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Clinical and immunologic implications of COVID-19 in patients with melanoma and renal cell carcinoma receiving immune checkpoint inhibitors

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ABSTRACT
The clinical and immunologic implications of the SARS-CoV-2 pandemic for patients with cancer receiving systemic anticancer therapy have introduced a multitude of clinical challenges and academic controversies. This review summarizes the current evidence, discussion points, and recommendations regarding the use of immune checkpoint inhibitors (ICIs) in patients with cancer during the SARS-CoV-2 pandemic, with a focus on patients with melanoma and renal cell carcinoma (RCC). More specifically, we summarize the theoretical concepts and available objective data regarding the relationships between ICIs and the antiviral immune response, along with recommended clinical approaches to the management of melanoma and RCC patient cohorts receiving ICIs throughout the course of the COVID-19 pandemic. Additional insights regarding the use of ICIs in the setting of current and upcoming COVID-19 vaccines and broader implications toward future pandemics are also discussed.

BACKGROUND
The SARS-CoV-2 pandemic and its associated COVID-19 have left a catastrophic impact on a myriad of socioeconomic and public health systems. Severe cases of this novel viral infection provide an elevated mortality risk that appears to manifest through a life-threatening constellation of cytokine storm,[1 2] prothrombotic hypercoagulability,[3 4] and lymphopenia.[5] Although a direct correlation between the severity of lymphopenia and COVID-19 mortality has been observed clinically,[5 6] with CD8+ T-cell depletion serving as a particularly poor prognostic marker,[7] the exact pathophysiological mechanisms of how these changes worsen mortality in patients infected with COVID-19 remain unclear. Studies have observed (1) highly heterogenous innate and adaptive immune response profiles in infected patients,[8] (2) acutely hyperactive CD8+ T cells containing abnormally high concentrations of cytotoxic granules in severe cases,[9] (3) increased markers of T-cell exhaustion in severe and chronically symptomatic cases,[6] as well as (4) prolonged immune dysregulation following an acute infection regardless of clinical severity.[8 10] These findings suggest that an initially overaggressive CD8+ T-cell response may negatively impact the clinical course of this novel viral infection through an initially hyperactive cytotoxic profile followed by a pro-apoptotic state with resultant lymphopenia in tandem with excessive levels of T-cell exhaustion and eventual impairment in memory T-cell production.[6 11]

Those with a cancer diagnosis during these unprecedented times constitute a large cohort of high-risk individuals who are facing a growing degree of complexity in the navigation of obtaining safe and adequate cancer care, especially through the stages of a COVID-19 infection.[12–16] Although patients with hematologic[17] cancers have exhibited the highest mortality risk of all cancer types to date, those with lung,[18] breast,[19] or any metastatic cancer[12] as well as patients with active comorbidities[20] also appear to exhibit a more severe clinical course. The complex and multifactorial pathophysiology between metastatic disease and severity of infection remains poorly understood, with early studies showing advanced age,[12] poor performance status,[21] and smoking history[13] as factors correlating with more severe outcomes.

The immunologic implications of advanced cancer and COVID-19 remains a topic of active study, as those with metastatic disease have been observed to express a baseline proinflammatory state and dysregulated immune profile that appears to worsen the severity and mortality of COVID-19 infections within this cohort.[13 22] Further, those receiving systemic anticancer therapy possess an additional level of complexity, as conflicting data have been observed regarding COVID-19 severity and mortality for those receiving chemotherapy[12 13] and immunotherapy.[23–25] For example, some studies have suggested that exposure to immune checkpoint inhibitor (ICI) therapies may serve as an independent risk factor for the development of a more severe clinical course of COVID-19 infection potentially due to increased T-cell cytokine production as well as ICI-induced immune-related pulmonary toxicities.[23 26–28] In contrast, multiple recent studies have not observed a significant risk in the contraction or mortality of a COVID-19 infection while receiving antiprogrammed cell death protein-1 (PD-1) ICIs in a variety of cancer types.[25 29 30]

