Title Page

Title: Repurposing of anticancer drugs expands possibilities for antiviral and anti-inflammatory discovery in COVID-19

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Jean-Marie Michot: Over the last 5 years, principal/sub-investigator of clinical trials for: Servier, Abbvie, Agios, Amgen, Argenx, Astex, AstraZeneca, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Genentech, Janssen, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Roche, Sanofi, Xencor

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Abstract

In 2020, the COVID-19 pandemic led to an unprecedented destabilization of the world's health and economic systems. The rapid spread and life-threatening consequences of COVID-19 have imposed testing of repurposed drugs, by investigating interventions already used in other indications, including anti-cancer drugs. The contours of anti-cancer drug repurposing have been shaped by similarities between the pathogenesis of COVID-19 and malignancies, including abnormal inflammatory and immunological responses. In this Review we will discuss the salient positive and negative points of repurposing anticancer drugs to advance treatments for COVID-19.

Statement of significance:

Targeting anti-inflammatory pathways with JAK/STAT inhibitors or with anti-cytokines therapies aiming to curb COVID-19-related cytokine storm, using antiangiogenic drugs to reduce vascular abnormalities or immune checkpoint inhibitors to improve anti-viral defenses, could be of value in COVID-19. However, conflicting data on drug efficacy point to the need for better patient selection and biomarker studies.
INTRODUCTION

A huge international effort has been made in the last 50 years to highlight cancers mechanisms of proliferation and dissemination (1). Beyond chemotherapy, new drugs such as targeted therapy, immunotherapy, epigenetic modifiers and more recently cellular therapies have been approved and have succeeded in improving lifetime expectancy and quality of life of patients living with cancer (2). Apart from their antitumor effects, anticancer drugs also increased knowledge about physiological pathways in healthy tissues. Outside of cancer indication, some anti-cancer agents were then developed in extended indications. For example, JAK inhibitors, first approved to treat myeloproliferative neoplasia with activating JAK2 mutations, have now extended indications in rheumatological diseases and are under development for several dysimmune diseases.

At the end of 2019, the world was destabilized by the emergence of new coronavirus called SARS-CoV-2 and the COVID-19 pandemic (3). International relationships were greatly impacted by the virus dissemination and government interventions to limit its spread (4,5). A huge effort by the scientific and biomedical community has sought to understand the pathophysiology and clinical manifestations of COVID-19. The full RNA sequence of the new coronavirus was identified with unprecedented speed, and insights into how it interacts with human cells quickly followed (6-8). Concomitantly, clinical studies worldwide revealed the different clinical aspects of severe COVID-19 manifestations characterized by brutal cytokine release syndrome and visceral inflammatory involvement, particularly pneumonitis (9).

The main risk factors for developing severe COVID-19 are age, male sex, obesity, cardiovascular comorbidities and diabetes (9,10). Laboratory science has shown that severe COVID-19 infections is mainly driven by immunopathological inflammatory pathways mediated by IL-6, IL-8, TNF alpha and interferon gamma (8). Large clinical trials has since evaluated antiviral drugs such as remdesivir (11), anti-cytokines approaches with anti-IL6 (12) and dexamethasone (13), passive immunotherapy such as patient convalescent plasmatherapy or recombinant cocktail antibodies against anti-spike antibody (14).

COVID-19 Pathological Mechanisms
Coronavirus disease 2019 (COVID-19) is a human infectious and inflammatory disease related with SARS-CoV-2 infection. A large number of individuals infected by SARS-CoV-2 do not develop symptoms or develop mild manifestations characteristic of flu-like syndrome and acquired immunity directed against the new betacoronavirus (15). However, about 10 to 15% of patients progress to severe pneumonia and respiratory distress and eventually require admission in the intensive care unit (ICU). Nearly 25-30% of patients admitted in the ICU will ultimately die. After an incubation phase and 7 to 10 days of symptoms, a sudden viral pneumonia characterized by profound hypoxemia and interstitial lung disease may occur, not only related to virus infection, but also to cytokine storm and immunothrombosis phenomenon (15).

Angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease TMPRSS2, expressed by human alveolar and endothelial cells, participate to the virus cell internalization and activate the spike (S) protein of SARS-CoV-2 into the human cells (16). Obesity is associated with ACE2 and TMPRSS2 overexpression at the surface of endothelial cells through dysregulation of leptin pathway (17). Also, TMPRSS2 is an androgen regulated protein, which could explain male sex predisposition to develop severe forms of COVID-19 (18). Primum movens to severe COVID-19 seems to be the immunothrombosis phenomenon, characterized by small blood vessels thrombosis associated with microangiopathy and inflammatory infiltration in alveolar capillary, which leads to alveolar oedema and associated systemic cytokine storm (19,20). Patients with severe COVID-19 develop an inflammatory state characterized by increased concentrations of plasmatic cytokines, chemokines and alarmins related to activation and recruitment of inflammatory cells, such as interleukin (IL)-1beta, IL-6, IL-8, tumor necrosis factor (TNF), granulocyte-colony stimulating factor (G-CSF), chemokine ligand (CCL)2 and calprotectin (S100A8 and S100A9) (21,22). The most severe COVID-19 infections correlate with low type 1 interferon concentration in blood and transcriptomic signature in peripheral blood mononuclear cells (PBMC) (23). Defects in type 1 interferon can be related to functional genetic polymorphisms or auto-immunity directed against type 1 interferon (24,25). Beside soluble inflammatory and immune factors, patients who develop most severe forms of COVID-19 present with pathological hematologic and immunologic features, such as increased neutrophilia, monocytopenia (with loss of non-conventional monocytes) and lymphocytopenia (22,26). Patients with severe COVID-19 have profound lymphocytopenia with low, but activated and exhausted, CD4+ and CD8+ T cells such as CD19+ B cells and particularly early plasmablasts, which do not succeed to establish effective antiviral immunity (27-29). Finally, patients with severe COVID-19 are also characterized in their blood and lungs by an emergency myelopoiesis
with immature neutrophils and monocytes with deleterious pro-inflammatory abilities and immunosuppressive function, which can limit the development of effective adaptive immunity (22).

Patients living with cancer are exposed to a significantly higher risk of severe SARS-CoV-2 infection and higher risk of death (30). Particularly, patients with hematological malignancies have a higher mortality rate related to COVID-19 than patients with solid tumors (31,32). Among patients with cancer, patients with more recent, disseminated and symptomatic diseases undergoing chemotherapy, are generally those with the most severe infections (33). The explanation for these increased risks remained unclear, such as the amplitude of viral load that could independently predict mortality in both patients' populations, which certainly reflects that immunosuppression related to cancer predisposes to a more intense viral replication (34). These data provide a basis for priority for COVID-19 vaccination in patients living with cancer (35).

Administration of anti-cancer treatments are also important factors that influence the risks of infectivity and severity of COVID-19 (36,37). While chemotherapy was shown to be associated with a higher risk of COVID-19 worsening, interestingly patients treated with immune checkpoint immunotherapies or targeted anticancer therapies were not (33,34,36-38). Other studies suggested that patients treated for cancer and receiving anti-androgenic treatments or anti-angiogenic drugs could have improved outcomes (39-41). As these treatments do not seem to increase COVID-19 severity and might improve outcomes of patients, the discussion of repurposing anticancer drugs for COVID-19 began (Figure 1). Anti-cancer drugs currently undergoing investigation in clinical trials for the treatment of COVID-19 are depicted in Table 1.

**REPURPOSING DRUGS from ONCOLOGY**

Anti-inflammatory drugs

*Dexamethasone.*

Corticosteroids, in particular dexamethasone, are commonly used drugs to treat hematological malignancies such as multiple myeloma, non-Hodgkin's lymphoma, or acute lymphoblastic leukemia. For the treatment of severe COVID-19 with viral pneumonia, the British Recovery study has shown that dexamethasone improves the overall survival of patients needing
respiratory support (either invasive mechanical ventilation or oxygen alone) (13). Dexamethasone then became the standard of care for patients hospitalized with COVID-19 with viral pneumonia requiring oxygen support.

