



Published in final edited form as:

*Cancer Discov.* 2022 February ; 12(2): 303–330. doi:10.1158/2159-8290.CD-21-1368.

## Learning Through a Pandemic: The Current State of Knowledge on COVID-19 and Cancer

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### Abstract

The ongoing COVID-19 pandemic has left patients with current or past history of cancer facing disparate consequences at every stage of the cancer trajectory. This comprehensive review offers a landscape analysis of the current state of the literature on COVID-19 and cancer including the immune response to COVID-19, risk factors for severe disease, and impact of anticancer therapies. We also review the latest data on treatment of COVID-19 and vaccination safety and efficacy in

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patients with cancer, as well as impact of the pandemic on cancer care, including the urgent need for rapid evidence generation and real-world study designs.

## Keywords

neoplasms; COVID-19; SARS-CoV-2

## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has caused an ongoing global pandemic. At the time of writing, over 257 million people have developed the resulting illness, COVID-19, and at least 5.1 million people have died (<https://coronavirus.jhu.edu/map.html>). Early on in the pandemic, it emerged that patients with certain risk factors or comorbidities including cancer were at heightened risk of severe outcomes.(1–3) In addition to the increased risk of transmission, severity, and risk of death from COVID-19 among patients with cancer, providing cancer care amidst this pandemic has proven to be an extraordinary and unprecedented challenge. Indeed, COVID-19 has affected every aspect of cancer care provision – from screening(4) and diagnosis, to changes in cancer therapies and delays in essential procedures, to lasting psychological consequences brought on by isolation(5) and distress among both patients and caregivers.(6)

These disparate repercussions on people with cancer have rippled deeply and globally. For example, early evidence points to a rise in metastatic cancer incidence, due to a decrease in screening either from healthcare avoidance or funneling of healthcare resources away from preventative care.(7)

This review aims to offer a landscape analysis of the current state of the literature on COVID-19 and cancer. The first section provides a framework to understand the physiologic immune response to SARS-CoV-2 infection with an in-depth view at how this response is affected by immunosuppressed states including cancer. The second section focuses on the spectrum of presentation of COVID-19 in patients with cancer including Post-Acute Sequelae of SARS CoV-2 infection (PASC a.k.a. “long-COVID”) as well as the risk factors for severe disease amongst patients with either a current or past diagnosis of cancer. The next section details the impact of cancer therapies on COVID-19, including therapies with both potential positive and negative effects on COVID-19 severity. We then describe the current best-practice guidelines, evidence, and advances in the treatment of COVID-19 in patients with cancer including general COVID-19 treatment and the importance of palliative care. Next, we summarize the most recent evidence on COVID-19 vaccine efficacy and safety in patients with cancer, followed by an outline on the impact of COVID-19 on cancer care delivery. We conclude with a discussion around real-world data in the COVID-19 era with a specific focus on research design and methodological considerations.

## COVID-19 Immune Response in Patients with Cancer

SARS-CoV-2 is an enveloped single-stranded RNA-virus of the  $\beta$ -coronavirus family, the members of which include SARS-CoV and MERS-CoV. (8) At the start of the pandemic,

epidemiologic studies identified risk factors associated with severe disease, notably advanced age and male sex(9). Further studies identified additional patient characteristics or underlying medical conditions also associated with poorer prognosis, including race and ethnicity, obesity, and active malignancy.(3,10–17) The early waves of the pandemic identified a “hyper-inflammatory” phenotype particularly among some critically ill patients, similar to known cytokine release syndromes (CRS), prompting numerous clinical studies to target dysregulated inflammation.(18–21) Thus, the demographic profile of the at-risk patient and the clinical syndrome of life-threatening disease were recognized early, although the mechanisms underlying these traits remain obscure. Since late 2020, the clinical complexity of COVID-19 is compounded by the emergence of sets of mutations in the virus, or variants of SARS-CoV-2 that can impact transmissibility and severity of COVID-19.(22)

The biologic basis for individual variability in clinical outcome has been partially clarified through immunologic investigations *in vitro*, in animal models, and in humans, enabling the construct of a two-step model of pathogenesis (Figure 1).(23,24) Glycosylated spike (S) proteins cover the surface of SARS-CoV-2 and attach to the host cell receptor angiotensin-converting enzyme 2 (ACE2).(25) Infection of the upper respiratory tract’s epithelial cells is mediated by the viral attachment to ACE2 (26–28). At this juncture, “Step 1”, one of the critical determinants of the disease course is the innate type I interferon (IFN) response. (24) Animal models susceptible to, or rendered permissive to, SARS-CoV-2 infection demonstrate early and robust induction of type I IFN following infection of the respiratory mucosa.(29,30) However, SARS-CoV-2 targets specific host proteins to suppress, but not abolish, the type I IFN response. Residual type I IFN response is presumably adequate to clear the infection in most hosts.(31–36) In a complementary series of investigations, pre-existing, neutralizing auto-antibodies to type I IFN have been found in ~15% of patients with severe COVID-19 (without genetic mutations), underscoring the importance of adequate type I IFN immunity at outset in mitigating human infection.(37–43) Thus, insufficient type I IFN at this juncture permits viral replication and propagation to the lungs and to extra-pulmonary sites.(44)

In “Step 2”, viral replication occurs in the lower airways and alveoli, 7-14 days following infection. This replication results in progressive recruitment and activation of leukocytes, with excessive production of various cytokines in an attempt to eradicate the virus. After primary exposure, adaptive immunity with development of plasmablasts and neutralizing antibodies, as well as virus-specific T-cells, attempt to clear the infection. Yet when type I IFN responses are impaired, a high viral burden in the lungs overwhelms *de novo* cell-mediated immunity (CMI).(18,20,28,45–48) In those with intact type I IFN responses, adaptive immunodeficiency (e.g. from iatrogenic immunosuppression) may blunt this process. This results in prolonged viral shedding and replication. However, dysregulation of CMI may produce exuberant responses that are detrimental. Progression to life-threatening disease is marked by significant immunopathology, including epithelial lung damage, endothelial dysfunction, and CRS.(19,21,47,49) Multiple complex interactions between malignant cells, the coagulation cascade, COVID-19 induced proinflammatory cytokines, and stasis secondary to prolonged illness and hospitalization shift hemostatic balance to a procoagulant state associated with a higher incidence of arterial and venous thromboembolism in patients with COVID-19 and active cancer.

Risk factors that define a high risk for severe COVID-19 include patients with past or active malignancy and patients that are post-cytotoxic chemotherapy.(21,50,51) In these patients, immune response is limited by the chronic immunosuppressed state, and one of the consequences of this is reduced plasmacytoid dendritic cells available to respond to infection.(52) Furthermore, these patients are subject to lower levels of adaptive immunity and antibody production in the context of SARS-CoV-2 infection.(53–55) This phenotype is associated with lymphopenias, neutropenia, and decreased types I and III IFN response. (19,28,48,56,57) Consistent with the model currently supported by the data, these findings suggest that patients with cancer are unable to mount an appropriate immune response to clear infection. This above description provides a framework for understanding how immune responses can be aberrantly affected in patients with cancer depending on the viral variant, host factors, type of underlying malignancy, and the impact of certain chemotherapeutic regimens on immunologic axes.

Recent studies have described some of the mechanisms behind the blunted immune response in patients with cancer.(58) In a study of patients with cancer hospitalized with COVID-19, patients with depletion of CD4<sup>+</sup> and CD8<sup>+</sup> T cells exhibited worse COVID-19 outcomes, and patients with hematologic malignancies had lower B cell immunity.(59) A second study confirmed distinct immune signatures of patients with solid malignancy compared to patients with hematologic malignancy. B cell cytopenia was over-represented in patients with hematologic malignancies. Moreover, patients with hematologic malignancy who recovered from COVID-19 displayed lingering immunological consequences with impaired adaptive lymphocytic and innate myelomonocytic parameters.(60)

An important consequence of this blunted immune response is prolonged viral clearance in patients with cancer, which can result in prolonged illness.<sup>26</sup> One study examined the nasopharyngeal swabs from over 1,000 patients with and without cancer to compare duration of viral shedding of SARS-CoV-2 by RT-PCR based cycle threshold (Ct) values and determined that an active malignancy conferred a longer shedding period associated with sustained presence of type 1 IFN.(61) In a study of 20 immunocompromised patients with COVID-19, viable virus could be isolated for up to 63 days post-symptom onset, while viral RNA was detectable for up to 78 days.(62) In clinical practice, prolonged viral shedding, even if the viral particles are no longer viable, usually precludes continuation of cancer therapy, with potential deleterious outcome of cancer progression.

With this background, we now turn to the manifestations of SARS-CoV-2 infection in patients with cancer.

## **COVID-19 Presentation, Severity, and Resolution in Patients with Cancer**

### **Increased rate of SARS-CoV-2 infection and transmission in patients with cancer**

Early reports indicated that patients with cancer have a higher risk of SARS-CoV-2 infection compared to cancer-free controls.(2,63,63) Differences in age, sex, and comorbidities, and increased reliance on the healthcare system have been postulated to account for differences in COVID-19 disease risk.(15,64,65) A large electronic health record (EHR) study of data from 360 hospitals, representing 20% of the United States population, found that

patients with a cancer diagnosis within the last year were seven times more likely to develop COVID-19 than patients without cancer, even after adjusting for age, race, sex, comorbidities, transplant status, and nursing home stays.<sup>25</sup> This increased risk may be due to immunocompromised state, frequent interactions with the healthcare system, and/or closer monitoring for infection among patients with cancer.<sup>21</sup>

### COVID-19 Presentation

Clinical presentation of SARS-CoV-2 infection in patients with cancer is similar to patients without cancer. Initial symptoms generally include fever, sore throat, fatigue, diarrhea, and anosmia.<sup>(64)</sup> There is a wide spectrum of presentation of COVID-19, ranging from asymptomatic infection to respiratory failure. In addition to other multiorgan complications, micro and macro vascular thrombosis both venous and arterial is a unique presentation in this infection; see “Anticoagulation” section below.<sup>(66)</sup> The most frequent symptoms in a report of over 900 patients with cancer were fever, cough, dyspnea, fatigue, and malaise.<sup>(3)</sup> Low or high absolute lymphocyte count, high absolute neutrophil count, low platelet count, and abnormal creatinine, troponin, lactate dehydrogenase, and C-reactive protein (CRP) levels were all associated with higher COVID-19 severity among hospitalized patients reported to the COVID-19 and Cancer Consortium (CCC19) registry.<sup>(16)</sup> In addition to these laboratory values, the OnCOVID registry<sup>(16,67)</sup> found that hypoalbuminemia, high ferritin, and elevated d-dimer were negatively associated with outcome. A recent study evaluated dynamic changes in albumin and lymphocytes (onCOVID inflammatory score) and found that it was independently associated with severe COVID-19.<sup>(68,69)</sup>

Clinical presentation in patients with cancer is further complicated by several cancer-specific factors. For example, there have been reports that patients with cancer may have increased prevalence of asymptomatic presentation due to reflex screening practices.<sup>(70)</sup>

