

## COVID-19 vaccination in patients with cancer: Position paper from the Indonesian Society of Hematology and Medical Oncology (ISHMO) of Semarang



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### ABSTRACT

Patients with active cancer (cancer on treatment, those planning to start treatment, and those immediately post-treatment) consider getting the COVID-19 vaccine, like the other vulnerable populations, to reduce the severe risk of SARS-CoV-2 infection. We suggest patients with cancer should be vaccinated with a non-lived COVID-19 vaccine. Specific consideration belongs to the type of cancer, current treatment, phase of disease along the cancer continuum, and optimal timing for vaccination; they should talk to their hematologist-medical oncologist. Vaccination with the live-attenuated and replicating-vector vaccine is strongly discouraged in patients with active cancer receiving chemotherapy and during other immunocompromising therapies. For patients those receiving intensive chemotherapy (e.g., induction or consolidation therapy in acute leukemia), anti-B-cell antibodies, hematopoietic stem cell transplantation (HSCT), and other immunocompromised conditions, we suggest postponing SARS-CoV-2 vaccination until reaching stable lymphocyte counts due to the risk of vaccine ineffectivity. Cancer survivors are considered to have the same risk as other persons with matched aged and other risk factors. They also should be vaccinated as early as possible. There are various other risk factors for cancer patients which must consider related to complications of COVID-19, such as age, other comorbid diseases, demographic and social factors. All of these factors should be judged as a comprehensive evaluation of an individual patient. The use of masks, physical distancing, hygienic activities such as washing hands with soap and hand sanitizers are still needed during this pandemic. Caregivers and households should certainly be included in the vaccination strategies.

**Keywords:** COVID-19, vaccine, cancer, recommendation.

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### INTRODUCTION

The world is currently impacted by the coronavirus disease 2019 (COVID-19) pandemic. It started in Wuhan, Hubei Province, China, and has brought many challenges to public health in various countries, including Indonesia. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly contagious virus associated with a considerable mortality rate. Indonesia has now reached over a million COVID-19 cases, with daily incidence hitting records from week to week in January 2021.<sup>1,2</sup> As

we all know, the COVID-19 pandemic has major catastrophic consequences on all aspects of life worldwide on the health and wellbeing. There are three ways out the pandemic 1) to continue stringent precautions forever, but people will get eventually infected, and it will spread for a long period with economic, psychological, political impacts that will be long lasting, 2) to obtain herd immunity, basically let the masses get infected but cost high toll of human lives or 3) to get enough people vaccinated to break this vicious cycle of infection and control the pandemic.<sup>3</sup> Currently, we already have

the SARS-CoV-2 vaccine that is used for the community. However, especially for cancer patients, there is still a lack of data on efficacy, safety, and immunogenicity.

The Indonesian Food and Drug Advisory Agency (*Badan Pengawas Obat dan Makanan*: BPOM) has granted the use of vaccine in Indonesia as an Emergency Use Authorization (EUA) to prevent COVID-19 disease supported by the availability of COVID-19 vaccine and scientific studies.<sup>4</sup> This position paper was formed to make practical considerations according to the latest information that may continue to evolve based on the latest

studies. Clinicians could use this position paper to consider COVID-19 vaccination for the cancer population under EUA until specific data are available.

## SCOPE OF THE PROBLEM

We know from other countries that patients with cancer may have more severe COVID-19 infection than those without cancer;<sup>5,6</sup> we are not particularly sure if they are at higher risk of getting it. It truly depends on what environment that they are living in. However, it is very important to think about cancer patients regarding any immunocompromised and defects in their immune system.

Cancer patients infected with COVID-19 had a significant risk of admission to ICU (OR 2.84; 95% CI 1.59-5.08,  $p < 0.01$ ) and death (OR 2.34; 95% CI 1, 15-4.77,  $p = 0.03$ ). The Case Fatality Rate (CFR) for hematologic cancer and lung cancer was found to have high percentages, namely 33.3% and 18.8%, respectively.<sup>5,6</sup> So, the population of cancer patients must be a priority for receiving the COVID-19 vaccine. A recent publication by Desai et al. of more than 5300 papers reports the outcome of this combination altogether: cancer and COVID-19. If we go through, from a meta-analysis, there is a very high risk of mortality ranging from 15 to 30% in hospitalized patients.<sup>7</sup> If we compared to the number in normal population only

2-3%, we can understand how much is the problem for this group of patients.<sup>1,2,8</sup>

The other important information is derived from the UKCC project, where the author reported all the comorbidities. For cancer, there is a higher risk of mortality. The highest risk is for cancer patients before five years of diagnosis, particularly in less than one year, mainly patients in active treatment.<sup>9</sup> A single hospital case series from New York, USA,<sup>6,10</sup> showed CFR in hematologic malignancies and solid cancer were 37% and 25%, respectively. COVID-19 outcomes in cancer patients are influenced by various factors such as old age, comorbid diseases, advanced disease, and quality of care.<sup>11</sup>

