ESMO Statements for vaccination against COVID-19 in patients with cancer

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What are the vaccines being developed and nearing approval?

The World Health Organization (WHO) currently counts 214 research projects for the development of a vaccine conferring protective immunity against the SARS-CoV-2 virus, among which 52 are in clinical development. New technologies, previous experience with vaccine projects against related viruses and the presence of a pandemic health hazard accelerated the usual development cycle from years to months. Presentation of SARS-CoV-2 antigens to the host, in the context of vaccine development, relied on technologies based on messenger RNA (mRNA), inactivated/attenuated or genetically modified viruses, synthetic long viral peptides and plasmid DNA vaccines. Two vaccines have been approved by some regulators, including one which has been approved by the European Medicines Agency (EMA) on 21 December 2021, and a third is expected to do so soon. Many more vaccines are being tested in placebo-controlled Phase III studies for efficacy and safety in a total of more than 100,000 participants. Specifically, one large trial on a novel mRNA-based vaccine against SARS-CoV-2 infection (BNT162b2) has been published. This is a Phase III trial which included 43,448 participants who received two doses of the vaccine or placebo (1:1 randomisation), 21 days apart. The primary endpoint was the efficacy of the vaccine in reducing the cases with laboratory-confirmed COVID-19 with onset at least 7 days after the second dose. After a median follow-up of 2 months, the number of COVID-19 cases was 8 versus 162 in the vaccine or placebo arm, respectively, with 1 versus 9 severe cases. Adverse events occurred in >50% of vaccinated participants and included local reactions as well as frequent systemic reactogenicity such as fatigue and headache. Fever (temperature >38°C) occurred in approximately 15% of participants who received the vaccine. Altogether, 6 participants died (2 in the vaccine arm and 4 in the placebo arm), all of them from unrelated causes. Approximately 3% of participants suffered from some form of malignant disease. Another Phase III trial investigating another mRNA-vaccine (mRNA-1273) with >30,000 participants will soon be published. Preliminary reports suggest a similar efficacy and safety profile as for BNT162b2.

The safety and efficacy of the ChAdOx1 nCoV-19 adenoviral vector-based vaccine was recently published in a pooled interim analysis of four trials that randomised 23,848 participants to two doses of the vaccine or placebo; a subset of 2741 patients in the UK trial received a half dose as their first dose (low dose, LD) and a standard dose (SD) as their second dose (LD/SD cohort). In participants who received two standard doses, vaccine efficacy was 62.1% (27 COVID-19 events in the ChAdOx1 nCoV-19 group versus 71 in the control group) and in participants who received a low dose followed by a standard dose, efficacy was 90.0% (three versus 30 disease events). Overall vaccine efficacy across both groups was 70.4%. From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. In total, 175 severe adverse events occurred in 168 participants; 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine.

A large array of other vaccine candidates against SARS-CoV-2 are currently under investigation applying various techniques such as mRNA-, protein subunit-, viral vector- or inactivated vaccines.

Overall mRNA-based vaccines have shown >90% protection from COVID-19 disease with good tolerance, whereas a non-replicating adenoviral vector-based vaccine has shown protection rates of 62%-90% conferred by different dosing regimens. Storage requirements and number of doses differ between vaccines and operational practicalities related to transport, administration, recording and follow-up of vaccinated people, pharmacovigilance are pivotal for the successful roll-out of vaccination programmes and their optimal impact on public health. Additional questions exist that necessitate generation of data, including long-term safety, duration of immunity, protective immunity against mild as opposed to severe cases of infection as well as immunity in the elderly, vaccine impact on contagious potential of vaccinated people and repeat vaccination intervals. Specifically, for patients with cancer or a history of cancer, such strategies will provide more insights on vaccine activity, optimal dose and frequency, safety, potential for interaction with malignant disease, antineoplastic therapies or other comorbidities. Consequently, prospective observational studies focusing on patients with active cancer receiving chemotherapy, targeted therapy or immunotherapy, as well as in patients in the chronic phase of

disease or in the survivorship phase are warranted and may lead to interventional clinical trials, if needed.

