, Wu G, Yao JX, Ding Q, Huang SA. CD4+CD25high regulatory cells in peripheral blood of cancer patients. *Neuro Endocrinol Lett* 2008; **29**: 240-245 [PMID: 18404145]

51 **Sarvaria A**, Madrigal JA, Saudemont A. B cell regulation in cancer and anti-tumor immunity. *Cell Mol Immunol* 2017; **14**: 662-674 [PMID: 28626234 DOI: 10.1038/cmi.2017.35]

52 **Murakami Y**, Saito H, Shimizu S, Kono Y, Shishido Y, Miyatani K, Matsunaga T, Fukumoto Y, Ashida K, Sakabe T, Nakayama Y, Fujiwara Y. Increased regulatory B cells are involved in immune evasion in patients with gastric cancer. *Sci Rep* 2019; **9**: 13083 [PMID: 31511630 DOI: 10.1038/s41598-019-49581-4]

53 **Li JH**, O'Sullivan TE. Back to the Future: Spatiotemporal Determinants of NK Cell Antitumor Function. *Front Immunol* 2021; **12**: 816658 [PMID: 35082797 DOI: 10.3389/fimmu.2021.816658]

54 **Zembower TR**. Epidemiology of infections in cancer patients. *Cancer Treat Res* 2014; **161**: 43-89 [PMID: 24706221 DOI: 10.1007/978-3-319-04220-6_2]

55 **Bitterman R**, Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. *Cochrane Database Syst Rev* 2018; **2**: CD008983 [PMID: 29388675 DOI: 10.1002/14651858.CD008983.pub3]

56 **Brydak LB**, Guzy J, Starzyk J, Machała M, Góźdź SS. Humoral immune response after vaccination against influenza in patients with breast cancer. *Support Care Cancer* 2001; **9**: 65-68 [PMID: 11147146 DOI: 10.1007/s005200000186]

57 **Pollyea DA**, Brown JM, Horning SJ. Utility of influenza vaccination for oncology patients. *J Clin Oncol* 2010; **28**: 2481-2490 [PMID: 20385981 DOI: 10.1200/JCO.2009.26.6908]

58 **Oates HF**, Stoker LM, Monaghan JC, Stokes GS. The beta-adrenoceptor controlling renin release. *Arch Int Pharmacodyn Ther* 1978; **234**: 205-213 [PMID: 213037 DOI: 10.1093/annonc/mdq728]

59 **Arrowood JR**, Hayney MS. Immunization recommendations for adults with cancer. *Ann Pharmacother* 2002; **36**: 1219-1229 [PMID: 12086557 DOI: 10.1345/aph.1A277]

60 **Velikova T**, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. *Rheumatol Int* 2021; **41**: 509-518 [PMID: 33515320 DOI: 10.1007/s00296-021-04792-9]

61 **Sen P**, Ravichandran N, Nune A, Lilleker JB, Agarwal V, Kardes S, Kim M, Day J, Milchert M, Gheita T, Salim B, Velikova T, Gracia-Ramos AE, Parodis I, Selva O'Callaghan A, Nikiphorou E, Chatterjee T, Tan AL, Cavagna L, Saavedra MA, Shinjo SK, Ziade N, Knitza J, Kuwana M, Distler O, Chinoy H, Agarwal V, Aggarwal R, Gupta L; COVAD Study Group. COVID-19 vaccination-related adverse events among autoimmune disease patients: results from the COVAD study. *Rheumatology (Oxford)* 2022; **62**: 65-76 [PMID: 35713499 DOI: 10.1093/rheumatology/keac305]

62 **Corti C**, Antonarelli G, Scotté F, Spano JP, Barrière J, Michot JM, André F, Curigliano G. Seroconversion rate after vaccination against COVID-19 in patients with cancer-a systematic review. *Ann Oncol* 2022; **33**: 158-168 [PMID: 34718117 DOI: 10.1016/j.annonc.2021.10.014]

63 **Khoury DS**, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27**: 1205-1211 [PMID: 34002089 DOI: 10.1038/s41591-021-01377-8]

64 **Earle KA**, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, Dull P, Plotkin SA. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 2021; **39**: 4423-4428 [PMID: 34210573 DOI: 10.1016/j.vaccine.2021.05.063]

65 **Slabakova Y**, Gerenska D, Ivanov N, Velikova T. Immune titers of protection against severe acute respiratory syndrome coronavirus 2: are we there yet? *Explor Immunol* 2022; **2**: 9-24 [DOI: 10.37349/ei.2022.00033]