The immune-mediated killing of various cancer cell types by ICIs, achieved through the interruption of several coinhibitory signaling pathways with antibodies targeting cytotoxic T lymphocyte antigen-4 (CTLA-4; ipilimumab), PD-1 (cemiplimab, nivolumab, pembrolizumab), and programmed cell death protein ligand-1 (PD-L1; atezolizumab, avelumab), has provided a tremendous impact on response and survival rates for a variety of solid and hematologic malignancies over the past decade,[31] and further investigation is warranted regarding the safety and immunologic implications of ICI therapy as it relates to COVID-19. Here, we provide a review of current literature and share additional immunologic and clinical insights into the implications of COVID-19 infection and vaccination as they relate to patients with cancer receiving immunotherapy through PD-1 blockade, with a specific focus on patients diagnosed with renal cell carcinoma (RCC) and melanoma given their high prevalence of ICI utilization as a widely accepted standard of care.[31 32]

COMMON THEMES OF THE ANTIVIRAL IMMUNE RESPONSE

The typical cellular response and immunologic profile associated with an acute viral infection begins with the activation of innate immune receptors, including several toll-like receptors (TLR3, TLR7, TLR8, and TLR9),[33] that trigger the secretion of proinflammatory type 1 interferons for localized cytotoxic control of viral spread[34] with simultaneous (1) activation of natural killer (NK) cells to destroy infected host cells,[35] (2) recruitment and activation of monocytes and macrophages to provide additional proinflammatory and free radical production,[36] and (3) ultimately facilitate the adaptive immune response, including the expansion and activation of CD4+ and CD8+ T cells.[37 38] This response, although critical to viral clearance and eventual establishment of antiviral immunity, is facilitated through highly cytotoxic pathways that often result in local tissue damage to organs harboring infected cells[39 40] as well as systemic tissue damage through a variety of complement[38] and antibody-mediated[41 42] inflammatory reactions.

Several immunologic countermeasures exist to control these inflammatory pathways and limit tissue destruction.[38] Key components of these tissue-protective mechanisms include the production of anti-inflammatory cytokines such as interleukin 10 (IL-10) and TGFβ by activated dendritic cells, macrophages, activated regulatory T cells (Treg), B cells and NK cells,[43–46] as well as the upregulation of inhibitory receptors by effector T cells including PD-1, CTLA-4, lymphocyte activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin domain 3 (TIM-3).[47–49]

Focusing specifically on the SARS-CoV-2 virus, initial infectivity appears to occur within nasopharyngeal mucosa and lung alveolar epithelial cells after interfacing with locally expressed angiotensin-converting enzyme 2 (ACE2) receptors to gain entry followed by S protein priming via the serine protease TMPRSS2.[50–52] Pathways involving the virulence and severity of this infection remain an active topic of study, with the initial innate response potentially triggered by a unique hyperactivation pattern by pulmonary bronchial mucosal-associated invariant T and γδ T cells,[53] with subsequent acute lung injury and systemic organ failure appearing to be associated with a proinflammatory storm of cytokines including TNF-α, IL-1β, IL-6, IL-8, IL-9, IL-10, bFGF, G-CSF, and GM-CSF[53] along with a hyperactive and lymphopenic immune profile of CD4+ and CD8+ T-cell subsets for which elevated neutrophil-to-lymphocyte ratios appear to serve as an independent prognostic biomarker of COVID-19 severity.[54] Further, the pulmonary tissue damage observed in more severe infections[55] appears to exhibit overactive cytotoxic CD8+ and Th17 T cells[9] as well as a unique prothrombotic immunologic milieu resembling macrophage activation syndrome[56 57] and a distinct endothelial-injury pattern that is topologically discordant to detectable virus within these tissues.[58] These findings, in addition to potential cross-reactive autoimmunity between viral spike surface proteins and host epitopes,[59] introduce a potentially viral-independent aberrant immune response causing the proinflammatory and prothrombotic sequalae observed in more severe cases of COVID-19.[57 60 61]