### Hospitalization and Mortality Rates

In addition to increased susceptibility to SARS-CoV-2 infection, patients with cancer also have higher risks of COVID-19 hospitalization and mortality. For example, among 4,966 patients from the primarily US-based CCC19 registry, 58% were hospitalized (N=2,872) and 14% (N=695) died.<sup>(16)</sup> A European study of 890 patients found a mortality rate of 33%.<sup>(67)</sup> A meta-analysis of 110 studies from 10 countries yielded a pooled in-hospital mortality rate among patients with cancer and COVID-19 of 14.1%.<sup>(71)</sup> Important comparisons were conducted using data from 360 hospitals in the US.<sup>(71)</sup> Patients with cancer who developed COVID-19 were hospitalized 47.5% of the time and had 14.9% mortality, versus 24.3% hospitalization and 5.3% mortality among COVID-19 patients without cancer, and 12.4% hospitalization and 4.0% mortality among patients with cancer but without COVID-19.<sup>(72)</sup> As demonstrated by these differing mortality rates, it is important to note the potential influence of geographic heterogeneity. A large study that examined case-fatality rates across the European Union (EU) vs United Kingdom (UK) showed that patients belonging to the UK group had higher case fatality rates which remained significant after multivariable analysis adjusting for known negative COVID-19 prognostic factors.<sup>(73)</sup>

Moreover, while the general population has seen improvements in COVID-19-related mortality over time, a large study conducted in Europe of more than 195,000 hospitalized patients suggested that mortality in the more than 15,000 patients with a history of cancer and more than 5,000 patients on active cancer treatment may be higher throughout and did not parallel the downward trends seen in patients with no history of cancer.(74) However, a recent report from the European OnCOVID registry recently presented at the ESMO 2021 conference showed improvement in COVID-19 mortality over time.(75)

A separate complicating factor is that the true rate of COVID-19 in patients with cancer remains incompletely quantified because the “full” denominator population is not known, e.g. there is a propensity for many of these studies to evaluate the risk of death in patients admitted to the hospital, and the actual number of all patients with cancer infected with SARS-CoV-2 may not fully reflect the proportion of asymptomatic or minimally symptomatic cases.(76)

### **Non-Cancer-Specific Clinical Factors Associated with COVID-19 Severity**

Patients with cancer represent a heterogeneous population with significant within-group variability. It is important to identify factors associated with worse outcomes to target surveillance and intervention efforts for high-risk patients. Similar to findings from the general public, demographic characteristics associated with worse prognosis in patients with cancer with COVID-19 include advanced age and male sex.(3,16,67,77) Similarly, comorbidities such as cardiovascular, pulmonary, and renal disease as well as their contribution to a higher Klabunde Comorbidity Index have all been associated with higher COVID-19 severity among patients with cancer.(16,78) Moreover, smoking as well as chronic pulmonary disease have been associated with worse outcomes in patients with lung cancer and COVID-19, and increased severity seen in smokers was also found in the lung-cancer specific TERA-VOLT study.(79)

### **Cancer Characteristics and Impact on COVID-19 Severity**

Impaired Eastern Cooperative Oncology Group (ECOG) performance status has been linked to higher morbidity and mortality among patients with cancer and COVID-19.(16,78) Several studies have reported that patients with lung cancer or hematological malignancies have worse outcomes than patients with other types of cancer.(3,16,77,80,81) This is likely due to the reduced respiratory capacity and more severe degrees of immunosuppression associated with these malignancies and their associated therapies. Among US Veterans with cancer and COVID-19, male genital cancer and thyroid cancer were also associated with higher mortality.(82) The literature on risks associated with other subtypes of cancer is still maturing. In addition to cancer type, cancer status is also important, as patients with advanced or progressive disease have been reported to have worse outcomes than patients in remission or that have stable disease.(3) Similarly, patients with recently diagnosed cancer have worse outcomes compared to patients with less recent (>6 months) diagnoses; this may be a surrogate for cancer therapy and/or therapy-related immunodeficiency.(1) For a discussion on risk related to specific anti-cancer therapies, please see the “COVID-19 and anti-cancer therapy” section below.



## Impact of Health Disparities

The COVID-19 pandemic has highlighted and exacerbated health disparities due to race and ethnicity.(83) Black and Hispanic patients with cancer are more likely to become infected with COVID-19 and to have severe disease than non-Hispanic White patients. (16,72,82) Early in the pandemic, Black patients with cancer were less likely to receive the experimental COVID-19 treatment remdesivir, likely due to differential access.(84) Furthermore, Black and Hispanic patients were less likely to use or have access to telehealth, and Hispanic patients were more likely to have pandemic-related delays in cancer care compared to White patients.(85) These disparities do not appear to have a biological basis but rather are symptoms of structural racism.(86–89)

## Post-acute sequelae of SARS-CoV-2 infection (PASC)

Similar to post-acute viral syndromes described in survivors of other coronavirus epidemics, there are increasing reports of long-term issues after recovery from acute COVID-19.(90–92) The PASC syndrome (colloquially, “long COVID”) is characterized by persistent and prolonged effects that extend beyond 4 weeks from the onset of symptoms; affected patients are sometimes referred to as “COVID long haulers”. While the pathophysiology has not been completely established, it is hypothesized that this long-term syndrome may be due a chronic inflammatory state, persistent viremia, and/or a general hypometabolic state. (93–95) Risk factors for PASC in the general population include older age, self-reported poor health status, and pre-existing comorbidities.(91,93) Based on these risk factors and pathophysiology, it is likely that patients with cancer will also have a higher risk of PASC. Although data in this field remain sparse, early evidence indicates that 15% of patients with cancer and COVID-19 have long term sequelae including respiratory symptoms and chronic fatigue, and that risk factors for PASC in patients with cancer include male sex, age of 65 years or older, 2 or more comorbidities, history of smoking, prior hospitalization for COVID-19, complicated disease, and prior COVID-19 therapy.(76,96) The impact of PASC on patients with cancer is an area of ongoing research and discovery.

Taken together, this section highlights the complexity of interacting factors which increase the risk of severity of COVID-19 in patients with cancer. Next, we will explore the added layer of anti-cancer therapies and their effects—both potentially negative and positive—on COVID-19.

## Anti-Cancer Therapies and COVID-19

The potential for exacerbation of COVID-19 severity from systemic anti-cancer therapy has remained a concern throughout the pandemic. This has stemmed from the fact that anti-cancer therapy could either suppress the host immune response (e.g., cytotoxic chemotherapy) or paradoxically exacerbate immune-mediated end organ damage (e.g., immunotherapy). Overall, the data linking COVID-19 severity to active oncologic treatment remains mixed. Elucidating the relationship between COVID-19 outcomes and specific systemic therapies remains challenging due to several factors: the heterogeneity of systemic therapy regimens, timing of therapy relative to COVID-19 exposure; and multiple patient-specific confounders. With a wide variety of single-agent and combinatorial regimens in use,

the number of patients receiving any given regimen who go on to develop COVID-19 is relatively small. This limits the analysis of specific treatments. Therefore, studies described below have largely focused on the effect of broad classes of systemic therapy with immunotherapy and cytotoxic chemotherapy as the two most studied examples. Additional targeted agents such as growth factor inhibitors, hormone modulators, or agents which exploit gene mutations have not been as thoroughly investigated.

### Immunotherapy

Efforts have focused on the impact of immune checkpoint inhibitors (ICIs) with anti-CTLA-4, PD-1 and PD-L1 as the most commonly prescribed and widely studied.<sup>(97)</sup> *A priori*, one could have speculated divergently: whether ICIs might actually be protective against symptomatic COVID-19 (with enhanced protective immunity or more rapid viral clearance), or whether they might exacerbate infection once it is established. Both of these hypotheses stem from their mechanism of action, which is to remove inhibitory signals from cytotoxic T-cells, thus enhancing T-cell function.<sup>(98)</sup> ICIs have been indeed associated with worse outcome in some studies,<sup>(99,100)</sup> but other studies have shown no effect on either COVID-19 severity or on the incidence of classical immune-related adverse events in patients who were infected.<sup>(82,101–105)</sup> A meta-analysis of sixteen studies has similarly shown no effect of recent ICI therapy on disease outcomes.<sup>(106)</sup> Another meta-analysis suggested a possible increased risk of hospitalization, but not attributing severe disease or mortality with ICI therapy.<sup>(97)</sup> These varying results may be explained by heterogeneity of the patient population included; ICIs are used in a broad array of cancers, some of which may have underlying predisposition to severe COVID-19, such as lung cancer.<sup>(2,79,101)</sup> In addition, many of the included studies have limited power due to the relatively low event rate of severe COVID-19 infection, which could miss a smaller but potentially clinically significant effect in certain patients. Amidst this data, no large study has demonstrated a protective effect for immunotherapy.

An additional complex subgroup are those patients with COVID-19 who experience immune-related adverse events as a result of immune checkpoint blockade. <sup>(107–109)</sup> These events may complicate the diagnosis of COVID-19 or could theoretically compound the effects of COVID-19 infection (e.g., T-cell mediated injury triggered by viral inflammation exacerbated by blockade of T-cell regulators). The interplay of these three conditions (pneumonitis, lung cancer, and COVID-19) and combined management strategy remains unknown and is an active area of study.<sup>(110)</sup>

### Cytotoxic chemotherapy

Cytotoxic chemotherapy has been implicated for increased risk of severe COVID-19, although the data supporting this suggestion is not universally conclusive. With intensely myelosuppressive regimens, there is a risk of impaired immune-mediated viral clearance leading to increased likelihood of severe consequences. Also, as with immunotherapy, there is a risk of chemotherapy-induced pneumonitis with certain agents (e.g., bleomycin, carmustine), compounding the risk of severe COVID-19 by reducing lung functional reserve. However, the evidence so far implicating chemotherapy as a class to increased COVID-19 severity remains mixed. The earliest study to report this was in the Chinese



case series by Zhang et al which reported a negative association between any recent anti-cancer therapy and outcome, but sample size of individual therapies, including chemotherapy were small.(111) Since then, there have been multiple studies showing that recent cytotoxic chemotherapy was detrimental.(16,79,100,105,112) Notably, in a large cohort study of risk factors for severe COVID among a general population, recent receipt of chemotherapy was identified as a predictor of severe COVID-19 and the risk increased with degree of myelosuppression.(113) Other studies have failed to find a difference in COVID-19 severity with chemotherapy use,(82,99,102,114) but it is unclear whether these studies were adequately powered. The OnCOVID study found that receipt of active anticancer therapy at the moment of COVID-19 diagnosis was associated with lower risk of complicated disease; however, type of systemic anticancer therapy, including cytotoxic chemotherapy was not associated with COVID-19 severity.(67) Although chemotherapy is the most common treatment modality for cancer management, several factors could explain the divergent results. Chemotherapy as a category is even more heterogeneous than immunotherapy, covering a wide range of cancers and producing varied degrees and duration of myelosuppression, and resulting functional impairment. Given this heterogeneity, conclusions may be particularly sensitive to the set of confounding variables adjusted for, which is inconsistent across studies. Moreover, severity of COVID-19 may be more sensitive to the timing of chemotherapy relative to SARS-CoV-2 exposure than immunotherapy, given the time-dependent nature of chemotherapy-induced myelosuppression (which is not consistently defined across studies). Thus, details of cycle length, numbers of cycles, intensity of regimen, and host responses to chemotherapy may abrogate a signal if one exists – unless specifically studied through appropriately powered subset analyses.

