Invited Comment

SARS-CoV-2 Vaccination and Phase I Cancer Clinical Trials of Investigational Agents during the COVID-19 Pandemic

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Given the current COVID-19 pandemic, there is now a rapid global roll-out of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines.[1] Approved SARS-CoV-2 vaccines currently include those from Pfizer-BioNTech[2], Moderna[3] and Oxford-AstraZeneca[4], but the WHO estimates 52 ongoing clinical research projects developing SARS-CoV-2 vaccines.[1] Different vaccine mechanisms have been explored using technologies based on messenger RNA (mRNA), synthetic long viral peptides, plasmid DNA vaccines, and inactivated/attenuated or genetically-modified viruses. Efficacy data are encouraging, with the mRNA-based vaccines reporting >90% protection rates from COVID-19 with good tolerability, although the durability of protection, and thus need for repeated vaccinations, is still uncertain.

Both COVID-19-associated morbidity and mortality rates of the cancer population range between 5-61% based on data from the COVID-19 and Cancer Consortium (CCC19) registry and other groups, clearly higher than overall population rates of 2-3%.[1] While such rates are associated with confounding biases, it is clear that cancer patients represent a very vulnerable population at high risk of serious COVID-19 infection. The efficacy of SARS-CoV-2 vaccines is likely to vary between patients depending on cancer type, disease burden, comorbidities and intrinsic or therapy-induced immunosuppression. To the best of our knowledge, SARS-CoV-2 vaccine trials have excluded patients on anticancer trials or immunosuppression, limiting our formal experience in this area and further data are needed to address concerns regarding the impact of various malignancies and anticancer drugs on vaccine efficacy. While policies covering the optimization of the timing of vaccinations during standard-of-care chemotherapy, tumor-

cell targeted agents, immunotherapy, radiotherapy and surgery are being introduced, there is less likely to be any formal guidance on experimental phase I clinical trials of investigational medicinal products (IMPs).[5,6] This is especially pertinent for first-in-human, first-in-class phase I trials of novel anticancer agents, where toxicity and efficacy profiles are limited to preclinical *in vitro* and *in vivo* data.

In general, with regards to phase I trials of anticancer agents, two key questions arise: What are the potential effects of such IMPs on the (1) efficacy and (2) toxicities of SARS-CoV-2 vaccinations; and vice versa. For example, the SARS-CoV-2 vaccine is likely to confer reduced protection in patients participating in phase I trials of experimental B cell-depleting antitumor agents, such as anti-CD10, anti-CD19 and anti-CD20 monoclonal antibodies, or CD19 CAR-T cells, given that such patients are unlikely to mount an optimal immune response.[7] From experience with influenza A vaccinations in patients receiving programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) monotherapies, seroconversion and seroprotection rates are generally high.[8] With regards to toxicity, it is particularly important when considering the impact of vaccinations on trials that involve IMPs with a high risk of immune toxicities including cytokine release syndrome (CRS), or novel agents given in combination with immunotherapeutics. While there is experience in administering well-established vaccinations in cancer patients on phase I trials, these tend to be limited to inactivated vaccines and exclude live-attenuated and replication-competent vector vaccines. This is in contrast to the currently available SARS-CoV-2 vaccines which are mRNA-based, live attenuated/non-replicating or more conventional protein subunit vaccines.

The current COVID-19 pandemic compels us to consider when patients participating in early clinical trials should get vaccinated.[5] Typically, the timing of vaccination has depended on the individual patient and the type of trial therapy; for example, vaccinations are recommended before systemic trial therapies commence, and are generally permitted on trial if the patient has already started systemic therapy. Current guidance on the administration of SARS-CoV-2 vaccines from trial sponsors has however been unclear, ranging from full approval for such vaccines to be given in parallel to the trial IMP, to a complete avoidance of the vaccine during IMP administration.