IMPLICATIONS OF IMMUNE CHECKPOINT INHIBITORS AND THE SARS-COV-2 ANTIVIRAL IMMUNE RESPONSE

Thorough reviews have outlined the immunologic patterns and clinical implications of chronic viral infections in patients receiving ICIs.[25 62 63] For example, the use of ICIs in patients with cancer with known RNA viral infections including HIV and hepatitis C have exhibited similar toxicity and efficacy rates as the general population[64 65] without a significant increase in viral reactivation risk.[66] Further, ICI therapy appears to improve effector memory viral-specific CD8+ T cells in patients with chronic HIV,[67] hepatitis B,[68] and hepatitis C[69] infections, reinvigorating antiviral immune responses. Some patients with cancer have also exhibited reduced hepatitis C viremia when treated with ICI therapy.[70 71]

Additional efforts to define the implications of ICI in the setting of acute infection are ongoing. For example, Pauken *et al* observed that acute influenza infections in PD-1 deficient mice led to increased proliferation and enhancement of effector CD8+ T-cell function, resulting in more rapid viral clearance than in PD-1 wild-type mice.[72]

However, this study further exposed that PD-1 blockade also appears to trigger higher rates of CD8+ T-cell apoptosis, impaired CD8+ T-cell memory, and compromised immunologic recall on viral rechallenge. Therefore, the timing of PD-1 blockade may pose a modulatory role in host immune responses that warrants further exploration within the clinical setting.[72–74] Lastly, evidence remains limited when attempting to define and understand the immunologic aberrancies associated with ICI treatment throughout a COVID-19 infection.[24 75–78]

Several hypotheses regarding the clinically detrimental effects of ICIs in patients infected with COVID-19 are currently under investigation. For example, ICIs are responsible for a multitude of immune-related adverse events (irAEs) with very rare associations to clinically significant inflammatory disorders such as cytokine release syndrome (CRS),[79] immune reconstitution inflammatory syndrome,[80] and hemophagocytic lymphohistiocytosis.[81] These conditions exhibit clinical and serologic similarities to the aforementioned proinflammatory state of severe COVID-19 infections, and early studies have suggested that ICIs may worsen the severity of the infection in a variety of cancer types.[12 24 82] Further, the irAE of pneumonitis is a rare but serious complication of ICI, with an observed incidence of 2.7% for all grade events and 0.8% grade 3 or higher for those on PD-1 blockade that results in a 40% mortality rate.[83] COVID-19-related lung injury has been observed to present with a clinical, radiographic, and serologic constellation of pulmonary damage that mimics ICI-induced pneumonitis and therefore provides a diagnostic dilemma to clinicians that may delay the proper diagnosis and life-saving interventions needed to control these irAEs.[84] Further, the management of such irAEs includes aggressive immunosuppressive regimens with high-dose corticosteroids, tumor necrosis factor alpha blockade, and occasionally IL-6 receptor inhibition, which may place patients at higher risk of contracting other serious infections.[25] In addition, the aforementioned potential to develop cross-reactive autoimmunity between COVID-19 viral spike surface proteins and host epitopes adds an additional degree of complexity in the safety and management of symptomatic patients on ICI with suspected or known COVID-19.[59 78]

