REVIEW ARTICLE
https://doi.org/10.1038/s43018-020-00122-3

nature cancer

The immuno-oncological challenge of COVID-19

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Coronavirus disease 2019 (COVID-19) and its causative virus, SARS-CoV-2, pose considerable challenges for the management of oncology patients. COVID-19 presents as a particularly severe respiratory and systemic infection in aging and immunosuppressed individuals, including patients with cancer. Moreover, severe COVID-19 is linked to an inflammatory burst and lymphopenia, which may aggravate cancer prognosis. Here we discuss why those with cancer are at higher risk of severe COVID-19, describe immune responses that confer protective or adverse reactions to this disease and indicate which antineoplastic therapies may either increase COVID-19 vulnerability or have a dual therapeutic effect on cancer and COVID-19.

After several local epidemics caused by coronaviruses (CoVs) in recent years, namely severe acute respiratory syndrome CoV (SARS-CoV) in 2002 and Middle East respiratory syndrome CoV (MERS-CoV) in 2012 and 2015, a novel virus, SARS-CoV-2, emerged at the end of 2019 and spread rapidly throughout the world to cause the pandemic known as COVID-19[1,2]. 22 million cases of COVID-19 and over 780,000 deaths had been reported worldwide by mid-August 2020, with a mortality rate that remains elusive due to uncertainty about the true number of infections. Mechanistically, infection by either SARS-CoV or SARS-CoV-2 involves the action of the virus spike protein (S), which engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor on the surface of target host cells[3], and the cooption of the cellular serine protease TMPRSS2, a member of the type II transmembrane serine protease family of proteins, which are implicated in both cancer and viral infections[4,5], for S protein priming[6,7]. The ACE2 receptor is highly expressed in lung alveolar type 2 cells, but is also present on endothelial and smooth muscle cells in various organs, including the heart, liver, kidney and digestive tract[8]. Although a substantial fraction of SARS-CoV-2-positive individuals are asymptomatic or paucisymptomatic carriers (the latter experiencing nonspecific symptoms similar to those of the common cold and sometimes gastroenteritis), severe COVID-19, which develops mostly in individuals with comorbidities, leads to acute respiratory failure, often associated with a cytokine storm, a prothrombotic immunopathology and profound lymphopenia, culminating in multiple organ dysfunction and death[9–12].

Patients with cancer were considered more susceptible to SARS-CoV-2 infection than individuals without cancer not only because of age, given that cancer incidence is strongly linked to advancing age, but also because of the high prevalence of cancer risk factors also associated with COVID-19—in particular, thoracic computed tomography (CT) scan abnormalities and smoking, along with cancer-associated metabolic disorders such as diabetes and hypertension—as well as the side effects of chemotherapy that might aggravate COVID-19, including arterial hypertension, cardiomyopathy, systemic immunosuppression[13] and accelerated cellular senescence[14,15]. Several reports have addressed the prevalence of patients with a clinical history of cancer in French, Chinese and Italian populations tested for SARS-CoV-2 infection[16–19]. One study of 84,246 consecutive individuals tested for SARS-CoV-2 from the Veneto region of Italy found that 5.7% had previously been diagnosed with cancer and, among those positive for SARS-CoV-2, 7.8% had a cancer diagnosis. Hence, the authors concluded that prevalence of cancer was not associated with risk of infection[16]. In contrast, two earlier studies reported an increased incidence of COVID-19 in patients diagnosed with cancer in China[17,18]. In the first report, patients with tumors were older and had a history of smoking or dyspnea or severe baseline CT scan manifestations, with 28% having been diagnosed with lung carcinoma[17]. In the second study, of 1,524 patients with cancer from a tertiary cancer center in China, the relative prevalence of COVID-19 was twice as high as in the general population[18]. Differences between the Italy-based studies versus China-based studies in the demographic profiles of their patient populations, such as a larger proportion of older males participating in the latter, may account for these apparent discrepancies.

The main risk factors of severe COVID-19 in the general population are gender (male/female sex ratio, 1.65:1), advanced age (median age >60), obesity and diseases such as congestive heart failure, coronary heart disease, diabetes, hypertension, hyperlipidemia and cancer[9]. Race and ethnicity are also associated with COVID-19 risk, with Black and Hispanic people being disproportionately affected compared with white people[9]. In contrast to the incidence, COVID-19 severity was found to increase when associated with cancer across studies and geographical sites, including France, China, the USA and Italy[16,20,21]. For instance, the study from the Veneto region of Italy reported a higher percentage of COVID-19-related hospitalizations (56% versus 34%) and deaths (14% versus 4%) among patients with a history of cancer than among those without such a history[16].

Cancer type, staging and specific therapies are additional risk factors for severe COVID-19 in this patient population. Patients with hematological, lung or breast cancer are more vulnerable than those with other cancers. In the Veneto study, breast and

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hematological cancers were associated with a higher risk of both hospitalization and death[16]. Lung cancer was associated with a four-fold risk of death due to SARS-CoV-2 infection[16]. A study reporting the clinical outcome of COVID-19 in 102 patients with lung cancer showed that the course of SARS-CoV-2 infection in these individuals was longer and more severe than that reported in the general US population[21]. About one-third of these patients experienced a relatively milder disease course and were treated as outpatients, two-thirds needed hospitalization and one-quarter died. Smoking status and chronic obstructive pulmonary disease (COPD) were the strongest determinants of severity[21]. 200 patients with COVID-19 and thoracic cancers from eight countries were identified and included in the TERAVOLT registry[22]. Univariate analyses identified age >65, current or former smoking, presence of any comorbidities and chemotherapy as being associated with increased risk of death. In line with the previous report[21], however, multivariate analysis revealed only smoking history as associated with increased risk of death[22]. In hematological malignancies at older age, diagnosis of acute myeloid leukemia, indolent and aggressive non-Hodgkin lymphoma or plasma cell neoplasms, and severe or critical COVID-19 were associated with worse overall survival[23]. A retrospective single-center analysis of 34 patients with hematological malignancies who developed COVID-19 during follow-up was conducted in Spain, reporting 11 deaths that could have been predicted by ECOG (Eastern Cooperative Oncology Group) status at disease onset[24]. Moreover, patients diagnosed with metastatic or stage IV carcinomas may be more susceptible to severe forms of COVID-19 than those with localized neoplasia[25]. Cancer treatments such as surgery, chemotherapy and immunotherapy have been reported to contribute to the severity of the COVID-19 among patients with cancer[19,21,23,25–27]. For example, a France-based study reported increased risk of deaths from COVID-19 in 178 patients with cancer with age >70, smoking status (current/former), ECOG score ≥2 at last follow-up visit, metastatic disease and use of cytotoxic chemotherapy in the past 3 months[19]. Separately, two studies reported that immunotherapy within the month before the first symptoms of COVID-19 developed was associated with increased severity and up to 30% death rates in 11 patients[27] and 31 patients[25], respectively. Age and receipt of immune-checkpoint inhibitor treatment remained significantly associated with COVID severity in a multivariate analysis of 563 patients with cancer[25].

Conversely, pediatric patients with cancer seem to be relatively resistant to SARS-CoV-2 infection and severe COVID-19. Among 120 asymptomatic pediatric cancer patients, only 2.5% were positive for SARS-CoV-2, contrasting with a 14.7% rate in their asymptomatic caregivers[18,19,28,29]. This latter finding favors the possibility that age is a more important risk factor for SARS-CoV-2 infection than cancer.

In conclusion, as of August 2020, it is not clear whether cancer is an independent risk factor for severe COVID-19 or whether the observed cancer-associated risk depends on the peculiar demography and comorbidities of oncology patients[30,31]. However, given that the time elapsing between cancer diagnosis and SARS-CoV-2 infection was reported to affect the risk of death (in that the shorter the time elapsed, the higher the risk)[16], we surmise that the role of therapies and co-medications may so far have been underestimated. Meta-analyses of well-described cancer cohorts, as well as prospective studies, are needed to fully disentangle the role played in COVID-19 severity by carcinogenesis and its clinical management, compared with age, sex and ECOG status.

Common risk factors for severe COVID-19 and cancer

In light of these intriguing data sets, it is important to elucidate the possible cause–effect relationship between severe COVID-19 and pre-existing pro-inflammatory and immunosuppressing conditions related to cancer (Fig. 1) and its treatments (Tables 1 and 2). In this section, we discuss the common risk factors between severe COVID-19 and cancer.

