premature deaths have been mainly seen in high-income countries. Disruptions caused by the COVID-19 pandemic—more than 40% of countries report partially or fully disrupted cancer services—are now expected to further exacerbate disparities in access to cancer care and increase excess mortality.[10] There must be renewed commitment to, and investments in, cancer control that spurs greater action and integration at all service levels, particularly primary care for prevention, early detection and palliative care, which also offer benefits in the broader prevention and control of non-communicable diseases.

Governments must include cancer interventions in universal health coverage as essential health services, with associated financial protection from the catastrophic expenditure experienced by so many patients with cancer. The vision of the World Cancer Declaration is still relevant and, to succeed in achieving its targets, we must do more. Millions of lives depend on it.

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1   Adams C, Torode J, Henshall S, Cazap E, Ryel AL, Grey N. The World Cancer Declaration: from resolution to action. *Lancet Oncol* 2011; **12:** 1091–92.
2   WHO. Assessing national capacity for the prevention and control of noncommunicable diseases: report of the 2019 global survey. Geneva: World Health Organization, 2020.
3   Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health* 2016; **4:** 453–63.
4   WHO. Report on the global tobacco epidemic, 2019: offer to help to quit tobacco use: executive summary. Geneva: World Health Organization, 2019.
5   Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1·6 million participants. *Lancet Child Adolesc Health* 2020; **4:** 23–35.
6   International Agency for Research on Cancer. World cancer report: cancer research for cancer prevention. In: Wild CP, Weiderpass E, Stewart BW, eds. Lyon: International Agency for Research on Cancer, 2020.
7   Union for International Cancer Control. International public opinion survey on cancer. Geneva: Union for International Cancer Control, 2020.
8   Abdel-Wahab M, Zubizarreta E, Polo A, Meghzifene A. Improving quality and access to radiation therapy—an IAEA perspective. *Semin Radiat Oncol* 2017; **27:** 109–17.
9   Worldwide Hospice Palliative Care Alliance, WHO. Global atlas of palliative care, 2nd edn 2020. http://www.thewhpca.org/resources/global-atlas-on-end-of-life-care (accessed Dec 1, 2020).
10 WHO. The impact of the COVID-19 pandemic on noncommunicable disease resources and services: results of a rapid assessment. Geneva: World Health Organization, 2020.

SARS-CoV-2 vaccination and phase 1 cancer clinical trials

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There is now a rapid global roll-out of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines as part of the response to the COVID-19 pandemic.[1] Approved SARS-CoV-2 vaccines include those from Pfizer-BioNTech,[2] Moderna,[3] and Oxford–AstraZeneca,[4] but WHO estimates that there are 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, and inactivated, attenuated, or genetically modified viruses. Efficacy data are encouraging, with the mRNA-based vaccines reporting more than 90% protection from COVID-19 with good tolerability, although the durability of protection, and thus the need for repeated vaccinations, is uncertain.

COVID-19-associated morbidity and mortality in patients with cancer range from 5% to 61% based on data from the COVID-19 and Cancer Consortium registry and other groups, more than the 2–3% observed in the general population.[1] Although these morbidity and mortality figures are associated with confounding biases, it is clear that patients with cancer are vulnerable and have a high risk of serious COVID-19 symptoms. 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 in anticancer trials or taking immunosuppressive drugs, which limits formal experience in this area and means that further data are needed to address concerns regarding the effects of malignancies and anticancer drugs on vaccine efficacy. Although policies covering the optimisation of the timing of vaccinations during standard-of-care chemotherapy, tumour-cell targeted drugs, immunotherapy, radiotherapy, and surgery are being introduced, it is unlikely that there will be any formal guidance on experimental phase 1 clinical trials of investigational medicinal products (IMPs).[5,6] This is especially pertinent for first-in-human, first-in-class phase 1 trials of novel anticancer drugs, in which toxicity and efficacy profiles are limited to preclinical in-vitro and in-vivo data.