Conversely, the use of ICIs has also been considered beneficial and even therapeutic, in multiple infectious scenarios including SARS-CoV-2.[62 63 67] In a recent review regarding the implications of various viral infections as they relate to the use of ICI, Gambichler *et al* emphasized the well-known concept of T-lymphocyte exhaustion as a distinguishing feature of several chronic viral infections, characterized by a functional loss of IL-2, impaired T-cell proliferation, and blunted cytotoxicity that simultaneously coincides with enhanced immunosuppressive cytokines including IL-10 and TGF-ß and overexpressed checkpoint receptors such as PD-1, CTLA-4, and Tim-3.[25] Similar immune profiles of T-cell exhaustion are well documented in various malignancies and are therefore known targets of ICI.[85] An additional potential benefit of ICI is to reduce the accumulation and upregulation of myeloid-derived suppressor cells which are associated with a proinflammatory state that subsequently impairs innate and adaptive immune responses in patients with cancer[86 87] as well as bacterial,[88] parasitic,[89] and viral[90] infections. The concept of utilizing ICI to enhance the antiviral immune response has been observed in a variety of settings[62 63 77 91 92] and is now under active investigation for patients infected with COVID-19 without a cancer diagnosis through several registered clinical trials including (1) a randomized, controlled, open-label, phase II clinical trial of anti-IL-6 (tocilizumab) in combination with pembrolizumab (MK-3475) in patients with COVID-19 pneumonia (NCT04335305), (2) an interventional parallel trial evaluating the efficiency of nivolumab versus standard of care in obese individuals with severe COVID-19 (NCT04413838), (3) an interventional parallel trial evaluating the efficacy of anti-PD-1 antibody versus thymosin versus supportive care in patients with COVID-19 pneumonia (NCT04268537), and (4) a phase II randomized open-label multicenter interventional trial evaluating the efficacy and safety of nivolumab compared with standard of care in hospitalized patients with COVID-19 (NCT04343144).

GENERAL CLINICAL CONSIDERATIONS REGARDING SARS-COV-2 AND ICI USE

The above hypotheses regarding ICIs as a potential risk factor impacting the susceptibility, severity, and mortality of SARS-CoV-2 has become highly disputed in a variety of clinical settings.[25 29 77 78 93 94] A recent meta-analysis of 16 studies containing 275 patients with cancer on ICIs with a COVID-19 diagnosis found no significant difference in the risk of severe disease and mortality between immunotherapy and control groups.[95] Additional cohort studies in various subsets of patients with cancer have provided similar findings regarding the safety of ICI use throughout a COVID-19 infection,[18] with an emphasis that patients with advanced cancers, active comorbidities, older age, and a history of smoking are to be considered potentially higher-risk categories that warrant close clinical monitoring.[14 29 96] Further, the utilization of high-dose systemic corticosteroids in the initial management of ICI-induced pneumonitis has also been increasingly observed to provide a mortality benefit in patients with severe COVID-19 infections.[97 98] Hence, there remains no clear evidence that the risk of a SARS-CoV-2 diagnosis be considered a contraindication to patients receiving or initiating ICIs at this time.

MELANOMA-SPECIFIC CLINICAL CONSIDERATIONS REGARDING SARS-COV-2 AND ICI USE

The scientific community has provided numerous resources regarding the negative effects and clinical constraints that SARS-CoV-2 poses on the diagnosis,[99] prognosis,[100] and outcomes[101] of patients with known or suspected melanoma. Suboptimal healthcare access due to administrative restrictions, psychological stressors, and infectious/symptomatic scenarios have led to significant delays in the diagnosis [100] and treatment of melanoma.[15 102] For example, a recent US-based single-center study observed that patients diagnosed with melanoma during the COVID-19 pandemic exhibited significantly higher tumor depth, mitotic rates, satellitosis, and pT3/T4 tumors compared with those diagnosed in the pre COVID-19 setting.[103] In addition, a multicenter Italian study of 169 patients with advanced (stages III and IV) melanoma on ICI found 49 (29%) of these patients to experience a delay in their ICI treatment for a median of 4 weeks due to clinician's concerns of frailty and increased risk of contracting COVID-19, while actual COVID-19 diagnoses of this entire cohort were ultimately found to be lower than the general population.[93] With no clear evidence suggesting that ICIs worsen the risk or course of a COVID-19 infection, many sources have concurred that patients with melanoma, particularly those of an advanced stage, be treated without hesitation via standard of care regimens including ICIs and targeted therapy pending individual serine–threonine protein kinase B-RAF (BRAF) mutational status.[30 95 104] We therefore agree with recently published consensus guidelines from the UK,[105 106] including continued use of front-line ICI therapies and to consider the approved alternative dosing regimens of either pembrolizumab 400 mg every 6 weeks as opposed to initial 3-week standard of care dosing per KEYNOTE-555 Cohort B data as well as nivolumab 480 mg every 4 weeks compared with every 2-week standard of care for those on nivolumab maintenance regimens.[107]