66 **Monin L**, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, Domingo-Vila C, Hayday TS, Graham C, Seow J, Abdul-Jawad S, Kamdar S, Harvey-Jones E, Graham R, Cooper J, Khan M, Vidler J, Kakkassery H, Sinha S, Davis R, Dupont L, Francos Quijorna I, O'Brien-Gore C, Lee PL, Eum J, Conde Poole M, Joseph M, Davies D, Wu Y, Swampillai A, North BV, Montes A, Harries M, Rigg A, Spicer J, Malim MH, Fields P, Patten P, Di Rosa F, Papa S, Tree T, Doores KJ, Hayday AC, Irshad S. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol* 2021; **22**: 765-778 [PMID: 33930323 DOI: 10.1016/S1470-2045(21)00213-8]

67 **Fendler A**, Shepherd STC, Au L, Wilkinson KA, Wu M, Byrne F, Cerrone M, Schmitt AM, Joharatnam-Hogan N, Shum B, Tippu Z, Rzeniewicz K, Boos LA, Harvey R, Carlyle E, Edmonds K, Del Rosario L, Sarker S, Lingard K, Mangwende M, Holt L, Ahmod H, Korteweg J, Foley T, Bazin J, Gordon W, Barber T, Emslie-Henry A, Xie W, Gerard CL, Deng D, Wall EC, Agua-Doce A, Namjou S, Caidan S, Gavrielides M, MacRae JI, Kelly G, Peat K, Kelly D, Murra A, Kelly K, O'Flaherty M, Dowdie L, Ash N, Gronthoud F, Shea RL, Gardner G, Murray D, Kinnaird F, Cui W, Pascual J, Rodney S, Mencel J, Curtis O, Stephenson C, Robinson A, Oza B, Farag S, Leslie I, Rogiers A, Iyengar S, Ethell M, Messiou C, Cunningham D, Chau I, Starling N, Turner N, Welsh L,

van As N, Jones RL, Droney J, Banerjee S, Tatham KC, O'Brien M, Harrington K, Bhide S, Okines A, Reid A, Young K, Furness AJS, Pickering L, Swanton C; Crick COVID19 consortium, Gandhi S, Gamblin S, Bauer DL, Kassiotis G, Kumar S, Yousaf N, Jhanji S, Nicholson E, Howell M, Walker S, Wilkinson RJ, Larkin J, Turajlic S. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: The CAPTURE study. *Nat Cancer* 2021; **2**: 1321-1337 [PMID: 34950880 DOI: 10.1038/s43018-021-00274-w]

68 **Miteva D**, Kitanova M, Batselova H, Lazova S, Chervenkov L, Peshevska-Sekulovska M, Sekulovski M, Gulinac M, Vasilev GV, Tomov L, Velikova T. The End or a New Era of Development of SARS-CoV-2 Virus: Genetic Variants Responsible for Severe COVID-19 and Clinical Efficacy of the Most Commonly Used Vaccines in Clinical Practice. *Vaccines (Basel)* 2023; **11** [PMID: 37514997 DOI: 10.3390/vaccines11071181]

69 **Greenberger LM**, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols G. L..Blood; 138:185, 2021 [DOI: 10.1182/blood-2021-151419]

70 **Rüthrich MM**, Giesen N, Mellinghoff SC, Rieger CT, von Lilienfeld-Toal M. Cellular Immune Response after Vaccination in Patients with Cancer-Review on Past and Present Experiences. *Vaccines (Basel)* 2022; **10** [PMID: 35214642 DOI: 10.3390/vaccines10020182]

71 **Ehmsen S**, Asmussen A, Jeppesen SS, Nilsson AC, Østerlev S, Vestergaard H, Justesen US, Johansen IS, Frederiksen H, Ditzel HJ. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. *Cancer Cell* 2021; **39**: 1034-1036 [PMID: 34348121 DOI: 10.1016/j.ccell.2021.07.016]

72 **Mairhofer M**, Kausche L, Kaltenbrunner S, Ghanem R, Stegemann M, Klein K, Pammer M, Rauscher I, Salzer HJF, Doppler S, Habringer A, Paar C, Kimeswenger S, Hoetzenecker W, Lamprecht B, Lee S, Schmitt CA. Humoral and cellular immune responses in SARS-CoV-2 mRNA-vaccinated patients with cancer. *Cancer Cell* 2021; **39**: 1171-1172 [PMID: 34450047 DOI: 10.1016/j.ccell.2021.08.001]