Other anti-inflammatory drugs targeting new molecular pathways may be tested for severe COVID-19 patients. Biological studies have shown that calprotectin is one of the key molecules implicated in the inflammatory cascade leading to severe forms of COVID-19 (22), suggesting calprotectin as a potential new therapeutic target.

**Anti-cytokines IL-6.**

In hematology oncology, cytokine release syndrome is known as a frequent complication associated with chimeric antigen receptor-T (CAR-T) cells or bispecific anti-tumor antibodies. Cytokine release syndrome (CRS) is characterized by fever, hypotension and eventually hypoxemia or biological abnormalities including coagulopathy (42), related to a sudden release of cytokines by the immune system when the latter encounters the tumor antigen under the effect of anticancer treatment (43). CRS is dominated by high levels of IL-6 in serum, which led to propose anti-IL6 receptor therapies to control CRS. (43). The respiratory distress and high fever during COVID-19 viral pneumonia may share similarities with CRS (44).

The cytokine storm induced by the SARS-CoV-2 virus is becoming better understood. Cytokines such as interleukin-6 (IL-6), interleukine-10 (IL-10) and Tumor Necrosis Factor alpha (TNFa), and the overactivation of the systemic complement pathways, namely substrates C5b-9 and C4d, are correlated with the severity of COVID-19 (45). This systemic inflammation and complement activation are also associated with the phenomenon of immunothrombosis, a hyper coagulopathy state affecting up to 16% of patients hospitalized for COVID-19 (46). Dysregulated neutrophil extracellular traps in endothelium of patients also contribute to immunothrombosis in severe COVID-19 patients, by propagating inflammation and microvascular thrombosis (46).

Several anti-cytokines therapeutics aiming to curb COVID-19-related cytokine storm have been investigated. Retrospective studies and randomized clinical trials evaluating the most used anti-IL6 receptor blockers tocilizumab antibody suggested a therapeutic effect of the drug (47-49), while other clinical trials failed to complete their efficacy endpoints (50-52). Overall, the results of additional clinical trials with longer follow-up of enrolled patients are needed to better
understand the magnitude of the therapeutic effect anti-IL6 receptor therapy in COVID-19 patients. A more precise, and probably more selective, definition of the patient population with COVID-19 who may or may not benefit from anti-IL6 receptor therapy remains to be clarified in future studies.

**Targeting BTK signaling pathway**

Bruton tyrosine kinase (BTK) inhibitors are approved therapies for treating lymphoid blood disorders such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), or Waldenstrom's disease (53). The SARS-CoV-2 virus can generate an overactivation of immune cells, including both B and T cells, leading to a "cytokine storm" thus contributing to acute lung injury and respiratory distress (21). BTK pathway effector molecules contribute to the cytokine storm and are potential targets for the drug therapy of COVID-19 (41). An observational study evaluating the use of acalabrutinib in 19 patients with COVID-19 hospitalized and requiring oxygen supplementation suggested potential efficacy. However, the BTK inhibition hypothesis must be interpreted with caution, because of the concomitant use of dexamethasone in initial studies. Definitive results of a randomized controlled clinical trial investigating acalabrutinib for patients with COVID-19 (CALAVI phase II trial: NCT04380688, NCT04346199) are pending, but a recent press communication reported that the study did not reach its primary endpoint as compared with best supportive care alone.