### **Hematologic malignancy-specific therapies**

A specific example concerning patients with hematologic malignancies in a subset analysis of CCC19 registry data has shown a concerning high mortality rate for patients receiving rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or DNA methyltransferase inhibitors (decitabine, azacitadine).(16) Possible confounders include host factors, as hematologic malignancies have been associated with a higher mortality rate in the pandemic.(81,112,115) In 318 allogeneic stem cell transplant recipients, primarily with underlying hematologic malignancies, development of COVID-19 within 12 months of transplantation was associated with a higher risk of mortality (compared to those without infection).(116) Data with regards to impact of CAR-T therapy in hematologic malignancies are limited. In a series of 57 patients treated with CAR-T therapy (the majority of whom had B-cell neoplasms in complete remission), the authors reported an unadjusted mortality rate of 41%; however, timing of CAR-T therapy did not impact degree of COVID-19 severity. (117)

### **Targeted anti-cancer therapies**

The impact of other therapies remains largely unknown. Interpretation of studies investigating non-chemo/immunotherapy agents grouped together, which alleviates the issue of small sample size, are complicated by the diverse mechanisms of action for these agents. There is very little data uncovering any effects of BRAF/MEK inhibitors, VEGF inhibitors,

EGFR inhibitors or anti-estrogen therapy use with COVID-19 severity. However, there are no obvious mechanistic concerns for disease exacerbation for most of these therapies.

### Localized anti-cancer therapies

With regards to localized or non-systemic treatment, available data suggests that postoperative mortality rates from SARS-CoV-2 infection are high. An international multicentric observational study of 1128 patients who had surgery during the first viral wave with confirmed SARS-CoV-2 infection within 7 days before or 30 days after surgery demonstrated that 30-day mortality was 24%. Of these, 80% of deaths were due to respiratory complications. In adjusted analyses, in addition to age and sex, cancer-related surgery was independently associated with increased 30-day mortality.(118) In a dedicated radiotherapy study of 350 patients who were infected with SARS-CoV-2 and who received radiation therapy at a single-center, 30-day mortality was 14%.(119) In a multivariate analysis, history of acute renal injury, shorter time between radiotherapy and COVID-19 diagnosis, and higher mean dose of radiation to the heart were associated with worse outcomes. This finding will require replication in a multi-institutional setting.

### Potential protective effect of certain anti-cancer therapies

Although the focus for anti-cancer directed systemic therapy has largely been on determining whether there is a detrimental effect, several therapies were hypothesized to play a preventative or ameliorative role. In particular, there were initial reports about a potentially beneficial effect from anti-androgen therapy against COVID-19 infection, (120,121) although subsequent studies have failed to reproduce this finding.(122–125) Some preliminary evidence suggested a potential benefit from the now rarely-used recombinant interferon in two (<80 patients) studies.(126,127) This finding has yet to be replicated in a larger setting. Furthermore, agents used for supportive care (e.g., steroids, tocilizumab) from cancer therapy toxicities may potentially mitigate COVID-19 severity, although any impact would depend on timing of administration relative to infection. A recent randomized controlled trial evaluating ruxolitinib in patients with severe COVID-19 did not meet its primary outcome.(128) A preclinical computational and in-vitro study identified nilotinib as a potential COVID-19 therapeutic.(129) However, overall, there is limited evidence that any systemic oncologic therapies are protective against COVID-19, although several phase 2 and 3 trials are ongoing (Table 1). In terms of potential locally-directed protective therapies, several studies are examining the therapeutic potential of low-dose radiotherapy for the treatment of patients for COVID-19.(130) A preprint version of a trial evaluated low-dose whole lung radiation therapy in 10 patients with COVID-19 who were hospitalized with matched controls. There was a trend for lower median time to clinical recovery as well as shorter hospital stay.(130) This approach remains to be validated as part of an ongoing randomized-controlled trial (ex: [NCT04466683](https://clinicaltrials.gov/ct2/show/study/NCT04466683)).

In the next section, we provide a synthesis of the current best practice evidence and advances in the treatment of COVID-19 in patients with cancer.

## Treatment of COVID-19 in Patients with Cancer

The optimal management and therapeutic approach to COVID-19 in patients with cancer has not been fully defined, in part due to their near systematic exclusion from prospective clinical trials.(131) Recommendations for the treatment of COVID-19 for patients with cancer have paralleled guidelines for the general population(132). Generally, guidelines for pharmacologic intervention have been dependent on the severity of symptoms requiring hospitalization, supplemental oxygen, noninvasive versus invasive ventilation, and intensive care unit (ICU) level care. A summary of treatments is provided in Figure 2.

### General Management for Non-Hospitalized Patients

For patients with mild symptoms not requiring hospitalization or supplemental oxygen, management relies on supportive care. Also, due to the increased risk of thrombosis in these patients (see “COVID-19 Presentation” section) and compounded in patients with active cancer, adequate mobilization is essential.(66,133–135)

Several neutralizing monoclonal antibodies have been developed and are under investigation for the treatment and prevention of COVID-19(136). The majority target the S (spike) protein limiting the ability of the virus to bind and fuse to the target host cell. Guidelines recommend the use of either casirivimab with imdevimab, or sotrovimab to treat non-hospitalized patients with mild/moderate COVID-19 who are at high risk of clinical progression, including patients with cancer on active treatment (<https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies>). While specific studies in patients with cancer are limited, a retrospective, single-center cohort of 38 patients with COVID-19 treated with bamlanivimab or casirivimab/imdevimab demonstrated that hospitalization and mortality rates due to COVID-19 were low compared to previously described rates among active patients with active cancer.(137) Currently, bamlanivimab plus etesevimab is not recommended given decreased activity against variants of concern, including the Delta variant, which has predominated globally. Additionally, while guideline panels recommend against the use of convalescent plasma to treat all stages of COVID-19, prospective studies conducted in patients with cancer specifically have been lacking. The CCC19 evaluated the utility of inpatient convalescent plasma administration in patients with hematologic cancer.(138) The observational study, which included 966 individuals, of whom 143 received convalescent plasma, demonstrated that convalescent plasma was associated with improved 30-day mortality. Prophylaxis of immunosuppressed patients with the oral antiviral molnupiravir (NCT04405739), ritonavir (NCT04960202) or repurposed medications such as fluvoxamine (NCT04405739), if confirmed effective in clinical trials, may be an alternative to monoclonal antibodies.(139)

### General Management for Hospitalized Patients

The approach for the treatment of COVID-19 in hospitalized patients with cancer is evolving, and most prospective trials have not studied cancer populations. Thus far, general clinical trial data support the use of remdesivir, dexamethasone, and tocilizumab or baricitinib (discovered during the pandemic using AI-guided in-silico experiments)(140),

with utilization dependent on the degree of respiratory support warranted. It is important to note that none of these trials evaluating these treatments reported the presence of cancer as a pre-existing condition (<https://www.covid19treatmentguidelines.nih.gov/management/clinical-1248management/hospitalized-adults--therapeutic-management/>) (141) (57) (142) (143) (144). Specific to tocilizumab, there have been reports of its successful use in patients with cancer, (145,146) however, concomitant immunotherapy poses a theoretical risk due to hyperactivation of the immune system causing cytokine storm(147).

Lastly, the COVID-19 pandemic has brought on a separate and dangerous pandemic related to the spread of false information.(148) Several theoretically promising agents with repeatedly negative studies have unfortunately had persistent support on some social media sites, despite the uniform lack of evidence of efficacy. A Cochrane meta-analysis of all randomized-controlled trials evaluating the use of chloroquine or hydroxychloroquine in the treatment of COVID-19 found that they were not effective in reducing COVID-19 mortality or severity.(149) In the same vein, there are no robust data to support the use of ivermectin, azithromycin, or vitamin C, or zinc in the treatment of patients with COVID-19.(150–153)

Given that prospective studies of COVID-19 directed therapies have been limited in patients with cancer, CCC19 investigated the association of hydroxychloroquine, azithromycin, remdesivir, high-dose corticosteroids, and tocilizumab on 30-day all-cause mortality in patients with invasive cancer and COVID-19.(84) In this observational study of 2186 patients, while there was no statistically significant difference in 30-day all-cause mortality with hydroxychloroquine alone, treatment with remdesivir indicated a potential benefit when compared to positive controls. Hydroxychloroquine in combination (most usually with azithromycin) and high-dose corticosteroids alone or in combination were associated with inferior outcomes in this population; further study is necessary to determine why corticosteroids were not associated with benefit in these patients with cancer.

### Anticoagulation

Venous thromboembolism (VTE) affects 1-8% of all patients with cancer receiving antineoplastic therapy and is the second most common cause of death in outpatients receiving chemotherapy.(154,155) A study of 2804 patients from CCC19 showed that 9.3% of hospitalized patients with cancer and COVID-19 had a VTE, which increased to 13.4% in 440 patients in the ICU. Apart from ICU admission, recent systemic therapy, active disease, and high-risk VTE cancer subtypes increased the risk of VTE in patients with cancer and COVID-19.(156,156) Prophylactic management recommendations for patients with cancer is hampered by under-representation in anticoagulation-based trials. Guidelines recommend low-molecular-weight heparin (LMWH) anticoagulation in outpatients with risk of VTE outweighing the risk of bleeding,(157,158) or in hospitalized patients with COVID-19. Consensus guidelines recommend initiating standard prophylactic dosing in all hospitalized patients who do not have contraindications for use(159,160). Treatment of acute thrombosis in the context of COVID-19 and cancer should follow those of guidelines (161–163)(164). IL-6 has a potent pro-thrombotic property. Therefore, concurrent use of anticoagulation and cytokine-reducing agents such as steroids and tocilizumab may cause dual blockade of IL-6 induced microvascular thrombosis pathway; however, this needs further investigation in

clinical trials.(165) The International Committee on Thrombosis and Haemostasis guidelines recommend extended post-discharge thromboprophylaxis for 2-6 weeks post-discharge in hospitalized patients who meet high VTE risk criteria, such as patients with active cancer. (159,164)

### **Palliative Care**

Studies have demonstrated that while early palliative care is an essential component of care coordination, it is underutilized in patients with cancer and COVID-19.(166) In a preliminary analysis by CCC19 on code status and utilization of palliative care, the majority (79%) of hospitalized patients were full code at the time of admission. Palliative care was involved in only 14% of cases and was associated with a 44% transition in code status to DNR+/- DNI (Do-not Resuscitate +/- Do-not intubate).(167) As patients with COVID-19 can deteriorate rapidly, it is crucial to establish advanced care directives(168) and identify a healthcare proxy early in disease management.(169) (166) Palliative care consultation in patients with cancer and COVID-19 has been shown to facilitate symptom control and improve discharge planning, and therefore should be initiated early-on.(170) Video communication has emerged as a practical, accessible, and acceptable method of communication in the palliative care setting, especially with different visitor restricting policies.(166)

In summary, there are many treatment options for COVID-19, but the data for the subgroup of patients with cancer is nearly completely lacking from prospective studies. Dedicated trials in this population, or at the very least more consistent reporting of cancer as a comorbidity in the major prospective RCTs, is needed to enable informed decision-making. Next, we turn to the prevention of COVID-19 through vaccination.