RCC-SPECIFIC CLINICAL CONSIDERATIONS REGARDING SARS-COV-2 AND ICI USE

Compared with the melanoma patient population, a less robust body of evidence is currently available regarding RCC patients and SARS-CoV-2. However, the available retrospective studies have once again observed no increase in the severity or mortality of a COVID-19 infection within patients with RCC,[12] including those receiving ICI.[108 109] In regard to systemic therapeutic approaches, no available evidence suggests that the use of ICI worsens the risk or severity of a COVID-19 infection and therefore standard guideline-based approaches to treatment remain recommended.[110] However, it is worth re-emphasizing current standards of care including the use of pembrolizumab plus axitinib based on KEYNOTE-426[111] and nivolumab plus ipilimumab based on CheckMate 214[112] led to 27% and 29% of patients, respectively, requiring ≥40 mg/day oral prednisone doses equivalents due to irAEs that included pneumonitis. Although alternatives to combination ICIs for patients with advanced RCC exist, such as antiangiogenic tyrosine kinase inhibitors combined with anti-PD1/PD-L1 agents,[111 113 114] these also possess a clinically meaningful side effect profile with up to 82.4% of patients developing grade 3 or higher adverse events.[115] It is therefore imperative to closely monitor patients on these regimens for such events and promptly rule out a COVID-19 infection at the time of symptom onset in order to appropriately and expeditiously treat a potentially life-threatening irAE.

In addition, should a patient with RCC on ICI therapy develop any life-threatening irAE or be considered at high risk of such events beyond 2 years of treatment, it is not unreasonable to consider indefinite discontinuation of ICI therapy in certain clinical scenarios, as members of the Society for Immunotherapy of Cancer have recommended stopping ICI in the setting of complete radiological response (94% recommended) or non-progressive disease (56% recommended) in patients with RCC following 2 years of treatment.[116]

SHARED CLINICAL CONSIDERATIONS FOR MELANOMA AND RCC

As outlined above, there remain no reliable data to suggest that the use of ICI poses any additional risk to the susceptibility or severity of a SARS-CoV-2 infection in either RCC or melanoma patient cohorts.[25 93 95 105] Besides the development of an acute COVID-19 infection, standard approaches to ICI therapy are advised throughout the course of the pandemic. One reasonable clinical consideration for these patients includes the utilization of approved dosing of pembrolizumab and nivolumab at longer intervals of every 6 and 4 weeks, respectively, in attempts to enhance practices of social distancing and limit healthcare-related exposures.[105 107] Further, the risk or history of a COVID-19 infection should not serve as a sole determinant of pursuing a non-ICI regimen such as targeted therapies. A summary of our above recommendations is provided in table 1.

ADDITIONAL CONSIDERATIONS REGARDING COVID-19 VACCINES IN PATIENTS RECEIVING ICI

As of June 6, 2021, a total of 84 COVID-19 vaccines are under active clinical investigation at varying phases of development and 11 are authorized for use on an international level.[117] Of those currently authorized, the most widely approved include the mRNA-based Pfizer/BioNTech and Moderna vaccines as well as the viral vector-based AstraZeneca and Johnson & Johnson (J&J) vaccines. The J&J vaccine has received publicized criticism for an initial reported efficacy of 66.1% in preventing moderate-to-severe COVID-19 28 days post vaccination as compared with the striking 94.1%[118] and 95%[119] efficacy reported in the Moderna and Pfizer/BioNTech vaccine trials, respectively. However, it is worth noting that the defined severity endpoints differed among these trials, and when comparing these three vaccines from a public health standpoint, the J&J vaccine is the only current option approved as a single dose with proven efficacy against the recently defined B.1.351 coronavirus variant.[120]

