Recommendations of the NCCN COVID-19 Vaccination Advisory Committee*

- Patients with active cancer and those on treatment should be prioritized for vaccination and should be immunized when any vaccine that has been authorized for use by the FDA is available to them.
- Immunization is recommended for all patients receiving active therapy, with the understanding that there are emerging efficacy data in these patients.
- Reasons for delay of vaccines are similar to those that impede delivery to the general public (eg, recent exposure to COVID-19), and there are also cancer-specific factors. Vaccination should be delayed for at least 3 months following hematopoietic cell transplantation (HCT) or engineered cellular therapy (eg, chimeric antigen receptor [CAR] T-cells) to maximize vaccine efficacy.
- Caregivers and household/close contacts should be immunized whenever possible.
- The committee supports use of any of the available EUA approved vaccines (Pfizer/BioNTech [BNT162b2 mRNA vaccine], Moderna [mRNA-1273 SARS-CoV-2 Vaccine] and Janssen/Johnson & Johnson [Ad26.COV2.S Adenovirus vector vaccine]) in patients who are eligible.

Table 1. COVID-19 Vaccination Recommendations for Cancer Patients**

<table>
<thead>
<tr>
<th>Patients Treatment/Cancer Type</th>
<th>Timing†‡¶</th>
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</thead>
<tbody>
<tr>
<td>Hematopoietic Cell Transplantation (HCT)/Cellular Therapy</td>
<td>At least 3 months post-HCT/Cellular therapy†‡¶</td>
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<tr>
<td>Allogeneic transplantation</td>
<td></td>
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<tr>
<td>Autologous transplantation</td>
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<tr>
<td>Cellular therapy (eg, CAR T-cell)</td>
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<tr>
<td>Hematologic Malignancies</td>
<td>Delay until absolute neutrophil count (ANC) recovery</td>
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<tr>
<td>Receiving intensive cytotoxic chemotherapy (eg, cytarabine/anthracycline-based induction regimens for acute myeloid leukemia)</td>
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<tr>
<td>Marrow failure from disease and/or therapy expected to have limited or no recovery</td>
<td>When vaccine available</td>
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<tr>
<td>Long-term maintenance therapy (eg, targeted agents for chronic lymphocytic leukemia or myeloproliferative neoplasms)</td>
<td>When vaccine available</td>
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<tr>
<td>Solid Tumor Malignancies</td>
<td>When vaccine available†¶</td>
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<tr>
<td>Receiving cytotoxic chemotherapy</td>
<td></td>
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<tr>
<td>Targeted therapy</td>
<td></td>
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<tr>
<td>Checkpoint inhibitors and other immunotherapy</td>
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<tr>
<td>Radiation</td>
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<tr>
<td>Major surgery</td>
<td>Separate date of surgery from vaccination by at least a few days</td>
</tr>
<tr>
<td>Caregivers and Household/Close Contacts</td>
<td>Any time eligible to receive the vaccine</td>
</tr>
</tbody>
</table>

**EUA for ≥18 years of age for Moderna and Janssen/Johnson & Johnson; ≥12 years of age for Pfizer/BioNTech
†COVID-19 vaccines and other vaccines may now be administered without regard to timing. This include simultaneous administration of COVID-19 vaccine and other vaccines on the same day, as well as coadministration within 14 days.
‡Discussion with clinical trial leads should be considered in advance to prevent protocol violations or exclusions.
¶CDC recommendations for timing of vaccination post-COVID-19 infection (after removal from isolation [minimum ≥20 days for cancer patients]), and/or post-SARS-CoV-2-specific monoclonal antibody or SARS-CoV-2 convalescent plasma (after 90-days).
**Table Footnotes**

a) Graft-versus-host disease (GVHD) and immunosuppressive regimens to treat GVHD (eg, systemic corticosteroids and targeted agents) are expected to blunt immune responses to vaccination. Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T-cell and B-cell immunity can be considered.

b) Patients on maintenance therapies (eg, rituximab, Bruton tyrosine kinase inhibitors, Janus kinase inhibitors) may have attenuated response to vaccination (see below).