In general, with regards to phase 1 trials of anticancer drugs, two key questions arise: what are the potential effects of such IMPs on (1) the efficacy and (2) the toxic effects of SARS-CoV-2 vaccinations; and vice versa. For example, a SARS-CoV-2 vaccine is likely to confer reduced protection in patients participating in phase 1 trials of experimental B cell-depleting antitumour drugs, such as monoclonal antibodies targeting CD10, CD19, or CD20, or CD19 chimeric antigen receptor T cells, given that such patients are unlikely to mount an optimal immune response.[7] From experience with influenza A vaccinations in patients receiving checkpoint inhibitors targeting PD-1 or PD-L1, seroconversion and seroprotection rates are generally high.[8] Toxicity is particularly important when considering the effects of vaccinations on trials that involve IMPs with a high risk of immune adverse events, including cytokine release syndrome, or novel drugs given in combination with immunotherapies. Although there is experience in administering well established vaccinations to patients with cancer in phase 1 trials, these tend to be limited to inactivated vaccines and exclude live-attenuated and replication-competent vector vaccines. This contrasts with the available SARS-CoV-2 vaccines that are mRNA-based, live attenuated, non-replicating, or that use more conventional protein subunits.

The COVID-19 pandemic requires consideration of when patients participating in early cancer clinical trials should get vaccinated.[5] Typically, the timing of

Panel: Recommendations for SARS-CoV-2 vaccination and phase 1 cancer trials

Not started phase 1 trial
Avoid starting trial investigational medicinal product (IMP) until 2–4 weeks after the second dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is administered safely for trial IMPs with cytokine release syndrome risk.

Already in phase 1 trial
Administer SARS-CoV-2 vaccine during the phase 1 trial but avoid vaccination on days of parenteral IMP dosing and the dose-limiting toxicity period.

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. However, guidance on the administration of SARS-CoV-2 vaccines from trial sponsors has been unclear, ranging from full approval for such vaccines to be given in parallel to the IMP, to a complete avoidance of the vaccine during IMP administration.

We are an international group of medical oncologists based across the USA, the UK, Canada, and Europe and are involved in treating patients with advanced cancers in early phase clinical trials. On the basis of the promising clinical data for approved SARS-CoV-2 vaccines, we believe that the benefits of vaccination in the COVID-19 pandemic should substantially outweigh the possible benefits of participating in a phase 1 trial in light of the high risk to these patients of contracting life-threatening SARS-CoV-2 infection. We believe that any unnecessary delays with SARS-CoV-2 vaccination should be avoided. We recommend applying risk stratification by considering trials with a risk of cytokine release syndrome (eg, certain immunotherapies) separately to those without such toxicities (eg, non-immunotherapy studies involving molecularly targeted drugs). We also recommend that patients participating in early trials of anticancer drugs with unknown safety and tolerability should avoid starting trial IMPs until 2–4 weeks after the second dose of the SARS-CoV-2 vaccine is administered safely, especially for those with a risk for cytokine release syndrome (panel). If the trial involves proven anticancer drugs with known benefits, this wait might

be more challenging for patients with progressing advanced cancers, and the risks and benefits of the delay must be carefully considered with the patient. We also recommend that patients avoid receiving their vaccine on days of parenteral IMP dosing (and receive it at a time as distanced as possible from IMP dosing) and the dose-limiting toxicity period if administration of the SARS-CoV-2 vaccine is mandated while the patient is participating in an early phase trial. This latter strategy will minimise the risk of confounding overlapping or added adverse events during the crucial trial period of the IMP. This is particularly pertinent for common SARS-CoV-2 vaccine adverse events, such as tiredness, headaches, muscle and joint aches, chills, and fever, which might 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, adverse events, and clinical outcomes, including those from both SARS-CoV-2 infection and complications from cancer. In patients who have cancer trial IMP-associated immune-related adverse events, such as colitis or pneumonitis, and are on steroids or other immunosuppressive drugs, the SARS-CoV-2 vaccine should probably be avoided until the event is fully resolved or markedly improved. Clearly, such decisions need to be individualised to each patient and IMP risk profile.

Because 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 consideration of any changing risk factors. SARS-CoV-2 infection has no doubt affected and delayed all components of care for patients with cancer, including screening, diagnosis, treatment, and monitoring and surveillance strategies, and has probably increased the risk of cancer-related morbidity and mortality.[9] The pandemic also affects oncology trials, including patient accrual and logistical and economic aspects, and has the potential to affect the long-term development of promising life-saving anticancer drugs.