### **Safety and Efficacy of COVID-19 Vaccination in Patients with Cancer**

The development of highly efficacious COVID-19 vaccines within one year from the identification of SARS-CoV-2 is a remarkable feat of vaccine development.(171,172) The FDA-approved vaccines for COVID-19 have demonstrated safety and efficacy in the general population. Their use is credited to have prevented many COVID-19 deaths.(173,174) However, their efficacy and safety profiles were not established in patients with cancer since participants undergoing active anti-cancer therapy were excluded from the seminal vaccination trials.(175–178) Nevertheless, patients with cancer were prioritized for the COVID-19 vaccine rollout because of higher case fatality rates or the mortality risks among SARS-CoV-2-infected patients with cancer. At the time of this rollout, no data existed for optimal dosing or interactions between active oncologic treatments and the ability of vaccination to induce protective immunity against COVID-19 in patients with cancer.(179–181)

Since the initial FDA EUA for the COVID-19 vaccines in Fall 2020, the safety profile for patients with cancer appears similar to the general population.(182–194) A summary of available data regarding vaccination effectiveness and safety in patients with cancer is provided in Table 2.

### **Safety of COVID-19 vaccination in patients with cancer**

Safety data available from these studies comes with the caveat that rare adverse events are unlikely to be captured at the scale of these smaller studies, and long-term adverse events have not been observed, given the timeframe of the vaccine rollout. Regardless, the data is reassuring against substantially increased risk consistent with safety data from other vaccination trials.(195) Moreover, the mRNA vaccine platform was initially developed for checkpoint-inhibitor-treated melanoma and was previously shown to be safe among patients with cancer.(196)

### **Antibody response/seroconversion of COVID-19 vaccination in patients with cancer**

There is now accumulating evidence for vaccine effectiveness against COVID-19 in patients with cancer.(58,182,184–187,194,197–212) In most patients with cancer, mRNA vaccination leads to seroconversion after the second dose, although antibody titers achieved tend to be inferior to non-cancer controls.(185–187,198,200,207–210,212) There is also emerging evidence that COVID-19 vaccines differ in antigenicity, for example mRNA-1273 (Moderna, Inc.) can generate higher median antibody titers than BNT162b2 (Pfizer and BioNTech).(198,204,213) However, consistent with the observation that patients with hematologic malignancies mount limited immune responses to SARS-CoV-2 infection,(214) seroconversion following COVID-19 vaccination tends to be lower in this group.(190,197–200,215) Patients undergoing chemotherapy and anti-CD20 therapies show further reduction in seroconversion.(185,186,190,198,199,204,215,216)

### **T and B cell vaccine immunity, and neutralization antibodies in patients with cancer**

It is important to note that most studies so far have focused on post-vaccine antibody titers to the viral spike protein (seroconversion) as the assessment of vaccine immunogenicity. Correlates of protection against COVID-19 are not yet fully established but seroconversion is frequently being used as a convenient, measurable and acceptable surrogate of immune protection from symptomatic SARS-CoV-2 infection.(199,217–221) However, antibody titer is an imperfect proxy for overall protection without other aspects of the immune response such as T-cell response being measured.(59,222,223) Despite decline of specific IgG, long-lasting memory T-cells reactive to the nucleocapsid proteins of SARS-CoV-2 can be found up to 17 years after the 2003 outbreak of SARS, suggesting long-lasting and cross-reactive T-cell immunity to this family of coronaviruses.(224) Spike-reactive memory T-cells, but not B-cells or antibodies, can be found in many individuals even before SARS-CoV-2 exposure or vaccination.(225–229) CD4+ T-cells induce antibody response and maintain B-cell memory 6 months after SARS-CoV-2 infection.(225)

In a study of patients with active solid and hematologic malignancies, 1 dose of BNT162b2 yielded a poor T cell response, further strengthening the recommendation of early (day 21) second dose of BNT162b2 vaccination in patients with cancer.(182) In patients with solid cancers on active therapy, after vaccination with two doses of BNT162b2, a T-cell response was observed in most, including nearly half who mounted undetectable neutralizing antibody responses.(192) (192)In a separate study, 77% of patients with hematologic cancer had detectable SARS-CoV-2-specific T-cell responses after COVID-19.(59) In a study of 239 patients with hematologic malignancy, vaccination with two BNT162b2 inocula resulted



in only 53% of the patients achieving effective T cellular protection against COVID-19. (230)

Aside from T or B cell immunity, neutralizing antibodies (antibodies which bind to cell-free virus and prevent it from infecting cells) have also emerged as a helpful surrogate for vaccine effectiveness. In a study of nearly 600 patients with cancer, examining protection against SARS-CoV-2 variants of concern, patients with hematological malignancies were more likely to have undetectable neutralizing titers and had lower median titers than those with solid cancers against both variants and WT SARS-CoV-2. By comparison with individuals without cancer, patients with hematological, but not solid, malignancies had reduced neutralizing antibody responses.(58) Of note, patients with inherited agammaglobulinemia or rituximab-induced complete B-cell depletion have recovered from COVID-19 in the absence of neutralizing antibodies.(222,223) It can be assumed that CD8+ T-cells can compensate to some degree for deficient humoral immunity against SARS-CoV-2 infection in some patients.(192)

### **Risk factors for impaired vaccine response in patients with cancer**

From the serology studies, type of malignancy and treatment agents have emerged as two major risk factors for inadequate vaccination response.(231) Since preliminary studies have investigated small cohorts, data on the impact of specific malignancies or treatment regimens is limited. Patients with hematologic malignancies tend to mount inadequate vaccine response, congruent with evidence of decreased humoral response, exhausted T-cell phenotype and prolonged viral shedding after COVID-19.(60) Studies of mixed solid tumor and hematologic cohorts have also independently identified hematologic malignancy as a risk factor for lower efficiency to seroconvert.(182,215,216,232) The risk for inadequate antibody response to vaccination may in part be due to the specific therapies used to treat hematologic malignancies – for example, the B-cell depleting agent rituximab is known to be particularly immunosuppressive.(233) However, hematologic malignancy itself is likely to be an independent contributor in blunted vaccine effectiveness since antibody titers were lower in patients with chronic lymphocytic leukemia even in the absence of therapy. (187,234)

Data so far suggests that immunosuppressive therapies, such as cytotoxic chemotherapy, are a risk factor for reduced antibody response. Multiple studies have demonstrated that although antibody response is preserved in patients with solid malignancies on cytotoxic therapy, the antibody titers in these patients, on average, are reduced compared to age-matched controls.(216,235) Comparatively, ICI therapy and endocrine therapy do not appear to reduce immune response.(215) Importantly, patients on rituximab-based combinations seem to be at the most risk for a reduced response. In a prospective cohort of 131 patients with mixed solid and hematologic malignancy, none of the 4 patients on anti-CD20 therapy developed an antibody response, compared with 15 out of 16 patients on endocrine therapy.(215) A recent study of longitudinal anti-spike and anti-nucleoplasmid antibodies found that B-cell targeted therapies were associated with decreased peak and sustained antibody responses.(210) In patients with leukemia, lymphoma, and multiple myeloma patients, treatment with Bruton tyrosine kinase inhibitors, venetoclax, phosphoinositide 3-

kinase inhibitors, anti-CD19/CD20, and anti-CD38/B-cell maturation therapies all hindered vaccination responses.(198,204)

### **Breakthrough infections, booster doses, and remaining questions**

The above preliminary studies reveal immunologic patterns but do not fully guide how they translate to protection from infection. Immunocompromised patients make up a disproportionately higher (40-44%) proportion of vaccinated people hospitalized with breakthrough COVID-19 infections despite making up about 3% of the U.S. adult population.(236–238) Vaccinated patients with hematological malignancies, in particular those on treatment, have a higher risk of severe COVID-19 outcomes than comparable vaccinated healthy people.(208) This has prompted the CDC to recommend an additional dose of an mRNA COVID-19 vaccine in moderately to severely immunocompromised people (<https://www.cdc.gov/media/releases/2021/s0813-additional-mRNA-mrna-dose.html>), and this may be especially important for patients with hematologic malignancies.(202,239) A phase 1 study in patients with solid tumors on active chemotherapy, examined the role of a third immunization. At 1 week after a third immunization, 16 participants demonstrated a median threefold increase in neutralizing antibody responses, but no improvement was observed in T cell responses.(192) In a prospective The Leukemia & Lymphoma Society National Registry study (NCT04794387), 55% patients with B cell malignancies who failed to make anti-S antibodies after full SARS-CoV-2 vaccines seroconverted after booster vaccination, and the immunogenicity of booster vaccination did not appear to be affected by disease type, vaccine type, homologous or heterologous vaccination pairing, or malignancy-target therapies.(202)

Studies have not yet extensively assessed the duration of vaccination effectiveness against COVID-19 from vaccination in patients with cancer relative to the general population. In a nationwide study of patients with cancer in the US Veterans Health administration, real world effectiveness from vaccination against SARS-CoV-2 infection was investigated. (201) In this retrospective matched cohort study of 58,304 patients with cancer, against the primary outcome of laboratory-confirmed SARS-CoV-2 infection, overall 14-day post-second dose effectiveness, defined as 1 minus the risk ratio of SARS-CoV-2 infection for vaccinated individuals compared to unvaccinated controls, was 57% among the patients receiving chemotherapy versus 76% for those receiving endocrine therapy. Patients who had their last dose of systemic therapy at least 6 months prior to vaccination exhibited 85% vaccine effectiveness. In limited studies, patients with cancer or those receiving anti-CD20 treatment have been shown to be at higher risk of vaccine breakthrough infections compared to the general population.(199,238,240) A more recent claims-based Israeli study examining breakthrough infections reported on 113 patients with hematologic malignancy who experienced COVID-19 infection after vaccination, of whom 70% had severe COVID-19 infection. Despite this high rate of severe infection, COVID-19-related mortality was 13%, which appears to be lower compared to mortality rates of patients with hematologic malignancies reported pre-vaccination rollout.(241) Overall, however, data on protection from severe complications of COVID-19 remains limited and future work on larger cohorts will be needed. The ultimate test of effectiveness of vaccination is protection against symptomatic and severe COVID-19 for which data is still emerging.