c) The committee recognizes that granulocytopenia does not, in itself, significantly affect immunologic response to vaccination. It is used in this setting of profound immunosuppression for patients with hematologic malignancies as a surrogate marker for recovery of adequate immunocompetence to respond to vaccines and sufficient platelet recovery to avoid bleeding complications from intramuscular administration. Due to short periods of neutropenia among solid tumor malignancies this is not used for timing of vaccination.

d) In patients receiving chemotherapy, optimal timing of vaccination in relation to cycles of chemotherapy is unknown. Given the variability of specific regimens and intervals between cycles, it is not possible to state whether immunization will be more effective if administered at the time of chemotherapy administration versus mid-cycle when the white blood cell (WBC) count might be at its nadir. In the absence of data, we recommend vaccination when available.

e) Theoretical risk of exacerbated immune-related adverse events in patients receiving immune checkpoint inhibitors, but early data so far has not demonstrated such findings. There are no data on timing of vaccine administration, so this may be considered on the same day as immunotherapy for convenience and to reduce added visits to the office whenever possible.

f) The primary reason for avoiding vaccine in the perioperative period is so that symptoms (eg, fever) can be correctly attributed to surgery versus vaccination. For more complex surgeries (eg, splenectomy or which may lead to an immunosuppressive state) surgeons may recommend a wider window (+/- 2 weeks) from the time of surgery.

g) Even if vaccinated, close contacts should continue to wear masks, maintain social distancing guidelines, and follow other recommendations for COVID-19 prevention.
OVERVIEW:
Large cohort studies have demonstrated that cancer patients are at high risk for COVID-19–associated complications.\(^1\)\(^-\)\(^4\) As an at-risk population, there is a clear need for vaccinating these patients to avoid excess morbidity and mortality during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. In addition, since immunosuppressed patients may be sources of prolonged viral shedding and development of variants\(^5\)\(^-\)\(^6\), prioritizing vaccinations to these vulnerable patients may provide an additional societal benefit. Individuals with active cancer or with active, recent (<6 months), or planned cancer treatment should be considered highest priority to receive one of the currently available COVID-19 vaccines that have received emergency use authorization (EUA) by FDA.\(^7\)\(^-\)\(^9\) This document, while focusing on approved vaccines in the US, can also be used to support vaccination approaches in cancer patients using vaccines approved in other parts of the world.

The National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee recommends that COVID-19 vaccines should be given to all cancer patients, as well as household contacts and caregivers, when they are eligible to receive the vaccine; the committee has no preference for any of the approved vaccines. Data from vaccine trials have demonstrated that vaccines decrease the incidence of COVID-19 disease and complications, and data suggest that these vaccines may additionally prevent SARS-CoV-2 infection and subsequent risk of transmission. However, due to early reports of less vaccine efficacy in cancer patients, patients and close contacts should continue to wear masks, maintain social distancing guidelines, and follow other recommendations for COVID-19 prevention even if vaccinated.

**Due to emerging data relating to vaccination efficacy in patients with active malignancy, recommendations are based on the expert opinion of the committee; as data continue to become available our approach will be modified accordingly.** Decisions about when to offer COVID-19 vaccines should also take into account the National Academies of Sciences, Engineering, and Medicine (NASEM) Framework for Equitable Allocation of COVID-19 Vaccine that includes: risk of infection, severe morbidity and mortality, excess burden of COVID-19 on specific communities, and transmission to others.\(^10\) The key principles are as follows:

1. There are emerging data for these vaccines in patients with cancer, but generating data for these populations, especially in those receiving active cancer therapy, remains a priority. Despite gaps in knowledge about specific patient populations and treatments, we strongly recommend that patients with cancer receive vaccination as soon as eligible given their increased risk of morbidity and mortality from COVID-19.

2. Persons with active cancer are at increased risk of complications from SARS-CoV-2, and efforts to limit spread in high-risk patients at cancer centers is imperative. Cancer centers should be specified locations where vaccines should be allocated to allow safe delivery to these high-risk patients.

3. A simple and rapid approach to vaccination is important.

4. Vaccine should be offered to cancer patients in a manner to assure inclusion of racial/ethnic minorities, non-English–speaking patients, and other at-risk groups (eg, patients with disabilities) to ensure equity in COVID-19 vaccine distribution; health care systems should make special efforts to take into consideration social vulnerability markers that have been demonstrated during this pandemic.