## IMMUNIZATION IN CANCER PATIENTS AT A GLIMPSE

Various studies with vaccines such as influenza, pneumococcus, and herpes zoster suggest vaccines' protective effect in cancer patients.<sup>12</sup> The influenza vaccination protected chemotherapy cycle disruption and the risk of death. However, cancer patients tend to have a poor antibody response compared to immunocompetent people<sup>13,14</sup>, but cancer patients' morbidity and mortality can be reduced with the vaccine administration.<sup>15</sup>

We are aware that there is insufficient data; patients with cancer requiring therapy and immunocompromised were usually

excluded from pivotal trials.<sup>12,16</sup> For those on active treatment, immunosuppressive therapy, chemotherapy, or those with immunotherapy, we do not have a specific study about the response in the SARS-CoV-2 vaccine. However, we can extrapolate data from other vaccine studies especially inactivated vaccines. From that data, cancer survivors, patients with stable disease, cure, or incomplete remission could mount an adequate immune response.<sup>11</sup> In general, vaccination in active cancer patients is not contraindicated.<sup>17-19</sup> However, specific requirements in terms of disease state, type of vaccine can be given safely according to immunity status, and the most important, vaccination timing.

Although specific data for SARS-CoV-2 vaccination in the cancer population is lacking, around 4% of patients included in the BNT162b2 mRNA vaccine trial had a prior history of malignancy (733 any malignancy, 22 lymphoma, 12 leukemia, and 4 solid metastatic tumors).<sup>20</sup> Although these peoples may not respond well to the vaccine, no particular safety concerns are anticipated. The benefit-to-risk ratio for patients with cancer is considered more beneficial than the possible risk for getting vaccinated because they may be at higher risk from COVID-19.<sup>20</sup>

A total of 56 vaccines for SARS-CoV-2 are in clinical development, of which 11 are in phase 3 trials and another 166 in preclinical development (information

**Table 1. Dose and type administration from available various SARS-CoV-2 vaccine in Indonesia**

Platform	Developer	Total dose	Schedule	Phase 1 / 2 trials	Phase 3 trials
Inactivated virus	Sinovac <sup>23</sup> Research and Development Co., Ltd.	2 (0.5 mL per dose)	Day 0, 14	NCT04551547 NCT04383574 NCT04352608	NCT04617483 NCT04582344 NCT04508075
Inactivated virus	Sinopharm <sup>24</sup> + Beijing Institute of Biological Products	2 (0.5 mL per dose)	Day 0, 21	ChiCTR2000031809 ChiCTR2000032459	N/A
Inactivated virus	PT Bio Farma	2 (0.5 mL per dose)	Day 0, 14	N/A	NCT04508075
Viral vector (non-replicating)	AstraZeneca <sup>25-27</sup> + University of Oxford	1 – 2 (0.5 mL per dose)	If 2 dosis, Day 0, 28	NCT04324606 NCT04400838	NCT04400838
Protein subunit	Novavax <sup>28</sup>	2 (0.5 mL per dose)	Day 0, 21	NCT04368988	NCT04611802 NCT04583995
RNA-based vaccine	Moderna <sup>29-31</sup> + National Institute of Allergy and Infectious Disease (NIAID)	2 (0.5 mL per dose)	Day 0, 28	NCT04283461	NCT04470427
RNA-based vaccine	Pfizer Inc. <sup>32</sup> + BioNTech	2 (0.3 mL per dose)	Day 0, 28	NCT04380701 NCT04523571 NCT04368728	NCT04368728

**Source:** Trial information is taken from <http://www.clinicaltrials.gov>. Their respective publications indicate completed trials.

as per January 26, 2021).<sup>2</sup> Indonesian Ministry of Health in the Decree of the Minister of Health document number HK.01.07/Menkes/12758/2020 has determined the SARS-CoV-2 vaccine available in Indonesia.<sup>21</sup> The lists are PT. Bio Farma, Oxford-AstraZeneca, Sinopharm, Moderna, Novavax, Pfizer-BioNTech, and Sinovac (Table 1). There is no basis for the preferential recommendation for one that could be better than the other vaccine under any circumstances. The choice is based on vaccine availability at one moment. Sinovac vaccines have been used since Wednesday, January 13, 2021. Little is known, and much is unknown about the COVID-19 vaccine; thus, until more information, it is wise to receive one type and not a different SARS-CoV-2 vaccine to be given to the same patient.<sup>22</sup>

Most COVID-19 vaccine currently under development does not employ a live virus. Exceptions are only made for non-replicating and replicating viral vector-based vaccines. Other vaccines (inactivated, nucleic acid, protein subunit, virus-like protein) are relatively safe for the immunosuppressed, hence, cancer patients. These vaccines generally exert reduced protection. It is suggested that it be beneficial to administer a second vaccine dose or prime booster to increase the seroconversion rate.<sup>18,33</sup>

## LEGALITY ASPECTS OF SARS-CoV-2 VACCINE IN INDONESIA

Recommendations for EUA use of COVID-19 vaccine for cancer patients in Indonesia are issued by the Indonesian Ministry of Health and the Indonesian Society of Internal Medicine (PAPDI).<sup>34,35</sup> This recommendation is prepared based on phase 1/2 publication data on the Sinovac vaccine and the results from phase 3 preliminary data from our population in Bandung (organized by Universitas Padjajaran and PT Bio Farma). The Indonesian Ministry of Health's main message that a recommendation for the COVID-19 vaccine is made for cancer survivors. However, PAPDI adds an important statement concerning both hematology malignancies and solid cancer should also get vaccinated. Accordingly, patients with cancer should have a consultation with their physicians before

receiving the SARS-CoV-2 vaccine. They should be advised to avail themselves of the SARS-CoV-2 vaccine as soon as it is offered to them.