73 **Oosting SF**, van der Veldt AAM, GeurtsvanKessel CH, Fehrmann RSN, van Binnendijk RS, Dingemans AC, Smit EF, Hiltermann TJN, den Hartog G, Jalving M,

Westphal TT, Bhattacharya A, van der Heiden M, Rimmelzwaan GF, Kvistborg P, Blank CU, Koopmans MPG, Huckriede ALW, van Els CACM, Rots NY, van Baarle D, Haanen JBAG, de Vries EGE. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. *Lancet Oncol* 2021; **22**: 1681-1691 [PMID: 34767759 DOI: 10.1016/S1470-2045(21)00574-X]

74 **Schmidt AL**, Labaki C, Hsu CY, Bakouny Z, Balanchivadze N, Berg SA, Blau S, Daher A, El Zarif T, Friese CR, Griffiths EA, Hawley JE, Hayes-Lattin B, Karivedu V, Latif T, Mavromatis BH, McKay RR, Nagaraj G, Nguyen RH, Panagiotou OA, Portuguese AJ, Puc M, Santos Dutra M, Schroeder BA, Thakkar A, Wulff-Burchfield EM, Mishra S, Farmakiotis D, Shyr Y, Warner JL, Choueiri TK; COVID-19 and Cancer Consortium. COVID-19 vaccination and breakthrough infections in patients with cancer. *Ann Oncol* 2022; **33**: 340-346 [PMID: 34958894 DOI: 10.1016/j.annonc.2021.12.006]

75 **Goshen-Lago T**, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, Hussein K, Fahoum L, Baruch M, Peer A, Reiter Y, Almog R, Halberthal M, Ben-Aharon I. Serologic Status and Toxic Effects of the SARS-CoV-2 BNT162b2 Vaccine in Patients Undergoing Treatment for Cancer. *JAMA Oncol* 2021; **7**: 1507-1513 [PMID: 34236381 DOI: 10.1001/jamaoncol.2021.2675]

76 **Waldhorn I**, Holland R, Goshen-Lago T, Shirman Y, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, Hussein K, Fahoum L, Peer A, Almog R, Shaked Y, Halberthal M, Ben-Aharon I. Six-Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors. *Cancer Discov* 2021; **11**: 2430-2435 [PMID: 34475136 DOI: 10.1158/2159-8290.CD-21-1072]

77 **Barrière J**, Chamorey E, Adjtoutah Z, Castelnau O, Mahamat A, Marco S, Petit E, Leysalle A, Raimondi V, Carles M. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. *Ann Oncol* 2021; **32**: 1053-1055 [PMID: 33932508 DOI: 10.1016/j.annonc.2021.04.019]

78 **Shroff RT**, Chalasani P, Wei R, Pennington D, Quirk G, Schoenle MV, Peyton KL, Uhrlaub JL, Ripperger TJ, Jergović M, Dalgai S, Wolf A, Whitmer R, Hammad H, Carrier A, Scott AJ, Nikolich-Žugich J, Worobey M, Sprissler R, Dake M, LaFleur BJ, Bhattacharya D. Immune responses to two and three doses of the BNT162b2 mRNA vaccine in adults with solid tumors. *Nat Med* 2021; **27**: 2002-2011 [PMID: 34594036 DOI: 10.1038/s41591-021-01542-z]

79 **Wagner A**, Garner-Spitzer E, Schötta AM, Orola M, Wessely A, Zwazl I, Ohradanova-Repic A, Weseslindtner L, Tajti G, Gebetsberger L, Kratzer B, Tomosel E, Kutschera M, Tobudic S, Pickl WF, Kundi M, Stockinger H, Novacek G, Reinisch W, Zielinski C, Wiedermann U. SARS-CoV-2-mRNA Booster Vaccination Reverses Non-Responsiveness and Early Antibody Waning in Immunocompromised Patients-A Phase Four Study Comparing Immune Responses in Patients With Solid Cancers, Multiple Myeloma and Inflammatory Bowel Disease. *Front Immunol* 2022; **13**: 889138 [PMID: 35634285 DOI: 10.3389/fimmu.2022.889138]