Aging, immunosenescence and inflammaging. Aging increases the incidences of both cancer and SARS-CoV-2 infection[32], with potential key commonalities relating to immunosenescence and inflammaging (Fig. 1). Immunosenescence defines a status of declining immune system function associated with, or causing, quantitatively insufficient or qualitatively maladaptive responses to vaccination, infection and neoplasia, as well as an increased incidence of debilitating autoimmune diseases in the elderly population[33,34]. For example, levels of C-reactive protein are positively associated with senescent CD8$^+$ T cells, plasmablasts and granulocytes in elderly people[35]. Notably, in patients with COVID-19, lower T cell counts are associated with clinical markers of inflammation, such as ferritin, D dimers and C-reactive protein, whereas high amounts of plasmablasts are associated with disease severity[36]. A recent immunophenotyping study of young and old individuals diagnosed or not diagnosed with COVID-19 confirmed that COVID-19 promotes age-induced immune cell polarization and gene expression related to inflammation and cellular senescence, and conversely, aging-associated dysregulated immune responses may at least partially account for vulnerability to COVID-19 in the elderly[37]. Moreover, the generation of naive T cells through thymopoiesis and their priming with novel antigens (such as tumor-specific neoantigens) or infectious agents (such as SARS-CoV-2) are compromised with aging[38–40]. This makes older people more vulnerable to both cancer and viral infections and less able to develop adaptive immune responses during SARS-CoV-2 infection or specific vaccination[41,42], unless T cell cross-reactivities against seasonal coronaviruses are also shown to be similarly protective and endowed with reduced risk of antibody-dependent amplified breakthrough infection, compared with SARS-CoV-2-specific immune responses in the elderly[43,44]. This contrasts with the fact that higher IgG and IgM responses to the SARS-CoV-2 S and N proteins have been observed in elderly patients during the early phase of COVID-19, notwithstanding their higher viral loads than those of younger patients[45].

A defect in dendritic cell (DC) fitness with aging has also been reported[46]. Peripheral germinal center follicular helper T cells are diminished in older people after seasonal influenza vaccination. This post-immunization impairment in the differentiation of follicular helper T cells was recapitulated in 2-year-old mice compared with younger mice, was linked to impaired T cell priming by conventional DCs (cDC2s) and could be restored by topical application of a Toll-like receptor 7 (TLR7) agonist[46]. Notably, the age-dependent increase in susceptibility to coronaviruses is also associated with an impaired ability of lung DCs to migrate to mediastinal lymph nodes and prime SARS-CoV-specific CD8$^+$ T cells[47–49]. Reduced numbers and impaired functions of DCs and T cells have been reported at the acute phase of severe COVID-19 in 17 patients[50]. Carcinogenesis is also associated with defective antigen presentation and DC functions, including DC loss and migration defects[51,52], which paves the way toward decreased antiviral T cell responses.

In addition to sex and genetics, age is a major factor influencing interindividual differences in transcriptional responses to bacterial, fungal and viral challenges in human peripheral blood mononuclear cells[53,54]. In the absence of stimulation, the expression of 85% of all genes in mononuclear cells is directly affected by age. After viral stimulation, reduced innate immune responses (for example, type I interferons (IFNs)) are observed in samples from individuals more than 30 years of age. Age (and sex) are also important determinants of humoral immunity, with older individuals (and women) showing higher rates of seropositivity for most antigens[53]. The reduced ability of aged B cells to increase their metabolism, characterized by a strong reduction in oxidative phosphorylation after activation,

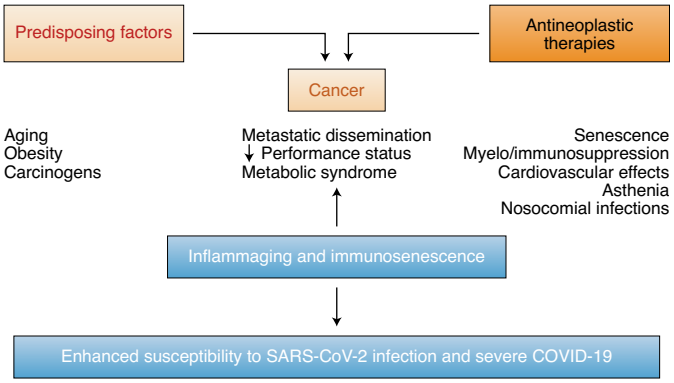

Fig. 1 | Intertwined relationships between cancer and its comorbidities or therapies in relation to COVID-19 susceptibility. Aging, obesity, metabolic syndrome and exposure to carcinogens are predisposing factors for cancer. Aging, obesity and metabolic syndrome also represent comorbidities that influence susceptibility to and severity of SARS-CoV-2 infection. In patients with cancer, metastatic dissemination and poor ECOG performance status also favor COVID severity. Many genotoxic chemotherapies administered before SARS-CoV-2 viral infection ultimately enhance its severity, likely by inducing immunosuppression and cellular senescence in normal tissues, which in turn maintain local and systemic inflammation, but also through therapy-related adverse events that may include cardiovascular effects, asthenia and propensity to nosocomial infections. Immunosenescence and inflammaging, which are also promoted by aging and obesity, result in declining functions of the innate and adaptive immune systems, exacerbating overt inflammation and cancer dissemination and also increasing vulnerability to SARS-CoV-2 infection and risk of severe COVID-19.

contributes to the weakened antibody responses of the elderly to vaccination in general[55]. A pivotal study analyzing immune responses to the Pandemrix H1N1 influenza vaccine concluded that age was a fundamental component of interindividual variations in the early response (by day 1) to the vaccine, dominated by type I and II IFN fingerprints. Only late (day 7) parameters, such as the rise in transitional plasmablasts usually found in responders, were not influenced by age[56].

Separate from such defects in innate and cognate immune responses, 'inflammaging' refers to a cytokine dysregulation associated with the age-dependent remodeling of the immune system, as well as to an inability to fine-tune systemic inflammation. Whereas acute, localized inflammation is required for tissue repair responses, systemic and chronic inflammation is harmful. Several common molecular pathways are associated with both aging and low-grade inflammation. For instance, changes in redox equilibrium, defects in the clearance of senescent cells, accumulation of cells with the senescence-associated secretory phenotype (SASP) and reduced autophagy are hallmarks of aging that activate the inflammasome platform, a key orchestrator of cellular inflammatory responses[57]. Interleukin 6 (IL-6), which has been referred to as the 'gerontologist's cytokine'[58], is normally present at low levels in the blood, but is increased with aging or frailty (sarcopenia and muscle loss)[59] and correlates with mortality[60,61]. IL-6 is involved in the pathogenesis of many chronic diseases, including cancer[62,63]. The IL-6–JAK–STAT3 pathway is hyperactivated in many types of cancer, driving the proliferation, survival and invasiveness of tumor cells and suppressing the antitumor immune response. Thus, strategies targeting this pathway have already received US Food and Drug Administration (FDA) approval to treat inflammatory conditions or myeloproliferative neoplasms and to manage certain adverse effects of chimeric antigen receptor–expressing T cells (CAR T cells)[64]. Given that IL-6 is therapeutically targeted by tocilizumab in the context of COVID-19 to reduce morbidity and mortality related to COVID-19 cytokine release syndrome[45], it is conceivable—although it remains to be demonstrated—that inflammaging favors the development of severe SARS-CoV-2 infection. In light of the critical pathophysiological impact of IL-6 and the severity of COVID-19 in individuals with hematological malignancies, prospective controlled studies testing IL-6 receptor (IL-6R) blockade or JAK or STAT3 inhibitors are warranted in this particular subset of patients.

Metabolic syndrome, cancer and COVID-19. Several meta-analyses have revealed an association between type 2 diabetes (T2D) and cancer, with the strongest relationship found for liver and pancreatic cancer, followed by endometrial cancer[65]. Similarly, morbidly obese individuals (body mass index ≥40 kg/m^2) with T2D are more likely to become infected by SARS-CoV-2 and are at a higher risk of complications and death from COVID-19[66]. Interestingly, individuals with T2D were also at increased risk for SARS and MERS[67]. Relevant to this, insulin is a key hormonal enhancer of tumor metabolism and growth in obesity-associated insulin resistance[68], and treatment of T2D during COVID-19 is being implemented to mitigate disease severity[69].

Although human and mouse data analyses revealed that individuals with T2D have reduced ACE2 expression[70], patients diagnosed with T2D also have elevated circulating levels of furin, a cellular protease that facilitates viral entry by cleaving the S1 and S2 domain of the SARS-CoV-2 spike protein (S)[71]. T2D inhibits neutrophil chemotaxis, phagocytosis and intracellular killing of microbes, resulting in impairments in adaptive immunity characterized by an initial delay in the activation of type 1 helper T cell (T_H1 cell)–mediated immunity and a late hyperinflammatory response often observed in patients with diabetes[72]. This could explain the observed links between T2D and increased risk of adverse outcomes for COVID-19 and cancer, both of which depend on protective T_H1/cytotoxic T cell type 1 (T_H1/Tc1) immune responses.

In addition to facilitating virus entry, the metabolic syndrome may compromise the integrity of the intestinal barrier, a location of SARS-CoV-2 replication. In mice, hyperglycemia increases the permeability of this barrier through glucose transporter 2–dependent transcriptional reprogramming of intestinal epithelial cells and disruption of tight and adherens junctions[73]. Similarly, in humans, systemic influx of intestinal microbiome products correlates with failing glycemic control[73]. Given that both SARS-CoV and SARS-CoV-2 can be recovered from feces, infect intestinal epithelial cells and cause diarrhea[74,75], hyperglycemia-induced dysfunction of the intestinal barrier might facilitate bacterial translocation, thus favoring systemic inflammation and immunosuppression. Interestingly, in a humanized mouse model of MERS-CoV infection on a high-fat diet, the course of infection was more severe and prolonged in male mice and was characterized by IL-17-producing helper T cell (T_H17 cell) responses[67], which are known to be pro-angiogenic and immunosuppressive in the course of cancer progression[76]. Notably, obese individuals contract more bacterial, viral and fungal infections than do lean counterparts, and respond relatively poorly to vaccination against influenza, hepatitis B, tetanus and rabies[77]. Obesity, alone or together with metabolic syndrome, induces defects in B cells similar to those associated with aging, contributing to systemic and B cell–intrinsic inflammation as well as to a surge in autoantibodies[77].