In the case of limited vaccine supply and high transmission rate of COVID-19 as today, the following criteria can be a priority consideration:<sup>17,36</sup>

- Patients with active cancer (e.g., cancer on treatment or newly start treatment) and who have just completed treatment (<6 months) consider for vaccination. Those who receive hormonal therapy can be managed as per a healthy population.
- Other risk factors such as old age, comorbid diseases, metastases, hematology, and lung-related cancers, as well as social and demographic factors, need to be considered because they are associated with complications of COVID-19.<sup>11</sup>

## INTERACTIONS BETWEEN VACCINES AND IMMUNE SYSTEM IN CANCER

This section described several important related considerations of vaccination for adult cancer patients. At least eight types of vaccines have been developed against the coronavirus: inactivated, live-attenuated, replicating vector, non-replicating vector, DNA, RNA, protein subunit, and virus-like particles.<sup>37</sup> Parts or all protein-based or polysaccharide-based viral components products are the main components of inactivated vaccines. Conjugation with protein is added to the polysaccharide vaccine to increase the immune response due to the low immunogenicity. Meanwhile, the induction of the immune response in active vaccines is carried out directly using attenuated pathogens. The recombinant vaccines containing inactive components of antigen with genetic engineering sometimes need to be weakened. Adjuvants can be found in both inactive and recombinant vaccines, aiming to increase the immune response and generate antibody production for specific diseases. All live-attenuated, including replication-competent vector vaccines, are considered contraindicated for patients with active cancer.<sup>11,18</sup> Fortunately, there is no live vaccine underdeveloped for SARS-CoV-2.

There are some patients with hematological malignancies have a higher risk of severe COVID-19 because their immune system has been weakened, patients who have been through hematopoietic stem cell transplant (HSCT), CAR-T therapy, or other treatments that are designed to knock down the immune systems do have an increased risk of complications related to the disease.<sup>12</sup>

As we learn from vaccination recommendations in cancer patients, the non-live vaccines are not contraindicated during chemotherapy.<sup>18,19</sup> Studies have shown that inactivated vaccines are safe for cancer patients where they reduce the disease-related incidence, although they have limited effectiveness.<sup>6,18</sup> However, it is not advisable to receive replicated competent vector vaccines or directly attenuated vaccines in patients undergoing aggressive chemotherapy or immunosuppressive agents.<sup>38</sup>

Below are considered an immunodeficiency state and immunocompromised conditions associated with an attenuated or blunted immune response to SARS-CoV-2 vaccine:<sup>22</sup>

- Primary and secondary immunodeficiencies involving adaptive immunity
- Post-splenectomy or functional asplenia
- The use of B lymphocyte-directed therapies (e.g., monoclonal antibodies against CD20 or CD22, bispecific agents like blinatumomab, CD19- or CD22-directed CAR-T cell therapies, BTK inhibitors)
- The use of T lymphocyte-directed therapies (e.g., calcineurin inhibitors, anti-thymocyte globulin (ATG), alemtuzumab)
- Cytotoxic chemotherapy, especially those receiving intensive regimen as in acute leukemia
- High-dose corticosteroids (>2 mg/kg daily of prednisone or equivalent)
- Hematopoietic stem cell transplantation (HSCT), especially within the first 3-6 months after autologous HSCT and longer after allogeneic HSCT.
- Graft versus host disease (GvHD)

**Table 2. Suggested timing for COVID-19 vaccination for patients in systemic cancer therapy**

Systemic anticancer therapy	Suggested timing
Cytotoxic chemotherapy	When blood counts have maximally recovered (towards the end of a cycle) – avoid on the same day of chemotherapy
Monoclonal antibodies (single agents) should not be a contraindication	No specific timing issues (providing that complete blood count is normal or within an acceptable range)
Monoclonal antibodies (with cytotoxic chemotherapy)	When blood counts have maximally recovered (towards the end of a cycle) – avoid on the same day of chemotherapy
CD20 – monoclonal antibodies, e.g., Rituximab	No specific timing issues – when blood counts are optimal. Where clinically possible vaccine should be given 4 weeks or more before rituximab. There may be suboptimal responses to the vaccine especially in patients within 6 months of their last dose or those on maintenance treatment.
Immunotherapy single agent	No specific timing issues (providing that complete blood count in normal or within an acceptable range)
Immunotherapy (with cytotoxic chemotherapy)	When blood counts have maximally recovered (towards the end of a cycle) – avoid on the same day of chemotherapy
Small molecule TKI	No specific timing issues (providing that complete blood count in normal or within an acceptable range)
Immunomodulator drugs (IMiDs)	When blood counts have maximally recovered (towards the end of a cycle) – avoid on the same day of chemotherapy
Protein kinase inhibitors e.g., Bortezomib, Ixazomib	When blood counts have maximally recovered (towards the end of a cycle) – avoid on the same day of chemotherapy
PARP inhibitors e.g. Olaparib	No specific timing issues (providing that complete blood count in normal or within an acceptable range)
CDK 4/6 inhibitors e.g. Abemaciclib, Ribociclib, Palbociclib	When blood counts have maximally recovered (towards the end of a cycle) – avoid on the same day of chemotherapy
Hormone treatments and other supportive treatments	No specific timing issues, vaccination at any time when available
High dose steroids (Prednisone or Prednisolone $\geq 2$ mg/kg/day or equivalent)	No specific timing issues If feasible, patients treated with steroids are vaccinated prior to therapy

