**Considerations for use of immune checkpoint inhibitors during COVID-19 pandemic\***

Current information suggests that cancer patients are a highly vulnerable group in the COVID-19 pandemic and have a poorer prognosis than those without cancer [1, 2]. To date, there is no conclusive clinical data to confirm whether immune checkpoint inhibitor (ICI) therapy increases, decreases, or has no effect on the severity of symptoms experienced with SARS-CoV-2 infection or the immune response associated with it [3], however, there is a theoretical risk that patients undergoing treatment with ICIs may respond to COVID-19 differently from other patients. Caution and additional monitoring is recommended when treating patients with confirmed COVID-19 who are undergoing treatment with PD-L1/PD-1 checkpoint inhibitors.

**Available Data**

In pre-clinical models, PD-L1/PD-1 blockade is associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection [4]. Clinical data to inform risk for patients on ICIs who develop acute SARS-CoV-2 infection is currently limited. There is accumulating clinical evidence that provides some reassurance about the safety of ICIs in patients with properly managed viral infections such as HBV, HCV, and HIV [5], but the relevance of this evidence in the context of COVID-19 is not clear. In a recent paper by Zhang et al., a strong association between anti-cancer therapy in the past 14 days and severe effects of COVID-19 was reported (HR=4.079, 95%CI 1.086-15.322, P=0.037). This retrospective analysis of 28 patients included 3 patients who received chemotherapy, 2 targeted therapy, 1 immunotherapy with chemotherapy and 1 radiotherapy, all who received treatment within 14 days before COVID-19 diagnosis [1].

**Theoretical Risks**

In the face of limited clinical information, the following theoretical risks are worthy of attention:

* Potential synergy or overlap in clinical and radiological features between immune mediated pulmonary toxicity with ICIs and coronavirus-related interstitial pneumonia [6], although there is some evidence which suggests that the type of lung damage in cancer vs infection may be different (e.g. “pneumonitis from checkpoint blockers respond to anti-TNF while pneumonitis from COVID-19 apparently does not”) [7].
* A subgroup of patients with severe COVID-19 may experience cytokine storm syndrome [8], and viral infections are a known trigger for hyperinflammation [secondary Hemophagocytic Lymphohistiocytosis (HLH)]. ICIs, especially when used in combination with other immune modulators or targeted agents, can also be associated with hyperinflammatory syndromes and may increase the potential for immune overreaction [Cytokine Release Syndrome (CRS), HLH spectrum] in COVID-19 patients.
* Individual patient characteristics like immune set point, current oncologic status and general medical condition may influence the risk of clinical translation (if any) of preclinical observations.

**Treatment Considerations**

* Prior to initiation of ICI therapy, individual patient risk for SARS-CoV-2 infection, current oncologic status and general medical condition should be considered. Screening for SARS-CoV-2 should be conducted in line with local or institutional guidance. Patients should be advised to follow local/WHO/CDC recommendations to avoid exposure to SARS-CoV-2 infections.
* For patients receiving ICIs, less frequent dosing intervals should be considered when locally approved and available for the patient’s indication [9, 10, 11] to minimize patient risk of infection.
* Currently, there are no evidence-based recommendations regarding use of corticosteroids to treat ICI associated immune mediated toxicities in context of COVID-19 pandemic; the relative merits of giving corticosteroids to patients with COVID-19 are a matter of debate [12, 13].
* Based on limited evidence from Zhang et al, ASCO recommends that clinicians consider interrupting anti-cancer treatment (not specific to ICIs) in patients with active COVID-19 [9]. For patients who develop COVID-19 while on ICI therapy, there is no data to inform decisions regarding continuation of therapy. Importantly, ICI discontinuation might not eliminate potential risk associated with ICIs given their long half-life which ranges from 6-27 days among molecules in this class [14].
* Considerations for chemotherapy treatment during the COVID-19 pandemic are set forth by ASCO [9], and this guidance should also be applicable for patients receiving ICIs in combination with chemotherapy.

While we await evidence-based recommendations, clinical decisions about administering ICI therapy in the context of COVID-19 pandemic should account for different immunological status in patients who receive ICI therapy compared with chemotherapy or targeted therapy [6], and be based on individual patient assessment of benefit/risk informed by type of tumor, line of therapy/intent of treatment, response and tolerance to treatment, general medical condition of the patient, risk of SARS-CoV-2 infection (or for COVID-19 positive patients, acuity of infection), and for those patients who do receive ICI therapy, caution and additional monitoring is recommended.

\* This statement represents the thinking as of Apr 10 2020, and given the dynamic situation with this pandemic, our knowledge and understanding is likely to evolve over time.

**References**

1. Zhang L, Zhu F, Xie L, et al., Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Annals of Oncology. 2020; 23 Mar. <https://doi.org/10.1016/j.annonc.2020.03.296> [Epub ahead of print]
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; published online Feb 14.:<https://doi.org/10.1016/S1470-2045(20)30096-6>
3. Uzzo R, Kutikov A. Coronavirus disease 2019 (COVID-19): Cancer care during the pandemic. UpToDate online accessed 07 Apr 2010
4. Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 17 December 2012; 209 (13): 2485–2499. doi: <https://doi.org/10.1084/jem.20121015>
5. Antonuzzo, A., Calabrò, F., Quaglino, P., et al. Immunotherapy in Underrepresented Populations of Patients with Cancer: Do We Have Enough Evidence at Present? A Focus on Patients with Major Viral Infections and Autoimmune Disorders. Oncologist. 2020; published online Mar 17. <https://doi.org/10.1634/theoncologist.2020-0035>.
6. Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Immunotherapy. Published Online 26 Mar 2020 <https://doi.org/10.2217/imt-2020-0067> [Epub ahead of print]
7. Humphrey R. What cancer immunologists are doing about COVID-19.  The Cancer Letter; Apr 03, 2020. [https://cancerletter.com/articles/20200403\_2](https://cancerletter.com/articles/20200403_2/)
8. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression, The Lancet, 2020, ISSN 0140-6736,<https://doi.org/10.1016/S0140-6736(20)30628-0>
9. ASCO Patient care: How should the care of cancer patients be modified by the COVID-19 pandemic. [https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-d](https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19)<https://doi.org/10.1016/S0140-6736(20)30628-0>[uring-covid-19](https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19). Accessed 07 Apr 2020
10. Banna G, Curioni-Fontecedro A, Friedlaender A, et al. How we treat patients with lung cancer during the SARS-CoV-2 pandemic: primum non nocere. ESMO Open 2020;5:e000765. <http://dx.doi.org/10.1136/esmoopen-2020-000765>
11. Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. Nat Rev Clin Oncol (2020). <https://doi.org/10.1038/s41571-020-0362-6>
12. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020; published online Feb 11. <https://doi.org/10.1016/S0140-6736(20)30361-5>
13. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; published online Feb 7. <https://doi.org/10.1016/S0140-6736(20)30317-2>
14. Picardo, S.L, Doi, J, Hansen, A.R. Structure and Optimization of Checkpoint Inhibitors. Cancers 2020, 12, 38. Published online 21 Dec 2019.  <https://doi.org/10.3390/cancers12010038>