**Implications of JAK/STAT inhibitors to treat COVID-19**

Janus Kinase (or Just Another Kinase) (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce signals transferred by the cytokines via the JAK-STAT signaling pathway. JAK/STAT pathway is overactivated by activating mutations in JAK2 hematological malignancies (54) such as myeloproliferative syndromes including myelofibrosis or polycythemia vera. The JAK/STAT pathway was recently highlighted as an important inflammatory signaling pathway in inflammatory diseases and JAK inhibitors are approved drugs in rheumatoid arthritis. JAK inhibitors are expected to reduce cytokine storms (55), therefore it was suggested as a promising therapy to mitigate the inflammatory cascade generated by COVID-19 (56). Preclinical studies in humans suggest that JAK inhibitors may restrict the expression of the ACE2 receptor - necessary for the entry of the SARS-CoV-2 virus - into human cells (57,58). A clinical study of 601 patients suggests that baricitinib, a JAK1/2 inhibitor, could improve the outcome of patients with severe COVID-19, primarily by reducing the rampant...
immune inflammation (58). A double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with COVID-19, concluded that baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19 (59). Data from randomized trials with a JAK inhibitor alone versus placebo for the treatment of COVID-19 are still pending (Table 1), while one trial was terminated early for futility (NCT04377620). In light of the hypercoagulability state of COVID-19, vigilance is recommended given the potentially increased risk of thrombosis reported with some JAK inhibitors (60).

**Antiangiogenics**

The immunothrombosis phenomenon is associated with upregulation of macrophages, complement substrates, platelet activation, thrombosis, and proinflammatory markers (61,62). Moreover, pro-angiogenic factors, such as VEGF and angiopoietin 2, are crucial factors implicated in vascular permeability and pulmonary edema of patients with COVID-19 (63). In an autopsy study performed on lungs from people who died from viral infections, the amount of new vessel growth associated with COVID-19 was 2.7 times higher as compared to those found in patients with H1N1 influenza virus. Pathological findings in COVID-19 patients indicate severe endothelial injury, disruptive cell membranes and widespread thrombosis (20). In severe forms of COVID-19, some researchers suggest antiangiogenics drugs may suppress pulmonary edema by inhibiting proangiogenic factors and by promoting a vascular normalization. In a single arm trial investigating bevacizumab plus standard of care in 26 patients with severe COVID-19 infection (NCT04275414), a single dose of 7.5 mg/kg of bevacizumab was associated with rapid improvement in PaO2/FiO2 ratios, improved oxygen support status in 92% of patients by day 28 (versus 62% in the external comparison cohort treated with standard of care only) and significant radiological reduction of pneumonia lesions within 7 days. Of note, no drug related serious adverse effects were reported (64). However, in this study, patients were excluded if they had received full-dose anticoagulant within 10 days before enrollment or had thrombosis within 6 months before enrollment, criteria which apply to a significant proportion of patients with cancer. Other ongoing clinical trials are investigating bevacizumab and results are pending (Table 1). A clinical trial (NCT04342897) evaluating the effect of targeting angiopoietin 2 in patients with COVID-19, was terminated early for futility. Further trials evaluating antiangiogenics should...
carefully assess the risk of thrombosis and probably offer concomitant anticoagulation treatments to control this risk of thrombosis.

**Immune checkpoint blockade**

An effective immune response against viral infections depends on the activation of host CD8+ T cells expected to eliminate cells containing the SARS-CoV-2 virus (65,66). In severe COVID-19 patients, there is a reduced number of CD4+ and CD8+ positive T cells, while the surviving T cells exhibit an exhausted phenotype, with higher level of PD-1 expression (67,68). The reduced T cells counts (total T cells <800/uL, CD8+ cells < 300/uL and CD4+ cells < 400/uL) in blood of patients with COVID-19 were negatively correlated with the levels of TNF-α, IL-6, and IL-10, (68). In an observational clinical study of 113 patients with cancer and laboratory confirmed COVID-19 while on treatment with immune-checkpoint inhibitors (ICI) without chemotherapy, the mortality by COVID-19 in patients under ICI did not seem to be higher compared to rates reported in the general cancer population (69). Another observational study conducted in 178 patients with cancer managed for COVID-19 did not identify increased risk of clinical worsening or death in patients treated with ICI for cancer. Conversely, patients receiving cytotoxic chemotherapy had an increased risk of clinical worsening and death in the univariable analysis and a trend towards a higher risk of death in the multivariable analysis, after adjusting for ECOG performance status and cancer status (33). Similarly, chemotherapy negatively impacted survival outcomes in patients with thoracic cancer and COVID-19 in the TERAVOLT cohort, as opposed to immunotherapy and targeted therapy (70,71). However, in another observational study including 423 cancer patients with symptomatic COVID-19, treatment with ICI (N=31) was a predictor for hospitalization and severe disease, while treatment with chemotherapy was not (72). Overall, these data are limited and their conflicting interpretation impose caution about potential interest of repurposing ICI for COVID-19. ICI might have a dual effect, it might enhance T-cell mediated viral clearance in the early phase, but it has been suggested to also facilitate late-inflammatory states by promoting T regulatory cells activation and the exacerbation of the cytokine storm (73,74). The sum of these data suggests that future trials evaluating the potential interest of ICI for COVID-19 should select the patient population to be treated, most likely considering treatment in the early phase of the disease and without a cytokine storm.