Source: Covid-19 vaccine in patients with hematological disorders – British Society of Haematology, 2020; MSK Covid-19 vaccine interim guidelines for cancer patients, 2021

**Table 3. COVID-19 vaccination suggestion for hematological malignancies patients**

Treatment	Vaccine Timing	Type of vaccine
<b>Hematological malignancies</b> <sup>19,36,40,42</sup>		
Receiving induction chemotherapy (e.g., Cytarabine / Anthracycline-based therapy for acute myeloid leukemia or multiagent chemotherapy in acute lymphoblastic leukemia)	Delay until absolute neutrophil count recovery	<b>Non-lived vaccine:</b> [RNA-based*, inactivated**, protein subunit**, and viral vector (non-replicating) vaccines**]
Marrow failure from disease and/or therapy expected to have limited or lack of predicted recovery		
Long-term maintenance therapy (e.g., targeted agents for chronic lymphocytic leukemia or myeloproliferative neoplasm)	Vaccinated at any time	

\*Based on a specific recommendation for SARS-CoV-2 vaccination<sup>40,42</sup>

\*\*Based on previous vaccination of other diseases in cancer patients<sup>18,19</sup>

- i. Low white blood cell count (absolute neutrophil count  $<500/\mu\text{L}$  and/or absolute lymphocyte count  $<200/\mu\text{L}$ )  
Healthy subjects and cancer patients showed similar antibody responses to SARS-CoV-2. Although previous reports stated that the induction of antibody production was insufficient with the administration of inactivated and unconjugated vaccines.<sup>19</sup> It is still a matter of debate whether vaccine effectiveness can be achieved in this subset of the population.<sup>39</sup> At present, there is still little data on cancer patients who have been involved in the phase 2/3 vaccine trial.<sup>11</sup> Cancer patients may be included in the trial based on inclusion criteria and exclusion criteria which are summarized in three categories: 1) previous cancer history; 2) current immunosuppressive therapy (chemotherapy, radiotherapy,

immunomodulating agents, systemic immunosuppressants); 3) immune deficiency and instability at the discretion of the investigators.<sup>11,16</sup>

## WHEN SHOULD CANCER PATIENTS RECEIVE THE COVID-19 VACCINE?

In essence, cancer patients are the priority for receiving the vaccine right after the healthcare workers.<sup>2,11,17</sup> They should be advised to avail of the SARS-CoV-2 vaccine as soon as it is offered to them. Vaccination timing for cancer and immunosuppressed patients must be adjusted as described below.

### Patients receiving cancer therapy (on treatment)

The concern about giving the vaccine to cancer patients is not a safety issue. We do not believe that cancer patients are at higher complication risk when getting vaccinated than the risk of severe and death due to COVID-19. The main issue is whether they will have enough immune response to the vaccine to protect them from the virus in the future because they may have immunosuppressed status because of cancer itself or associated with the treatment. Thus, receiving a COVID-19 vaccine before treatment starts may improve its effectiveness. Nevertheless, on several occasions, patients may need to start treatment before having the vaccine.<sup>40</sup> Below are several different scenarios that may encounter concerning cancer patients (Table 2).

Individuals with cancer who should recommend avoiding vaccination would be very limited. Those who have had a severe allergic reaction to the first vaccination or individuals who had a recent stem cell transplantation would be individuals who have had a severe allergic reaction. Individuals with a recent stem cell transplantation may still be immunosuppressant medication, compromising their immune system and ability to tolerate the vaccination. It seems to be significantly better to give vaccine shots between cycles than at the same time as the cytotoxic chemotherapy using the influenza vaccine as a prototype.<sup>18</sup> The timing of vaccination is ideal before they start systemic therapy. However, it is still

reasonable to vaccinate cancer patients if the patient has already started systemic therapy. Vaccines can be given during systemic therapy with several precautions as described below.<sup>11</sup>

Patients with rituximab have the highest risks for COVID-19-associated morbidity and mortality if infected by SARS-CoV-2. Also, a low immune response is seen in patients taking rituximab. It is recommended that patients should be vaccinated before initiation of therapy, when feasible. A similar treatment was applied for other anti-CD20, anti-thymocyte globulin (ATG), and alemtuzumab. Consideration of delaying the vaccine can be made considering completion of 6 months of therapy or lymphocytes has shown recovery evidence.<sup>40</sup>

