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Current Perspective

Severe acute respiratory syndrome coronavirus 2 vaccination for patients with solid cancer: Review and point of view of a French oncology intergroup (GCO, TNCD, UNICANCER)



David Tougeron ^{a,*}, Maxime Hentzien ^b, Barbara Seitz-Polski ^c, Firouze Bani-Sadr ^b, Jean Bourhis ^d, Michel Ducreux ^e, Sébastien Gaujoux ^f, Philippe Gorphe ^g, Boris Guiu ^h, Khê Hoang-Xuan ⁱ, Florence Huguet ^j, Thierry Lecomte ^k, Astrid Lièvre ^l, Christophe Louvet ^m, Léon Maggiori ⁿ, Laura Mansi ^o, Pascale Mariani ^p, Pierre Michel ^q, Amélie Servettaz ^b, Juliette Thariat ^r, Virgine Westeel ^s, Thomas Aparicio ^{t,1}, Jean-Yves Blay ^{u,1}, Olivier Bouché ^v, for Thésaurus National de Cancérologie Digestive (TNCD), réseau de Groupes Coopérateurs en Oncologie (GCO), Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER), Association de Chirurgie Hépatobilio-Pancréatique et Transplantation (ACHBT), Association de Recherche sur les Cancers Gynécologiques-Groupes d'Investigateurs Nationaux pour l'étude des Cancers Ovariens et du Sein (ARCAGY-GINECO), Fédération Francophone de Cancérologie Digestive (FFCD), Groupe Coopérateur multidisciplinaire en Oncologie (GERCOR), Groupe d'Oncologie Radiothérapie Tête et Cou-Intergroupe ORL (GORTEC-Intergroupe ORL), Intergroupe Francophone de Cancérologie Thoracique (IFCT), InterGroupe Coopérateur de Neuro-Oncologie/Association des Neuro-Oncologues d'Expression Française (IGCNO-ANOCEF), Société Française de Chirurgie Digestive (SFCD), Société Française d'Endoscopie Digestive (SFED), Société Française de Radiothérapie Oncologique (SFRO), Société Française de Radiologie (SFR), Société Nationale

* Corresponding author: Gastroenterology department, Poitiers University Hospital, Poitiers, France. Fax: +5 49 44.38.35.

E-mail address: david.tougeron@chu-poitiers.fr (D. Tougeron), Twitter: [@david_tougeron](https://twitter.com/david_tougeron) (D. Tougeron).

¹ Equally contributor.

Française de Colo-Proctologie (SNFCP), Société Nationale Française de Gastroentérologie (SNFGE)

- ^a Hepatology and Gastroenterology Department, Poitiers University Hospital and University of Poitiers, FFCD, Poitiers, France
- ^b Internal Medicine and Infectious Diseases Department, Reims University Hospital, Reims, France
- ^c Immunology Laboratory, UR2CA, Nice University Hospital, Nice, France
- ^d Radiotherapy Department, Vaud University Hospital, GORTEC/Intergroupe ORL, Lausanne, Switzerland
- ^e Digestive Oncology Department, Gustave Roussy Institute, Paris-Saclay University, UNICANCER, Villejuif, France
- ^f Digestive Surgery Department, Pitié-Salpêtrière Hospital, AP-HP, ACHBT, Paris, France
- ^g Cervico-Facial Department, Gustave Roussy Institute, Paris-Saclay University, Intergroupe ORL, Villejuif, France
- ^h Radiology Department, Montpellier University Hospital, SFR, Montpellier, France
- ⁱ Neurology Department, Pitié-Salpêtrière Hospital, AP-HP, Paris-Sorbonne Université, IGCNO-ANOCEF, Paris, France
- ^j Radiotherapy Department, Tenon Hospital, Sorbonne Université, APHP, Institut Universitaire de Cancérologie, SFRO, Paris, France
- ^k Hepatology, Gastroenterology and Digestive Oncology Department, Tours University Hospital and UMR INSERM 1069 N2C, Tours University, SFED, Tours, France
- ^l Gastroenterology Department, Pontchaillou University Hospital, INSERM UMR 1242, COSS “Chemistry, Oncogenesis, Stress Signaling”, Rennes, SNFGE, France
- ^m Medical Oncology Department, Institut Mutualiste Montsouris, GERCOR, Paris, France
- ⁿ Digestive Surgery Department, Saint Louis Hospital, APHP, SNFCP, Paris, France
- ^o INSERM, EFS BFC, UMR1098, RIGHT, University of Bourgogne Franche-Comté, Interactions Greffon-Hôte-Tumeur/ Ingénierie Cellulaire et Génique, Department of Medical Oncology, University Hospital of Besançon, GINECO, Besançon, France
- ^p Oncology Digestive Surgery Department, Curie Institute, SFCD, Paris, France
- ^q Hepatology and Gastroenterology Department, Rouen University Hospital, Normandie University, UNIROUEN, Inserm U1245, IRON Group, FFCD, Rouen, France
- ^r Radiotherapy Department, François Baclesse Center, Normandie Université, GORTEC/Intergroupe ORL, Caen, France
- ^s Pneumology Department, Jean Minjot Hospital, CHU Besançon, INSERM UMR 1098, Franche-Comté University, IFCT, Besançon, France
- ^t Gastroenterology and Digestive Oncology Department, Saint Louis Hospital, APHP, Université de Paris, GCO, Paris, France
- ^u Medical Oncology Department, Léon Bérard Center, UNICANCER, Lyon, France
- ^v Digestive Oncology Department, CHU Reims University Hospital, TNCD, Reims, France