80 **Reimann P**, Ulmer H, Mutschlechner B, Benda M, Severgnini L, Volgger A, Lang T, Atzl M, Huynh M, Gasser K, Grabher C, Mink S, Fraunberger P, Petrausch U, Hartmann B, Winder T. Efficacy and safety of heterologous booster vaccination with Ad26.COV2.S after BNT162b2 mRNA COVID-19 vaccine in haemato-oncological patients with no antibody response. *Br J Haematol* 2022; **196**: 577-584 [PMID: 34872162 DOI: 10.1111/bjh.17982]

81 **Thomas SJ**, Perez JL, Lockhart SP, Hariharan S, Kitchin N, Bailey R, Liau K, Lagkadinou E, Türeci Ö, Şahin U, Xu X, Koury K, Dychter SS, Lu C, Gentile TC, Gruber WC. Efficacy and safety of the BNT162b2 mRNA COVID-19 vaccine in participants with a history of cancer: subgroup analysis of a global phase 3 randomized clinical trial. *Vaccine* 2022; **40**: 1483-1492 [PMID: 35131133 DOI: 10.1016/j.vaccine.2021.12.046]

82 **Lee LYW**, Starkey T, Ionescu MC, Little M, Tilby M, Tripathy AR, Mckenzie HS, Al-Hajji Y, Barnard M, Benny L, Burnett A, Cattell EL, Charman J, Clark JJ, Khan S, Ghafoor Q, Illsley G, Harper-Wynne C, Hattersley RJ, Lee AJX, Leonard PC, Liu JKH; NCRI Consumer Forum, Pang M, Pascoe JS, Platt JR, Potter VA, Randle A, Rigg AS,

Robinson TM, Roques TW, Roux RL, Rozmanowski S, Tuthill MH, Watts I, Williams S, Iveson T, Lee SM, Middleton G, Middleton M, Protheroe A, Fittall MW, Fowler T, Johnson P. Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): a population-based test-negative case-control study. *Lancet Oncol* 2022; **23**: 748-757 [PMID: 35617989 DOI: 10.1016/S1470-2045(22)00202-9]

83 **Thakkar A**, Pradhan K, Duva B, Carreno JM, Sahu S, Thiruthuvanathan V, Campbell S, Gallego S, Bhagat TD, Rivera J, Choudhary G, Olea R, Sabalza M, Shapiro LC, Lee M, Quinn R, Mantzaris I, Chu E, Will B, Pirofski LA, Krammer F, Verma A, Halmos B. Study of efficacy and longevity of immune response to third and fourth doses of COVID-19 vaccines in patients with cancer: A single arm clinical trial. *Elife* 2023; **12** [PMID: 36975207 DOI: 10.7554/eLife.83694]

84 **Polack FP**, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**: 2603-2615 [PMID: 33301246 DOI: 10.1056/NEJMoa2034577]

85 **Haynes L**. Aging of the Immune System: Research Challenges to Enhance the Health Span of Older Adults. *Front Aging* 2020; **1**: 602108 [PMID: 35822168 DOI: 10.3389/fragi.2020.602108]

86 **Zangemeister-Wittke U**, Simon HU. Myelosuppression. In: Schwab M. Encyclopedia of Cancer. Springer, Berlin, Heidelberg. Encyclopedia of Cancer 2011; 2437-2440 [DOI: 10.1007/978-3-642-16483-5_3940]

87 **Ba Y**, Shi Y, Jiang W, Feng J, Cheng Y, Xiao L, Zhang Q, Qiu W, Xu B, Xu R, Shen B, Luo Z, Xie X, Chang J, Wang M, Li Y, Shuang Y, Niu Z, Liu B, Zhang J, Zhang L, Yao H, Xie C, Huang H, Liao W, Chen G, Zhang X, An H, Deng Y, Gong P, Xiong J, Yao Q, An X, Chen C, Shi Y, Wang J, Wang X, Wang Z, Xing P, Yang S, Zhou C. Current management of chemotherapy-induced neutropenia in adults: key points and new challenges: Committee of Neoplastic Supportive-Care (CONS), China Anti-Cancer

Association Committee of Clinical Chemotherapy, China Anti-Cancer Association. *Cancer Biol Med* 2020; **17**: 896-909 [PMID: 33299642 DOI: 10.20892/j.issn.2095-3941.2020.0069]

88 **Weinblatt ME**, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, Trentham DE. Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985; **312**: 818-822 [PMID: 3883172 DOI: 10.1056/NEJM198503283121303]