### Cancer phase-specific suggestion for COVID-19 vaccine

Cancer patients do not represent a homogenous population. In this section, we are deemed to separate this population into three different pathways and scenarios: 1) patients with active disease, newly diagnosed patients or already on treatment, 2) those with the chronic disease after specific treatment, and 3) patients in the survivorship phase. Among these criteria, along with other vulnerable populations, the priority of COVID-19 vaccination in patients with active cancer needs to be considered.<sup>6</sup> Surprisingly, not only those with active cancer but also patients with cancer history or within the survivorship phase also carry a higher risk of COVID-19-related complications than the noncancer population in terms of risk of hospitalization, ICU admission, and 30-day mortality.<sup>41</sup> A large percentage of our cancer populations may be cancer survivors. Like the general population, cancer survivors are at risk of getting COVID-19. We encourage all of these individuals to get vaccinated.

## DISEASE-SPECIFIC SUGGESTION FOR COVID-19 VACCINE

### Patients with hematological malignancies (non-HSCT setting)

Patients with hematological malignancies are at the highest risk among other cancer who will develop more severe

complications associated with SARS-CoV-2 infection. Concerning the high community transmission in Indonesia currently, vaccination is continued to patients when a vaccine is available and offered to them. Patients with hematological malignancies, particularly patients on or planned to have a B lymphocyte depleting therapies, should consult the optimal vaccination timing to their hematologist – medical oncologist.

Hematologic malignancies patients have to meet these criteria:<sup>40</sup> The candidates for vaccination should have an adequate cellular and humoral immune response. Vaccination can be given in these requirements and timing (Table 3):

- Patients who have not yet started lymphocyte-depleting therapies can receive 2-dose scheduled 14 days before initiating lymphocyte-depleting therapy.
- Patients that have completed therapy with stable lymphocyte counts (Absolute Lymphocyte Count (ALC)  $\geq$  to 1.0 (normal range: 1.3 - 4.0 x 10<sup>3</sup> cells/uL) or B cell counts  $\geq$  50 cells per microliter).
- Patients on therapy with stable lymphocyte counts.

### Acute leukemia and aggressive lymphoma

Vaccination should not be delayed in patients with acute leukemia and aggressive lymphoma with induction chemotherapy for a newly diagnosed disease. The consolidation or maintenance phase was the recommended time which the vaccine should be given due to the patient showing hematologic recovery. The vaccination doses should be given before steroid pulse. In lymphoma, the vaccine can be planned after completing therapy. We must assume they did not require further therapy and already in remission. For relapsed or refractory disease, systemic therapy should not be deferred for vaccination. Only the optimal timing should be adjusted to give the optimal immunologic response.<sup>18,19,40</sup>

### Multiple myeloma

Vaccination in myeloma patients does not have contraindications related to specific diseases or treatments. Vaccination can

**Table 4. COVID-19 vaccination suggestion in HSCT patients**

Treatment	Vaccine Timing	Type of vaccine
<b>Hematopoietic stem cell transplantation or cellular therapy</b> <sup>11,19,36</sup>		
Autologous transplantation Allogeneic transplantation Cellular therapy (e.g., CAR-T cell)	At least 3 to 6 months post-HSCT or cellular therapy, except if remains on immunosuppression	<b>Non-lived vaccine:</b> [RNA-based*, inactivated**, protein subunit**, and viral vector (non-replicating) vaccines**]

\*Based on a specific recommendation for SARS-CoV-2 vaccination<sup>40,42</sup>

\*\*Based on previous vaccination of other diseases in cancer patients<sup>18,19</sup>

**Table 5. COVID-19 vaccination suggestion in solid cancer**

Treatment	Vaccine Timing	Type of vaccine
<b>Solid cancer</b> <sup>11,36,40</sup>		
Cytotoxic chemotherapy  Targeted therapy, hormone therapy Checkpoint inhibitor Major surgery	In the middle of the cycle to assure better mounting of the immune response, just before the next cycle of chemotherapy Vaccinated at anytime Vaccinated at anytime Separate date of surgery from vaccination by at least a few days	<b>Non-lived vaccine:</b> [RNA-based*, inactivated**, protein subunit**, and viral vector (non-replicating) vaccines**]

\*Based on a specific recommendation for SARS-CoV-2 vaccination<sup>40,42</sup>

\*\*Based on previous vaccination of other diseases in cancer patients<sup>18,19</sup>

be given to patients on lymphodepletion therapy (e.g., high-dose melphalan with SCT, cyclophosphamide/fludarabine, or anti-CD52 monoclonal antibody conditioning for cellular therapy) according to cellular therapy guidelines and HSCT with proven lymphocyte recovery. Before vaccination, make sure the patient is not neutropenic (ANC <500/ $\mu$ L).<sup>40,42,43</sup>