Received 20 February 2021; accepted 14 March 2021

Available online 1 April 2021

KEYWORDS

COVID-19;
SARS-CoV-2;
Vaccination;
Coronavirus;
Solid cancers;
Chemotherapy;
Radiotherapy

Abstract The impacts of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic on cancer care are multiple, entailing a high risk of death from coronavirus disease 2019 (COVID-19) in patients with cancer treated by chemotherapy. SARS-CoV-2 vaccines represent an opportunity to decrease the rate of severe COVID-19 cases in patients with cancer and also to restore normal cancer care. Patients with cancer to be targeted for vaccination are difficult to define owing to the limited contribution of these patients in the phase III trials testing the different vaccines. It seems appropriate to vaccinate not only patients with cancer with ongoing treatment or with a treatment having been completed less than 3 years ago but also household and close contacts. High-risk patients with cancer who are candidates for priority access to vaccination are those treated by chemotherapy. The very high-priority population includes patients with curative treatment and palliative first- or second-line chemotherapy, as well as patients requiring surgery or radiotherapy involving a large volume of lung, lymph node and/or haematopoietic tissue. When possible, vaccination should be carried out before cancer treatment begins. SARS-CoV-2 vaccination can be performed during chemotherapy while avoiding periods of neutropenia and lymphopenia. For organisational reasons, vaccination should be performed in cancer care centres with messenger RNA vaccines (or non-replicating adenoviral vaccines in non-immunocompromised patients). Considering the current state of knowledge, the benefit-risk ratio strongly favours SARS-CoV-2

vaccination of all patients with cancer. To obtain more data concerning the safety and effectiveness of vaccines, it is necessary to implement cohorts of vaccinated patients with cancer. © 2021 Elsevier Ltd. All rights reserved.

1. Introduction

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an exceptional pandemic with a high impact on cancer care pathways. Morbidity and mortality from COVID-19 in patients treated for solid tumour is high, with approximately 35% of severe diseases and 20–30% of deaths [1,2]. Severity and mortality from COVID-19 are mostly due to patients' comorbidities, with a low impact of cancer treatments [1–3]. COVID-19 is also associated with delay in treatment and loss of chances in terms of cancer treatment and quality of life (postponement of chemotherapy, radiotherapy and/or surgery, limited access to supportive care and so on).

Immunocompromised patients have longer viral clearance owing to late and low humoral immunity [4]. Moreover, anti-SARS-CoV-2 humoral and T-cell immune response is less effective in patients with cancer, raising questions about the effectiveness of vaccination. Indeed, patients with cancer do not develop as much humoral immunity as non-cancer subjects and may remain contagious and able to spread SARS-CoV-2 for two months or more [5]. Consequently, it seems appropriate to vaccinate all patients who are frequently treated in cancer care centres.

In addition to the morbidity and mortality associated with COVID-19, the impact on the healthcare system for cancer care from cancer screening to palliative care is major [6]. While the prognostic impacts of diagnosis and treatment delays are not yet known, existing modelling analyses are worrisome [7]. Several recommendations for the cancer treatment strategy have been proposed during the SARS-CoV-2 pandemic [8–13].