**Anti-androgenic treatment**
SARS-CoV-2 virus harness the TMPRSS2 receptors to enter within the host human cell and these receptors are regulated by the androgen receptor (16). TMPRSS2 gene is strongly upregulated in prostate cancer cells and it has a testosterone-activated response element, suggesting potential anti-androgenic treatment in patients with COVID-19. In a cohort of men with prostate cancer, COVID-19 infection was less likely to be reported in patients treated with androgen deprivation therapy (ADT) as compared with those without (ADT 4/5273 cases versus 114/37, odds ratio 4.05, 95% confidence interval 1.55–10.59, P = 0.00043) (39). However, ADT effect seems to be modest, as the number of patients needed to treat with ADT for the prevention of one case of COVID-19 was 434. This minimal potential therapeutic effect yields ADT a less appealing option in case of patients without prostate cancer, also considering the associated side effects of ADT (75). Moreover, preliminary data from multicenter registries do not support a decrease in COVID-related mortality with antiandrogenic drugs (76). Ongoing trials testing bicalutamide, enzalutamide or GnRH antagonists are ongoing (Table 1). Also, camostat mesylate, a direct TMPRSS2 inhibitor is currently investigated in several clinical trials for COVID-19 as monotherapy or in combination with bicalutamide, with the aim of reducing the SARS-CoV-2 viral burden and forestall complications of COVID-19 (NCT0435328, NCT04583592, NCT04608266, NCT04524663, NCT04652765).

The targeting of host interacting proteins and kinases dysregulated during infection

Recent preclinical studies on SARS-CoV-2 infected cells found important interactions between human proteins and SARS-CoV-2, and a dramatic rewiring of phosphorylation on host and viral proteins, highlighting how the virus uses the host’s post-translational regulatory systems to induce rapid signalling changes (77-79). The mapping of proteomic changes to pharmacological modulators identified promising target-drug pairs that might trigger robust anti-viral effects (77,78). For instance, eEF1A was identified in SARS-CoV virions (80,81) and plitidepsin, an eEF1A inhibitor approved in Australia for the treatment of multiple myeloma, was shown to have a potent anti-SARS-CoV-2 antiviral activity in preclinical studies (IC90= 0.88 nM) (81). Plitidepsin was 27.5-fold more potent than remdesivir in vitro, while having limited toxicity (81). These data indicated promising therapeutic repurposing for plitidepsin as antiviral therapy for COVID-19 and phase II/III trials are pending.