Multiple questions on the future of vaccination for patients with cancer remain unanswered. It is unclear how effective current vaccines will remain against future SARS-CoV-2 variants, and what strategies will be most effective to protect a vulnerable patient population. Booster vaccinations recommendations are still evolving, and preliminary evidence suggests that booster vaccinations are safe,(242,243) and potentially effective against new variants.(244) A trial in adults with solid tumors showed that a third immunization with BNT162b2 boosted neutralizing antibody titers in most participants to protective level, but the improvements were fairly modest and circulating spike-specific T-cell frequencies did not change.(192) Data are lacking on how effective booster vaccinations will be in the heterogeneous cancer patient population, whether “mix-and-match” approaches with in-class and across-class vaccines are effective(245), and how booster vaccinations should be optimally timed with anticancer therapy. These questions remain important directions for future studies.

In the final sections of this review, we turn to the effects of COVID-19 on the whole population with or at risk of cancer, followed by a discussion of the methodologic challenges of studying COVID-19 in patients with cancer.

## The Impact of COVID-19 on Cancer Care Delivery

At the onset of the COVID-19 pandemic, inaccessible testing and protective personal equipment (PPE) shortages were widespread. Therefore, recommendations of adaptive care strategies (aimed at maintaining continuity and quality of cancer care while mitigating risk of infection transmission within the contingencies of the healthcare system) were made by expert panels,(246,247) and oncology societies.(248–251) This resulted in widespread temporary suspensions of essential cancer services such as screening, diagnostic procedures, and treatments.(4) The reorganization of cancer management had unintended consequences of significant decreases in cancer screening, cancer management visits, cancer surgeries, access to healthcare delivery, and cancer research.(252) Frequent determinants for disruptions in cancer care were provider- or systems-based due to reduction in service availability with impact on treatment, diagnosis, or general health service.(253) It is important to consider the patient perspective in the midst of all of these and other changes (Figure 3).

### Cancer Screening and Prevention

Due in part to the decreased capacity for non-COVID care and decrease in primary care visits, both primary and secondary prevention of cancer were negatively impacted.(252,254) In contrast to 2019, a cross-sectional study suggests that the diagnosis of cancer decreased by 46% overall in 2020. Examples range from a 25% drop in pancreatic cancer diagnoses to a 52% decrease for new breast cancer diagnoses, early in the pandemic.(255) Data from US central cancer registries will further inform this observation but will not be available until 2022 at the earliest, given the normal lag in registry reporting. During the pandemic, routine cancer screening rates have also declined. In the United Kingdom screening declined across all studied cohorts, most notably breast cancer screening by 90% and in colorectal cancer screening by 85%.(256) In the U.S. screenings for breast, colon, prostate, and lung

cancers in older adults were lower by 85%, 75%, 74%, and 56%, respectively,(257) and there were reduced cervical cancer screenings for women aged 21 to 65 years.(258) Studies tracking observed versus expected cancer cases(259) and modeling studies(7,260,261) suggest a significant reservoir of undiagnosed cancer due to pandemic-related decreases in screening. Compared to pre-pandemic figures, a UK-based population modeling study estimates increased mortality and avoidable deaths ranging from 4% to 17%, depending on tumor type, due to pandemic-related diagnostic delays.(7)

The impact of delayed diagnosis is disproportionately profound in vulnerable populations, which will result in widening disparities.(258) Researchers in Canada and Scotland reported on the negative impact of the pandemic on all cancer screening programs and identified older age and low neighborhood income as factors associated with diagnostic delays.(262,263) DeGross et al. further reported decreases in screening and recovery among women from underrepresented minority populations.(264) In another study, disparities seen at the onset of the pandemic remained persistent when screening resumed.(265)

### Cancer Therapy

Around the world, and even within locales, there has been variability in individual treatment decision-making in an attempt to maintain evidenced-based cancer care during the pandemic while ensuring patient safety. In addition to delays and cancellations of surgeries, modifications included the use of local or regional anesthesia in place of general anesthesia when feasible(266), change in surgical technique to decrease aerosol generation(267), and enhanced recovery protocols to decrease hospital stays(268). Within radiation therapy there are often multiple dose/fractionation regimens that can have clinical parity for a particular disease entity, allowing for the consideration of truncated treatment times.(269) In some cases a modality change was recommended; for example, consensus panels often eschewed surgical therapies in favor of radiation or chemoradiation.(246) Systemic regimens were altered with prolonged dosing intervals,(270) intravenous regimens being replaced by oral or subcutaneous agents(271) or the type of systemic therapy was chosen to decrease the likelihood of hematologic toxicity.(272) In an example of an extreme modification, stem cell transplants in hematologic malignancies were replaced with radiotherapy.(266) In the OnCOVID registry, among 466 patients who had recovered from COVID-19 who were on systemic anti-cancer therapy, 15% permanently discontinued therapy, and 38% resumed treatment with a dose or regimen adjustment; permanent treatment discontinuation was independently associated with an increased risk of death, while dose or regimen adjustments were not associated with worse outcome.(76)

For patients with cancer, a delay in surgery has the potential to increase the likelihood of advanced disease and decreased survival.(7) Data from an observational modeling study examining the effect of COVID-19 on surgery delays and outcomes showed that delays by 3 to 6 months reduced life-years gained by surgery by 19% and 43% respectively.(273) Another study reported a 6-8% increase in the risk of death for every four-week delay across surgical, systemic therapy, and radiotherapy indications for seven analyzed cancers.(274) A large international prospective study of over 20,000 people awaiting surgery found that 10% of patients did not receive surgery for a COVID-19-related reason, with moderate and

full lockdowns being associated with non-operation.(275) The aggregate effects of these alterations to standard of care therapy will be the subject of ongoing study for several years and may lead to insights to guide practice in future pandemics. Early estimates of the 1-year impact of reduced supply and demand of cancer services by 40% resulted in 78% excess deaths in survivors of cancer.(275)

### Telehealth

Driven by the need to preserve PPE, minimize physical contact within healthcare facilities, and reduce potential exposure to infection, COVID-19 has propelled the use of telemedicine. There have been mixed reactions among patients to the telehealth experience, with an appreciation for the accessibility, ease, and convenience that it allows, against the challenges of available access to internet/technology.(276,277)

The increased use of virtual consultation ushers in a new set of concerns including maintenance of cybersecurity, confidentiality, delivery of medications, and documentation. (278) The pivot to telemedicine(279) highlights challenges mediated by sociodemographic factors(280) potentially deepening the divide for disadvantaged and marginalized groups. In particular, despite increased telehealth visits during the pandemic, Black and Hispanic patients were less likely to have an increase in telehealth utilization.(85) In addition to changes in direct patient contact, videoconferencing has been adopted by many centers for multidisciplinary tumor boards. This has the advantage of improved ease of attendance for participants, but with mixed results in regard to efficiency because of potential audiovisual sharing difficulties and delays in supporting information like pathology slides and imaging. (4,281) The rapid and successful deployment of virtual medicine has transformed cancer care and will likely become a permanent aspect of its delivery, although this outcome is highly dependent on regulatory decisions.

### Access to Care, Social Isolation, and Rationing

Additional effects of the pandemic have been omnipresent and have affected all patients with cancer. These include the barriers of accessing in-person and telemedicine care during provider shortages and re-assignments, cancellation of procedures due to healthcare system capacity issues, social isolation due to visitor limitations at healthcare facilities, and general avoidance of social outings. Preliminary research suggests that the “fear of COVID” is common in patients with cancer and can lead to debilitating anxiety.(282) In a study of 1000 patients with cancer carried out during the early and late pandemic, fear of COVID-19 was linked to psychological distress and persisted throughout the pandemic among under-resourced patients with cancer. The authors concluded that timely psychosocial support is critical to meet increased care needs experienced by patients with cancer during the COVID-19 pandemic. Early on in the pandemic, in exceptional circumstances, certain patients with cancer were not being offered potentially life-saving therapies such as ECMO or intubation.(96)

## Statistical and Research Design Considerations

Underlying all aspects of COVID-19 research—from disease characterization to potential treatment and vaccination evaluation to appropriate public health communication—is data generation. The abundance of data on COVID-19 has been very valuable. However, when muddled or inaccurate, data can be detrimental. Because of the urgency to answer public health questions amid a dearth of randomized trial data early in the pandemic, real-world data (RWD) have emerged as useful tools to understand and contextualize emerging situations. This provides an opportunity to rapidly characterize natural history including disease progression and risk factors, examine health equity, and evaluate treatments.

The rapid rise in use of RWD applied to COVID-19 is accompanied by the inherent challenges to the use of observational data that vary in their purpose, type, completeness, and granularity. Data quality is a salient—if not the greatest—challenge in the use of RWD for generating inference. Measures of data quality can include plausibility, reliability, conformance, completeness, accuracy, and reliability. Assessment of whether a dataset is fit to answer a research question requires a high level of data familiarity. Furthermore, transparency and reproducibility in methods is integral to interpretation (<https://www.strobe-statement.org/>). (283,284)

Observational studies are subject to the potential for inherent confounding and bias in the absence of randomization, including selection bias, measured and unmeasured confounding, residual confounding, and collider bias. For example, collider bias can infer associations between two or more variables which affect the likelihood of an individual being sampled, misrepresenting the true associations between these variables in the sample. (285) In COVID-19 research designs, confounding by indication (e.g., evaluating ACE inhibitor and angiotensin receptor blocker treatment effects on COVID-19) and confounding by severity (e.g., differential nature of underlying comorbidities or more severe disease) are particularly relevant. Moreover, temporal and geographic biases can arise from the spatiotemporal patterns in the pandemic, public health mitigation strategies (i.e., masking), available treatments and authorizations, testing, as well as vaccine uptake. These time and geographical-varying aspects have created measurement challenges in data capture—for example inaccurate estimates of vaccine exposure or severity outcomes which could lead to the potential for information bias, where the exposure may be misclassified due to incomplete capture.

Consistent definitions for data elements and outcomes, such as the ordinal WHO clinical progression scale, (286) could better facilitate replication and synthesis of results across studies and populations. While advanced statistical methods are available that attempt to generate causal inference from observational data, these methods require additional, sometimes untestable, assumptions that must be considered in each individual context.” (287) At minimum, selection of appropriate comparators for both positive and negative controls are essential. (288) Because the total eligible population for a convenience sample is not easily estimable, the definition of a denominator remains elusive meaning that population inferences are challenging. For example, a commonly reported statistic is the percentage of inpatients with SARS-CoV-2 infection or that are vaccinated versus



unvaccinated. However, the more logical statistic for public health communication to explain risk perception would be the percentage of vaccinated people that are hospitalized. This illustrates a more general problem that is widespread in an incomplete data ecosystem. Because of these intricate methodological considerations, RWD design and analysis requires a collaborative, multidisciplinary approach to ensure appropriate data selection and analysis to provide the best possible evidence for patient and clinician decision-making. Attention to data quality assessment, protocol development, and *a priori* statistical analysis plans are necessary.(289) RWD can contribute meaningfully to rapid categorization and understanding of broader patient populations than those included in trials, which is particularly important in evaluating COVID-19 treatment and vaccination effectiveness in patients with cancer. While randomized controlled trials remain the gold standard, efforts during the COVID-19 pandemic have demonstrated the potential opportunity for registry-based studies, observational cohort studies, and pragmatic trials to improve care delivery and clinical research to provide for more inclusive improvement of patient health outcomes.(290)

In addition to challenges related to RWD during this health crisis, several ethical concerns related to informed consent for participation in research have been highlighted. While many institutions have adopted innovative methods such as e-consent, implementation has not always been seamless due to lack of personnel and infrastructure (especially in underserved communities), user-friendly interfaces, and availability of translators for non-English language speaking individuals.(291,292) These hurdles have highlighted the need to improve technology and accessibility for e-consent, assure presence of translators, and to simplify the e-consent process by reducing the lengths or number of forms required.(293)

## Conclusion

This landscape analysis provides the reader with the current state of knowledge along with many of the challenges faced in determining evidence for patients with COVID-19 and cancer. Overall, our collective understanding is remarkably advanced less than two years into a generational pandemic, but many gaps and unanswered questions remain. In comparison to the early years of the last generational pandemic (HIV/AIDS), the number of basic, translational, and clinical researchers tackling COVID-19 has been nothing short of remarkable. Many of these researchers pivoted from pre-existing programs, and the effects on their unrelated cancer and infectious diseases research remain to be determined. International grassroots efforts have been catalyzed by social media in a way that would have been unimaginable before the internet.(290,294,295) The next chapter of the pandemic is yet to be written, but it is clear that much remains to be learned so that the direct and indirect effects of the pandemic on patients with cancer are mitigated to the fullest extent possible.