No drug treatment, except corticosteroid and tocilizumab, has been shown with a high level of evidence to achieve a decreased rate of severe COVID-19. The SARS-CoV-2 vaccine consequently represents a major hope for patients with cancer, by not only limiting severe COVID-19 infection but also maintaining 'normal' cancer care.

2. Methodology

The current perspective is focused on SARS-CoV-2 vaccination of adult patients with solid tumours (excluding vaccination of physicians and patients with haematologic malignancies). Our proposals are based on the scientific data concerning SARS-CoV-2 vaccines

available on 19th February 2021; recommendations from the European Society for Medical Oncology (ESMO) [14], the American Association for Cancer Research [15], the American Society of Clinical Oncology [16], the Society for Immunotherapy of Cancer [17], and the French National Cancer Institute (INCa) and collaborative reflection of a French oncology intergroup (Thésaurus National de Cancérologie Digestive [TNCD], réseau de Groupes Coopérateurs en Oncologie [GCO] and Fédération Nationale des Centres de Lutte Contre le Cancer [UNICANCER]) enriched by the expertise of immunologists and infectious disease specialists. In many respects, the available data are sparse, with a low level of evidence (expert agreement or expert opinion).

3. Immune response to SARS-CoV-2 infection in patients with cancer

In about 80% of symptomatic cases of COVID-19, patients do not require special monitoring. In less than 20% of cases, COVID-19 progresses to severe symptoms including acute respiratory syndrome with a cytokine storm partially related to an insufficient type I and II interferon response [18]. The interferon response decreases not only with age but also in patients with cancer [19]. More specifically, severe COVID-19 in patients with cancer is due to the cancer itself, treatments and the severe comorbidities that are frequently present in these patients.

4. The different SARS-CoV-2 vaccines and data on patients with cancer

Based on the country, different SARS-CoV-2 vaccines are available, and several have been approved or are in development (Table 1). The spike protein is the 'key' that allows SARS-CoV-2 to enter into our cells and is the target of vaccines. The first two vaccines approved by the European Medicines Agency (EMA) and the US Food and Drug Administration are two messenger RNA (mRNA) vaccines (BNT162b2 [Comirnaty®] from Pfizer/BioNTech and mRNA-1273 [COVID-19®] from Moderna) [20,21]. Both vaccines have demonstrated an interferon increase after injection associated with a specific CD4+ and CD8+ T-cell response and neutralising antibodies directed against the spike protein (humoral and cellular immune response). In some phase III trials with these vaccines, patients with cancer could be

Table 1
Main vaccines available or in the ongoing phase II–III.

Vaccines	Type	Trial	Population	Usable in immunocompromised patients
Comirnaty® BNT162b2 Pfizer/BioNtech	mRNA	Phase III Approved by the EMA and FDA	Exclusion of patients with cancer with ongoing chemotherapy (no subgroup result available)	Yes
mRNA-1273 Moderna/NIH	mRNA	Phase III Approved by the EMA and FDA	Exclusion of patients with cancer with ongoing chemotherapy or immunotherapy more than 14 days during the past 6 months (no subgroup result available)	Yes
CVnCoV CUREVAC	mRNA	Phase III	Exclusion of patients with cancer with ongoing treatment (no subgroup result available)	Yes
AstraZeneca/Oxford University AZD1222	Adenovirus	Phase III Approved by the EMA	Exclusion of patients with cancer history except curative treatment and low risk of recurrence according to the investigator	Yes
Ad26.COV2.S/JNJ-78436735 Beth Israel Deaconess Medical Center and Johnson & Johnson (Janssen)	Adenovirus	Phase III Approval request	Exclusion of patients with cancer since less than one year	Yes
Gam-Covid-Vac (Sputnik V®) Russia MH/Gamaleya Research Institute	Adenovirus	Phase III	Exclusion of patients with a cancer history	Yes
Ad5-nCoV/Convidecia CanSino Biologics	Adenovirus	Phase III	Exclusion of patients with cancer with ongoing treatment (no subgroup result available)	Yes
GRAd-COV2 Italy ReiThera	Adenovirus	Phase II	Exclusion of patients with a cancer history	Yes
WIBPCorV Wuhan Institute of Biological Products/ Sinopharm	Inactivated SARS-CoV-2	Phase III	Exclusion of patients with a cancer history	Yes
BBIBPCorV Beijing Institute of Biological Products/ Sinopharm	Inactivated SARS-CoV-2	Phase III	Exclusion of patients with a cancer history	Yes
NVXCoV2373 Novavax	Recombinant protein	Phase III	Exclusion of patients with a cancer history and with treatment completed since less than 1 year	Yes
CoVLP Medicago/GSK	Virus-like particles	Phase III	Exclusion of patients with a cancer history and with chemotherapy completed since less than 3 months	Yes