Another target is the virus-induced upregulation of casein kinase 2 (CK2), that might facilitate cell-to-cell spread by driving actin polymerization. CK2 inhibition with silmitasertib, currently tested in recurrent medulloblastoma (NCT03904862), showed robust anti-viral activity in SARS-
CoV-2 infected cells (77). Phosphatidylinositol-3-Phosphate/Phosphatidylinositol 5-Kinase (PIKfyve) is a protein that resides in early endosomes, being involved in endomembrane homeostasis. Its inhibition has the potential to inhibit viral entry, making it a promising target for the treatment of early COVID-19 infection. *In vitro* experiments showed that apilimod, a specific PIKfyve kinase inhibitor investigated in early phase clinical trials for the treatment of non-Hodgkin lymphoma, successfully inhibited viral replication during entry (82). Apilimod is currently evaluated for its impact on SARS-CoV-2 viral load in patients with confirmed COVID-19 infection treated in an out-patient setting (NCT04446377). SARS-CoV-2 also increases the phosphorylation of cyclin dependent kinase 2 (CDK2) and promotes cell cycle arrest in the S/G2 phase, that may facilitate viral replication (77,83). Accordingly, strong antiviral activity for the CDK inhibitor dinaciclib was observed across two SARS-CoV-2 infected cell lines (77). Other examples of promising target-drug pairs include AXL and gilteritinib (FDA approved for relapsed or refractory acute myeloid leukemia with FLT3 mutations) or p38 and p38 inhibitors, such as ralimetinib (undergoing development in ovarian cancer) (77).

**Conclusion**

A better understanding of molecular mechanisms associated with COVID-19 as well as clinical observations from patients with COVID-19 and concomitantly treated for cancer generate various hypotheses concerning potential anti-cancer drug repositioning. While strong clinical evidence is still lacking, the sum of these data suggests anticancer drugs could be regarded as potent antiviral therapies, with both direct antiviral effects and indirect effects by blocking signaling pathways such as JAK/STAT or abnormal angiogenesis. Clinical trials for hypothesis testing of anticancer drugs is an encouraging strategy for discovering new possible therapies for COVID-19.