## Funding

National Cancer Institute grant P30 CA068485 to Alicia Beeghly-Fadiel, Benjamin French, Sanjay Mishra & Jeremy L. Warner

### Conflict of Interest Disclosures

Dr. Elkrief reports salary support from Canadian Institute of Health Research, the Royal College of Physicians and Surgeons of Canada (Detweiler Travelling Fellowship), and the Henry R. Shibata Fellowship outside the submitted work.

Dr. Jhavar declares grant from Varian Medical Systems; outside the submitted work.

Dr. Johnson declares Advisory boards/consulting for BMS, Catalyst, Jansen, Iovance, Merck, Mosaic ImmunoEngineering, Oncosec, Pfizer, Targovax, and research funding from BMS and Incyte.

Dr. McKay received research funding from Bayer, Pfizer, Tempus; serves on Advisory Board for AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Merck, Novartis, Pfizer, Sanofi, Tempus; is a consultant for Dendreon, Myovant, Sorrento Therapeutics, Vividion; serves on the molecular tumor board at Caris.

Dr. Vinh declares salary support through the clinician-scientist scholar Junior 2 program from *Fonds de la recherche en santé du Québec* (FRQS); Grants or contracts from Canadian Institutes of Health Research, COVID Immunity Task Force, Jeffrey Modell Foundation to his institution; Consulting fees from Qu Biologics, UCB Biosciences GmbH; Payment or honoraria from CSL Behring, Merck Canada, Novartis Canada, Shire; Support for attending meetings and/or travel from CSL Behring; Patents pending (PCT/US2021/042875; United States Provisional Application No. 63/280,983); Leadership or fiduciary role as Chair of AMMI Canada Guidelines committee; member of Clinical Immunology Society Education Committee; ass outside the submitted work.

Dr. Mishra reports support from National Cancer Institute (P30 CA068485), and the International Association for the Study of Lung Cancer to his institution) during the conduct of the study; personal fees from National Geographic for writing articles outside the submitted work.

Dr. Warner reports grants from NIH and the International Association for Study of Lung Cancer during the conduct of the study; grants from AACR; personal fees from Westat, Melax Tech, Flatiron Health, and Roche; equity in [HemOnc.org](https://www.hemonc.org) LLC, outside the submitted work.

Drs. Beeghly-Fadiel, Enriquez, French, Glover, Jani, Reuben, Rivera, Surbhi Shah, Mansi Shah, Shaikh, Wu; and Stacey Tinianov has nothing to disclose.

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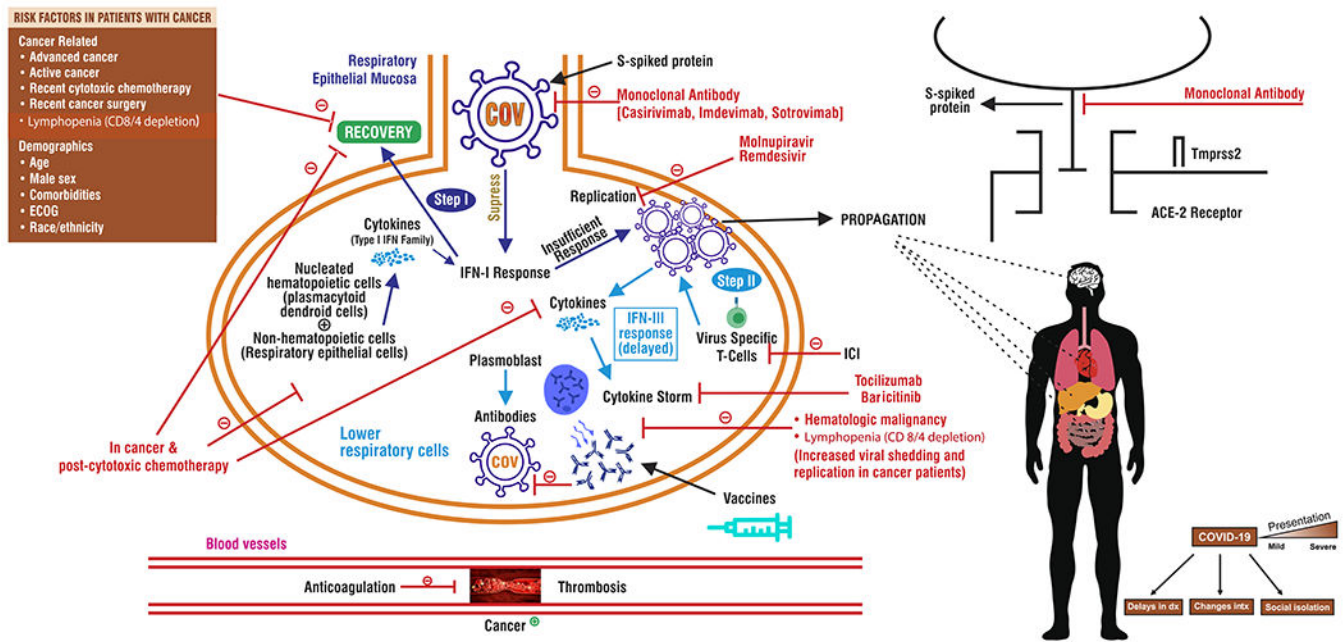


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**Statement of Significance:**

Patients with cancer have faced severe consequences at every stage of the cancer journey due to the COVID-19 pandemic. This comprehensive review offers a landscape analysis of the current state of the field regarding COVID-19 and cancer. We cover the immune response, risk factors for severe disease, and implications for vaccination in patients with cancer, as well as the impact of the COVID-19 pandemic on cancer care delivery. Overall, this review provides an in-depth summary of the key issues facing patients with cancer during this unprecedented health crisis.



**Figure 1: Biological framework for understanding the immune response to COVID-19 in patients with cancer.**

Step 1: Infection of the upper respiratory tract's epithelial cells

Step 2: Viral replication occurs in the lower airways and alveoli

ACE-2: Angiotensin Converting Enzyme

S-protein: Spike protein

COV: SARS-CoV-2




ECOG: Eastern Cooperative Oncology Group

ICI: Immune Checkpoint Inhibitor

IFN-I: Type-I Interferon response

IFN-II: Type-II Interferon response

VTE: Venous Thromboembolism

Guidelines for COVID-19 treatment	Anticoagulation
 <p><b>Outpatient</b></p> <ul style="list-style-type: none"> <li>• <b>Supportive and symptomatic care:</b> <ul style="list-style-type: none"> <li>• Adequate hydration</li> <li>• Antipyretics</li> <li>• Analgesics</li> <li>• <b>Cough:</b> breathing exercises, self-proning, cough suppressants (dextromethorphan or benzoate)</li> </ul> </li> <li>• <b>Neutralizing monoclonal antibodies</b> (casirivimab plus imdevimab or sotrovimab)</li> <li>• <b>Future therapies:</b> molnupriavir</li> </ul>	<ul style="list-style-type: none"> <li>• Adequate mobilization</li> <li>• LMWH anticoagulation in patients with risk of VTE outweighing risk of bleeding</li> </ul>
 <p><b>In-patient</b></p> <ul style="list-style-type: none"> <li>• <b>Dexamethasone:</b> Should be used only in hospitalized patients requiring oxygen.</li> <li>• <b>Remdesivir:</b> Patients in the early stage of disease requiring oxygen and not having any contraindications to its use.</li> <li>• <b>Severe disease/ critically ill patients:</b> Can consider adding Tocilizumab or Baricitinib</li> <li>• <b>Palliative care:</b> <ul style="list-style-type: none"> <li>• Pain management</li> <li>• Goals of care discussion</li> <li>• Management of cancer and cancer therapy related complications</li> <li>• Breathlessness: Opioid management</li> <li>• Anxiety and agitation: Benzodiazepines</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Prophylaxis:</b> <ul style="list-style-type: none"> <li>• UH 5000 units bid or tid or LMWH 40 mg q24h</li> <li>• Therapeutic dosing ** (LMWH 1 mg/kg q12h)</li> </ul> </li> <li>• <b>Treatment:</b> <ul style="list-style-type: none"> <li>• LMWH 1 mg/kg q12 h</li> <li>• DOAC</li> <li>• Warfarin</li> </ul> </li> </ul>
 <p><b>Post-Discharge</b></p> <ul style="list-style-type: none"> <li>• No current treatment guidelines.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Post-discharge thromboprophylaxis:</b> For 2-6 weeks post discharge in patients who meet high risk VTE criteria like cancer patients (ISTH).</li> </ul>

**Figure 2: Summary of evidence for COVID-19 treatment in patients with cancer.**

This is a synthesis of much of the available evidence but should not be taken as a guideline or endorsement of a particular clinical strategy. CDC: Center for Disease Control and prevention, WHO: World Health Organization, NICE: National Institute for Health and Care Excellence. ISTH: International Society on Thrombosis and Haemostasis. VTE: Venous thromboembolism. LMWH: Low molecular weight heparin. UH: Unfractionated heparin. DOAC: Direct oral anticoagulant.

**Box 1. Perspectives from a cancer survivor and patient advocate.**

Much of the published COVID19 and cancer research has focused on clinical risks, appropriate treatments, and poor outcomes at the intersection of a SARS-CoV-2 infection and cancer. But, for those with a diagnosis or history of cancer, the impacts of the COVID19 pandemic have had a cascade of effects well beyond the co-morbidity of a cancer diagnosis. These impacts have been felt in different ways, and to different degrees, depending on a myriad of cancer-related characteristics as well as social/environmental factors.