Immunosuppression, lymphopenia, neutrophilia and interferon deficiency. Through their participation in immunosurveillance, lymphocytes control the incidence, progression and therapeutic response of cancers[78]. CD4$^+$ and CD8$^+$ T lymphocytes recognize tumor cells expressing immunodominant epitopes presented by major histocompatibility complex class II and class I, respectively. CD4$^+$ lymphopenia, a hallmark of immunosuppressive viral infection,

Table 1 | Drugs (by class) with anticancer effects or used for best supportive cancer care repurposed to become antivirals

Drugs	Mode of action	Cancer indication	Antiviral indication	Type of study	Ongoing clinical trials
Interferon-based therapies					
IFNα2b or IFNβ1b, alone or combined with antivirals	Stimulation of innate immunity	RCC, melanoma, HCC, CML, hairy-cell leukemia[163] AIDS-related Kaposi sarcoma Follicular lymphoma Condylomata acuminata	Hepatitis B and C	Clinical trial against COVID-19[106,131,132]	NCT04344600, NCT04350671,NCT04343768 NCT04343976, NCT04254874,NCT04320238 ChiCTR2000029387, NCT04315948, NCT04276688
IFNγ	Activation of lung macrophages	Cancer[130] cancer comorbidities: e.g., COPD, idiopathic pulmonary fibrosis	Synergy with IFNβ to block SARS-CoV-2 replication	Clinical trial with inhaled IFNγ[133]	
TLR3 agonists Hiltonol (poly-ICLC)	Induction of type I IFNs and protection against respiratory virus–induced immunopathology[109]	Adjuvant for cancer vaccines Therapeutic in addition to immunogenic chemotherapy	Preclinical study in BALB/c mice against SARS-CoV: prophylactic and therapeutic effects of poly-ICLC by intranasal route [109]	No trials	
Immune checkpoint inhibitors					
Anti-PD-1 Abs Pembrolizumab Nivolumab	Reactivation of exhausted antiviral and antitumor CTLs[134]	Multiple stage IIIc/IV cancer indications (various cancers)[134]	Prevention of EBV-induced HLH[137] Non-inferiority in case of concomitant NSCLC and COVID-19[138]	Retrospective analysis on 62 patients with lung cancer adjusted for gender and smoking status Randomized trials with anti-PD-1	NCT04335305: pembrolizumab NCT04333914: nivolumab
IL-6–JAK–STAT3					
Anti-IL-6R Abs Tocilizumab	Cytokine storm and HLH, prevention of immunothrombosis, lung and systemic inflammation, reduction of neutrophilia[144]	FDA approved for iatrogenic responses to immunostimulation (e.g., CAR T cell therapies) and myeloproliferative neoplasms. In assessment for multiple myeloma, many solid and hematological malignancies and acute GVHD[64]	FDA approved in China for severe COVID-19	Pilot studies or Randomized clinical trials Observational study in 21 Chinese patients with COVID-19[139] Translational research studies[139–141]	NCT04332094, NCT04359667, NCT04317092, NCT0433291, NCT04335071, NCT04346355, NCT04306705, NCT04331795, NCT04377659, NCT04377750, NCT04363853, NCT04320615, NCT04315480, NCT04331808, NCT04310228, NCT0433391, NCT04339712, NCT04331808
Ruxolitinib	JAK1/2 inhibitor Decreases T_H1 lymphocyte activation, reduces pro-inflammatory cytokine secretion	FDA/EMA approved for GVHD	Effects on host immune cells; no direct antiviral activity	Clinical trials: 8 trials against COVID-19 started /ongoing	NCT0435579, NCT04362137, NCT04377620, NCT04334044, NCT04337359, NCT04338958, NCT04348695, NCT04354714
Baricitinib	JAK1/2 inhibitor	Rheumatoid arthritis, trials as cancer treatment	SARS-CoV-2[190]	Clinical trials: 8 trials against COVID-19 started /ongoing	NCT04358614, NCT04340232, NCT04373044, NCT04393051, NCT04320277, NCT04399798, NCT04346147, NCT04362943
Androgen-deprivation therapy					
Androgen receptor deprivation therapies (ADT)	ADTs decrease TMPRSS2 in lung and prostate tissues[5,146]	Prostate cancer (expressing TMPRSS2)[5]	TMPRSS2 induces spike protein priming; its inhibition by camostat mesylate has antiviral effect[6]	Retrospective Italian study, N = 4,532 patients; ADT decreased COVID-19 incidence (OR: 4.05)[147]	NCT04397718

Continued

Table 1 | Drugs (by class) with anticancer effects or used for best supportive cancer care repurposed to become antivirals (continued)

Drugs	Mode of action	Cancer indication	Antiviral indication	Type of study	Ongoing clinical trials
Other small molecules					
Anti-CD26/ DDP4 Begelomab	Alternate receptor for SARS-CoV-2 (in addition to ACE2)[191] Preservation of Cxcl10 biological activity and anticancer synergistic effects between CD26 blockade and anti-PD-1 Ab[158]	Steroid refractory acute GVHD[161]	MERS Diabetes[162]	No trials	
Imatinib mesylate or saracatinib	Abl kinase activity involved in coronavirus fusion with endosomal membrane as well as cell–cell fusion late in infection[192,193]	FDA approved for CML and GIST	Infectious bronchitis virus (IBV) SARS-CoV1 MERS[158]	Randomized clinical trial	NCT04357613, NCT04356495, NCT04346147
Ibrutinib	TKI Bruton kinase and IL-2-inducible T cell kinase inhibitor that blunts T cell activation and reduces cytokine release syndrome[159]	Steroid-refractory chronic GVHD CLL Waldenström disease[163]	Effects on host immune cells; no direct antiviral activity	Retrospective observation in Waldenström macroglobulinemia: reduced COVID-19 incidence[159]	No trials
Zotatifin; Plitidepsin	eIF4A inhibitor; eEF1A inhibitor	Preclinical activity against multiple forms of KRAS mutant and receptor tyrosine kinase mutant cancers currently being evaluated in multiple myeloma	eIF4H, an Nsp9 interactor, is a partner of eIF4A; eIF4A inhibitor zotatifin shows strong antiviral effect eIF4A inhibitor ternatin-4 has antiviral effects	Phase 1/2 clinical trial in patients with a targeted set of solid tumors[153,154]	NCT04092673 NCT04382066
Anakinra	Interleukin (IL)-1 receptor antagonist	Currently being evaluated to prevent or treat severe side effects in patients receiving CAR-T cell therapy (NCT04148430)		Clinical trials in cytokine storm syndrome secondary to COVID-19[194,195]	NCT04443881
Other strategies					
BCG	Trained immunity Epigenetic reprogramming of myeloid cells[196]	FDA approved in non-muscle invasive bladder urothelial cancers	No data Negative epidemiological data[197]	Phase 3 randomized controlled clinical trials	NCT04328441, NCT04327206, NCT04379336, NCT04327206, NCT04348370
Chlorpromazine	High concentrations in lung and saliva Anti-inflammatory (more IL-10, less TNFα, IFNα) Antiproliferative via suppression of AKT–mTOR or sirtuin 1 inhibition	Phenothiazine derivative used to treat psychotic disorders Control of nausea and vomiting in cisplatin-treated cancer patients Weak indication in drug repurposing: antineoplastic properties in colon cancer and glioblastoma in vitro	Inhibition of clathrin-dependent endocytosis[192,193,198–200]	Clinical trials	NCT04366739, NCT04354805
Low-dose radiotherapy	Immunomodulation Reprogramming of iNOS$^+$/M1 phenotype of pulmonary macrophages[164,165]	Low-grade lymphoma Lung cancer	Pneumonia	Preclinical models of lung inflammation induced by TLR3 or TLR4L[165] Preclinical models of viral pneumonia[168]	NCT04377477, NCT04390412, NCT04366791, NCT04380818, NCT04394182

Continued

Table 1 | Drugs (by class) with anticancer effects or used for best supportive cancer care repurposed to become antivirals (continued)

Drugs	Mode of action	Cancer indication	Antiviral indication	Type of study	Ongoing clinical trials
Vitamin D3 (cholecalciferol)	Extraskeletal bioactivity in prevention of infections, T1D and T2D, cardiovascular disease, obesity, asthma, inflammatory bowel disease and cancers (colon, breast, prostate and ovarian)	Induction of apoptosis, stimulation of cell differentiation and anti-inflammatory and antiproliferative effects and inhibition of angiogenesis, invasion and metastasis Reduction of death by cancer but no benefit in preventing cancer incidence	Protective effect of vitamin D in settings of pneumonia, cytokine hyperproduction and ARDS[172–174] Vitamin D repurposed for influenza A H5N1 virus–induced lung injury	**Observational studies:** Daily supplementation with 2000–5000 IU/day vitamin D_3 in older adults with Parkinson disease may offer protection against COVID-19[175,179,180,201,202] **Association studies:** Between vitamin D deficiency and community-acquired pneumonia[176] **Genetic studies:** Vitamin D receptor gene (*VDR*) alleles associated with increased susceptibility to respiratory or viral infections[177] **Animal models of ARDS:** Reduced lung permeability by modulation of renin–angiotensin system activity and ACE2 expression[178]	NCT04399746, NCT04344041,NCT04372017, NCT04386850