### Indolent lymphoma

Except for indolent lymphomas, where the asymptomatic disease will be managed conservatively, B-cell depleting therapy should be postponed until 1 month after completing the vaccination series. If they need systemic therapies, the proposed strategy would be different. For asymptomatic patients, B-cell depleting therapy could be postponed until 1 month after completion of vaccination dosages. For patients that need systemic therapies, the proposed strategy would be different. We would recommend treating with the induction regimens followed by complete vaccination dosages, and the maintenance therapy might be temporarily postponed until there is evidence of B lymphocyte recovery. During the high transmission rate, such as the current situation, vaccination is still advocated to generate T-cell memory responses.<sup>18,19,40,42</sup>

### Myeloid malignancies

This section covers acute myeloid leukemia (AML), myelodysplasia syndrome, myeloproliferative disorders, and chronic myeloid leukemia (CML). In AML, induction therapy should be given, and vaccination can be given during the consolidation phase. MDS patients treated with hypomethylating agents (HMA) should also be considered for vaccination, as well as polycythemia vera, essential thrombocytosis, or primary myelofibrosis while on active treatment or just observation. CML patients receiving tyrosine kinase inhibitors (TKI) should also be considered for vaccination at any time, with or without remission.<sup>18,19,40,42</sup>

## SPECIAL CONSIDERATIONS IN HSCT

Hematopoietic stem cell transplantation is an integral part of treatment in many hematological malignancies. Whether the COVID-19 vaccination will be planned before autologous stem cell transplantation (ASCT), then plan to complete the schedule before stem cell harvest (Table 4).<sup>40,43</sup> If considering vaccination post-ASCT, then the administration's timing should be initiated within 3 months, and COVID-19 vaccination should prioritize the regular vaccination schedule.<sup>44</sup>

For patients receiving tandem ASCT, vaccination should be initiated after the last planned stem cell infusion. Allogeneic HSCT patients still are regarded as immunosuppressed for two years post-transplant. A live-attenuated vaccine should not be given until these two years, as long as no GvHD, no immunosuppressive medication is needed, no relapse, and no recent administration of immunoglobulin.<sup>19,45,46</sup> However, vaccination may be initiated as early as 3-4 months post-HSCT with a non-live vaccine (time-frame within 6 months based on local vaccine availability and transmission rate in the community).<sup>47</sup> During that time, stay at home, double down on social distancing, wash hands frequently, and avoid contact with other people, especially large groups.

## PATIENTS WITH SOLID CANCER

Patients with solid cancers should be offered for vaccination as long as vaccine components are not contraindicated. The impact of the humoral and cellular responses is variable across solid tumor types and treatment paradigms. Special caution on lung cancer treated with immune checkpoint inhibitors; existing data suggested that they are at a higher risk for severe COVID-19 (Table 5).<sup>48,49</sup>

If vaccine supplies are constrained, those patients should be prioritized along with other high-risk cancer patients: age >74 years old, multiple comorbidities, active treatment, and metastatic disease.<sup>40,50</sup>

There is generally no contraindication to receipt of the COVID-19 vaccine across the broad range of cancer therapies. In the high COVID-19 transmission rate currently, clinicians should not hold or pause cancer therapy for vaccination. Optimal vaccination timing concerning cytotoxic chemotherapy and other cancer-directed therapies has not been established, giving data paucity. But whichever type of chemotherapy is chosen for particular cancer, vaccination should be planned at the furthest possible time point away from the cytotoxic effect (i.e., nadir point) during a given cycle is recommended.<sup>18,40,42</sup>

Radiotherapy can also cause indirect immunosuppression. However, the degree of immunosuppression depends on the type, and total-body irradiation (TBI) seems to cause obvious white blood cell reduction. TBI is typically given to hematological malignancies before HSCT as part of the conditioning regimen.<sup>40</sup> For cancer patients undergoing surgery, no specific timing is recommended relative to surgery except for elective splenectomy. The first dose of vaccination should occur  $\geq 2$  weeks before splenectomy in the post-surgical period after recovery. In patients with asplenia, the COVID-19 vaccine should also be prioritized over other recommended vaccine schedule.<sup>51</sup>

## POST-VACCINATION FOLLOW-UP

At this time, post-vaccine serologies are not recommended in the general population. Post-vaccine serologies monitoring should be considered in clinical studies only. Further clinical studies to measure humoral and cell-mediated immunity to COVID-19 vaccination is recommended.<sup>40</sup>

## CONCLUSION

Given the global plans made by national health authorities in every country worldwide for the widespread vaccination in individuals against SARS-CoV-2, the ISHMO of Semarang chapter herein presents the latest information concerning to-date authorized vaccinations as well

as the peer-group position about the vaccination in cancer patients. In general, a non-live vaccine can be safely given to immunocompromised patients. Live-attenuated and replicating viral vector vaccine should not be administered to patients who are considered to be highly immunocompromised. All the SARS-CoV-2 vaccine types planned to be distributed in Indonesia do not contain live viruses, which theoretically leads us to conclude that SARS-CoV-2 vaccination in cancer patients is considered safe. It is clear that we need more data and specific studies in patients with cancer, but this should not delay access to priority vaccination. As we see, patients interested in vaccination should discuss with their hematologist-medical oncologist to check if they met the vaccination requirements. We also encourage social distancing, mask-wearing, good hand washing, and limiting exposure as much as possible. Caregivers and household or close contact with the patients should also encourage to have vaccinated

## DISCLOSURES

None to disclosed.