Although phase 1 oncology trials have unknown toxicity risks and are done primarily to recommend safe doses for future studies, the potential benefit to patients 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 drugs. Patient motivations and expectations of phase 1 oncology trials are varied. It will therefore be essential for decisions to be made on an individual basis with patients and their advocates to assess the risk–benefit balance by considering known IMP mechanisms and adverse events, and key patient characteristics, such as age, comorbidities, prognosis, and social factors. This is an opportunity for, 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 effect on the development of COVID-19, toxicity of anticancer drugs, and eventual cancer outcomes. As the vaccination programmes roll out globally, this early experience is likely to affect the timing, safety, and efficacy of SARS-CoV-2 vaccination for a considerable period.

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1   European Society for Medical Oncology. ESMO statements for vaccination against COVID-19 in patients with cancer. https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination (accessed Jan 7, 2021).

See **Online** for appendix

2   Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.

3   Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med* 2020; **383:** 1920–31.

4   Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2020; **397:** 99–111.

5   Curigliano G, Banerjee S, Cervantes A, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Ann Oncol* 2020; **31:** 1320–35.

6   Society for Immunotherapy of Cancer. SITC statement on SARS-CoV-2 vaccination and cancer immunotherapy. https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy (accessed Jan 7, 2021).

7   Yri OE, Torfoss D, Hungnes O, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. *Blood* 2011; **118:** 6769–71.

8   Bayle A, Khettab M, Lucibello F, et al. Immunogenicity and safety of influenza vaccination in cancer patients receiving checkpoint inhibitors targeting PD-1 or PD-L1. *Ann Oncol* 2020; **31:** 959–61.

9   Sud A, Torr B, Jones ME, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. *Lancet Oncol* 2020; **21:** 1035–44.

10 Adashek JJ, LoRusso PM, Hong DS, Kurzrock R. Phase I trials as valid therapeutic options for patients with cancer. *Nat Rev Clin Oncol* 2019; **16:** 773–78.

Quality assurance and cancer medicines in low-income and middle-income countries

Substandard medicines are medicines that fail to meet their quality standards, whereas falsified medicines are those that have been deliberately misrepresented in their identity, composition, or source.[1] Both substandard and falsified medicines are a major burden on health and economic outcomes, particularly in low-income and middle-income countries (LMICs).[1] WHO reports that one in ten medicines in LMICs might be substandard or falsified,[1] although a systematic review suggests higher rates of 11–48%.[2] These medicines impact a broad range of therapies, including cancer treatments, antibiotics, and other life-saving therapies.[1]

There is vast global inequality in cancer outcomes,[3] which is attributed to factors such as sparse implementation of prevention strategies, delayed diagnosis, and difficulty accessing treatment. Cancer control requires early diagnosis, effective intervention, and palliative care.[3] Treatment of cancer often leads to catastrophic financial costs for patients and their families,[3] which exacerbates existing income inequalities, hinders socioeconomic progress in marginalised groups, and causes poverty cycles.[4] These impacts are compounded by the infiltration of substandard or falsified medicines into health-care settings. The out-of-pocket spending and indirect costs of cancer (eg, due to work loss) increase if patients purchase ineffective medicines.

Substandard or falsified medicines reduce patient confidence in health-care systems, which can lead to disengagement if patients do not perceive effective treatments to be available, or if they fear prolonged physical pain, or are worried about becoming a financial burden on their families.[4] Access to quality-assured medicines is integral to tackling inequality in cancer outcomes and for fostering a global patient-centred public health approach, which has increasingly been called for during the COVID-19 pandemic.[5]

Delivery of quality-assured medicines at the point of access requires a robust regulatory system. When the regulatory system is deficient, substandard or falsified medicines can be accessed through formal supply routes that serve public facilities. Although initiatives between high-income countries and LMICs are helping to strengthen regulatory control,[1] challenges related to a scarcity of testing facilities, regulatory workforce and expertise, oversight, administration, and communications still exist.[6]

There is a need to simultaneously strengthen the formal supply chain workforce to maintain the quality

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