Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

SARS-CoV-2 vaccines for cancer patients treated with immunotherapies: Recommendations from the French society for ImmunoTherapy of Cancer (FITC)

Marie-Léa Gauci [a,*], Clélia Coutzac [b], Roch Houot [c], Aurélien Marabelle [d,e], Céleste Lebbé [a] on behalf of the FITC

[a] Université de Paris, AP-HP Dermatology, INSERM U976, Saint Louis Hospital, Paris, France
[b] Centre Léon Bérard, Cancer Research Center of Lyon (CRCL), Lyon, France
[c] Centre Hospitalier Universitaire de Rennes, Service D'Hématologie Clinique, Rennes, France
[d] Gustave Roussy, Université Paris-Saclay, Département D'Innovation Thérapeutique et D'Essais Précoces, Villejuif, France
[e] Gustave-Roussy, Université Paris-Saclay, INSERM U1015 & CIC1428, Villejuif, France

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Dear Editor,

Since December 2019, the emergence of the severe acute respiratory syndrome (SARS)- coronavirus (CoV)-2, responsible for COVID-19 and its worldwide spread led to devastating medical, economic and social consequences. Recently approved anti-SARS-CoV-2 vaccines (SC2V) offer a new hope to end this crisis.

Cancer patients (CPs) represent a group at higher risk of severe COVID-19 because of the underlying disease, mostly during the five years after cancer diagnosis and in case of active disease [1] but also because of their age and preexisting conditions [2].

Two mRNA-based SC2V have been recently approved by the EMA (BNT162b2, Pfizer Inc./BioNTech SE; and mRNA-1273, Moderna Inc.) and consist of lipid-nanoparticles- encapsulated mRNA that encodes the SARS-CoV-2 spike protein (SSP). On cell penetration, mRNA will be translated into the SSP,

* *Corresponding author*: Dermatology department, INSERM U976 Saint-Louis Hospital 1, Avenue Claude Vellefaux 75010, Paris, France.
E-mail address: marie-lea.gauci@aphp.fr (M.-L. Gauci).

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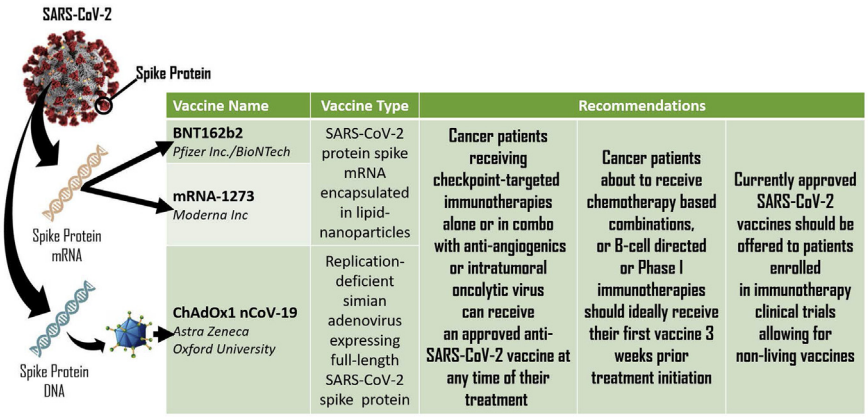
Table 1
FITC recommendations for COVID-19 vaccination in cancer patients treated with immunotherapy.



Vaccine Name	Vaccine Type	Recommendations		
BNT162b2 *Pfizer Inc./BioNTech*	SARS-CoV-2 protein spike mRNA encapsulated in lipid-nanoparticles	Cancer patients receiving checkpoint-targeted immunotherapies alone or in combo with anti-angiogenics or intratumoral oncolytic virus can receive an approved anti-SARS-CoV-2 vaccine at any time of their treatment	Cancer patients about to receive chemotherapy based combinations, or B-cell directed or Phase I immunotherapies should ideally receive their first vaccine 3 weeks prior treatment initiation	Currently approved SARS-CoV-2 vaccines should be offered to patients enrolled in immunotherapy clinical trials allowing for non-living vaccines
mRNA-1273 *Moderna Inc*				
ChAdOx1 nCoV-19 *Astra Zeneca Oxford University*	Replication-deficient simian adenovirus expressing full-length SARS-CoV-2 spike protein			

where degraded peptides are presented by MHC molecules to trigger an antigen-specific cellular and humoural immune response (IR) against SSP epitopes. Of note, the viral mRNA is subsequently degraded, thus it cannot interfere significantly with the host genome nor persist overtime. Phase 3 clinical trials (CTs) evaluating these vaccines versus placebo demonstrated remarkable efficacy with more than 90% (95 and 94.1%, respectively) protection against COVID-19 development and a favourable safety profile [3,4]. Although the efficiency of vaccination to prevent SARS-CoV-2 asymptomatic infection and transmission was not robustly explored in these phase 3 CTs, there was a trend in a decrease in PCR positivity before the second injection in the vaccine group (0.1% versus 0.3%) [3]. Further studies are needed to address this question.