Due to patients with cancer on active systemic therapy being excluded from initial vaccine registration trials, the safety and efficacy of COVID-19 vaccinations in patients

Table 1 Summarized treatment and vaccination recommendations for various clinical scenarios

Clinical scenario	ICI recommendation	Vaccination recommendation*†‡
No comorbidities or AID	Treat with SOC or clinical trial* without delay	Vaccinate promptly with first-available approved option
Known history of AID	Use of clinical judgment is advised If deemed fit for ICI, prioritize treatment with SOC or clinical trial*. Consider delay if AID exhibiting active and clinically significant flare Consider approved longer interval of ICI doses§	Prioritize prompt vaccination with first-available approved option¶
High risk of COVID-19 severity or mortality (advanced metastatic cancer,[22] poor performance status,[21] elderly,[12] active comorbidities,[20] smoking history)[13]	Use of clinical judgment is advised If deemed fit for ICI, prioritize treatment with SOC or clinical trial* without delay Consider approved longer interval of ICI doses§	Prioritize prompt vaccination with first-available approved option
Contraction of COVID-19 infection while receiving, or prior to initiation of, ICI therapy	Recommend withholding ICI therapy regardless of symptoms On resolution of acute illness (if symptomatic) and meeting criteria to discontinue isolation, use of clinical judgment is advised. If deemed fit for ICI, prioritize treatment with SOC or clinical trial* without delay‡ Consider approved longer interval of ICI doses§	► No treatment with monoclonal antibodies or convalescent plasma: Asymptomatic: prioritize prompt vaccination 14 days following positive test Symptomatic: vaccination recommended pending clinical judgment at 28 days from diagnosis or on symptom resolution, whichever is first** Temporary delay in booster dose appears to be reasonable in case of vaccine shortages ► Treated with monoclonal antibodies or convalescent plasma: Recommend at least 90-day delay from time of treatment to vaccine, regardless of vaccine series

*If enrolling in phase I trial involving investigational medicinal products with known or theoretical risk of cytokine release syndrome, as well as if administered in combination with ICI, consider waiting 2–4 weeks following completion of all COVID-19 vaccination(s) prior to the initiation of investigational treatment.[132]

†If two-dose vaccine provided, strongly recommend adherence to receiving second dose within timeframe of pivotal trials in attempts to optimize immunologic seroconversion.[117 118] Deferral of vaccinations is ill advised and consideration to do so should be based on individual clinical context along with regional infectivity rates.

‡Clinical caution and shared decision-making are advised as provided recommendations are synthesized from available trial data that lack cancer and ICI-treated patients.

§Consider utilization of approved dosing of pembrolizumab and nivolumab at longer intervals of every 6 and 4 weeks, respectively, in attempts to enhance practices of social distancing and limit healthcare-related exposures.[105 107]

¶Vaccination is recommended regardless of use of immunosuppression. However, if immunosuppressive agent is temporary in patients with low risk of severe COVID-19 and adequately low regional infectivity rates, they may consider delaying vaccination until completion of immunosuppression in attempts to optimize immunologic seroconversion.[133]

**Vaccination appears safe in previously infected patients. Delay in vaccination is recommended in order to avoid both symptomatic transmission within healthcare facilities as well as misrepresentation of viral symptoms as adverse events to vaccine and advisable based on favorable immune profile of previously infected non-cancer patients.[134]

AID, autoimmune disease; ICI, immune checkpoint inhibitor; SOC, standard of care.