As an international group of medical oncologists based across the USA, UK, Canada and Europe involved in treating such patients with advanced cancers on early phase clinical trials, based on the promising clinical data presented to date with approved SARS-CoV-2 vaccines, we believe that the benefits of vaccination in the current COVID-19 pandemic should substantially outweigh the possible benefits of participating in a Phase I trial in light of the high risk of contracting life-threatening COVID-19 infection in this vulnerable population. We believe that any unnecessary delays with SARS-CoV-2 vaccination should be avoided. We recommend applying risk stratification by considering trials with a CRS risk (e.g. certain immunotherapeutics) separately to those that do not harbor such toxicities (e.g. non-immunotherapy studies involving molecularly targeted agents). We also recommend that patients participating in early trials of anticancer drugs with unknown safety and tolerability should: (1) Avoid starting trial IMP until 4-weeks after the second dose of the SARS-CoV-2 vaccine is administered safely, especially for those

with a CRS risk **(Text Box)**. If the trial involves proven anticancer drugs with known benefits, this wait may be more challenging for patients with progressing advanced cancers, where the delay must be carefully weighed up with the patient. (2) Avoid days of parenteral IMP dosing (and as distanced as possible from IMP dosing) and the dose-limiting toxicity (DLT) period**,** if administration of the SARS-CoV-2 vaccine is mandated while the patient is participating on an early phase trial. This latter strategy will minimize the risk of confounding overlapping or added toxicities during the crucial trial period of the IMP. This is particularly pertinent for common SARS-CoV-2 vaccine toxicities, such as tiredness, headaches, muscle/joint aches, chills and fever, which may be particularly prominent after the second vaccine dose or if the patient has already been exposed to asymptomatic SARS-CoV-2 infection. Close monitoring of patients in 'real-time' after SARS-CoV-2 vaccination will be essential to assess potential interactions, toxicities and clinical outcomes, including those from both COVID-19 infection and complications from cancer. In patients who experience cancer trial IMP-associated immune-related adverse events, e.g. colitis, pneumonitis, etc and are on steroids or other immunosuppressive agents, the SARS-CoV-2 vaccine should probably be avoided until the toxicity is fully resolved or markedly improved. Clearly, such decisions need to be individualized to each patient and IMP risk profile.

Since it is currently unclear how long immunity will last after vaccination, with this response likely to be temporary and lasting months to years, rather than decades or a lifetime, repeat vaccinations are likely to be required during a patient's lifetime. Repeat vaccination decisions will therefore require further consideration of any changing risk

factors. COVID-19 infection has no doubt impacted and delayed all components of the cancer patient's journey, including screening, diagnosis, treatment and monitoring/ surveillance strategies, and likely increasing the risk of cancer-related morbidity and mortality.[9] This also has knock-on effects on oncology trials, including patient accrual, logistical and economic aspects, and with potential impact on the long-term development of promising life-saving anticancer agents.

While there is no doubt that phase I oncology trials have unknown toxicity risks and are conducted primarily to recommend safe doses for future studies, the potential of imparting benefit is well-described.[10] These factors need to be judiciously balanced with the unknown effects of the IMP on SARS-Cov-2 vaccination and the risk of such vaccines worsening the toxicity of a subset of novel anticancer agents. Patient motivations and expectations of phase I oncology trials are variable and it will be critically important for decisions to be made on an individual case-by-case basis with patients and their advocates to assess the risk-benefit balance by taking into consideration known IMP mechanisms and toxicities, and key patient characteristics, such as age, co-morbidities, prognosis and social factors. This is an opportunity and indeed a duty of treating oncologists, trial sponsors and regulatory agencies to monitor, document and communicate outcomes of the different SARS-Cov-2 vaccines during anticancer drug administration, as well as their impact on the development of SARS-Cov-2 disease, toxicity of anticancer agents, and eventual cancer outcomes. As the vaccination programs roll out globally, this early experience is likely to influence the timing, safety and efficacy of SARS-Cov-2 vaccination for a considerable period of time.

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Text Box: Recommendations for SARS-CoV-2 Vaccination and Phase I Cancer Trials

Not started Phase I trial	Avoiding starting trial IMP until 2-4 weeks after 2nd dose of SARS-CoV-2 vaccine is administered safely for trial IMP with CRS risk
Already on Phase I trial	Administer SARS-CoV-2 vaccine during phase I trial but avoid days of parenteral trial IMP dosing and the DLT period