EMA: European Medicines Agency; FDA: US Food and Drug Administration.

included; unfortunately, no results in this subgroup of patients have been reported to date (Table 1).

Three first non-replicating viral vectors (human and non-human adenoviruses) have been developed by the University of Oxford/AstraZeneca (non-replicating chimpanzee adenovirus AZD1222 vaccine), by Russia/the Gamaleya Research Institute (Gam-COVID-Vac [Sputnik V®]) and by Johnson & Johnson/Janssen (JNJ-78436735) (two non-replicating human adenovirus vaccines). The first of these, which is 60–70% effective, was recently been approved by the EMA but remains restricted to the population aged younger than 65 years, pending ongoing studies in elderly patients [22]. Recently, the Russian Sputnik V® vaccine showed 91.6% efficacy in a phase III study [23]. To date, although there exist no specific data on patients with cancer, it bears mentioning that these viral vectors,

which are non-replicating, are not contraindicated in immunocompromised patients.

Vaccines based on the inactivated whole virus, or based on part of the virus, most often combined with an adjuvant to enhance immune response, are currently under development (Sinopharm®, China). Although they do not seem to be particularly immunogenic, they may be of use in patients with cancer.

5. Immunogenicity and safety of SARS-CoV-2 vaccines in immunocompromised patients

While most immunosuppressive agents may negatively impact vaccine efficacy and duration of humoral (antibody) and cellular (T-cell) vaccine immune responses, there are few specific data currently available on SARS-

CoV-2 vaccines. Preliminary data suggest that anti-SARS-CoV-2 IgG concentrations after vaccination are not different between healthy patients and those with cancer. However, these results do not necessarily imply optimal protection for this population [24].

Immunosuppressive treatments lead to a decrease in immunogenicity (decrease in the number and functionality of CD4+ T cells, IgM and IgA) and potentially in the efficacy of vaccines. Indeed, although immunocompromised patients have presented a lower seroconversion rate after influenza vaccine, clinical efficacy is preserved (78% decrease in mortality) [25].

Research on mRNA vaccines started 20 years ago, especially on anticancer vaccines with no safety issues [26]. In phase II/III trials with the Pfizer/BioNTech BNT162b2 vaccine, 4% of patients had previous HIV infection or cancer [20]. Results in this group are not available, but vaccine safety in the overall population was excellent. There is no reason that immunosuppression can lead to adverse events after mRNA vaccines.

Regarding non-replicating viral vectors, in the phase III trial with Astra Zeneca/University of Oxford AZD1222 vaccine, immunosuppression was an exclusion criterion [22]. By contrast, it is not an exclusion criterion for the Johnson & Johnson/Jansen adenoviral vaccine, for which the first results are expected in March/April 2021.

6. Contraindications and adverse events of SARS-CoV-2 mRNA vaccines

The single definitive contraindication to mRNA vaccines is a history of severe allergy to a component of the vaccine (in particular, polyethylene glycol or polysorbate) or an immediate severe reaction (generalised urticaria, bronchospasm and/or anaphylaxis) to the first vaccine dose. Other relative and temporary contraindications are ongoing infectious disease, flare of inflammatory or autoimmune disease, symptomatic COVID-19 less than 3 months ago and an influenza vaccination less than 3 weeks ago or another vaccine less than 2 weeks ago.

Immunosuppression and autoimmune diseases (excluding the flare-up period) are not contraindications. An allergy not qualified as anaphylaxis (for example, to pets, venom, pollen, latex or drugs) does not contraindicate vaccination. A history of immediate severe reaction (generalised urticaria, bronchospasm and/or anaphylaxis) to another vaccine or to an unidentified drug requires an allergist's opinion before vaccination and longer follow-up after SARS-CoV-2 vaccination.