5. To date, there are no reports of increased risk for side effects of the COVID-19 vaccines in patients with cancer as compared to the general population.
6. Vaccine efficacy in the setting of cancer care and a weakened immune system is thought to be less robust than in the general population, particularly for hematologic malignancies. However, vaccination is still strongly recommended for all eligible cancer patients.

7. Those immediately around patients under cancer care (eg, spouses, household members) are the most likely to be sources of transmission and should be vaccinated as soon as possible.

**VACCINE SAFETY AND EFFICACY IN CANCER PATIENTS:**

Cancer patients should be counseled that although these vaccines have been shown to be safe and effective in the general population, data on their effectiveness in immunosuppressed patients is emerging. The data on COVID-19 vaccine immunogenicity are mostly limited to measurement of post-vaccine antibody titers to the viral spike protein. Early data has demonstrated blunted antibody responses in patients with solid tumors and hematologic malignancies, particularly patients on active treatment;\(^{24-28}\) data among other immunosuppressed populations also indicates more limited antibody responses.\(^{29}\) Antibody responses are particularly poor among patients with hematologic malignancies, including those receiving monoclonal antibodies targeting CD20 (eg, rituximab). Antibody responses should be interpreted with caution, as they are only a surrogate marker for vaccine protection. Some studies have demonstrated additional T-cell responses to vaccination,\(^{30}\) although the strength and duration of neutralizing antibody responses or cellular immunity are not known at this point. Importantly, outcomes data (eg, COVID-19 disease, hospitalization, death) among fully vaccinated cancer patients are not available. All cancer patients should receive education regarding the importance of following all current prevention guidance post-vaccination. Caregivers and household/close contacts should be strongly encouraged to get vaccinated.

There are no safety signals that suggest increased adverse events specifically among patients with cancer receiving currently available COVID-19 vaccines; although rare case reports have been reported in cancer populations.\(^{31}\) Current SARS-CoV-2 mRNA vaccines (eg, Pfizer/BioNTech, Moderna) do not contain live virus and do not pose an immediate safety risk for immunosuppressed patients. The available single dose SARS-CoV-2 viral vector (Adenovirus-type 26 [AdV-type 26]) vaccine (Janssen/Johnson & Johnson) is safe for use in immunosuppressed hosts, as the adenovirus vector has been modified to make it replication incompetent.\(^{11}\) Although other vaccines are currently available in other parts of the world (eg, Astra-Zeneca COVID-19 vaccine, Sputnik [Ad35V26, AdV5 vaccine], Covaxin [killed whole virus vaccine with adjuvant], Sinovac (killed whole virus vaccine]) they are not currently available for use in the US.

All three EUA approved and available vaccines (in the US) have been shown to be safe in the general population, although post-vaccination arm soreness, fatigue, fever and headache, among other side effects are not uncommon.\(^{7-9}\) Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors has been reported.\(^{23}\) Anaphylaxis has been reported with both mRNA vaccines, although incidence is very low, ranging from 2.5-4.9 cases per million doses administered\(^{12}\); severe allergic responses have also been reported with the AdV-type 26 vector vaccine. Although more data are required to evaluate the safety of COVID-19 vaccination in patients with cancer including those receiving immunotherapy, targeted regimens, and investigational therapies, the results so far show an acceptable safety profile of COVID-19 vaccination.

**Post-vaccine thrombosis:** The available single dose SARS-CoV-2 viral vector (AdV-type 26) vaccine (Janssen/Johnson & Johnson) has been associated with an exceedingly rare risk of thrombosis with low platelets after vaccination (Thrombosis with Thrombocytopenia syndrome [TTS]); similar findings have
been linked to the Astra-Zeneca (AdV-type 26) vaccine. The mechanism that causes TTS is not fully understood. To date there have been no associations in cancer patients, but patients who have a history of heparin-induced thrombocytopenia and/or thrombosis should be counseled to receive another vaccine.