Statements:

- Effective and safe vaccines against COVID-19, authorised after thorough, independent and robust scientific review by regulatory authorities, should be administered in the context of operationally sound vaccination programmes [V]. A pharmacovigilance plan is mandatory in the context of the vaccination programme.
- Continued research in the context of clinical trials and registries as well as in-trial and post-trial follow-up is advised in order to generate more data on vaccine efficacy and safety in the general population as well as in special populations, including patients with cancer or history of cancer [V].

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- **What is the incidence and severity of COVID-19 in patients with cancer, and where should they be positioned in vaccination priority policies?**

Cancer patients as a group have been shown to be at higher risk of severe COVID-19 [1]. Among cancer patients, it seems that haematological and lung malignancies and the presence of metastatic disease are associated with a persistently increased risk. Solid tumour patients appear to suffer an increased risk, particularly in the first year after diagnosis which drops to baseline if diagnosis is >5 years ago [2]. For any malignancy, active disease confers a significantly increased risk of severe COVID-19 [IV] [3, 4].
However, the higher incidence and severity of COVID-19 in patients with cancer, as opposed to those without cancer, are observations based on non-comparative retrospective studies. Data on the true incidence and direct comparisons remain elusive. Most studies do not have the full denominator to calculate the true incidence [IV].
Severity and mortality rates from the COVID-19 and Cancer Consortium (CCC19) registry and other cohorts have ranged from 5% to 61% (meta-analysis showed 26%) which is much higher than in the overall population (~2%-3%), but this is with caveats of unadjusted rates, while the cancer population is an older population with more comorbidities, poorer performance status, and many unmeasured confounding and selection biases [IV].
SARS-Cov-2 infection may also result in significant and devastating delays in screening, diagnosis, treatment and monitoring/surveillance strategies in patients with cancer which can ultimately cause an increased risk of cancer-related morbidity and mortality, as well as major economic burden and high patient volumes needing care in the healthcare systems. Moreover, the impact on clinical trials accrual appears to be very significant and detrimental, although it is hard to measure [V].
Although evidence regarding vaccination in cancer patients is limited, there is enough evidence to support anti-infective vaccination in general (excluding live-attenuated vaccines and replication-competent vector vaccines) even in cancer patients undergoing immunosuppressive therapy [5-7].
Reduced protective effects are probable in patients treated with B cell-depleting agents (anti-CD19, anti-CD20, anti-CD10 monoclonal antibodies and CD19 CAR-T cells) in view of suboptimal immune response [8-12]. Based on data extrapolation from other vaccines and the mechanism of action of the COVID-19 vaccines (not live), it is conceivable that the efficacy and safety of vaccination against COVID-19 may be estimated to be similar to that of patients without cancer, although data from clinical trials are lacking [V]. The level of efficacy may be expected to be generally reduced in certain populations of cancer patients with intense immunosuppression, such as recipients of haematopoietic stem cell transplantation [V] [5-7]. Beyond stem cell transplantation, the efficacy of COVID-19 vaccines can also vary in patients with distinct contexts of malignant disease (tumour type, disease extent, intrinsic or therapy-induced immunosuppression); however, the benefits of vaccination seem to significantly and substantially outweigh the risks [V].
The timing of vaccination depends on individual therapy scenarios and may ideally occur before systemic therapy starts; however, if the patient has already started systemic therapy, it is reasonable to vaccinate during therapy [V].
Vaccinating healthcare staff against influenza has been shown to reduce nosocomial transmission of the infection in cancer care [13]. Furthermore, certain immunocompromised cancer patients might not achieve a sufficient immune response to vaccination. This provides a rationale for vaccinating healthcare staff who work in a high-risk setting against COVID-19 as well [Evidence III for influenza].

Statements:

- Cancer patients with an increased risk of severe COVID-19 (i.e. haematological malignancy requiring chemotherapy or active, advanced solid tumour or history of solid tumour <5 years ago) should be vaccinated against SARS-CoV-2 regardless of any other indications (i.e. age) and positioned at high prioritisation [V]. Patients who have received B cell depletion in the past 6 months may derive reduced protection. The time-point for vaccination after allogeneic stem cell

transplantation should follow general recommendations – usually, in the absence of graft-versus-host disease (GvHD), the vaccine can be applied 6 months post stem cell transplantation [V].