## CONFLICT OF INTERESTS

The authors certify that we have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the materials discussed in this manuscript.

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All authors have contributed to this review from drafting and conceiving, literature searching, and preparing the article review.

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Not applicable

## REFERENCES

1. WHO. The current COVID-19 situation [Internet]. World Health Organization. 2020. Available from: <https://www.who.int/countries/idn/>

2. WHO. Draft landscape and tracker of COVID-19 candidate vaccines [Internet]. World Health Organization. 2021. Available from: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>
3. Gallagher J. Coronavirus: When will the outbreak end and life get back to normal? [Internet]. British Broadcasting Corporation. 2020. Available from: <https://www.bbc.com/news/health-51963486>
4. BPOM. Penerbitan Persetujuan Penggunaan Dalam Kondisi Darurat Atau Emergency Use Authorization (EUA) Pertama Untuk Vaksin COVID-19 [Internet]. Badan Pengawas Obat dan Makanan (BPOM) - Republik Indonesia. 2021. Available from: <https://www.pom.go.id/new/browse/more/pers/28-01-2020/28-01-2021/1>
5. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multi-center study during the COVID-19 outbreak. *Cancer Discov.* 2020;10(6):783–91.
6. Ribas A, Sengupta R, Locke T, Zaidi SK, Campbell KM, Carethers JM, et al. Priority COVID-19 Vaccination for Patients with Cancer while Vaccine Supply Is Limited. *Cancer Discov.* 2021;11(2):233–6.
7. Desai A, Sachdeva S, Parekh T, Desai R. COVID-19 and Cancer: Lessons From a Pooled Meta-Analysis. *JCO Glob Oncol.* 2020;(6):557–9.
8. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708–20.
9. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430–6.
10. Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. *Cancer Discov.* 2020;10(7):935–41.
11. Garassino M, Giesen N, Grivas P, Jordan K, Francesca L, Mir O, et al. ESMO Statements for Vaccination Against COVID-19 in Patients with Cancer [Internet]. European Society for Medical Oncology. 2020. Available from: <https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination>
12. Shah MK, Kamboj M. Immunizing Cancer Patients: Which Patients? Which Vaccines? When to Give? *Oncology (Williston Park).* 2018;32(5):254–8, C3.
13. Brydak LB, Guzy J, Starzyk J, Machała M, Góźdz SS. Humoral immune response