with cancer have become major topics of interest within the medical and scientific community. However, the US Centers for Disease Control and Prevention, American Society of Clinical Oncology, European Society for Medical Oncology, American Association for Cancer Research, and National Comprehensive Cancer Network have unequivocally recommended that all patients with cancer seek expeditious vaccination based on the observed safety profiles of currently approved vaccines, the historical tolerance to vaccines against other viruses, and the high rates of COVID-19 morbidity and mortality within this cohort.[121–123]

The ideal vaccine choice in patients with cancer, as well as the general population, has yet to be elucidated. A small amount of evidence has suggested that current mRNA vaccines may provide relatively favorable efficacy following a single dose, especially in those previously infected with COVID-19,[124] which could challenge support of the J&J vaccine. However, such an approach should be avoided until the generalizable efficacy of incomplete vaccine series is supported by peer-reviewed objective evidence, as the production and duration of neutralizing antibodies appear to decline prior to the second booster doses across all studied age groups[125] and may ultimately lead to an increased susceptibility of contracting vaccine resistant variants.[126] In addition, increasing age[124] and early data from patients with cancer, especially those with hematologic malignancies,[127] are cohorts who appear to exhibit suboptimal immune responses to mRNA vaccines following a single dose, further supporting strict adherence to the vaccination schedules as studied in their initial clinical trials.[125] Therefore, a current approach to vaccine prioritization should simply focus on whichever approved option becomes available for these patients until additional efficacy data are observed.[128 129]

Although the ideal timing of these vaccines in relation to ICI administration has yet to be elucidated, eligible patients on ICI are encouraged to receive this vaccine as it becomes available to them in efforts to provide much-needed mitigation of the short-term and long-term complications of a COVID-19 infection and its associated delays in cancer treatment.[15 102] A minor caveat to consider should eventual prospective data for ICI-treated patients parallel the general population is to potentially consider avoidance of vaccine administration within 24–48 hours prior to scheduled ICI, especially in investigational regimens, as the transient fever and occasionally severe side effect profiles more frequently observed following the second dose of currently accepted Moderna and Pfizer/BioNTech vaccines may lead to misattribution of treatment-related adverse events and potentially interfere with a patient's ability to attend and receive their scheduled ICI treatments.[130] Patients with nonhematologic cancers actively participating in clinical trials should also be prioritized for COVID-19 vaccination, with additional efforts to provide at least the first vaccine dose during the screening process for those being considered for enrollment.[131] Although more detailed considerations regarding the approach to vaccine timing and clinical trials for various solid and hematologic malignancies are beyond the scope of this article and well-articulated elsewhere,[131] a noteworthy example by Yap *et al* recommends that patients enrolling in experimental phase I clinical trials involving investigational medicinal products (IMPs), for which human toxicity profiles remain unknown, should consider waiting 2–4 weeks following completion of all COVID-19 vaccination(s) prior to the initiation of an IMP, especially should these drugs confer any known or theoretical risk of CRS as well as if administered in combination with ICI.[132] Lastly, patients on ICI who have previously been infected with COVID-19 are to follow guidelines outlined for the general population until prospective data within this cohort becomes available,[128 129] including a delay in vaccination for (1) at least 90 days if COVID-19 infection was treated with monoclonal antibodies or convalescent plasma, (2) approximately 14 days from diagnosis in asymptomatic patients, and (3) either 28 days from diagnosis or on symptom resolution in symptomatic patients (whichever occurs first).[133 134] These recommendations are summarized in table 1.

Additional risk assessment regarding the impact of ICI therapy on the efficacy and safety of these vaccines are under active investigation. Previous encouraging safety and immunologic efficacy profiles have been observed with influenza vaccines for those on ICIs[121 135] and only a single report is currently available at the time of this review regarding a case of CRS following the Pfizer/BioNTech vaccine in a patient on long-standing ICI therapy.[136] In addition, although the presence of PD-1 is known to enhance CD8+ T-cell exhaustion during chronic infection and cancer,[137] the exact timing of PD-1 blockade during CD8+ T-cell differentiation in the setting of an acute viral infection, as outlined in section III, may pose a modulatory role in host immune responses.[72–74] Such observations, although compelling given the theoretic implications of suboptimal long-term T-cell memory or variable immune responses on vaccination in ICI-treated patients, require further study within the clinical setting.