With mRNA SARS-CoV-2 vaccines, anaphylactic reactions are exceptional, with a rate of 11.3 cases per million people vaccinated with the Pfizer-BioNTech BNT162b2 vaccine and 2.5 cases per million people vaccinated with the Moderna mRNA-1273 vaccine [27].

Therefore, vaccinated people should be monitored for at least 15 min after injection and 30 min if there is a history of anaphylaxis. The other known side-effects are expected and non-specific [20–22].

7. Vaccination of patients treated with immune checkpoint inhibitors

Immune checkpoint inhibitors, anti-cytotoxic T lymphocyte-associated antigen 4 and programmed cell death protein 1/programmed death ligand 1, do not increase the risk of viral infection, but can induce autoimmune adverse events to be treated with immunosuppressive agents. Despite the lack of data on mRNA vaccines in patients treated with immune checkpoint inhibitors, SARS-CoV-2 vaccination is not expected to have an impact on autoimmune adverse events. Influenza vaccination is safe (no increased risk of immune-induced adverse events) and effective in patients treated with immune checkpoint inhibitors [28]. All SARS-CoV-2 vaccines are possible in patients with cancer treated with immune checkpoint inhibitors (Table 2) [17]. Nevertheless, it seems reasonable to postpone vaccination in patients with an ongoing severe autoimmune side-effect.

8. Which cancer target population for SARS-CoV-2 vaccination?

On 8th January 2021, the ESMO launched a triple call towards the European states: to vaccinate all patients with cancer, especially those on active anticancer treatment; to monitor effects of the vaccine and to instill confidence among patients and the public (Table 2) [14].

The target cancer population is determined on the basis of available scientific data. The availability of vaccines and national priorities will impact this target population. Scientific evidence suggests that immunosuppression after cancer treatment, especially chemotherapy, persists for several months. Therefore, all patients with cancer with an ongoing treatment or treatment completed less than 3 years ago should be vaccinated, as should people living in the same household. This target population represents millions of persons, approximately 5–10% of the population in European countries. Patients with planned major cancer surgery should also be vaccinated a few weeks before surgery to limit the risk of developing severe COVID-19 after surgery or surgery postponement [29]. In addition, other risk factors for severe COVID-19 should be taken into account: male gender, poor general condition and/or severe comorbidities (heart disease, diabetes, chronic pulmonary disease, chronic renal failure, cirrhosis, body mass index >40 kg/m², complicated high blood pressure and transplantation) [1]. In addition, the doctor-patient relationship is important in the vaccination decision-

Table 2

Summary of recommendations (expert agreement).

1) Indications of SARS-CoV-2 vaccination

- Indication for patients with cancer under treatment or whose treatment ended less than 3 years ago.
- Priority for patients with cancer treated with chemotherapy.
- Ultrapriority for (1) patients with curative intent treatment (including surgery) excluding basal cell skin carcinoma, (2) patients on palliative first- or second-line chemotherapy and (3) patients receiving radiotherapy for a primary thoracic tumour with a large lung volume, radiotherapy on large lymph node areas and/or radiotherapy on a large volume of haematopoietic tissue.
- Patients treated only with hormone therapy and recent patients with COVID-19 are not ‘ultrapriority’.
- Vaccination of the immediate entourage of patients with cancer (the person living in the same house and frequent contacts [home helps, nurses and so on]) (expert opinion).

2) SARS-CoV-2 vaccination in patients with cancer treated with immune checkpoint inhibitors

- SARS-CoV-2 vaccination is recommended for patients with cancer treated with immune checkpoint inhibitors.
- In case of severe immune-related adverse events due to immune checkpoint inhibitors, it seems reasonable to postpone SARS-CoV-2 vaccination.

3) Strategy of SARS-CoV-2 vaccination

- Vaccination could be carried out using mRNA vaccines (or using a non-replicating adenoviral vaccine in non-immunocompromised patients younger than 65 years).
- If possible, vaccination is recommended at least 10 days before the start of chemotherapy.
- For patients with cancer already on chemotherapy, vaccination can be carried out during chemotherapy, avoiding periods of bone marrow aplasia.
- There is no need to postpone the chemotherapy course for SARS-CoV-2 vaccination.
- If a chemotherapy holiday is planned soon, the SARS-CoV-2 vaccination can be postponed for a few days and carried out during this chemotherapy holiday.
- Serological monitoring after vaccination could be useful (if possible in a specific cohort) (expert opinion).
- Patients with cancer who are vaccinated must continue to follow SARS-CoV-2 protection.