89 **Alqarni AM**, Zeidler MP. How does methotrexate work? *Biochem Soc Trans* 2020; **48**: 559-567 [PMID: 32239204 DOI: 10.1042/BST20190803]

90 **Koźmiński P**, Halik PK, Chesori R, Gniazdowska E. Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers. *Int J Mol Sci* 2020; **21** [PMID: 32423175 DOI: 10.3390/ijms21103483]

91 **Kapetanovic MC**, Roseman C, Jönsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum* 2011; **63**: 3723-3732 [PMID: 21834061 DOI: 10.1002/art.30580]

92 **Kapetanovic MC**, Saxne T, Sjöholm A, Truedsson L, Jönsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2006; **45**: 106-111 [PMID: 16287919 DOI: 10.1093/rheumatology/kei193]

93 **Nived P**, Pettersson Å, Jönsson G, Bengtsson AA, Settergren B, Skattum L, Johansson Å, Kapetanovic MC. Methotrexate reduces circulating Th17 cells and impairs plasmablast and memory B cell expansions following pneumococcal conjugate immunization in RA patients. *Sci Rep* 2021; **11**: 9199 [PMID: 33911135 DOI: 10.1038/s41598-021-88491-2]

94 **Ogino MH**, Tadi P. Cyclophosphamide. 2023 Jul 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan- [PMID: 31971727]

95 **Gauthier SA**, Weiner HL. Cyclophosphamide therapy for MS. *Int MS J* 2005; **12**: 52-58 [PMID: 16417815]

96 **Elkhalifa A**, Weiner H. Cyclophosphamide Treatment of MS: Current Therapeutic Approaches and Treatment Regimens. *Int MS J* 2010; **17**: 12-18 [PMID: 20663416]

97 **Ahlmann M**, Hempel G. The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy. *Cancer Chemother Pharmacol* 2016; **78**: 661-671 [PMID: 27646791 DOI: 10.1007/s00280-016-3152-1]

98 **Madondo MT**, Quinn M, Plebanski M. Low dose cyclophosphamide: Mechanisms of T cell modulation. *Cancer Treat Rev* 2016; **42**: 3-9 [PMID: 26620820 DOI: 10.1016/j.ctrv.2015.11.005]

99 **de Lavallade H**, Khoder A, Hart M, Sarvaria A, Sekine T, Alsuliman A, Mielke S, Bazeos A, Stringaris K, Ali S, Milojkovic D, Foroni L, Chaidos A, Cooper N, Gabriel I, Apperley J, Belsey S, Flanagan RJ, Goldman J, Shpall EJ, Kelleher P, Marin D, Rezvani K. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. *Blood* 2013; **122**: 227-238 [PMID: 23719297 DOI: 10.1182/blood-2012-11-465039]

Table 1 Some of the more significant studies conducted on the efficacy and safety of COVID-19 vaccination with different approved COVID-19 vaccines in oncological patients with solid tumors

Ref.	Type of vaccine	Type of study	Subjects (diagnosis, other specific characteristics)	Data on efficacy	Data on safety (main side effects)
OnCovid study group[5]	NA	A multicenter observational registry-based study	All PTs included *n* = 2634 (100%); PTs with advanced tumor stage *n* = 1244 (46%); PTs with receipt of anti-cancer therapy within 4 wk of COVID-19 diagnosis *n* = 1305 (51.8%); malignancy type: Breast *n* = 493 (18.9%); gastrointestinal *n* = 476 (18.2%); gynecologic/genitourinary *n* = 530 (20.3%); hematologic *n* = 357 (13.7%)	The difference in the necessity of hospitalization due to COVID-19, oxygen therapy requirement, mechanical ventilation requirement, and 14-d CFR between PTs stratified across time 5 phases and 2 major outbreaks of the pandemic; hospitalization requirement: 1st phase-64.7% to 5th phase-42.7% ($P < 0.01$); proportion ot PTs requiring O2: therapy, phase 1-62.6%, to phase 5-46.0% ($P < 0.001$); mechanical ventilation: Phase 1-12.1% to phase 5-11.8% ($P = 0.01$); CFR: 1st outbreak-25.6% to-2nd outbreak 16.2% ($P < 0.001$)	NA
Khoury *et al*[63], 2021	mRNA and adenoviral vector vaccines			20.2% of subjects had (95%CI) 50% protective neutralization level	NA