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References


### Table 1. Examples of cancer drugs currently tested for COVID-19

<table>
<thead>
<tr>
<th>Targeted pathway</th>
<th>Drug</th>
<th>MoA related to Covid pathogenesis</th>
<th>COVID-19 severity</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-cytokines</strong></td>
<td></td>
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<tr>
<td>IL-6</td>
<td>Tocilizumab</td>
<td>Prevents the “cytokine storm”</td>
<td>Severe</td>
<td>NCT04377659 Phase II</td>
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<td></td>
<td>Severe</td>
<td>NCT04363853 Phase II</td>
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<td></td>
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<td></td>
<td>Requiring hospitalization</td>
<td>NCT04317092 (TOCIVID-19)</td>
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<td></td>
<td>Requiring hospitalization</td>
<td>NCT04372186 (EMPACTA) Phase III</td>
</tr>
<tr>
<td>IL-8</td>
<td>BMS-986253</td>
<td>Prevents the “cytokine storm”</td>
<td>Severe</td>
<td>NCT04347226 Phase II</td>
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<tr>
<td><strong>JAK inhibitors</strong></td>
<td>Pacritinib (JAK2i)</td>
<td>Blocks multiple, pro-inflammatory cytokines; anti-viral effects by impeding cellular viral endocytosis</td>
<td>Severe</td>
<td>NCT04404361 (PRE-VENT) Phase III</td>
</tr>
<tr>
<td></td>
<td>Baricitinib (JAK1/2i) + antiviral therapy</td>
<td></td>
<td>Moderate and severe</td>
<td>NCT04373044, Phase II</td>
</tr>
<tr>
<td></td>
<td>Baricitinib</td>
<td></td>
<td>Moderate and severe</td>
<td>NCT04346147, Phase II NCT04390464, Phase IV</td>
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<tr>
<td></td>
<td>Ruxolitinib (JAK1/2i)</td>
<td></td>
<td>Severe</td>
<td>NCT04331665</td>
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<tr>
<td><strong>BTK</strong></td>
<td>Ibrutinib</td>
<td>Abrogation of pulmonary inflammatory cytokines, lung injury</td>
<td>Requiring hospitalization</td>
<td>NCT04439006 Phase II</td>
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<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04375397 (iNSPIRE) Phase II</td>
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<td></td>
<td>Acalabrutinib</td>
<td></td>
<td>Requiring hospitalization</td>
<td>NCT04346199 (CALAVI) Phase II</td>
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<td>TL-895</td>
<td></td>
<td>Requiring hospitalization</td>
<td>NCT04419623 Phase I/II</td>
</tr>
<tr>
<td><strong>Antiangiogenic</strong></td>
<td>Bevacizumab</td>
<td>Inhibits VEGF, a key factor to increase vascular permeability and induce pulmonary edema caused by inflammatory exudation in COVID-19 infection</td>
<td>Severe</td>
<td>NCT04305106 (BEST-RCT)</td>
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<td></td>
<td>Severe</td>
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<td>NCT04275414 (BEST-CP)</td>
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<td>Requiring more than 3L of oxygen</td>
<td></td>
<td>NCT04344782 (CORIMMUNO-BEVA)</td>
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<td><strong>Androgen blockade</strong></td>
<td>Bicalutamide</td>
<td>Blocks TMPRSS2</td>
<td>Mild/moderate COVID-19 requiring hospitalization</td>
<td>NCT04374279 (RECOVER)</td>
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<td></td>
<td></td>
<td>Symptomatic</td>
<td></td>
<td>NCT04509999</td>
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<td></td>
<td>Degarelix</td>
<td>Suppresses androgens, that might regulate TMPRSS2 expression in lung tissue</td>
<td>Veterans hospitalized for COVID-19 (severity 3,4,5 on the influenza scale)</td>
<td>NCT04397718 (HITCH)</td>
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<td>Enzalutamide</td>
<td>antiandrogen inhibiting the expression of androgen regulated proteins, such as TMPRSS2</td>
<td>High risk COVID-19 male patients, mild symptoms, not requiring hospitalization</td>
<td>NCT04456049</td>
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<td></td>
<td></td>
<td>Mild/severe COVID-19 requiring hospitalization</td>
<td></td>
<td>NCT04475601 (COVIDENZA)</td>
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<tr>
<td><strong>Other</strong></td>
<td>Interferon alpha</td>
<td>Abrogates type I IFN deficiency in severe Covid19</td>
<td>Severe</td>
<td>NCT04534725 (C-SMART)</td>
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<td>IMM-101</td>
<td>Stimulates dendritic cells</td>
<td>Prevention of severe COVID-19</td>
<td>NCT04442048 (COV-IMMUNO)</td>
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<td>FT516</td>
<td>engineered NK cells expressing CD16, that destroy antibody-coated target cells</td>
<td>Hospitalized COVID-19 patients with hypoxia</td>
<td>NCT04363346</td>
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<td></td>
<td>Rintatolimod +/− IFN alpha</td>
<td>mimics viral infection, stimulates the immune system to limit viral replication</td>
<td>Mild/moderate</td>
<td>NCT04379518</td>
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<td></td>
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<td>Double stranded RNA</td>
<td></td>
<td>Phase I/II</td>
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<tr>
<td>Mechanism of Action</td>
<td>Drug</td>
<td>Pharmacological Effect</td>
<td>Disease Severity</td>
<td>Clinical Trial ID</td>
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<td>PI3K - AKT</td>
<td>Duvelisib (PI3K inhibitor)</td>
<td>Inhibit aberrant hyperactivation of the innate immune system</td>
<td>Severe</td>
<td>NCT04487886 (DAMPEN-CI)</td>
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<td>Severe</td>
<td>NCT04372602</td>
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<td>MAPKAPK2 (MK2) inhibitor</td>
<td>(ATT)-450 (HSP inhibitor)</td>
<td>Inhibits multiple inflammatory cytokines</td>
<td>Moderate or severe</td>
<td>NCT04481685</td>
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<td>HSP</td>
<td>MPT0B640 (HSP inhibitor)</td>
<td>Inhibits defective HSP in Covid19, to avoid the “cytokine storm”</td>
<td>Requiring hospitalization</td>
<td>NCT04526717</td>
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<td>SK2</td>
<td>Opaganib (SK2 selective inhibitor)</td>
<td>Anti-inflammatory and anti-viral activity</td>
<td>Requiring supplemental oxygen at baseline</td>
<td>NCT04414618</td>
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<td>Nucleo-cytoplasmic transport inhibitor</td>
<td>Selinexor (selective inhibitor of XPO1)</td>
<td>Anti-inflammatory activity, reduction of pro-inflammatory cytokines levels</td>
<td>Severe</td>
<td>NCT04534725 (C-SMART)</td>
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<td>SUMO</td>
<td>TAK-981</td>
<td>Inhibits SUMOnylation, a process involved in the posttranslational modification of the coronavirus N protein</td>
<td>Moderately severe</td>
<td>NCT03648372</td>
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<td>eEF1A inhibition</td>
<td>Plitidepsin</td>
<td>Anti-viral activity by the inhibition of eEF1A, identified in in SARS-CoV-2 virions</td>
<td>Requiring hospitalization</td>
<td>NCT04382066 (APLICOV-PC)</td>
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<td>eEF4A inhibition</td>
<td>Zotatifin</td>
<td>Antiviral activity by impairing the cap-dependent mRNA translation of SARS-CoV-2</td>
<td>Mild or moderate</td>
<td>NCT04632381 (PROPEL)</td>
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<tr>
<td>CK2 inhibition</td>
<td>Silmitasertib</td>
<td>Anti-viral activity by inhibiting CK2, involved in viral replication and virus-induced cytoskeleton organization</td>
<td>Moderate</td>
<td>NCT04663737</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>NCT04668209</td>
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ALI: acute lung injury; ARDS: acute respiratory distress syndrome; CK2: casein kinase 2; eEF1A: Eukaryotic translation elongation factor 1 alpha 1; GM-CSF: granulocyte macrophage-colony stimulating factor; HSP: heat shock protein; IFN: interferon; MoA: mechanism of action; MoAb: monoclonal antibody; NF-kB: Nuclear Factor kB; SK2: sphingosine kinase-2; TMPRSS2: Transmembrane protease, serine 2; VEGF: vascular endothelial growth factor.
Figure Legends