- after vaccination against influenza in patients with breast cancer. *Support Care Cancer*. 2001;9(1):65–8.
14. Meisel R, Kuypers L, Dirksen U, Schubert R, Gruhn B, Strauss G, et al. Pneumococcal conjugate vaccine provides early protective antibody responses in children after related and unrelated allogeneic hematopoietic stem cell transplantation. *Blood*. 2007;109(6):2322–6.
  15. Bitterman R, Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. *Cochrane Database Syst Rev*. 2018;2018(2):CD008983.
  16. Doshi P. Covid-19 vaccine trial protocols released. *BMJ*. 2020;371:m4058.
  17. Dooling K, Marin M, Wallace M, McClung N, Chamberland M, Lee GM, et al. The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine. 2020;
  18. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3).
  19. Rieger CT, Liss B, Mellinghoff S, Buchheidt D, Cornely OA, Egerer G, et al. Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors—Guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). *Ann Oncol*. 2018;29(6):1354–65.
  20. Committee for Medicinal Products for Human Use (CHMP). COVID-19 mRNA vaccine (nucleoside-modified) – assessment report [Internet]. European Medicine Agency Science Medicines Health. Amsterdam; 2020. Available from: [https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf)
  21. Harsono FH. Menkes Budi Gunadi Tetapkan 7 Jenis Vaksin COVID-19 untuk Vaksinasi [Internet]. 2021. Available from: <https://www.liputan6.com/health/read/4446237/menkes-budi-gunadi-tetapkan-7-jenis-vaksin-covid-19-untuk-vaksinasi>
  22. Auletta J, Chemaly R, Khawaja F, Papanicolaou G, Hill J, Kanter J, et al. ASH-ASTCT COVID-19 and Vaccines: Frequently Asked Questions [Internet]. American Society of Hematology. 2020. Available from: <https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines>
  23. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(2):181–92.
  24. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis*. 2021;21(1):39–51.
  25. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet*. 2020;396(10249):467–78.
  26. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2020;396(10267):1979–93.
  27. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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*. 2021;397(10269):99–111.
  28. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *N Engl J Med*. 2020;383(24):2320–32.
  29. Anderson EJ, Roupael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N Engl J Med*. 2020;383(25):2427–38.
  30. Jackson LA, Anderson EJ, Roupael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. *N Engl J Med*. 2020;383(20):1920–31.
  31. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403–16.
  32. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603–15.
  33. Sandherr M, Hentrich M, von Lilienfeld-Toal M, Massenkeil G, Neumann S, Penack O, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2015;94(9):1441–50.
  34. Hidayat MB. Petunjuk Teknis Pelaksanaan Vaksinasi Dalam Rangka Penanggulangan Pandemi Corona Virus Disease 2019 (COVID-19) [Internet]. Jakarta, Indonesia; 2021. Available from: [https://covid19.go.id/storage/app/media/Regulasi/2021/Januari/Final\\_SK\\_Dirjen\\_Juknis\\_Vaksinasi\\_COVID-19\\_02022021.pdf](https://covid19.go.id/storage/app/media/Regulasi/2021/Januari/Final_SK_Dirjen_Juknis_Vaksinasi_COVID-19_02022021.pdf)
  35. PAPDI. Rekomendasi PAPDI tentang Pemberian Vaksinasi covid-19 (CoronaVac) pada Pasien dengan Penyakit Penyerta/ Komorbid (Revisi 9 Februari 2021) [Internet]. Pengurus Besar Perhimpunan Ahli Penyakit Dalam Indonesia (PAPDI). 2021. Available from: <https://www.papdi.or.id/berita/info-papdi/1009-rekomendasi-papdi-tentang-pemberian-vaksinasi-covid-19>
  36. Pergam S, Baden L, Abel G, Bunnell C, Cinar P, Hamdan A, et al. Preliminary Recommendations of the NCCN COVID-19 Vaccination Advisory Committee [Internet]. National Comprehensive Cancer Network (NCCN). Montgomery; 2021. Available from: [https://www.nccn.org/covid-19/pdf/COVID-19\\_Vaccination\\_Guidance\\_V1.0.pdf](https://www.nccn.org/covid-19/pdf/COVID-19_Vaccination_Guidance_V1.0.pdf)
  37. Callaway E. The race for coronavirus vaccines: a graphical guide. *Nature*. 2020;580(7805):576–7.
  38. Corti C, Curigliano G. Commentary: SARS-CoV-2 vaccines and cancer patients. *Ann Oncol*. 2021;S0923-7534.
  39. Marra A, Generali DG, Zagami P, Gandini S, Cervoni V, Venturini S, et al. LBA77 Anti-SARS-CoV-2 antibody response in patients with cancer and oncology healthcare workers: A multicenter, prospective study. *Ann Oncol*. 2020;31:S1206.
  40. Kamboj M, Hohl T, Vardhana S, Knorr D, Lesokhin A, Papanicolaou Z, et al. MSK COVID-19 Vaccine Interim Guidelines for Cancer Patients [Internet]. Vol. 4. New York; 2021. Available from: [https://www.asco.org/sites/new-www.asco.org/files/content-files/2021-MSK\\_COVID19\\_VACCINE\\_GUIDELINES\\_final\\_V.2.pdf](https://www.asco.org/sites/new-www.asco.org/files/content-files/2021-MSK_COVID19_VACCINE_GUIDELINES_final_V.2.pdf)
  41. Sun L, Surya S, Le AN, Desai H, Doucette A, Gabriel P, et al. Rates of COVID-19–Related Outcomes in Cancer Compared

- With Noncancer Patients. *JNCI Cancer Spectr.* 2021;5(1).
42. Howard J, Snowden J, Ashcroft J. COVID-19 Vaccine in patients with haematological disorders British Society for Haematology [Internet]. British Society of Haematology. United Kingdom; 2020. Available from: <https://b-s-h.org.uk/media/19195/haematology-covid-19-v10-vaccination-statement-231220.pdf>
  43. Recommendations for anti-Covid-19 vaccination in patients with multiple myeloma (MM) and related conditions, AL amyloidosis and other monoclonal gammopathies of clinical significance [Internet]. 2020. Available from: [http://cms.cws.net/content/beta.myelomasociety.org/files/PM\\_COVID\\_vaccination\\_in\\_MM\\_guidelines\\_The\\_Final.pdf](http://cms.cws.net/content/beta.myelomasociety.org/files/PM_COVID_vaccination_in_MM_guidelines_The_Final.pdf)
  44. DeMarco C. COVID-19 and stem cell transplants: What you should know [Internet]. MD Anderson Cancer Center. 2020. Available from: <https://www.mdanderson.org/cancerwise/covid-19-and-stem-cell-transplants-what-you-should-know.h00-159380367.html>
  45. Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Krüger W, et al. Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. *Ann Hematol.* 2016;95(9):1435–55.
  46. Cordonnier C, Einarsdottir S, Cesaro S, Di Blasi R, Mikulska M, Rieger C, et al. Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis.* 2019;19(6):e200–12.
  47. Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. *Blood.* 2016;127(23):2824–32.
  48. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet.* 2020;395(10241):1907–18.
  49. Robilotti E V., Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. *Nat Med.* 2020;26(8):1218–23.
  50. Garassino MC, Whisenant JG, Huang L-C, Trama A, Torri V, Agustoni F, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol.* 2020;21(7):914–22.
  51. Lee GM. Preventing infections in children and adults with asplenia. *Hematology.* 2020;2020(1):328–35.



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