Monin *et al*[66], 2021	mRNA	Prospective observational study	PTs with oncologic disease *n* = 151: With solid cancer *n* = 95; with hematological malignancy *n* = 56; and healthy controls *n* = 54	Surrogate marker of efficiency: Seroconversion after 1st dose: 32 of 34 (94%) HCs, 21 of 56 (38%), PTs with solid cancer, 8 of 44 (18%), PTs with hematologic malignancies; after 2nd dose: 12 of 12 (100%) HC; 18 of 19 (95%), PTs with solid, 3 of 5 (60%), PTs with hematologic malignancies	AE: Injection-site pain within 7 d following the first dose in: 23 of 65 (35%) patients with cancer; 12 of 25 (48%) healthy controls; no vaccine-related deaths were reported
Greenberger *et al*[69], 2021	mRNA and adenoviral vector vaccines	Retrospective cohort study	PTs with hematologic malignancies, *n* = 3300		
Ehmsen *et al*[71], 2021	mRNA	Prospective cohort study (comparison between groups with different malignancies; no healthy controls)	PTs with cancer, *n* = 524, of whom: 201 (38%) with solid cancer; 323 (62%) with hematologic cancer; 524 (100%) had a blood sample drawn at a median of 36 d after the second dose of vaccine; and 247 (47%) had a second blood sample drawn	Seropositivity rate for anti-S IgG 36 d after vaccination: PTs with solid cancer 187 of 201 (93%); PTs with hematologic cancer 215 of 323 (66%); seropositivity rate for anti-S IgG 3 mo after vaccination: PTs with solid cancer-86%, PTs with hematologic cancer-53%; anti-S IgG titers; between 36-d and	N/A

		3 mo after the second dose of the vaccine	3-mo samples declined from a median of 429 BAU/mL to a median of 139 BAU/mL (P = 0.03, Student's t-test); T-cell reactivity: PTs with solid cancer-92 (46%), 70 (76%) mounted both CD4+ and CD8+ T cell responses, 21 (23%) elicited only a CD8+ T cell response, PTs with hematologic cancer-144 (45%), 81% were positive for both CD4+ and CD8+ T cells, 26 (18%) only elicited a CD8+ T cell response, 76% of the seronegative patients did not elicit a T cell response; PTs with solid cancer: only 1 of the 14 (7%) seronegative PTs elicited a T cell response; PTs with hematologic cancer: 28 of 108 (26%) patients elicited T cell response	
Oosting *et al*[73], 2021	mRNA	Prospective, multicentre, non-inferiority trial	Cohort A: Individuals without cancer (control cohort); cohort B: PTs with solid tumors, regardless of	Presence of SARS-CoV-2-binding antibodies after the second vaccination; at 28th d, 6 mo after 12 mo after a spike-specific T-cell	N/A

			stage and histology, treated with immunotherapy; cohort C: PTs treated with chemotherapy; and cohort D: PTs treated with chemoimmunotherapy	response was defined as a two times or more significant increase in the number of spot-forming cells	
Polack *et al*[84], 2020	mRNA vaccines	Placebo-controlled, observer-blinded, pivotal efficacy trial (randomized 1:1 vaccine *vs* placebo)	All patients included n = 43548; patients with liver disease n = 217 (0.6%)	95% efficacy (9 vaccinated *vs* 169 controls with COVID-19); 10 cases of severe COVID-19 infection *vs* 9 in the placebo group; Flares: NR	Systemic AEs: (1) Fatigue (34%-51%); (2) headache (25%-39%); fever (11%); injection site reactions; (4) pain (71%-83%); (5) redness and swelling (< 7%); and (6) serious AE < 4%
Fendler *et al*[67], 2021	BNT162b2 or AZD1222 vaccines (CAPTURE, NCT03226886)	Prospective cohort study	585 patients, the seroconversion rates after two doses of BNT162b2 or AZD1222 vaccines given over 12 wk were assessed	After two doses of BNT162b2 or AZD1222 vaccines given over 12 wk, seroconversion was 85% and 59% in patients with solid and hematological malignancies, respectively;	N/A

				vaccine-induced T-cell responses were found in 80% of patients regardless of the vaccine or type of cancer	
Goshen-Lago *et al*[75], 2021	BNT162b2 vaccine	Prospective study	One hundred fifty-four patients with solid tumors and 135 controls (health workers)	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; analysis by age, sex, or disease stage has no significant differences within the patient cohort; 15% of the seropositive patients became seronegative after six months, comparable to the control group	N/A
Waldhorn *et al*[76], 2021	BNT162b2 vaccine	Prospective study	154 patients with solid tumors and 135 controls	Six months postvaccination 79% of patients and 84% of healthy controls were seropositive (P = 0.32); dramatically decreased	