Ab, antibody; ADT, androgen deprivation therapy; ARDS, acute respiratory distress syndrome; BC, breast cancer; BCG, Bacillus Calmette–Guérin vaccine; BiTE, bispecific T cell engagers; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; EBV, Epstein–Barr virus; EMA, European Medical Agency; GC, gastric cancer; GVHD, graft-versus-host disease; HCC, hepatocarcinoma; HLH, hemophagocytic lymphohistiocytosis; iNOS, inducible nitric acid synthase; NSCLC, non-small-cell lung cancer; OR, odds ratio; poly-ICLC, polyinosinic–polycytidylic acid; RCC, renal-cell carcinoma.

occurs in ~20% of patients with advanced pancreatic cancer, melanoma, non-Hodgkin's lymphoma, breast cancer, sarcomas or hepatocellular carcinoma but is rare (~2%) in patients with localized disease[79–82]. In fact, cancer-associated lymphopenia, mostly affecting $CD4^+$ T cell counts, has been reported to increase the risk of comorbidities (febrile neutropenia), resistance to a range of therapies and mortality across many cancer types[79]. Lymphopenia often accompanies cancer diagnosis, treatment or progression and is a side effect of chemotherapy and steroids. Radiotherapy also negatively impacts circulating lymphocyte counts[83]. An increased number of circulating neutrophils is often combined with decreased lymphocyte counts, resulting in a marked elevation of the neutrophil-to-lymphocyte ratio[84]. A high neutrophil-to-lymphocyte ratio is a poor prognostic marker and predicts short cancer-specific progression-free survival after blockade of programmed cell death protein 1 (PD-1)[84], as well as severe COVID-19[85]. Beyond lymphopenia, a reduction in T cell receptor diversity and a functional impairment of other lymphoid and myeloid immune cells (such as natural killer (NK) cells, monocytes, DCs, and memory $CD4^+$ and $CD8^+$ T cells) have been detected in patients with localized primary tumors such as breast cancer, colon carcinoma and hepatocellular carcinoma[79,86–88].

Given the critical role of T effector lymphocytes in eliminating virus-infected cells, an attenuated and functionally compromised T cell pool may pave the way toward the higher incidence and severity of COVID-19 in patients with cancer. Indeed, the outcome of COVID-19 may be determined by a 'race' between the cellular immune system that mounts a response to eliminate virus-infected cells and the immunosuppressive action of the pathogen[89] (Fig. 2). Individuals who present with detectable memory B and T cell responses against seasonal coronaviruses may be able to mobilize a pool of effector T cells and mount neutralizing antibody responses that may, at least in part, prevent the thrombotic microangiopathy associated with SARS-CoV-2 viral endothelial infection[90–92]. Moreover, MERS-CoV and SARS-CoV-2 trigger apoptosis and necroptosis of T cells and reduce lymphopoietin IL-7 as an immunosuppressive strategy[93].

If people with cancer start this 'race' with a handicap due to pre-existing T cell defects, this makes them particularly susceptible to COVID-19-associated severe pneumonia or systemic organ failure[93]. Conversely, it is unclear whether cancer-associated immunosuppressive cells—such as regulatory T cells, T_H17 cells, myeloid-derived suppressor cells and 'exhausted' PD-1 ligand–positive T cells—might mitigate lung inflammation caused by SARS-CoV-2[79,94–97]. Longitudinal high-dimensional immunomonitoring will help delineate favorable and deleterious cancer-associated immune factors for each stage of COVID-19 infection.

Type I and II IFN responses are intertwined and essential for long-term protective anticancer and antiviral immune responses[98–100]. Defective type I IFN responses by conventional or plasmacytoid DCs during natural immunosurveillance, or by tumor cells after chemotherapy or radiotherapy, are associated with tumor progression[101–104]. Intestinal dysbiosis, as well as tumor-intrinsic genetic defects, account for aberrant IFN-α/β receptor (IFNAR) signaling, preventing full efficacy of immunotherapy in patients with tumors[101]. RNA viruses engage pattern-recognition receptors (e.g., TLR3, TLR7 and TLR8, RIG-I, MDA5) on antigen-presenting cells, culminating in the induction of type I IFNs and an endoplasmic reticulum stress response that shuts down viral protein translation while igniting innate effector cells, such as NK cells or DCs[105,106]. Elegant studies have revealed the beneficial role of type I IFN signaling at early steps of infection and the protective impact of type II IFNs released by airway memory $CD4^+$ T cells, or intranasal instillations of recombinant IFNγ, against SARS-CoV infection in mice[107]. Separately, treatment with the TLR3 agonist poly(I:C) protected mice

Table 2 | Anticancer drugs that potentially increase vulnerability to COVID-19

Anticancer therapies	FDA-approved indication	Side effects/risk factors for COVID-19	Side-effect mechanism
Anti-angiogenic agents			
Bevacizumab	Various cancers	Hypertension, dilated cardiomyopathy, thrombosis, proteinuria	Pathologic remodeling in response to pressure overload, increase arterial thrombosis[203], increased vascular permeability
Chemotherapy			
Anthracyclines	Lymphoma, leukemia, sarcoma, BC	Cardiac dysfunction[204], heart failure[205], cardiomyopathy[206]	Troponin I production, oxidative stress, mitochondrial dysfunction[207]
Chemotherapy (anthracyclines, gemcitabine, cisplatin, taxanes)	Various cancers	Myelosuppression, immunosuppression	Cell senescence[208]
Cytotoxic drugs	Various cancers	Premature aging including skin, nail, and hair changes	Cell senescence[208], mitotic catastrophe[209]
Gemcitabine	NSCLC, pancreatic cancer, BC	Interstitial pneumonitis[210]	Unknown; proposed release of cytokines in the body[211]
Mitomycin C	Pancreatic and stomach cancer	Interstitial pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease[212,213]	Apoptosis in fibroblasts
Hormonotherapy			
LH-RH agonists (leuprorelin, goserelin, triptorelin, buserelin) and antagonist (degarelix)	Prostate cancer, BC	Increase fat mass, obesity, insulin resistance, serum cholesterol and triglyceride levels, cardiovascular disease, infarct[214]	Low adiponectin levels and elevated resistin levels in mice
Androgen depletion therapy, anti-aromatase inhibitors	Various cancers	Osteoporosis, accelerated bone loss[215]	Hypoestrogen states[216], early menopause[217], direct toxic effects on bone, local tissue atrophy characterized by loss of functional osteoblasts, marrow adiposity and microvascular impairments[218]
Radiotherapy			
Radiotherapy	Various cancers	Premature aging including skin, nail, and hair changes, myelosuppression, immunosuppression	Cell senescence[208], mitotic catastrophe[209]
Radiotherapy	Lung tumors	Interstitial fibrosis	Epithelial cell death, senescence and SASP, EMT, myofibroblast, NADPH oxidase, macrophage reprogramming, M2 and T_H2 responses[209,219]
Radiotherapy	Various cancers	Osteoporosis, accelerated bone loss[215]	Hypoestrogen states[216], early menopause[217] direct toxic effects on bone, local tissue atrophy characterized by loss of functional osteoblasts, marrow adiposity and microvascular impairment[217]
Targeted monoclonal antibodies			
Anti-HER2 agents (trastuzumab)	BC, GC	Dilated cardiomyopathy, congestive heart failure, systolic dysfunction[220]	Impairment of contractility rather than loss of myocytes[221]
Epidermal growth factor receptor (EGFR)-targeted agents	NSCLC, BC, CRC	Interstitial pneumonitis	On- and off-target effect[222]
Immunotherapies			
Anti-PD-1 inhibitors (pembrolizumab, nivolumab)	Various cancers	Hyperglycemia, T1D, metabolic effects Pneumonitis	Autoimmune destruction of pancreatic islet cells[223], excessive immune activation[222]
Anti-CTLA-4 inhibitors (tremelimumab, ipilimumab)	Various cancers	Autoimmune-mediated side effects such as hypophysitis, hepatitis, iridocyclitis or exacerbation of lupus nephritis and pre-existing comorbidities	Excessive immune activation[224]
CAR T cell therapy, BiTE therapy	Lymphoma, acute lymphoblastic leukemia	Cytokine release syndrome, increased serum troponin, cardiovascular events	Mediated by IL-6, IL-1 and nitric oxide produced by recipient macrophages[225]

Continued

Table 2 | Anticancer drugs that potentially increase vulnerability to COVID-19 (continued)

Anticancer therapies	FDA-approved indication	Side effects/risk factors for COVID-19	Side-effect mechanism
Small molecules			
mTOR inhibitors (everolimus, temisrolimus, sirolimus)	RCC, neuroendocrine tumors; as anti-rejection agents in solid organ transplantation	Hyperglycemia, T1D, metabolic effect, hyperlipidemia, hypophosphatemia Noninfectious pneumonitis[226] Interstitial pneumonitis[227]	Reduced glucose-stimulated insulin secretion and increased apoptosis; reduced glucose uptake and muscle mass[228] Autoimmune response leading to lymphocytic alveolitis[229]
Tyrosine kinase inhibitors (sunitinib, sorafenib, cabozantinib)	RCC, neuroendocrine tumors, GIST	Hypertension, rhythm disturbances, heart failure[230]	Mitochondrial dysfunction and cardiomyocyte apoptosis and cardiac contractile dysfunction[231]