- Healthcare workers caring for cancer patients with increased risk should be prioritised in receiving vaccination to minimise nosocomial transmission [III].
- The efficacy and duration of immunity in patients with cancer are still unknown and unexplored. Given the often-immune compromised status and the frailty of these patients, we suggest monitoring in the context of registries and dedicated clinical trials [V].
- Close surveillance and monitoring of patients with cancer is required after COVID-19 vaccination to assess potential adverse events and measure clinical outcomes, e.g. infection, severity and mortality from COVID-19, complications from cancer, etc. [V].
- Physical distancing measures, masks, face shields, sanitizers and other hygiene measures are still required during the pandemic, including for patients with cancer, and should certainly accompany the vaccination strategies [V].

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- **What is the ability of cancer patients to mount an immune response following vaccination?**

Data on humoral and cellular immune response to antiviral vaccination in cancer patients are scarce, and mostly address the issue of influenza vaccination [1,2]. Observational clinical studies indicate that lower mortality and morbidity rates from influenza are observed in cancer patients receiving influenza vaccination [II] [3], suggesting an efficient immune response.
In lung and breast cancer patients, the humoral immune response to vaccination appears adequate, although not all patients were receiving chemotherapy [IV] [4,5]. In a study of patients with various solid tumours, the response to vaccination was better than in patients with lymphoma [IV] [6].
In patients receiving chemotherapy, seroconversion and seroprotection rates are expected to be lower than in the general population [IV] [7], but not in patients receiving single-agent immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) [IV] [8].
In patients receiving chemotherapy, multiple doses of vaccine might help to reach adequate seroconversion and seroprotective rates. As an illustration, in a non-randomised Phase II study on 65 patients with solid tumours receiving chemotherapy (+/- molecular targeted agents) during the 2009 influenza season, 5% of patients had vaccine strain titres of specific haemagglutination inhibition antibodies that were ≥1:40 at baseline. After one and two doses of AS03A-adjuvanted H1N1v vaccine, seroprotection rates (i.e. the proportion of participants with antibody titres ≥1:40) were 48% and 73%, respectively, and seroconversion rates were 44% and 73%, respectively [III] [9].
Whenever possible, the administration of the vaccine should be performed before initiation of chemotherapy [V] [2]. In patients who have already initiated chemotherapy, the existing data do not support a specific timing of administration with respect to chemotherapy infusions [III] [2, 9].
In order to generate protective immunity following vaccination, intact host immunity is needed, particularly with respect to antigen presentation, B- and T-cell activation. In this context, vaccination may be less effective in patients receiving anti–B-cell antibodies or intensive chemotherapy (e. g. induction or consolidation chemotherapy for acute leukaemia) because the antibody response may be low, due to B-cell depletion, though the role and potential protective effect of T-cell immunity has not been studied extensively [V] [2].
The level of evidence is weak, due to the small number of studies and their methodology; placebo-controlled randomised controlled trials of antiviral vaccination among adults with cancer being often considered ethically questionable [V] [2].

Statement:

- Accumulated evidence from influenza vaccinations suggests that patients with cancer are able to mount a protective immune response from anti-SARS-CoV-2 vaccines, though the level of immunity may be modulated by a range of factors (type of malignancy, antineoplastic therapies and timing of administration, pre-existing immune dysfunction, fitness) [V]. Data on the interaction of such factors with vaccine-induced immunity in patients with cancer are needed.