Figure 1. Anticancer drugs proposed for drug repurposing in COVID-19 infection and presented according to their potential therapeutic targets. In mild to moderate COVID-19, anti-PD1 reinforces the T cell immune system and may improve viral clearance. Antiandrogen drugs block the TMPRSS2 receptor used by the virus for entry into the cell. In severe COVID-19, JAK/STAT or BTK inhibitors mitigate the inflammatory signaling cascade into the cell and help control the cytokine storm. Anti-cytokines (anti-IL6 receptor) directly reduce the cytokine storm by blocking IL6 receptor in cell surface. Antiangiogenics drugs could limit vascular abnormalities induced by the virus in endothelium. Other anticancer drugs, such as plitidepsin and apilimod, have antiviral activity against SARS-CoV-2 by targeting the host protein eEF1A or by impacting endosomal homeostasis, respectively.
Mild / moderate COVID-19

- **T cells**
  - PD-1
  - PD-1 inhibitors
  - Antiandrogen drugs
  - TMPRSS2
  - ACE
  - Apilimod
  - Plitidepsin
  - TMPRSS2-ERG fusion in prostate cancer (nucleus)

Severe COVID-19

- **Host cell**
  - JAK inhibitors
  - BTK inhibitors
  - TLR7/8
  - NF-kB
  - NLRP3 inflammasome

- **vascular abnormalities**
- **Antiangiogenic drugs**
- **Sars-CoV2**; **T-cell**; **ACE**: angiotensin-converting enzyme 2; **TMPRSS2**: Transmembrane Serine Protease 2; **macrophage**; **interleukin receptor**; **TLR 7/8**: Toll-like receptor 7/8; **NLRP3**: NLR family pyrin domain containing 3 inflammasome; **neutrophil**; **inhibition**.

Figure 1
Repurposing of anticancer drugs expands possibilities for antiviral and anti-inflammatory discovery in COVID-19

Mihaela Aldea, Jean-Marie Michot, Francois-Xavier Danlos, et al.

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