ADT, androgen deprivation therapy; BC, breast cancer; BiTE, bispecific T cell engagers; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; EMT, epithelial–mesenchymal transition; GC, gastric cancer; GIST, gastrointestinal stromal tumor; GVHD, graft-versus-host disease; HCC, hepatocarcinoma; HER2, human epidermal growth factor receptor 2; HLH, hemophagocytic lymphohistiocytosis; LH-RH, luteinizing hormone–releasing hormone; NSCLC, non-small-cell lung cancer; poly-ICLC, polyinosinic–polycytidylic acid; RCC, renal cell carcinoma; SASP, senescence-associated secretory phenotype; T1D, type 1 diabetes mellitus.

against highly pathogenic coronavirus species, including group 2c (MERS-like) coronaviruses[108,109]. Similarly, TLR signaling through the TRIF adaptor protein protected mice from lethal SARS-CoV disease[110]. However, in stark contrast to other beta coronaviruses, SARS-CoV-2 fails to induce—or perhaps subverts—a type I IFN response in immune cells[111]. Thus, in response to SARS-CoV-2, the host does not increase the production of type I and type III IFNs but instead produces high levels of inflammatory chemokines and cytokines, particularly IL-6, thus stimulating emergency hematopoiesis and attracting granulocytes and monocytes to lung lesions[111–113] (Fig. 2). As a failing immune response enables sustained viral replication, a positive feedback loop becomes established, eventually allowing the virus to prevail. These findings have been substantiated by in vitro studies in which normal lung parenchyma from five healthy human donors was infected with SARS-CoV versus SARS-CoV-2. In contrast to SARS-CoV, SARS-CoV-2 was highly replicative and poorly immunogenic, failing to trigger a type I IFN response and T_H1 chemokine release[114].

However, the timing of activation of the type I IFN pathway is key for antiviral and antitumor immune responses. For example, in separate mouse-based studies, delayed IFNβ treatment failed to effectively inhibit virus replication of SARS-CoV-2[115] and MERS-CoV[116], increased infiltration and activation of monocytes, macrophages and neutrophils in the lungs[115,116] and enhanced the expression of pro-inflammatory cytokines, resulting in fatal pneumonia during SARS-CoV infection[116,117] and in tumor resistance to PD-1 blockade[115–118].

Altogether, these results imply that cancer and COVID-19 may be concomitantly aggravated by comorbidities such as aging, metabolic disorders, and innate and cognate immunosuppression (Fig. 1). These comorbidities may also compromise the efficacy of immune-based anticancer and antiviral therapies.

Cancer therapeutics with possible pro-COVID-19 effects

Tumor control achieved by oncological treatments is counterbalanced by the cardiovascular toxicities of cytotoxic agents, which often cause premature discontinuation of an effective therapy or undermine overall survival. An association between cancer and cardiovascular diseases, as well as a direct relationship between hypertension and cancer incidence and mortality, have been documented[119]. Thus, arterial hypertension (AHT) is both the most common comorbidity of cancer and a frequent adverse effect of antineoplastic therapies[120]. Pre-existing AHT is known to increase the risk of other cardiac adverse events due to oncologic treatments, in particular heart failure[121]. Many antineoplastic treatments (of which a non-exhaustive list is provided in Tables 1 and 2), particularly small molecules or antibodies targeting the growth factor VEGF or its receptor VEGF-R2 and tyrosine kinase inhibitors, cause AHT, compromising the long-term outcome of chemotherapy[120]. All these side effects theoretically complicate the prognosis of COVID-19[25]. However, and notwithstanding the high serum VEGF levels found in patients suffering from severe SARS-CoV-2, clinical trials in China are currently assessing the effect of targeting VEGF with bevacizumab in COVID-19 (NCT04275414) in preventing immunothrombosis.

Cytotoxic drugs administered at ablative or non-myeloablative dosages stimulate bone marrow progenitors and the exodus of both immature and mature cells, including granulocytes, monocytes and platelets. As previously reported, the resulting leukocytosis and production of the cytokine G-CSF could facilitate the differentiation of myeloid-derived suppressor cells and modulate neutrophil-to-lymphocyte ratios, paving the way to tumor progression, metastasis and poor clinical outcome[122].

Genotoxic chemotherapies induce cellular senescence in normal tissues, where they promote local and systemic inflammation that causes or exacerbates the debilitating effects of chemotherapy[15]. In mice, ablating senescent cells reduces many side effects of cytotoxic agents, including cancer recurrence, cardiac dysfunction and myelosuppression[15]. Moreover, the risk of chemotherapy-induced asthenia is higher in people with increased expression of a senescence marker in T cells before chemotherapy[15]. Accordingly, after and during chemotherapy, patients with cancer are particularly susceptible to severe COVID-19[19].

Radiation-induced pulmonary fibrosis (RIPF) is a common complication of thoracic radiotherapy for lung and breast cancer, observed in 16–28% of patients[123]. RIPF leads to irreversible destruction of lung architecture and disruption of gas exchange. Because the pathophysiology of RIPF features epithelial cell dysfunction and senescence, pro-inflammatory cytokine release and dysfunction of innate and adaptive immunity, it is not surprising that patients with lung cancer may have an elevated susceptibility to severe COVID-19[21,124]. Nevertheless, with appropriate dosing and timing, radiotherapy may be beneficial against acute respiratory distress syndrome, with single-fraction radiation or short courses of radiation being recommended[125,126].

An association of checkpoint inhibitor–based immunotherapy with the aggravation of COVID-19, including increased hospitalization and severe respiratory conditions, was first reported in 31 patients[25]. This negative prognostic link was independent of age, cancer type and other comorbid conditions or coadministered

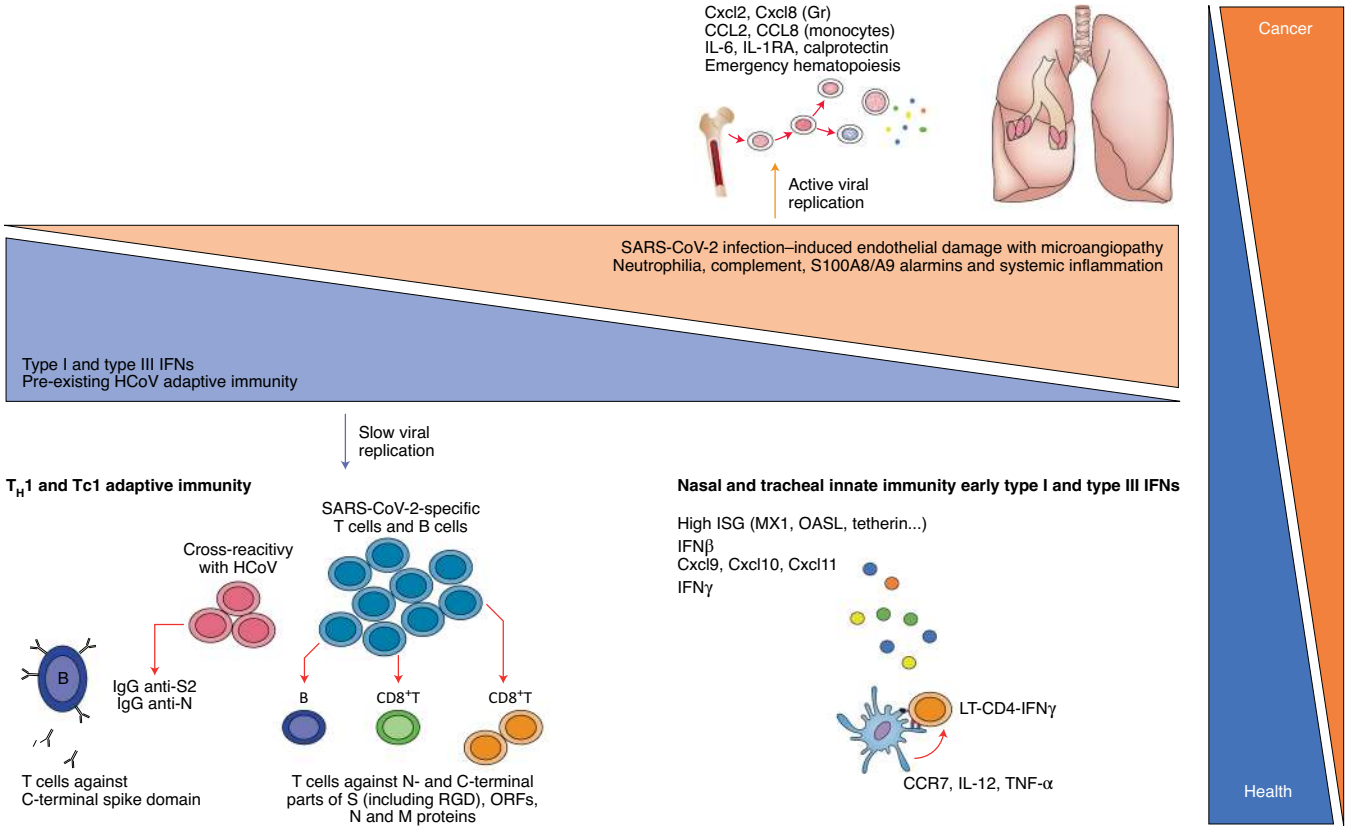

Fig. 2 | A race between viral replication and effective innate and cognate immune responses in cancer. Cancer, at an advanced or metastatic stage, may compromise the delicate equilibrium between viral replication and appropriate innate (for example, type I and III IFN) and cognate immune responses (for example, memory T_H1 responses and antibody-secreting cell cross-reactivity with other beta coronaviruses) in the lung alveolar epithelium and mediastinal lymph nodes. The SARS-CoV-2 virus infects endothelial cells of the lung alveolar capillaries, inducing microthrombi and severe endothelial injury. The failure of the immune system to control early viral replication and to prevent endothelial injury may lead to a marked release of chemokines, cytokines and/or alarmins and a viral sepsis initiated or maintained by pulmonary or medullary hematopoiesis. Gr, granulocyte; HCoV, human coronavirus; IFN, interferon; IL, interleukin; ISG, interferon-stimulating gene; ORF, open reading frame; RGD, Arg-Gly-Asp.