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- **What is the risk of interaction of a SARS-CoV2 vaccine with antineoplastic therapies?**

No SARS-CoV-2 vaccine trial is enrolling patients receiving immunosuppressive therapy, though data from some patients with cancer have been accrued. Most trials require patients to be off immunosuppression for a certain period in order to be eligible for vaccination.
Currently developed SARS-CoV-2 vaccines are either live attenuated/non-replicating vaccines (using vectors as adenovirus or measles virus), mRNA-based vaccines or more conventional protein subunit vaccines [1].
Live vaccines are, in general, contraindicated in patients under immunosuppressive therapy [V] [2,3]. Indeed, serious adverse events are possible, as was shown with BCG (Bacillus Calmette–Guérin) [3]. One of the anti-SARS-CoV-2 live virus vaccines developed utilised a replication-deficient simian adenoviral vector (ChAdOx1).
There are no published data on the immunogenicity and interaction of mRNA-based antiviral vaccines with antineoplastic therapies in cancer patients. Some of these vaccines are encapsulated in small liposomes, vectors that are expected to accumulate in tumour tissues. An increased uptake of these liposomes in tumour tissues is theoretically possible and might impact the immunogenicity of such vaccines [V] [4]. Otherwise, mRNA-based vaccines against non-communicable diseases (e.g. melanoma) have been tested in cancer patients for the past 10 years, without raising specific safety concerns [5]. Retrospective datasets suggest good tolerability and safety of influenza vaccination in patients with cancer receiving immune checkpoint inhibitors [6-8], as well as in patients on cytotoxic therapy or targeted agents [9, 10].
Finally, regarding protein subunit vaccines, there is no conclusive evidence regarding the use of adjuvanted versus non-adjuvanted inactivated influenza vaccines in cancer patients [II] [11].

Statement:

- Although no obvious safety concerns are evident, there is a clear need to generate data on preference of vaccine technology and interaction of SARS-CoV-2 vaccines with antineoplastic therapies in patients with cancer, potentially impacting on efficacy, dosing or toxicity, via in-trial, post-trial and registry monitoring [V].

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- **What are the priority considerations to be implemented for patients with cancer so as to identify groups with varying benefits from a SARS-CoV2 vaccine?**

Vaccination strategies have been published worldwide, in order to prioritise vaccine administration in the different populations [1]. The World Health Organization (WHO) considers the elderly and healthcare professionals as first priorities (respectively phases 1b and 1a), and cancer patients are positioned in phase 2 [2, 3]. In the United States (US), professionals are considered priorities (1a), followed by cancer patients and the elderly ≥65 years old (1b) [4]. In Australia, professionals, those with comorbidities such as cancer and the elderly are the first priority for vaccination against COVID-19 [5]. In Europe, the UK and France base their recommendation priorities on age before comorbidities such as cancer [6, 7]. Belgium, Luxembourg and Sweden will vaccinate in priority cancer patients and healthcare professionals [8-10]. In a German joint position paper "persons (groups of persons) who have a significantly increased risk of serious or fatal disease progression due to their age or underlying medical condition" are prioritised [11]. However, patients with cancer do not represent a homogeneous population.

In general, cancer disease reveals three aspects of pathways: patients with active disease on treatment, those with chronic disease after specific treatment and patients in the survivorship phase. In the "survivorship" phase, previous studies revealed a higher risk of complications related to influenza in cancer patients compared to a cancer-free control cohort, specifically in haematological cancer survivors [12]. Consequently, vaccination seems essential to protect survivors along with patients in the chronic phase of their cancer without active treatment [V]. The question is more uneasy in patients with active disease on anticancer therapy for whom vaccination could have reduced efficacy or adverse events. Additionally, there are no granular data that dissect the vaccine role in protection from COVID-19, protection from SARS-CoV-2 infection (at the mucosal level) and protection from SARS-CoV-2 transmission in patients with cancer.

Acceptability of COVID-19 vaccination has reached 69% among adults in the US, notably if their healthcare provider would recommend vaccination [13]. Informed consent and shared decisions should be the rule to discuss benefits and risks of the anti-COVID-19 vaccination to prevent patients from a double jeopardy: cancer and infection.

Statement:

- While acknowledging the need to generate data in the context of trials or registries, in order to refine the risk/benefit profile and prioritise subgroups of patients with cancer for anti-SARS-CoV-2 vaccination, we propose a four-step process [V]:
    - Step 1: Consider the phase of malignant disease and therapy: active cancer on treatment, chronic disease after treatment or survivor care.
    - Step 2: Consider age, fitness and comorbidities as general risk factors; specifically, obesity, hypertension, diabetes, respiratory, cardiac and renal disorders.
    - Step 3: Consider vaccine-related interactions on the tumour and on the treatment efficacy.
    - Step 4: Secure informed consent and improve shared decision making.