Post-vaccine lymphadenopathy and Imaging Studies in Cancer Patients: Reactive lymphadenopathy has been reported in up to 16% of the patients following COVID-19 vaccination with the mRNA (Pfizer/BioNTech, Moderna) vaccines; this side effect has not been reported to date with the AdV-type 26 vector vaccine (Janssen/Johnson & Johnson). To reduce the number of unwarranted biopsies, several reports with guidance on imaging studies have been published. Vaccination history and site of injection should be included in medical history to provide the radiologists with the clinical background for accurate interpretation. The Society of Breast Imaging recommends consideration of scheduling screening breast imaging 4-6 weeks following the completion of the COVID-19 vaccination, when possible. Unilateral lymphadenopathy noted on chest CT may likely be reactive following the vaccine unless it persists beyond six weeks following the second dose of the vaccine; abnormal FDG uptake with PET scanning has also been reported. With the currently available data, we recommend delay of imaging studies by 4-6 weeks following the COVID-19 vaccine if it will not result in a delay that will affect patient outcomes. For patients whose scans cannot be delayed in relation to the vaccination, careful consideration of the clinical context should be made by the treating oncologists and radiologists when interpreting the imaging studies. For patients who have a history of breast cancer, the vaccine should be administered in the contralateral arm whenever possible.

ANTIBODY TESTING POST-VACCINATION:
Emergency use authorized (EUA) vaccines have not been systematically evaluated in patients with active cancer or recipients of cellular therapy (hematopoietic cell transplant/ chimeric antigen receptor T-cell) as these populations were mostly excluded from clinical trials; although both the Pfizer/BioNTech and Janssen/Johnson & Johnson vaccine clinical trials did include cancer patients. Assessment for long-term immunity after vaccination with serologic testing (against spike protein of SARS-CoV2) in the cancer population and the general population outside of the clinical trial are lacking, so utility of such post-vaccine testing is unclear.

The correlation between antibody titers (against spike protein) and immunity as well as the duration of protection is not known at this time. Additionally, it is postulated that vaccine induced T-cell immunity may play a role in protection. Immunologic data from trials are still pending and at present standardized commercially available assays evaluating T-cell responses are lacking. Furthermore, the diversity of antibody tests, include non-vaccine targets such as the viral nucleocapsid, make interpretation of results even more complicated. The FDA does not recommend routine post-vaccine antibody testing. Antibody testing is complicated and may be difficult to interpret in the post-vaccination phase, but testing in select situations, such as part of research protocols can be considered; antibody testing for vaccine immunity, if ordered, should target the SARS-CoV-2 spike protein. Testing of antibodies to the nucleocapsid protein is used to assess prior SARS-CoV-2 infection, not vaccine immunity.

IMPORTANCE OF COVID-19 VACCINATION AMONG PATIENTS WITH CANCER, THEIR HOUSEHOLD MEMBERS, AND THE GENERAL POPULATION:
In prior version of NCCN guidelines, patients with cancer were prioritized for vaccination based on a number of factors that included those with active cancer on treatment, those planned to start therapy,
and those < 6 months post completion of therapy (excluding those receiving only hormonal therapy). The guidelines also recommended consideration of older age and comorbidities that increase the risk of COVID-19-related morbidity and mortality (e.g. chronic lung, cardiovascular, or renal disease) and social and demographic factors such as poverty, limited access to healthcare, and underrepresented minorities. Although barriers to vaccine access still exist, the need for prioritization of cancer patients has been mitigated by widespread vaccination throughout the country. Seen in this light, patients with cancer face two major obstacles regarding vaccination: lack of effective immune responses due to their underlying disease and/or therapy; and vaccine hesitancy in the general population that impedes the development of herd (community) immunity. Emerging data demonstrate that certain patients with cancer (e.g., those receiving B cell-depleting agents) may not have protective antibody titers following vaccination. Although we strongly continue to recommend that these patients be immunized because the vaccine may still confer some protection against COVID-19, the most effective protection for specific immunocompromised patients with cancer is likely to be through a reduction of community spread of SARS-CoV-2 by widespread vaccination. **We also note the particular importance for household members and other close contacts of patients with cancer to be immunized.**

**Vaccination of cancer patients enrolled/planning to enroll in clinical trials:** Patients currently being treated on clinical trials, or considering enrollment on a clinical trial should not defer COVID-19 vaccination, or be ineligible for enrollment or continuation on a clinical trial because of COVID vaccination, unless there is a specific scientific contraindication. The same should apply to COVID-19 antibody treatment. Clinical trials currently ongoing or nearing initiation should allow for COVID-19-related interventions without excluding candidacy or ongoing participation. The COVID-19 and Cancer Clinical Trials Working Group also recommended that patients with cancer enrolled in clinical trials should be prioritized for COVID-19 immunization, which should not affect clinical trial eligibility.  