medications such as steroids[25]. In this case, immune-checkpoint inhibitors may have exacerbated immune-related pneumonitis or T cell cytokine release, as previously discussed[127]. Given that many therapeutic actions currently used in oncology may increase the risk of severe SARS-CoV-2 infection, current guidelines related to cancer care during the COVID-19 crisis advise the postponement of all non-mandatory cancer therapies[128].

In recent years we have accumulated an unprecedented understanding of the molecular pathways and immune-tolerance mechanisms governing the incidence and severity of human neoplasia, leading to a large swath of targeted anticancer therapies and immunotherapies. Despite their specificity, however, small-molecule inhibitors and antibody-based therapies induce both on- and off-target effects—the latter including immune-related pneumonitis and diabetes, among other conditions—that could increase the susceptibility of patients with cancer to COVID-19 (Fig. 3, Tables 1 and 2).

Cancer therapeutics with potential anti-COVID-19 effects

The quest for safe agents capable of inhibiting SARS-CoV-2 infection and replication has been intense over the past several months, spurring screening campaigns aimed at drug repurposing[129]. We have identified a number of antiviral drugs with potential antineoplastic properties and, reciprocally, anticancer agents with potential antiviral effects (Tables 1 and 2). In this section we discuss some of these therapeutic agents.

Interferon-based therapies. Recombinant IFNγ and IFNα2b have been widely used against cancer, alone or combined with other cancer treatment modalities[130]. Because SARS-CoV-2 compromises the paradigmatic type 1 interferon antiviral response[111,113,114], IFN administration—either locally by vapor inhalation or systemically, and alone or in combination with ribavirin[106,131], lopinavir/ritonavir, remdesivir[132] or hydroxychloroquine—has arisen as a promising treatment approach against COVID-19[131] (Tables 1 and 2). IFNγ as an inhaled aerosol has been found to be effective against tuberculosis in a controlled clinical trial and to be safe and ameliorate pulmonary function in a phase 1 clinical trial of patients with idiopathic pulmonary fibrosis[133]. Thus, inhaled IFNγ has been proposed as a treatment against COPD, tuberculosis and idiopathic pulmonary fibrosis[133]. It will be interesting to follow SARS-CoV-2 viral loads, virulence and the expression of type I IFN–related genes in the blood and lungs of patients with cancer over the course of their cytotoxic therapies, to estimate the suitability of IFN supplementation in treating COVID-19. Alternatively, another way to increase the systemic circulating levels of type I IFNs would be to use pattern-recognition-receptor agonists. For instance, subcutaneous administrations of a TLR9 agonist increases circulating levels of type I IFNs and decreases hepatitis C viral loads[107].

Immune-checkpoint blockers. On theoretical grounds, immunotherapy with immune-checkpoint blockers might simultaneously boost cytotoxic T lymphocyte (CTL) immune responses[134]

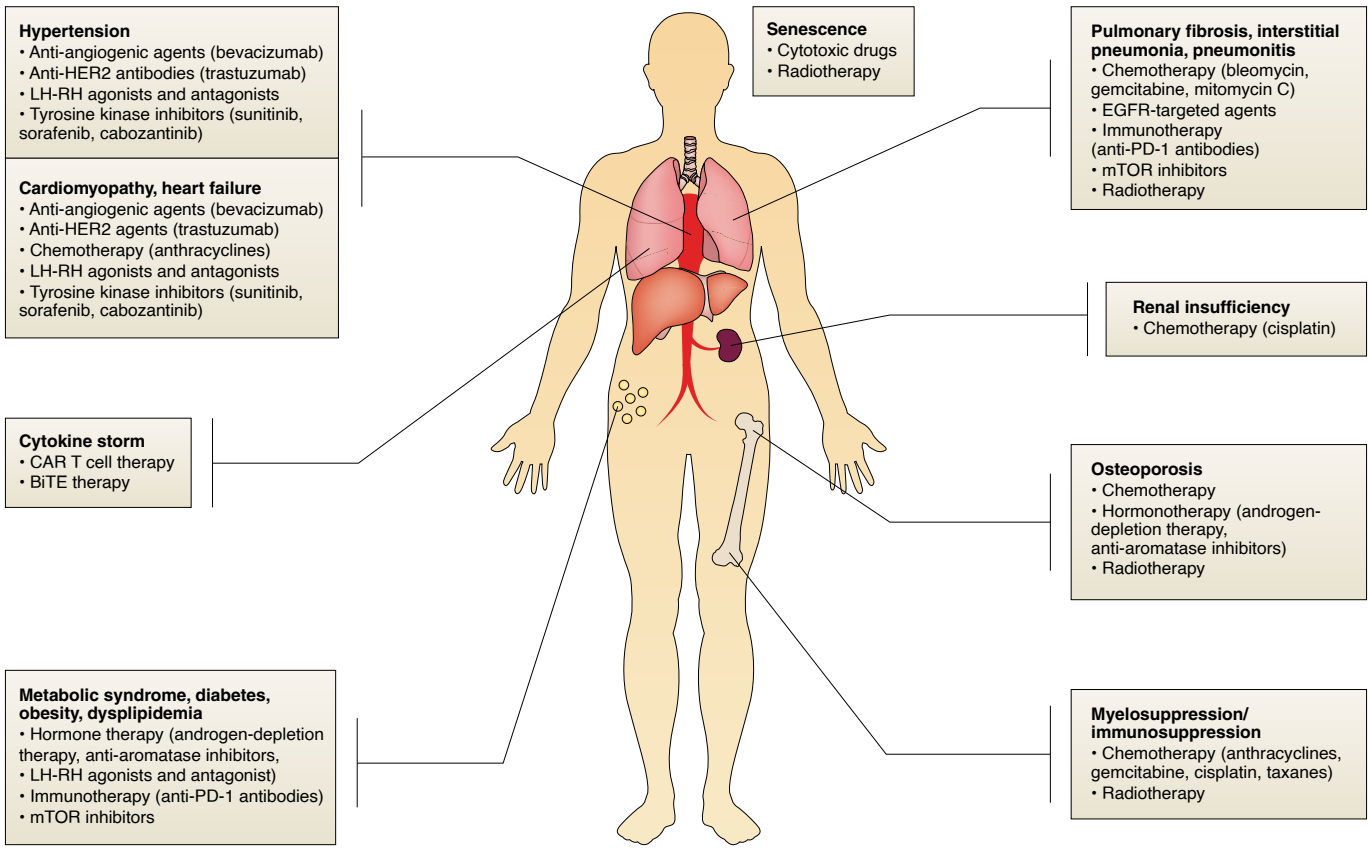

Fig. 3 | Side effects of cancer therapeutics that represent aggravating comorbidities of COVID-19. Major side effects triggered by the main classes of compounds in the oncological armamentarium, including conventional therapies (such as cytotoxic chemotherapy, hormone therapy and radiotherapy), targeted therapies (such as TKI and mTOR inhibitors) and immunotherapies (such as immune-checkpoint inhibitors and CAR T cells), that can exacerbate COVID-19. On- or off-target unwanted effects of the drugs listed in each rectangle are indicated in uppercase letters. See also Tables 1 and 2. BiTE, bispecific T cell engagers; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; LH-RH, luteinizing hormone–releasing hormone; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

against virus-infected and neoplastic cells. At this stage, however, there is little information on the role of T cells during the severe phase of COVID-19. Indeed, T cells also might cause lung immunopathology, meaning that their therapeutic reactivation would exacerbate the disease[135]. In contrast, it is also possible that CTL exhaustion accompanying respiratory virus–induced pneumonitis might render such cells unable to eliminate inflammatory myeloid cells, in which case immune-checkpoint blockers might have anti-inflammatory effects. Indeed, virus-induced secondary hemophagocytic lymphohistiofibrosis (HLH) has been reported to result from inappropriate and prolonged macrophages activation[10,136]. Supporting the view that T cell exhaustion might be causal in the HLH syndrome, a recent clinical study showed a remarkable efficacy of anti-PD-1 antibodies in treating HLH induced by Epstein–Barr virus in four out of six patients treated[137]. However, although a retrospective analysis of 62 patients with lung cancer adjusted for gender and smoking status showed the non-inferiority of anti-PD-1 treatment in cases of concomitant COVID-19 and non-small-cell lung cancer[138], the contrary effect has been reported recently across various malignancies, as discussed above[25].