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ESMO Levels of Evidence:

I - Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity

II - Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

III - Prospective cohort studies

IV - Retrospective cohort studies or case–control studies

V - Studies without control group, case reports, expert opinions

Appendix

Table 1: Coronavirus vaccine candidates investigated as of November 30, 2020.

Vaccine	Company	Clinical Trial Identifier	Exclusion Criteria for cancer patients
mRNA-1273 (Lipid nanoparticle-mRNA)	Moderna / NIAID	NCT04470427	People who have received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to screening.
BNT162b2 (Lipid nanoparticle-mRNA)	BioNTech, Pfizer, Fosun Pharma	NCT04368728	People receiving Immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g. for cancer.
Ad5-nCoV (Non-replicating Adenovirus Type 5 Vector)	CanSino Biologics	NCT04526990 NCT04540419	People with current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma *in situ*)
Gam-Covid-Vac (Sputnik V) Adeno-based (rAd26-S+rAd5-S)	Gamaleya Research Institute	NCT04530396 (RESIST) NCT04564716	History of any malignant tumours.
Ad26.COV2.S / JNJ-78436735 (Adenovirus Type 26 vector)	Beth Israel Deaconess Medical Center and Johnson & Johnson (Janssen)	NCT04505722 (ENSEMBLE) NCT04614948 (ENSEMBLE 2)	Malignancy within 1 year before screening, except squamous and basal cell carcinomas of the skin and carcinoma *in situ* of the cervix, or other malignancies with minimal risk of recurrence. Patients receiving chemotherapy, immune-modulating drugs or radiotherapy within 6 months before administration of vaccine and/or during the study.
ChAdOx1 nCov-19 (AZD-1222) (Non-Replicating Viral Vector)	University of Oxford/ AstraZeneca	NCT04516746 NCT04540393 (COV002 and COV003) ISRCTN89951424 CTRI/2020/08/027170	History of primary malignancy except for malignancy with low potential risk for recurrence after curative treatment or metastasis (for example, indolent prostate cancer) in the opinion of the site investigator.
NVX-CoV2373 (Protein Subunit)	Novavax	(UK) 2020-004123-16 / 2019nCoV-301 (US) NCT04611802 / 2019nCoV-301	(UK) Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma *in situ*, at the discretion of the investigator). (US) Active malignancy on therapy within 1 year prior to first study vaccination (with the exception of malignancy cured via excision, at the discretion of the investigator).
CoVLP (Plant-derived VLP adjuvanted with GSK or Dynavax adjs)	Medicago /GSK	NCT04636697	Any confirmed or suspected immunosuppressive condition, including cancer. Investigator discretion is permitted. People receiving cytotoxic, antineoplastic, or immunosuppressants within 36 months prior to vaccination.
COVID-19 Vaccine	Chinese	NCT04466085	History of any malignant tumours.

(Protein Subunit)	Academy of Medical Sciences/ Anhui Zhifei Longcom	(ph 2) Phase III announced on November 20, 2020.	
BBIBP-CorV (Inactiva-ted)	Wuhan Institute of Biological Products / Sinopharm	ChiCTR2000034780 ChiCTR2000039000 NCT04612972	History of any malignant tumours.
CoronaVac (Inactiva-ted)	Sinovac Biotech	NCT04456595 (PROFISCOV) 669/UN6.KEP/EC/2020 NCT04582344 NCT04617483	Use of chemotherapy or radiotherapy within 6 months prior to enrolment or planned use within the 2 years following enrolment. History of malignancy or antineoplastic chemotherapy, radiotherapy, immunosuppressants in the past 6 months.
Covaxin (Inactiva-ted)	Indian Council of Medical Research / Bharat Biotech	CTRI/2020/11/028976	Treatment with immunosuppressive or cytotoxic drugs or use of anticancer chemotherapy or radiotherapy within the preceding 36 months.
BCG	Murdoch Children's Research Institute	NCT04327206 (BRACE)	History of any malignant tumours.