				serology titer	
Shroff *et al*[78], 2021	BNT162b2	Phase 1 cohort trial	53 patients with solid tumors on active cytotoxic anti-cancer therapy and 50 healthy cohort	Neutralizing antibodies were detected in 67% of patients with cancer after the first immunization, followed by a threefold increase in median titers after the second dose	Adverse events were mild: Temperature, fever, headache, redness, and swelling on the injection site
Barrière *et al*[77], 2021	BNT162b2	VMO for vaccinated patients under active treatment in the Department of Oncology of the Saint Jean Polyclinic, Nice, France	194 evaluable patients with solid tumors and 31 healthy controls	Fifty-eight patients had neutralizing antibodies, although the median levels were significantly lower than those in the control group; the data demonstrating impaired immunogenicity of the BNT162b2 vaccine in immunocompromised patients; % of efficacy is not reported	N/A
Thomas *et al*[81], 2022	BNT162b2 mRNA	Phase 3 randomized clinical trial	3813 participants had a history of neoplasm: Most common malignancies were breast (n = 460), prostate (n = 362), and melanoma (n = 223)	Vaccine efficacy was 94.4% (95%CI) after up to 6 mo of follow-up post-dose 2	N/A

Wagner *et al*[79], 2022	mRNA-1273 or BNT162b2	Prospective, open-label, phase four trail	263 patients with solid tumors: (SOT, *n* = 63), multiple myeloma (MM, *n* = 70), inflammatory bowel diseases (IBD, *n* = 130) and 66 controls	A month after the two-dose primary vaccination, the highest non-responder rate was found in MM patients (17%); six months after the second dose, 18% of patients with MM, 10% with SOT and 4% with IBD became seronegative compared to the control group; the vaccination with mRNA-1273 led to higher antibody levels than with BNT162b2; booster vaccination increased antibody levels 8-fold in seropositive individuals and induced responses in those with undetectable pre-booster antibody levels	N/A
Lee *et al*[82], 2022	BNT162b2, ChAdOx1 nCov-19, or mixed and	Population-based test-negative case-control study	Cancer cohort comprised 377194 individuals, of whom 42882 had breakthrough SARS-CoV-2	Overall vaccine effectiveness was 69.8% in the control population and 65.5% in the cancer cohort; vaccine	N/A

	other		infections; the control population consisted of 28010955 individuals, of whom 5748708 had SARS-CoV-2 breakthrough infections	effectiveness at 3-6 mo was lower in the cancer cohort (47.0%) than in the control population (61.4%)	
Reimann *et al*[80], 2022	Ad26.COV2.S after BNT162b2 mRNA		32 oncological non-responders to double-dose BNT162b2	The overall response rate was 31%	Mainly mild local and systemic reactions
Thakkar *et al*[83], 2023	Two doses of mRNA or one dose of AD26.CoV2.S vaccine and administered a third dose of mRNA vaccine	Single-arm prospective clinical trial	106 cancer patients	A third dose of the COVID-19 vaccine induces durable immunity in cancer patients, leading to seroconversion in 57% of patients who did not respond to primary vaccination; eighteen patients with blood cancer and severe immune suppression had no response after three doses; and the fourth dose boosted the immune response by 2/3 of	N/A

	patients, with neutralizing activity against the Omicron variant

VMO: Vaccine monitoring observatory; N/A: Not applicable.; 95%CI: confidence interval; AE: PT:

86646_Auto_Edited.docx

ORIGINALITY REPORT

16%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.wjgnet.com Internet	88 words — 1%
2	www.mdpi.com Internet	71 words — 1%
3	Angelika Wagner, Erika Garner-Spitzer, Anna-Margarita Schötta, Maria Orola et al. "SARS-CoV-2-mRNA Booster Vaccination Reverses Non-Responsiveness and Early Antibody Waning in Immunocompromised Patients – A Phase Four Study Comparing Immune Responses in Patients With Solid Cancers, Multiple Myeloma and Inflammatory Bowel Disease", Frontiers in Immunology, 2022 Crossref	64 words — 1%
4	Bernhard Englinger, Christine Pirker, Petra Heffeter, Alessio Terenzi, Christian R. Kowol, Bernhard K. Keppler, Walter Berger. "Metal Drugs and the Anticancer Immune Response", Chemical Reviews, 2018 Crossref	62 words — 1%
5	bsdwebstorage.blob.core.windows.net Internet	60 words — 1%
6	A. Meerveld-Eggink. "Response to influenza virus vaccination during chemotherapy in patients with breast cancer", Annals of Oncology, 09/01/2011 Crossref	58 words — 1%