IL-6–JAK–STAT3 blockade. As outlined above, overt inflammation accompanied by elevated plasma IL-6 levels is associated with severe COVID-19[10] and disseminated malignancies[64]. Despite the absence of a causative link between the manifestation of a cytokine release syndrome and COVID-19 severity, investigators have attempted to interfere with this inflammatory cascade. Tocilizumab, an anti–human IL-6R monoclonal antibody, was recently approved to treat severe SARS-CoV-2-related pulmonary complications by the National Health Commission of the People's Republic of China. Observational studies conducted in China in patients with severe COVID-19 receiving tocilizumab showed an improvement of clinical and radiological outcome[139] and attenuation of the hyperactivated inflammatory immune responses[140] as well as restoration of a robust T cell-associated adaptive immunity[141] in these patients[142,143]. Meta-analyses of studies of IL-6R blockade to treat rheumatoid arthritis revealed a drastic reduction of neutrophil counts in chronically treated patients[144]. Such neutrophil depletion might alleviate lung inflammation in severe COVID-19, as emergency hematopoiesis and bone marrow exodus of immature neutrophils and pre-neutrophils may predict the switch between moderate and severe cases[112]. However, given that the first randomized trial assessing the efficacy of IL-6R blockade in overt pneumonia (the COVACTA phase 3 trial, NCT04320615) did not reach its primary endpoint[145], stratification of patients may be necessary to reach clinical significance.

Androgen-deprivation therapy. Androgen-receptor signaling enhances TMPRSS2 expression in non-prostatic tissues, including lungs[146], potentially contributing to the increased vulnerability of male individuals to SARS-CoV-2. Androgen-deprivation therapy (ADT) decreases the levels of TMPRSS2 and may be used to counter the severity of SARS-CoV-2 infection in male patients, potentially in combination with other inhibitors of viral entry or replication.

Table 3 | Antiviral drugs proposed against SARS-CoV-2 infection displaying antitumor effects

Antiviral drugs	FDA indication	Anti-CoV-2 effect in vitro	Antitumor effect in vitro	Antitumor effect in vivo	Anticancer mechanism	Ongoing clinical trials for viral or cancer indications.
Azithromycin	Acute bacterial sinusitis Acute bacterial infections n COPD Community-acquired pneumonia Pharyngitis/tonsillitis Skin infections Urethritis and cervicitis Genital ulcer disease	Yes[184]	BC cells Pancreatic cancer cells[232] HCC cells[233] Colon cancer, GC cells[234] Myeloma cells[235]	**In mice** Colon cancer[234] Lung cancer[236]	Autophagy inhibition (upregulation of DR4 and DR5)[234] Inhibition of angiogenesis (suppression of VEGF receptor 2 signaling) Apoptosis via both intrinsic and extrinsic pathway[233]	NCT04341207: (+ hydroxychloroquine) SARS-CoV-2 in cancer patients; NCT04369365: COVID-19 prophylaxis in cancer patients; NCT04392128: (+ hydroxychloroquine) COVID-19 treatment in patients with hematological malignancies
Camostat mesylate	No	Yes[237]	No	No	No	No
Favipiravir	No	Yes[188]	No	No	No	No
Hydroxychloroquine	COVID-19 (China with cautions) Malaria Autoimmune diseases	Yes[185]	Glioblastoma cells[238] BC cells[239] Stomach cancer cells[240] Pancreatic cancer cells[241] Kidney cancer cells[242] CRC cells[243] Endometrial cancer cells[244] Myeloma cells[245] Lymphoblastic cells[246] Leukemic cells[247] Lymphoma cells[248] Melanoma cells[249]	**In mice:** Neuroblastoma[250] Gastric cancer[251] Prostate cancer[252] CRCI[243] Melanoma[253] **In humans:** Phase 1 trial in melanoma, glioblastoma and myeloma[254] Phase 1/2 in glioblastoma[255] Prostate[252]	Autophagy inhibition[254] p53 pathway activation[238] Akt signaling pathway inhibition G_2/M cell cycle arrest[239] Bcl2 inhibition[249] Increase in CTL response[256]	**Viral indications:** NCT04341207: SARS-CoV-2 in cancer patients; NCT04381988: COVID-19 prevention in patients receiving RT; NCT04392128: (+ azithromycin) COVID-19 and hematological malignancy **Cancer indications:** NCT01266057, NCT01023737, NCT01480154: advanced cancer; NCT03774472, NCT03774472, NCT03032406: BC; NCT03377179: cholangiocarcinoma; NCT04214418, NCT04145297: gastrointestinal adenocarcinoma; NCT04201457: glioma; NCT03037437: HCC; NCT02722369, NCT00977470: lung cancer; NCT04163107: myeloma; NCT03754179, NCT02257424: melanoma; NCT03081702: ovarian cancer; NCT03598595: osteosarcoma; NCT04132505, NCT03825289, NCT01506973, NCT01494155: pancreatic cancer; NCT03513211, NCT04011410, NCT04011410: prostate cancer; NCT01023737, NCT03015324, NCT04316169: solid tumors

Continued

Table 3 | Antiviral drugs proposed against SARS-CoV-2 infection displaying antitumor effects (continued)

Antiviral drugs	FDA indication	Anti-CoV-2 effect in vitro	Antitumor effect in vitro	Antitumor effect in vivo	Anticancer mechanism	Ongoing clinical trials for viral or cancer indications.
Lopinavir	HIV	Yes at very high dose[257]	Primary effusion lymphoma cells[258] Melanoma cells[259] Lymphoblastic and myeloid leukemia cells[260]	**In mice:** Prostate cancer Colon cancer[261] Melanoma[259] Primary effusion lymphoma[258]	Caspase-dependent apoptosis[258] Suppression of NF-κB activity by inhibition of IKK phosphorylation in PEL cells[258] Inhibition of proliferation, transient activation of Akt and inhibition of P70 S6 kinase[259] ER stress Cell signaling induction, including Akt and mTOR[262] Caspase-dependent apoptosis[260]	No
Nitazoxanide	*Giardia lamblia* diarrhea; *Cryptosporidium parvum* diarrhea	Yes[186]	Glioblastoma cells[263] Breast lymphoma and colon carcinoma cells[264] Colon cancer cells[265] Osteosarcoma cells[266]	**In mice:** CRC[267]	G_1-phase cell cycle arrest, inhibition of protein translation via the mTOR–c-Myc–p27 pathway[264] Decreased ING1 cleavage, autophagy inhibition and ING1 upregulation[263] c-Myc inhibition[266] Growth inhibition and induction of GSTP1-dependent cell death[265]	No
Nafamostat	No	Yes[187]	GC cells CRC cells Gallbladder cancer cells Pancreatic cancer cells HCC cells[268]	**In mice:** HCC[269] Gallbladder cancer[270] Pancreatic cancer[271,272]	Induce mitochondria-dependent apoptosis Canonical NF-κB signaling blockade TNFR1-stimulated cleavage of caspase family members[270]	No
Oseltamivir	Influenza virus infection	Limited[273]	BC cells[274] Pancreatic cancer cells[275]	**Pro-tumorigenic effects in mice:** Increased aggressiveness of canine mammary tumor xenografts[276]	Increase of cleaved caspase 3 expression[274] Blockade of Neu 1 activity[275]	No
Penciclovir	Recurrent herpes labialis	Yes[277]	Oral hairy leukoplakia[278]	No	Accumulation of cells in S phase and apoptotic death[279]	No
Remdesivir	No[109]	Yes[48]	No	No	No	No
Ribavirin	HCV HCC co-infected with HIV	Yes[188] (high dose)	Glioblastoma cells[280] Retinoblastoma[281] SCC[282] HNSCC cells[283] Cervical and colon cancer cells[284] HCC cells[285] RCC cells[286] Prostate cancer cells[286] Lymphoma cell line (Hut78 cells, a cutaneous T cell lymphoma cell line)[287] Lymphoblastic leukemia cells[288] Atypical teratoid/rhabdoid tumor cells[289]	**In mice:** Glioma[280] Glioblastoma[280] Thyroid tumor[290] HCC[285] RCC[291] Leukemia[292] Teratoid/rhabdoid tumor[289] Osteosarcoma[293]	GTP depletion in HeLa cervical cancer cells[283] Cell-cycle arrest and cell death apoptosis (modulation of the eIF4E, EZH2 and ERK pathways)[280] Growth inhibition, STAT1 depletion and IFNγ[287] eIF4E inhibition[282] Potentiation of the effect of IFNα immunotherapy and switch from T_H2 to T_H1[286]	NCT02109744: AML; NCT01268579, NCT02308241: HPV-related malignancies; NCT03585725: indolent follicular lymphoma and mantle cell lymphoma; NCT02940496: liver cancer; NCT01268579: tonsil and/or base of tongue SCC

Continued

Table 3 | Antiviral drugs proposed against SARS-CoV-2 infection displaying antitumor effects (continued)