**Active Treatment & the Newly Diagnosed**

Cancer therapies are never a walk in the park but, for many, these activities were previously endured with the physical and emotional support of care partners, family and friends. Pandemic restrictions intended to protect the vulnerable cancer population further isolated individuals in a time of great need. For newbies, there is a rich community of support, but the pandemic quashed much of the connection opportunities. The newly diagnosed are usually educated to bring a second set of eyes and ears to visits yet, in many instances, only the patient was allowed in the room. Second opinions and oncology check-ins moved to televisits, and clinical trials slowed recruitment or halted altogether. In many places support groups, a sacrosanct space for many during and following treatment, stopped meeting in person. Treatment and recovery became a solo, or at least socially distanced, sport. And, for those with a technology barrier too steep to overcome, the isolation was deafening. For those with progressing metastatic disease, and a mandate of living while dying, bucket list modifications were devastating.

**Previvors & Cancer Survivors**

For previvors, especially for those with a germline mutation, delays in routine screening became a major issue clinically as well as psychologically. For those with a history of malignancy, “cancer” became a key comorbidity, yet individuals were left to untangle what exactly put them at risk. Did a history of cancer, a history of cytotoxic treatments, or perhaps late and long-term effects of treatment put them at additional risk? Would exposure to SARS-CoV-2 awaken dormant cancer cells in those who had been enjoying a long dance with NED? These questions remain in urgent need of answers so that individuals can better understand their risk profile.

**Silver Linings & Takeaways**

To be clear, there is no ‘upside’ to the death of over 5 million individuals to an infectious disease. That said, we witnessed swift changes in healthcare that show promise in right-sizing cancer care moving forward. Beyond collectively limiting mis- and dis-information rampant with respect to COVID19, we should consider what to maintain from the pandemic reality. Telehealth should remain an available option. Clinical trials that had originally paused now follow a decentralized model making trials easier to access addresses issues for both the patient and research communities. In the patient and advocacy community, true silver linings appeared in the form of gratis registration to oncology conferences and the proliferation of open access webinars with clinical and research leaders. To look at COVID-19 impacts on any community without addressing the combined impact of politics, economy, racial upheaval would be to perpetuate the existing misstep of looking at healthcare and cancer care as isolated entities. It was a hard year for all of us. By the same token, to continue to meet the needs of population health and those with a diagnosis or history of cancer, we must look beyond the boundaries of what is commonly considered healthcare toward a collaborative and systems-based approach.

**Figure 3:**  
Perspectives from a cancer survivor and patient advocate.

**Table 1.**

Systemic anticancer therapies undergoing prospective evaluation in the treatment of COVID-19. 58 of 1243 (5%) ongoing phase 2 or 3 trials registered on [ClinicalTrials.gov](https://clinicaltrials.gov), as of November 23, 2021, utilize one or more drugs with known anti-cancer effects, many of which have FDA cancer-specific indications. Corticosteroids (dexamethasone, prednisone, etc.) are not included in this list, nor are tofacitinib/baricitinib, which are Janus kinase inhibitors but do not have known anti-cancer activity. Drugs listed only by code name on [ClinicalTrials.gov](https://clinicaltrials.gov) were also not further evaluated for inclusion in this table.

Drug	Drug class	Cancer indication <sup>1</sup>	Clinical trials
Acalabrutinib	BTK inhibitor	CLL/SLL; Mantle cell lymphoma	Phase 3: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04647669">NCT04647669</a>
ATRA	Retinoid	Acute promyelocytic leukemia	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04568096">NCT04568096</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT05077813">NCT05077813</a>
BCG	Non-specific immunotherapy	Bladder cancer	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT02081326">NCT02081326</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04659941">NCT04659941</a> Phase 3: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04327206">NCT04327206</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04328441">NCT04328441</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04350931">NCT04350931</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04379336">NCT04379336</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04384549">NCT04384549</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04461379">NCT04461379</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04475302">NCT04475302</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04542330">NCT04542330</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04648800">NCT04648800</a>
Bevacizumab	Anti-VEGF antibody	Breast cancer; Cervical cancer; Colorectal cancer; Glioblastoma; HCC; NSCLC; Ovarian cancer; RCC	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04344782">NCT04344782</a>
Dasatinib	TKI	CML; Ph+ ALL	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04830735">NCT04830735</a>
Decitabine	Hypomethylating agent	CMML; MDS	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04482621">NCT04482621</a>
Duvelisib	PI3K inhibitor	CLL/SLL; Follicular lymphoma	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04372602">NCT04372602</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04487886">NCT04487886</a>
Enzalutamide	ARI	Prostate cancer	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04456049">NCT04456049</a>
Etoposide	Topoisomerase inhibitor	Testicular cancer; SCLC	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04356690">NCT04356690</a>
Ibrutinib	BTK inhibitor	CLL/SLL; Mantle cell lymphoma; Marginal zone lymphoma, Waldenström macroglobulinemia	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04439006">NCT04439006</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04665115">NCT04665115</a>
Imatinib	TKI	CML; DFSP; GIST; MDS; Ph+ ALL; Systemic mastocytosis	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04346147">NCT04346147</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04794088">NCT04794088</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04953052">NCT04953052</a> Phase 3: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04394416">NCT04394416</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04422678">NCT04422678</a>
Interferon <sup>2</sup>	Non-specific immunotherapy	CML; Follicular lymphoma; Hairy cell leukemia; Kaposi sarcoma; Melanoma	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04379518">NCT04379518</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04988217">NCT04988217</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04480138">NCT04480138</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04356495">NCT04356495</a> Phase 3: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04534725">NCT04534725</a>
Isotretinoin	Retinoid	None <sup>3</sup>	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04730895">NCT04730895</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04577378">NCT04577378</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04578236">NCT04578236</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT05077813">NCT05077813</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04389580">NCT04389580</a> Phase 3: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04353180">NCT04353180</a>
Masitinib	TKI	None <sup>4</sup>	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT05047783">NCT05047783</a>
Melphalan	Alkylating agent	Multiple myeloma; Ovarian cancer	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04380376">NCT04380376</a>
Methotrexate	Antimetabolite	ALL; Breast cancer; GTD; Head & neck cancer; Meningeal leukemia; Mycosis fungoides; NHL; NSCLC; Osteosarcoma; SCLC	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04352465">NCT04352465</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04610567">NCT04610567</a>
Nintedanib	TKI	None <sup>4</sup>	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04338802">NCT04338802</a> Phase 3: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04541680">NCT04541680</a>
Nivolumab	Anti-PD-1 antibody	Bladder cancer; Colorectal cancer; Esophageal cancer; Gastric cancer; Head & neck	Phase 2: <a href="https://clinicaltrials.gov/ct2/show/study/NCT04343144">NCT04343144</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04356508">NCT04356508</a> , <a href="https://clinicaltrials.gov/ct2/show/study/NCT04413838">NCT04413838</a>



Drug	Drug class	Cancer indication <sup>1</sup>	Clinical trials
		cancer; HCC; Hodgkin lymphoma; Melanoma; Mesothelioma; NSCLC; RCC	
Pembrolizumab	Anti-PD-1 antibody	Bladder cancer; Cervical cancer; Colorectal cancer; Cutaneous SCC; Endometrial cancer; Esophageal cancer; Gastric cancer; Head & neck cancer; HCC; Hodgkin lymphoma; Melanoma; Merkel cell carcinoma; MSI-H or dMMR solid tumors; NSCLC; PMBCL; RCC; TMB-H solid tumors; TNBC	Phase 2: <a href="#">NCT04335305</a>
Ruxolitinib	JAK inhibitor	Myelofibrosis; Polycythemia vera	Phase 2: <a href="#">NCT04581954</a> , <a href="#">NCT04348695</a> , <a href="#">NCT04403243</a> , <a href="#">NCT04414098</a> Phase 3: <a href="#">NCT04424056</a>
Selinexor	XPO1 inhibitor	DLBCL; Multiple myeloma	Phase 3: <a href="#">NCT04534725</a>
Sirolimus	mTOR inhibitor	None <sup>3</sup>	Phase 2: <a href="#">NCT04341675</a> , <a href="#">NCT04461340</a>
Tamoxifen	SERM	Breast cancer	Phase 2: <a href="#">NCT04389580</a> , <a href="#">NCT04568096</a>
Thalidomide	Immunomodulator (IMiD)	Multiple myeloma	Phase 2: <a href="#">NCT04273529</a> , <a href="#">NCT04273581</a>
Uproleselan	E-selectin antagonist	None <sup>4</sup>	Phase 2: <a href="#">NCT05057221</a>

<sup>1</sup>US Food and Drug Administration approved indication. Many of these drugs have additional off-label uses, which are not reported here

<sup>2</sup>Includes alpha interferons, but not beta or lambda interferons, which do not have an established role in anti-cancer treatment

<sup>3</sup>No FDA-approved cancer indication; used off-label for some cancer conditions

<sup>4</sup>Not yet FDA-approved for any indication; has preliminary data or non-FDA approval for some cancer conditions

**Acronyms:** ALL: acute lymphoblastic leukemia; ARI: androgen receptor inhibitor; ATRA: all-trans retinoic acid; BCG: Bacillus Calmette-Guérin; BTK: Bruton tyrosine kinase; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; CMML: chronic myelomonocytic leukemia; DFSP: dermatofibrosarcoma protuberans; DLBC: diffuse large B-cell lymphoma; dMMR: mismatch repair deficient; GIST: gastrointestinal stromal tumor; GTD: gestational trophoblastic disease; HCC: hepatocellular carcinoma; JAK: Janus kinase; MDS: myelodysplastic syndrome; MSI-H: microsatellite instability-high; mTOR: mammalian target of rapamycin; NHL: non-Hodgkin lymphoma; NSCLC: non-small cell lung cancer; PD-1: programmed death receptor-1; Ph+ ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; PI3K: phosphoinositide 3-kinase; PMBCL: primary mediastinal B-cell lymphoma; RCC: renal cell carcinoma; SCC: squamous cell carcinoma; SCLC: small cell lung cancer; SERM: selective estrogen receptor modulator; SLL: small lymphocytic lymphoma; TKI: tyrosine kinase inhibitor; TMB-H: tumor mutational burden-high; TNBC: triple-negative breast cancer; VEGF: vascular endothelial growth factor; XPO1: exportin 1



Table 2:

Summary of safety and efficacy vaccination studies in patients with cancer

Cohort	n	Median age years (IQR)	Vaccine studied	Safety	Efficacy	Reference
Single center (London); solid cancers, 88.5% receiving anti-cancer therapy (36.2% parenteral chemotherapy and 15.3% immunotherapy)	373	56 (19–65)	First dose of Pfizer, BioNTech, Oxford, AstraZeneca, Moderna	mild reactogenicity (sore arm, tiredness, and headaches); No grade 4/5 or anaphylaxis	Not reported	(191)
Three London hospitals; solid cancer, hematological cancer	151	73.0 (64.5–79.5)	One and two doses of BNT162b2	fewer adverse symptoms reported compared with healthy controls; No differences between patients with hematological cancer and those with solid cancer.	38% seroconversion in solid cancer & 18% in hematological cancer after one dose; second dose significantly increased seroconversion in solid cancer within 2 weeks at day 21 after the first dose; better overall T-cell response than antibody response	(182)
Single center (Israel) cancer treated with immune checkpoint inhibitors alone or in combination with chemotherapy	170	72 (29–93)	BNT162b2	Same as healthy controls but patients with cancer had more common muscle pain, none required hospitalization, similar side-effects in treatment groups.	Not reported	(183)
Single center (New York City)	200	67 (27–90)	Two doses of the mRNA vaccines (BNT162b2 or mRNA-1273) or one dose of the adenoviral vaccine (AD26.COV2.S)	no adverse effects overall	Seroconversion; significantly lower rate in hematologic malignancies, particularly following immunosuppressive therapies (anti-CD20 therapies, stem cell transplantation)	(215)
The Leukemia & Lymphoma Society National Registry; B-cell-derived hematologic malignancies	1,445	68 (16–110 years)	Two doses of mRNA vaccines (mRNA-1273 or BNT162b2)	Not reported	Seroconversion; 75% of all patients with hematologic malignancies produced antibodies	(197)
The Leukemia & Lymphoma Society National Registry; B-cell-derived hematologic malignancies	49	66 (31–80)	Heterologous and homologous booster of the mRNA vaccines (BNT162b2 or mRNA-1273) or adenoviral vaccine (AD26.COV2.S)	Not reported	Seroconversion; 55% patients with B-cell malignancies who failed to make anti-S antibodies after full SARS-CoV-2 vaccines seroconverted after booster vaccination	(202)
The Leukemia & Lymphoma Society National Registry	3,574	Not given	At least one dose: COVOD-19 vaccine (BNT162b2 or mRNA-1273, AD26.COV2.S, AZD)	13% reported no adverse events; distribution similar compared to age-matched healthy individuals	Not reported	<a href="https://www.ils.org/news/covid-19-vaccine-safety-among-blood-cancer-patients">https://www.ils.org/news/covid-19-vaccine-safety-among-blood-cancer-patients</a>

Cohort	n	Median age years (IQR)	Vaccine studied	Safety	Efficacy	Reference
One site (Pittsburgh); hematologic malignancies	67	70 (62.5 – 73.5)	two doses of either the mRNA-1273 (Moderna) or the BNT162b2 (Pfizer) vaccine	Not reported	Seroconversion; 46% did not produce antibodies and were vaccine non-responders.	(296)
Two sites (San Antonio, Geneva) solid and hematological malignancies.	140	63 (55–69)	two doses of mRNA vaccines (mRNA-1273 and BNT162b2)	Not reported	Seroconversion; 94% seroconverted after two vaccine doses, significantly lower seroconversion rates and antibody titers in patients with hematological malignancy than with solid tumors. Patients anti-CD20 treatment 6 months prior did not develop antibodies.	(216)
Single center (Italy); multiple myeloma, myeloproliferative malignancies on active treatment	92	70 (28–80) for MPM; 73 (47–78) for MM	Two doses of BNT162b2	no serious adverse event	Seroconversion; lower titers in MPM and MM patients; particularly those on anti-CD38-based treatment	(205)
single center (Israel); solid tumors undergoing active treatment	102	66 (56-72)	Two dose of mRNA vaccine (BNT162b2)	Not reported	Seroconversion; 90% were seropositive after the second vaccine dose; lower titers in patients with cancer, affected by chemotherapy plus immunotherapy	(235)
Single center (France); solid tumors; under treatment or within 6 months after treatment	13	17 (16-21)	BNT162b2 mRNA vaccine	Well tolerated; mild pain at the site of injection and fatigue were most frequent systemic symptoms	Seroconversion; 7 of 10 patients developed antibodies before second vaccine dose, and 9 of 10 patients developed antibodies one month after the second injection.	(203)
2 independent cohorts of hematological and solid tumors on active therapy (8.6% were previously infected)	595	67 (19-96)	BNT162b2, mRNA-1273, or AZD1222 COVID-19 vaccines	Not reported	Seroconversion; improved titers after second dose; lower levels in patients on treatment with B-cell-targeting agents	(200)
multicenter (US Veterans Health administration); solid or hematologic malignancy	58,304#	Not available	Any COVID-19 vaccine	Not reported	Laboratory confirmed SARS-CoV-2 infection; 57% for chemotherapy within three months prior to first vaccination dose; 76% for endocrine therapy and 85% for those off systemic therapy for at least six months prior.	(201)
lymphoplasmacytic Single patient case study; lymphoma	1*	59	Two doses of the BNT162b2 mRNA vaccine; 1 dose of INJ-78436735	mild malaise and headache	Seroconversion; No detectable antibodies after 2 doses of BNT162b2; low but detectable antibodies after heterologous booster	(243)
Single center; solid tumors on treatment	53	63.7	two and three doses of the BNT162b2 mRNA vaccine	Not reported	Seroconversion and T-cell assay; all patients seroconverted but had lower overall antibody and T-cell responses in patients with cancer.	(192)
Single center; Chronic myelogenous leukemia (CML) on TKI	16	45.6	first injection of BNT162b2 vaccine	Tolerable; localized inflammation in 56.3% and transient flu-like illness in 23.5% patients	Seroconversion and T-cell response; 87.5% of the patients with CML had detectable antibodies and developed a neutralizing antibody response; 93.3% had T-cell response	(297)
hematologic malignancy patients, on treatment	551	65 (22-97)	two doses of the mRNA vaccines (BNT162b2 or mRNA-1273)	Not reported	Seroconversion; positive seroconversion rates (51.5% at 1 month and 68.9% at 3 months), lower antibody titers and diminished neutralizing capacity (26.3% at 1 month and 43.6% at 3 months)	(204)

Cohort	n	Median age years (IQR)	Vaccine studied	Safety	Efficacy	Reference
multiple myeloma	320		Fully vaccinated (BNT162b2, mRNA-1273, and some unknown); 18.8% had COVID-19 prior to immunization	Not reported	Serology: 81.3% seroconverted after receiving the second vaccine dose; antibody levels highly variable; 15.8% did not have detectable levels	(198)
Single center; Youths and young adults with history of acute lymphoblastic leukemia and allergy to PEG-asparaginase	32	16 (12–29)	BNT162b2, mRNA-1273	No patients had signs or symptoms of allergic reaction	Not reported	(193)
Single center; lymphoma	67	71 (24–90)	BNT162b2, mRNA-1273	Not reported	Seroconversion; Treatment-naïve lymphoma patients induce IgG antibody response same as healthy controls; but patients on recent anti-CD20 therapy had sub-detection seroconversion.	(206)
Chronic lymphocytic leukemia (CLL)	167	71.0 (63.0–76.0)	BNT162b2	Mild local reactions (pain at the injection site, local erythema or swelling); no statistical difference between the first and second dose of the vaccine; more frequent systemic adverse events after the second dose; no differences in the rate of adverse events for patients on active treatment.	Seroconversion; significantly reduced antibody response rate among patients (39.5%); after treatment (79.2%), in treatment-naïve patients (55.2%) and in patients under treatment (16.0%); considerably low response in patients recently treated with Bruton's tyrosine kinase inhibitors (16%) or venetoclax ± anti-CD20 antibody (13.6%)	(187)
myeloproliferative neoplasm patients receiving JAK1 and JAK2 inhibitor (JAKi) ruxolitinib	30	60.8 (36.9–80.3)	first injection BNT162b2 or	Not reported	Seroconversion; significantly lower in patients receiving ruxolitinib; compared to healthy controls only 33.3–38.8% patients seroconverted	(207)
Israel nationwide; patients with hematological neoplasms with some on therapy for an active disease	32,516#	70 (59–79)	Two doses of mRNA BNT162b2 vaccine	Not reported	Vaccinated patients with hematological neoplasms, compared with vaccinated matched controls, had an increased risk of infections, symptomatic covid-19, covid-19 related hospitalizations, severe covid-19, and covid-19 related death.	(208)
multiple myeloma	44	65	Two doses of mRNA SARS-CoV-2 vaccine (BNT162b2; mRNA-1273 Moderna)	Not reported	B and T cell responses; seronegative MM patients had lower B cells and total CD4+ T cell; only 40% had spike-protein-reactive B cells; Seropositive MM patients had spike reactive B cells and activated CD4+ cells same as healthy controls	(209)
CAPTURE (COVID-19 antiviral response in a pan-tumor immune monitoring study)	357	59 years	unvaccinated	Not applicable	detected SARS-CoV-2-specific CD4+ T cells in 77 of 100 patients (77%) and CD8+ T cells in 49 of 100 patients (49%)	(298)
SeroNet-CORALE U.S. wide cohort of adult patients with solid tumors or hematological malignancies	366	65 (56–73) years	Two doses of mRNA SARS-CoV-2 vaccine (BNT162b2; mRNA-1273 Moderna)	Not applicable	antibody levels at prior to vaccination; 2–12 weeks; and 16–28 weeks after second dose. Lower antibody levels in cancer	(210)

Cohort	n	Median age years (IQR)	Vaccine studied	Safety	Efficacy	Reference
Single center (New York City); hematologic malignancy and solid tumor; 73% on active treatment	88	69 (30–91) years	Booster vaccination with mRNA vaccine (BNT162b2 or mRNA-1273) following previous 2 doses of BNT162b2	Not reported	56% of seronegative patients (hematologic malignancies) after previous full vaccination seroconverted after the booster vaccination; Prior anti-CD20/BTK inhibitor therapy was associated with reduced seroconversion even after boosters; patients with prior COVID-19 infection had more robust vaccine responses	(211)
Multicenter, Netherlands (Vaccination Against COVID in Cancer (VOICE) trial)	791	55 – 73 years	2 doses of mRNA-1273	Fatigue was most prevalent solicited systemic adverse event; fatigue, fever, chills, headache, myalgia, joint pain, and nausea were higher up to 7 days after the second vaccination; serious adverse events included fever, diarrhea, and febrile neutropenia	Seroconversion and spike-specific T-cell response; Most patients of solid tumor cancer developed adequate antibody response to mRNA-1273 vaccination while receiving chemotherapy, immunotherapy, or both; 2% of cohort did not develop antibody or T-cell response	(194)
Patients on remission after receiving CD19 or anti-CD22 targeting CAR T-cell treatments (CART)	12	53 (16-74) years	2 doses of mRNA vaccines (BNT162b2 or mRNA-1273)	Not reported	Seroconversion and T-cell response; Significantly lower RBD-IgG but comparable T-cell induction among the CART cohort compared to healthy controls; strong SARS-CoV-2-specific CD4 T-cell responses even after robust B-cell depletion by CAR T cells	(212)
Israel, single center, Patients with solid tumors on active therapy	37	67 (43-88)	Booster vaccination with BNT162b2 after 2 doses of mRNA vaccine BNT162b2	Not reported	Serology; most recipients had enhanced antibodies after 3rd booster, including those with moderate or minimal response following the second vaccine dose	(299)
Single site, patients with plasma cell neoplasms	276	74 (62–80)	two doses of the BNT162b2 or one dose of the AZD1222 vaccine	Not reported	Seroconversion, lower production of neutralizing antibodies in patients with MM compared with controls; independent of anti-CD38 or belantamab mafodotin and lymphopenia at the time of vaccination	(300)

# EHR extraction

\* Single patient case study