CONCLUSIONS

Patients with cancer, although comprised of a large and heterogenous cohort, are to be considered a high-risk population amidst a global pandemic. Although additional studies are needed to conclusively define the implications of ICI and the SARS-CoV-2 virus, we are in agreement with the most up-to-date consensus guidelines stating that the current pandemic should not be considered a contraindication to ICI initiation or continuation,[105] that ICI should be held on diagnosis of a COVID-19 infection until clinical stability is ensured, and that patients on ICI be expeditiously vaccinated.[122] Although our understanding of these topics is rapidly evolving, patients should be made aware that many of our current clinical approaches are based on consensus rather than controlled empirical evidence and that our vaccination guidelines are currently based on non-ICI treated and non-cancer patients.

Several knowledge gaps remain regarding the clinical and immunologic relationships between the SARS-CoV-2 virus and anti-PD-1 therapies. Currently available literature appears to suggest that the use of ICI does not pose a significantly increased risk in the susceptibility or severity of a SARS-CoV-2 infection when adjusted for comorbidities and other potential confounding factors,[25 93–95 105] although many of these studies remain underpowered and will require expanded sample sizes and longer observational periods in order to achieve adequate significance and generalizability. Further, the majority of available evidence supporting the safety and efficacy of ICI in the setting of a known viral infection are based on a chronic rather than acute viral infection status,[67–70] requiring clinicians to remain vigilant to their ICI-treated patients throughout the course of a COVID-19 infection. Lastly, the impact of the innate and adaptive immune response in ICI-treated patients following COVID-19 infection and/or vaccination is largely unknown.

Given the sparsity and mostly underpowered literature currently available regarding cancer patients and COVID-19, larger and controlled prospective studies are needed to further investigate the potential risks and benefits of anti-PD-1 therapeutic pathways on the short-term and long-term clinical course and immunologic profiles associated with both the SARS-CoV-2 virus and various COVID-19 vaccines. One such dedicated project includes the COVID-19 Antiviral Response in a Pan-tumor Immune Monitoring (CAPTURE) Study (NCT03226886), evaluating longitudinal clinical outcomes and immune profiles in cancer patients and healthcare workers in attempts to cultivate an enhanced understanding and evidence-based clinical framework to minimize viral transmission and optimize cancer treatment approaches.[129] CAPTURE study is actively evaluating B-cell and T-cell response to vaccination in patients with cancer, especially those with renal cell cancer and melanoma who are receiving immune checkpoint blockade. In addition, the 'Vaccination Against COVID in Cancer' Project (NCT04715438) is an exciting prospective, national, multicenter, longitudinal, multicohort study observing the short-term and long-term immunologic profiles of patients with solid tumor cancers on multiple treatment modalities including ICI with a primary endpoint of a sufficiently mounted immune response 28 days following the completion of an mRNA vaccine series.[128] This project will also further define the T-cell immunity observed against these vaccines, which will provide valuable insights into the potential differences of ICI-treated cohorts. Lastly, several aforementioned clinical trials utilizing various anti-PD-1 therapies in attempts to reinvigorate the exhausted T cells observed in patients infected with COVID-19 and thereby promote viral clearance and immunity are ongoing.[10 25 62]

We eagerly await long-term clinical and immunologic analyses of how the SARS-CoV-2 virus and vaccine may impact the antitumor and antiviral responses for those receiving anti-PD-1 therapy. These topics will most assuredly remain the source of many active and fruitful scientific projects in the near future, providing practice-changing insights toward the navigation of current and future pandemics within both the oncologic and general population.

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