Antiviral drugs	FDA indication	Anti-CoV-2 effect in vitro	Antitumor effect in vitro	Antitumor effect in vivo	Anticancer mechanism	Ongoing clinical trials for viral or cancer indications.
Ritonavir	HIV	No	Glioma cells[294] Thymomas EL4-T cells[295] Cervical cancer cells[296] HNSCC cells[297] BC cells[295] Prostate cancer cells[298] Myeloma cells[299] Leukemia cells[262] Lymphoblastoid B cells[300] Kaposi sarcoma cells[301]	**In mice:** Thymoma[295] HNSCC[90] BC[302] Renal cell cancer[303] Myeloma cell line[299] Kaposi sarcoma[301] Prostate cancer[298] **In humans:** Glioma—no efficacy[294]	Inhibition of chymotrypsin-like activity of the proteasome[304] Cell signaling induction including Akt and mTOR[262,299] Suppression of pro-survival BCL-2 family member and MCL-1 expression[262,299] Cell-cycle arrest at G_1 phase and apoptosis via downregulation of cyclin D2 and anti-apoptotic gene ER stress[296] Suppression of NF-κB transcriptional activation[300] Inhibition of primary endothelial cell proliferation[301] Decreased TNF-α, IL-6, IL-8 and VEGF production[301]	NCT02948283: multiple myeloma, CLL
Umifenovir	No	Yes[305]	No	No	No	No

AML, acute myeloid leukemia; AMP, adenosine monophosphate–activated protein; BC, breast cancer; BCL-2, B cell lymphoma 2; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; CTL, cytotoxic T lymphocytes; CRC, colorectal cancer; eIF4E, eukaryotic initiation factor 4; ER, endoplasmic reticulum; ERK, extracellular signal–regulated kinase; EZH2, enhancer of zeste homolog 2; FDA, US Food and Drug Administration; GC, gastric cancer; GSTP1, glutathione-S-transferase Pi; GTP, guanosine triphosphate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HNSCC, head and neck squamous-cell carcinoma; HIV, human immunodeficiency virus; HPV, human papillomavirus; IFN, interferon; IL, interleukin; ING1, inhibitor of growth 1; IKK, IκB kinase; MCL-1, myeloid cell leukemia 1; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; NSCLC, non-small-cell lung cancer; PKB, protein kinase B; PEL, primary effusion lymphoma; RCC, renal-cell carcinoma; RT, radiotherapy; SCC, squamous-cell carcinoma; SCLC, small-cell lung cancer; STAT1, signal transducers and activators of transcription protein; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor 1; VEGF, vascular endothelial growth factor.

Accordingly, in one study, patients with prostate cancer receiving ADT had a significantly lower risk of severe COVID-19 than patients who did not receive ADT[147]. An even greater difference was found when comparing patients with prostate cancer receiving ADT to patients with other types of malignancies[147]. Hence, ADT with luteinizing hormone–releasing hormone (LH-RH) modulators or AR inhibitors (Tables 1 and 2) may be worth evaluating as interceptive medications against COVID-19 in prophylactic therapy[148], as well as therapeutic measures for high-risk male patients[147].

Other small molecules. Based on its capacity to inhibit autophagy, hydroxychloroquine (HCQ) is being evaluated in clinical trials to treat autophagy-dependent cancers[149]. In spite of initial reports that HCQ might reduce the duration of SARS-CoV-2 infection and the severity of COVID-19[150], later reports failed to confirm significant effects of the drug[151,152], suggesting that the simultaneous treatment of cancer and COVID-19 with HCQ is not advisable. Nonetheless, there may be other small molecules with dual anticancer and anti-SARS-CoV-2 properties. For example, inhibitors of translation elongation factors may have such a dual activity because both cancer cells and coronaviruses rely on cap-dependent mRNA translation. A recent study that screened a large library of compounds for their capacity to inhibit the replication of SARS-CoV-2 identified inhibitors of elongation factor 1A (eEF1A) and eukaryotic initiation factor 4A (eIF4A)[153] that are currently being evaluated to treat multiple myeloma and *KRAS*-mutated cancers, respectively[153,154](Tables 1 and 2). A separate report screened a library of FDA-approved drugs for inhibitors of coronavirus replication and identified Abelson (ABL) kinase inhibitors, including the anticancer drug imatinib mesylate, as inhibitors of both SARS-CoV and MERS-CoV in vitro[155], and a later study confirmed that imatinib mesylate inhibits SARS-CoV-2 replication in cultured cells as well[156]. Although no in vivo data are yet available, the use of imatinib mesylate to treat COVID-19 is an active area of research (Tables 1 and 2). It should be noted that imatinib mesylate has the capacity to stimulate T and NK lymphocyte–mediated anticancer responses, suggesting that it has immunostimulatory effects[157]. Whether it can also stimulate immune responses against SARS-CoV-2 remains to be investigated. Other small molecules (including JAK1/2 inhibitors[158,159] and anti-CD26 antibody[160–162]; see Tables 1 and 2) currently in use for hematological malignancies to alleviate graft-versus-host disease, cytokine storms or overt inflammatory responses may also be of interest against severe COVID-19, as discussed elsewhere[159,163]. Many additional antiviral and tumoricidal therapeutics or interceptive strategies (such as the anti-inflammatory use of low-dose thoracic irradiation[164–171] or prophylactic vitamin D[172–180]) listed in Tables 1 and 2 are currently under investigation.

Conclusions and future directions

The current COVID-19 crisis has a lesser impact on healthy and fit children and adolescents, while claiming its deadly toll among all other segments of the population: the sick, the unfit and the elderly, including patients with cancer. Malignant disease predisposes to severe COVID-19 for multiple reasons, primarily because (i) patients with cancer fall into general at-risk categories because of their average advanced age, predisposing factors such as obesity

and smoking, and comorbidities such as T2D and hypertension; (ii) cancer intrinsically has negative effects on patients' general health status; and (iii) antineoplastic therapies such as surgery, chemotherapy and radiotherapy may debilitate the immune system and cause immunosenescence and inflammaging. However, whether cancer per se is an independent risk factor for severe COVID-19 remains to be elucidated. It should also be kept in mind that during the COVID-19 outbreak, morbidity and mortality of patients with cancer may have been substantially affected not only by the viral disease itself but also by the extreme pressure exerted by COVID-19 on the healthcare system, which led to the postponement of cancer treatments and the allocation of scarce resources, such as intensive care beds and ventilators, to patients with better prognoses[181–183]. During the present COVID-19 pandemic, oncology departments are frequently confronted with the challenge of treating patients with both cancer and COVID-19, raising a strong argument for exploring therapeutic strategies that could simultaneously improve both diseases. Several drugs that have direct inhibitory effects on SARS-CoV-2 replication in vitro[184–188] (and that still require further characterization in clinical trials; Table 3) are also known for their potential anticancer effects, supporting the idea that such agents, including imatinib mesylate and inhibitors of cap-dependent translation, might have a dual therapeutic activity against cancer and COVID-19. Given the uncertainties about the benefits of PD-1 and/or PD-L1 or IL-6R blockade[25,145], other possibilities are being investigated, such as passive transfer of neutralizing anti-SARS-CoV-2 antibodies for frail patients at a moderate to severe stage of COVID-19[189]. Finally, active vaccination will be an option for patients at high risk of developing severe COVID-19 but still capable of mounting protective antiviral T cell responses[41]. However, candidate vaccines will have to undergo large-scale phase 3 clinical trials to assess their effectiveness and safety, so the earliest regulatory approvals and roll-outs are not expected before late 2020 or early 2021. All these possibilities await urgent investigation to allow clinical oncologists to navigate between cancer and COVID-19 in full compliance with the Hippocratic Oath: *primum non nocere*—first, do no harm.

Received: 28 May 2020; Accepted: 2 September 2020;
Published online: 2 October 2020

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Acknowledgements

L. Z. and G. K. are supported by the Ligue contre le Cancer (équipe labellisée); Agence Nationale de la Recherche (ANR)–Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; AMMICa US23/CNRS UMS3655; Association pour la recherche sur le cancer (ARC); Association "Le Cancer du Sein, Parlons-en!"; Cancéropôle Ile-de-France; Chancelerie des universités de Paris (Legs Poix), Fondation pour la Recherche Médicale (FRM); a donation by Elior; European Research Area Network on Cardiovascular Diseases (ERA-CVD, MINOTAUR); Gustave Roussy Odyssea, the European Union Horizon 2020 Project Oncobiome; Fondation Carrefour; High-end Foreign Expert Program in China (GDW20171100085), Institut National du Cancer (INCa); INSERM (HTE); Institut Universitaire de France; LeDucq Foundation; LabEx Immuno-Oncology (ANR-18-IDEX-0001); RHU Torino Lumière; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and Personalized Medicine (CARPEM). A. M. has received pre-clinical and clinical cancer research funding from the Fondation MSD Avenir and Malakoff Médéric. L.D. has received support by the Philanthropia Fondation. L. D. and L. Z. are supported by the Gustave Roussy–sponsored clinical study on COVID-19 (ONCOVID; NCT04341207 supported by the Gustave Roussy Fondation, the Dassault family and Malakoff Humanis.

Competing interests

The authors declare no competing interests.

Additional information

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