7	elifesciences.org Internet	58 words — 1%
8	Lennard Y W Lee, Thomas Starkey, Maria C Ionescu, Martin Little et al. "Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): a population-based test-negative case-control study", The Lancet Oncology, 2022 Crossref	57 words — 1%
9	covid19dataportal.es Internet	46 words — 1%
10	J. Barrière, E. Chamorey, Z. Adjtoutah, O. Castelnau, A. Mahamat, S. Marco, E. Petit, A. Leysalle, V. Raimondi, M. Carles. "Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors", Annals of Oncology, 2021 Crossref	36 words — 1%
11	www.cdc.gov Internet	34 words — < 1%
12	www.esp.org Internet	34 words — < 1%
13	Stephen J. Thomas, John L. Perez, Stephen P. Lockhart, Subramanian Hariharan et al. "Efficacy and safety of the BNT162b2 mRNA COVID-19 vaccine in participants with a history of cancer: subgroup analysis of a global phase 3 randomized clinical trial", Vaccine, 2021 Crossref	30 words — < 1%
14	www.nature.com Internet	28 words — < 1%
15	hdl.handle.net	

Internet

27 words — < 1%

16 pro.uptodatefree.ir
Internet

27 words — < 1%

17 Ithai Waldhorn, Roy Holland, Tal Goshen - Lago, Yelena Shirman et al. "Six Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors", Cancer Discovery, 2021
Crossref

26 words — < 1%

18 Kaiyin Huang, Yamei Yan, Dan Chen, Ya Zhao, Wei Dong, Xiaoxiong Zeng, Youlong Cao. " Ascorbic Acid Derivative 2- -β- -Glucopyranosyl- -Ascorbic Acid from the Fruit of Modulates Microbiota in the Small Intestine and Colon and Exerts an Immunomodulatory Effect on Cyclophosphamide-Treated BALB/c Mice ", Journal of Agricultural and Food Chemistry, 2020
Crossref

26 words — < 1%

19 Tim Hulsen. "Literature analysis of the efficacy of COVID-19 vaccinations", Cold Spring Harbor Laboratory, 2022
Crossref Posted Content

24 words — < 1%

20 files.covid19treatmentguidelines.nih.gov
Internet

23 words — < 1%

21 www.covid19reviews.org
Internet

23 words — < 1%

22 Anastasios Dimou. "Areas of Uncertainty in SARS-CoV-2 Vaccination for Cancer Patients", Vaccines, 2022
Crossref

22 words — < 1%

23	Tsvetelina Velikova, Tsvetoslav Georgiev. "SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis", Rheumatology International, 2021 Crossref	22 words — < 1%
24	www.frontiersin.org Internet	21 words — < 1%
25	www.science.gov Internet	21 words — < 1%
26	www.cell.com Internet	20 words — < 1%
27	orizon.ori-capital.com Internet	18 words — < 1%
28	Christine R. Cuthbertson, Zahra Arabzada, Armand Bankhead, Armita Kyani, Nouri Neamati. "A Review of Small-Molecule Inhibitors of One-Carbon Enzymes: SHMT2 and MTHFD2 in the Spotlight", ACS Pharmacology & Translational Science, 2021 Crossref	17 words — < 1%
29	Przemysław Koźmiński, Paweł Krzysztof Halik, Raphael Chesori, Ewa Gniazdowska. "Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers", International Journal of Molecular Sciences, 2020 Crossref	17 words — < 1%
30	Alberto Pinzon-Charry, Tammy Maxwell, Michael A McGuckin, Chris Schmidt, Colin Furnival, J Alejandro López. "Spontaneous apoptosis of blood dendritic cells in patients with breast cancer", Breast Cancer Research, 2005 Crossref	16 words — < 1%

31	www.researchgate.net Internet	16 words — < 1%
32	Mutsa Tatenda Madondo, Michael Quinn, Magdalena Plebanski. "Low dose cyclophosphamide: Mechanisms of T cell modulation", Cancer Treatment Reviews, 2016 Crossref	15 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 15 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 10 WORDS