4) Contraindications of SARS-CoV-2 vaccination

- No ‘oncological’ contraindication.
- Definitive contraindications to mRNA vaccines are history of allergy to one of the vaccine components (in particular PEG or polysorbate) or anaphylactic reaction during the first dose.
- Temporary contraindications requiring postponement of vaccination:
 - Pregnancy or breastfeeding
 - Ongoing infectious disease
 - Flare of inflammatory or autoimmune disease
 - Symptomatic COVID-19 less than 3 months previous
 - Influenza vaccination less than 3 weeks previous or with another vaccine less than 2 weeks previous
 - History of severe reaction to another vaccine or to an unidentified drug requires an allergist’s opinion before vaccination and longer follow-up after SARS-CoV-2 vaccination (30 min)

5) SARS-CoV-2 vaccination and cancer clinical trials

- The vaccine strategy is identical for patients participating in clinical trials, but specific recommendations have been proposed for phase I [30]:
 - Not started phase I trial: avoid starting trial investigational medicinal products until 2–4 weeks after the second dose of the SARS-CoV-2 vaccine and administered safely for the trial with risk of cytokine release syndrome.
 - Already in phase I trial: administer the SARS-CoV-2 vaccine during the phase I trial, but avoid vaccination on days of parenteral investigational medicinal product dosing and the dose-limiting toxicity period.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; mRNA: messenger RNA; PEG: polyethylene glycol; COVID-19: coronavirus disease 2019.

making process, especially in the context of short-term life expectancy owing to cancer progression (Table 2).

People around an immunocompromised patient are a potential source of SARS-CoV-2 transmission. Owing to the potential lower immunogenicity of the vaccination in patients treated by chemotherapy, it seems appropriate to vaccinate household/close contacts (wives, nurses, home helps and so on). In addition, patients with cancer who are vaccinated must continue to follow SARS-CoV-2 protection because vaccine protection is not immediate, not 100%, of uncertain duration and possibly less effective in patients under

chemotherapy and of varying efficacy depending on the variants of SARS-CoV-2.

Three vaccines are now approved in most European countries (Pfizer/BioNtech BNT 162b2, Moderna/NIH mRNA-1273 and AstraZeneca AZD1222), but limited availability has led health authorities to prioritise populations at high risk of severe COVID-19. In France, the INCa defined ‘ultrapriority’ patients with cancer for vaccination against SARS-CoV-2 as (1) patients with curative intent treatment excluding basal cell carcinoma, (2) patients on palliative first- or second-line chemotherapy and (3) patients receiving radiotherapy

for a primary thoracic tumour with a large lung volume, radiotherapy on large lymph node areas and/or radiotherapy on a large volume of haematopoietic tissue. Patients older than 75 years or with a severe comorbidity should also be vaccinated regardless of cancer history. Patients treated only with hormone therapy, as well as patients with recent COVID-19, are not in the ‘ultra-priority’ population. In addition, for patients with short life expectancy due to cancer progression, vaccination should be discussed on a case-by-case basis, especially in case of best supportive care. Although the vaccine strategy is identical for patients participating in clinical trials, specific recommendations have been proposed for phase I cancer trials [30]. Finally, mRNA vaccines are recommended in most European countries, and the adenoviral vaccine (AstraZeneca AZD1222) is limited for patients younger than 65 years.

9. Conclusion

Indications for SARS-CoV-2 vaccination, based on available scientific data, are patients with solid cancer under treatment or patients with treatment completed less than 3 years ago and household and close contacts. However, owing to limitations in vaccine doses, ‘ultra-priority’ patients with cancer are those under chemotherapy and/or with other curative intent treatment. It is essential to set up specific clinical studies or cohorts dedicated to patients with cancer, the objective being to determine the safety and effectiveness of SARS-CoV-2 vaccines in this population.

Author contributions

D.T. and O.B. contributed to study conception and design. All authors contributed to analysis and interpretation of data. D.T., M.H., B.S.-P., T.A., J.-Y.B. and O.B. contributed to draft manuscript preparation. All authors reviewed the manuscript and approved the final version.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank Jeffrey Arsham as he helped with the English language revision of the manuscript.

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