In the BNT162b2 CT (Pfizer Inc./BioNTech SE) only, 4% of patients in the vaccine group suffered of any malignancy. Metastatic solid tumour, leukaemia and lymphoma represented 0.2% of all patients. Although robust data on efficacy and safety in this category of patients are lacking and because none of these patients received immunosuppressive treatment such as chemotherapy [3,4], it is expected that the safety of such non-live vaccines should be similar to that of patients without cancer. The ability of CP to build a strong, durable anti-SARS-CoV-2 IR with these mRNA-based vaccines shall be investigated in future trials.

Recently, the EMA has approved of the ChAdOx1 nCoV-19 codeveloped by AstraZeneca and Oxford University based on the results of 4 randomised CTs demonstrating an efficacy of ~60% with only mild local and systemic reactions [5]. This vaccine is a replication-deficient simian adenovirus expressing full-length SSP used here as a vector for transfection of SSP nucleic acid sequence into host cells, which will express SSP without viral replication. Therefore, it cannot be considered as a "live" vaccine such as BCG. Of note, its efficacy in the elderly population could not be formally demonstrated because few patients in those trials were over 55 years old. However, COVID-19 protection is expected in these patients given that an IR against the SSP was generated in this age group. The vaccine can be used in adults aged >55 years as per EMA recommendation.

Immune checkpoint inhibitors (ICI), such as anti-PD-(L)1 and anti-CTLA-4, restore an efficient anti-tumor IR by blocking inhibitory synapses. Considering their mechanism of action and based on preclinical data, ICI are likely to enhance rather than diminish IR against vaccines. Although the susceptibility of immunotherapy-treated patients to infections has not been specifically investigated, immunosuppression is not expected with these treatments and efficient postvaccinal seroconversion was already demonstrated with influenza vaccines [6,7]. However, CPs receiving steroids or cytokine blockers to manage immune-related side effects may not mount a robust IR against vaccines, but this aspect has not yet been evaluated. Patients with haematologic malignancies receiving B-cell-directed immunotherapies, typically CD19, CD20 or CD22-targeted therapies, may also be less responsive to SC2V [8]. In light of these data, the FITC (French society for ImmunoTherapy of Cancer) elaborated the following recommendations (summarised in Table 1) on the EMA-approved SC2Vs for CPs treated with immunotherapy:

- Healthcare workers caring for CPs treated with immunotherapy should receive SC2V to minimise virus transmission (based on data on influenza vaccine [9]). Because it is not yet formally proven that the vaccine prevents transmission of the virus to others, we recommend to maintain social distancing and masking even after vaccination [10].
- Anti-SARS-CoV-2 vaccination should be made available broadly to CPs under immunotherapy but considered individually, notably in patients with known severe food, drug or excipient allergies.
- CPs receiving ICI alone or in combination with anti-angiogenics or intratumoral oncolytic virus should receive an approved SC2V at any time of their treatment.

- ❖ CPs treated with a combination of ICI and chemotherapy should be prioritised due to their immunocompromised condition. They shall ideally receive their first SC2V dose 3 weeks before starting their chemotherapy or in ongoing treatment conditions, as close as possible and before the next chemotherapy to improve its immunogenicity.
- ❖ CPs treated with B-cell-directed immunotherapies (monoclonal antibodies, bi-specific T-cell engagers or CAR-T cells) should ideally receive their first dose of vaccine 3 weeks before starting treatment (including conditioning regimen for CAR-T cells). For patients who have already received haematopoietic stem cell transplantation or a CAR-T cell therapy, we recommend starting vaccination at least 3 months after therapy to allow immune recovery and optimise vaccinal response.
- ❖ Patients in CTs should not be prevented from receiving SC2V and efforts are needed for CT protocols and sponsors to allow for concurrent vaccination. In phase I immunotherapy trials, patients should ideally receive a first vaccine dose at least 3 weeks before cycle 1 but should not receive any dose during the DLT period to avoid confusing unrelated adverse events.
- ❖ Close monitoring of CPs treated with immunotherapy and vaccinated against SARS-CoV-2 should be performed through CTs and registries to assess potential adverse events, measure biological and clinical outcomes, and determine optimal protocols for anti-SARS-CoV-2 immunisation, notably:
  - The capacity to build a strong anti-SARS-CoV-2 IR.
  - The impact of the sequence of vaccination/immunotherapy on the efficacy/safety of both vaccination and immunotherapy and potential interactions.

Finally, continued research with CTs and registries should be encouraged to generate more data on vaccine efficacy/safety in immunotherapy-treated CPs. FITC's recommendations could be modified on availability of new data.

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Conflict of interest statement

Authors declare no competing interest in relation with this letter.

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