**SOCIETAL CONSIDERATIONS:**

It is imperative that all patients have equitable access to the vaccines. The NASEM guidelines have recommended the incorporation of social vulnerability indices to mitigate health inequities that have clearly arisen during the COVID-19 pandemic. Notably, similar to the general non-cancer population, Black/African American, Hispanic/Latino, and Native American patients with cancer have been observed to have increased risk of developing COVID-19. Consequently, we encourage health systems to incorporate social vulnerability markers tailored to their populations to address the myriad of health inequities that have arisen during this pandemic. In addition, patients who may not have access to electronic health record platforms or email should be considered when vaccine invitation and scheduling are being operationalized. Special efforts should also be made to engage and incorporate those patients with limited English proficiency. Finally, health systems are encouraged to collect—to the extent possible—both race-ethnic and socioeconomic data for patients who receive the vaccine, so that these data can be periodically reviewed, and if inequities develop, aggressively addressed.

**POST-VACCINE PREVENTION:**

Recommendations from the CDC for loosening restrictions for the general public ≥ 2 weeks after completion of COVID-19 vaccination (2 weeks post second dose for Pfizer/BioNTech and Moderna, 2 weeks after first dose of Janssen/Johnson & Johnson), may not be reflective of what is best for the cancer community. The committee strongly recommends continued vigilance for cancer patients. As cancer patients are at increased risk for COVID-19 complications and may have less protection from available vaccines, patients should continue to wear masks, maintain social distancing, avoid crowds and follow guidelines and other pre-vaccine recommendations for COVID-19 prevention. Future studies on
boosters/re-vaccination are expected but without data, are currently not recommended by the committee. Efforts to protect patients should also expand to families, caregivers and household contacts, where targeted vaccination approaches can help assure patients are less likely to acquire SARS-CoV-2 from those closest to them.35

PRIORITIZATION AMONG CANCER PATIENTS IN SETTINGS OF LIMITED VACCINE AVAILABILITY:
Currently in the US vaccine supply is not an issue. COVID-19 vaccine availability varies in different regions of the world, and limitations exist for ability to vaccinate large populations efficiently (eg, rural vs. urban communities). These realities may still necessitate prioritization of an order in which patients with cancer are offered immunization. This prioritization must be evidence-based but also values-based as possible; even so, debate and disagreements exist. In situations of vaccine shortage, risk factors for COVID-19–related morbidity and mortality (eg, advanced age, chronic lung disease, cardiovascular disease) and cancer-specific factors should be considered in prioritization. Those with active cancer and/or therapy should be prioritized over those who completed therapy and those without evidence of disease. For those addressing shortages, the committee cannot issue a recommendation on prioritization based on chemotherapy, surgery, radiation, targeted therapy, or immunotherapy; however, patients without active cancer who are receiving hormonal therapy only would have lower prioritization.

Prioritization is challenging to develop when considering the diverse population of patients with their varied comorbidities, demographic and social factors known to increase risk of COVID-19 acquisition, morbidity, and/or mortality. The following criteria can be used to help determine local guidance to consider when developing such decisions*:

1) Prioritize patients with active cancer on treatment (including hematopoietic and cellular therapy), those planned to start treatment, and those immediately (<6 months) post-treatment, except those receiving only hormonal therapy.

2) Consider additional risk factors for such patients and other factors linked to adverse COVID-19 complications including, but not limited to:
   a. Patients with advanced age (eg, ≥65 years of age)
   b. Patients with comorbidities (eg, chronic pulmonary, cardiovascular, or renal disease)
   c. Social and demographic factors that include poverty, limited access to health care, and underrepresented minorities

*The current vaccine recommendations and prioritization guidelines will be updated regularly based on availability of new data. There are important gaps in knowledge on vaccine immunogenicity in specific patients with cancer and therapies. We will learn more about specific therapies that limit vaccine efficacy and would warrant vaccine delay. The durability of vaccine protection is being investigated in the general population and is expected to be attenuated in immunocompromised patients with cancer.
REFERENCES:


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