Recommendations of the National Comprehensive Cancer Network® (NCCN®) Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis*

▪ The committee endorses vaccination for all eligible persons based on FDA-approved indications or emergency use authorization (EUA). With the widespread availability of highly effective and safe vaccines, the committee reiterates the need for patients with cancer to be fully immunized, including receiving third doses and boosters.

▪ Vaccination is also recommended for caregivers, household/close contacts, and the general public. This statement reflects the evidence that patients with cancer or other immunocompromising conditions are most effectively protected from COVID-19 when they are immunized and their close contacts and general community are also vaccinated.

▪ Vaccination should be delayed for at least 3 months following hematopoietic cell transplantation (HCT) or engineered cellular therapy (eg, chimeric antigen receptor [CAR] T-cell therapy) to improve vaccine efficacy. Vaccine delays in patients with cancer should also include those recommended for the general public (eg, recent exposure to COVID-19, recent monoclonal antibody therapy).

▪ The committee supports use of any of the available FDA-approved or EUA vaccines but with strong preference for mRNA vaccines (Pfizer/BioNTech [BNT162b2/Comirnaty®] or Moderna [mRNA-1273]) over the Janssen/Johnson & Johnson [Ad26.COV2.S Adenovirus vector] vaccine as recommended by the CDC-ACIP Vaccine Advisory Committee.

▪ The committee strongly supports mandates for health care worker vaccination.

Table 1. COVID-19 Vaccination Recommendations for Patients with Cancer**
(see next section for details on third doses)

<table>
<thead>
<tr>
<th>Patients Treatment/Cancer Type</th>
<th>Timing to Start Series⁴,†,‡,¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic Cell Transplantation (HCT)/Cellular Therapy</td>
<td></td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>At least 3 months post-HCT/cellular therapyᵃᵇ</td>
</tr>
<tr>
<td>Autologous transplantation</td>
<td></td>
</tr>
<tr>
<td>Cellular therapy (eg, CAR T cell)</td>
<td></td>
</tr>
<tr>
<td>Hematologic Malignancies</td>
<td></td>
</tr>
<tr>
<td>Receiving intensive cytotoxic chemotherapy (eg, cytarabine/anthracycline-based induction regimens for acute myeloid leukemia)</td>
<td>Delay until absolute neutrophil count (ANC) recovery or for those not expected to recover, as soon as possible</td>
</tr>
<tr>
<td>Marrow failure from disease and/or therapy expected to have limited or no recovery</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Long-term maintenance therapy (eg, targeted agents for chronic lymphocytic leukemia, myeloma, or myeloproliferative neoplasms)</td>
<td>As soon as possibleᵉ</td>
</tr>
<tr>
<td>Solid Tumor Malignancies</td>
<td></td>
</tr>
<tr>
<td>Receiving cytotoxic chemotherapy</td>
<td>As soon as possible⁵,ᵈ</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Checkpoint inhibitors and other immunotherapy</td>
<td>As soon as possible⁶</td>
</tr>
<tr>
<td>Radiation</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Separate date of surgery from vaccination by at least a few daysᶠ</td>
</tr>
<tr>
<td>Caregivers and Household/Close Contacts</td>
<td>Any time eligible to receive the vaccine⁸</td>
</tr>
</tbody>
</table>
**The Pfizer/BioNTech mRNA vaccine is FDA approved for persons ≥16 years of age; it remains under EUA for persons aged 5–15 years (children <12 years should receive the pediatric formulation of the vaccine). The Moderna and Janssen/Johnson & Johnson vaccines are under EUA for those ≥18 years of age.

†COVID-19 vaccines and other vaccines may now be administered without regard to timing. This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day, as well as coadministration within 14 days.

‡ In rare instances, clinical trials (eg, involving anti-cancer vaccines) may exclude or require modification of timing of standard-of-care vaccines, including COVID-19 vaccines. This should be discussed with clinical trial investigators to ensure that the COVID-19 vaccine is initiated as soon as feasible.

¶CDC recommendations for timing of vaccination post-COVID-19 infection (after removal from isolation [minimum ≥20 days for patients with cancer]), and/or post-SARS-CoV-2–specific monoclonal antibody or SARS-CoV-2 convalescent plasma (after 90 days). Guidance for timing of vaccination post tixagevimab plus cilgavimab (Evusheld) is not currently available.

---

**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, anti-CD20 monoclonal antibodies, Bruton tyrosine kinase inhibitors, Janus kinase inhibitor, anti-CD38 antibodies) 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 as soon as possible to avoid delays in vaccination.

e) There may be theoretical risk of exacerbated immune-related adverse events in patients receiving immune checkpoint inhibitors, but early data so far have 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 CDC recommendations for COVID-19 prevention.
THIRD DOSE RECOMMENDATIONS:
The FDA issued an update to the EUA for the Pfizer-BioNTech mRNA vaccine (Comirnaty®) and the Moderna mRNA vaccine (mRNA-1273) to include an additional dose after an initial 2-dose series for moderately to severely immunocompromised patients. The amendment applies to mRNA COVID-19 vaccines and was based on a growing body of literature showing that immunocompromised patients can have impaired immune responses to vaccination. Limited data in solid organ transplant recipients show a substantial effect of an additional dose in augmenting antibody responses to vaccination after completion of a 2-dose series.1 For patients receiving an initial Janssen/Johnson & Johnson AD26–based COVID-19 vaccine, a second dose of the Janssen/Johnson & Johnson vaccine or an mRNA vaccine (preferred) should be given.

The CDC recommends a third dose of the mRNA vaccines for moderately to severely immunocompromised people, defined as:
- Those who have been receiving active cancer treatment for tumors or cancers of the blood
- Those who have received an organ transplant and are taking medicine to suppress the immune system
- Those who have received an HCT within the last 2 years or are taking medicine to suppress the immune system
- Those with moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Those with advanced or untreated HIV infection
- Those on active treatment with high-dose corticosteroids or other drugs that may suppress immune response

The NCCN Committee fully supports a third dose for immunocompromised patients. Below, we provide consensus recommendations on patients with cancer who should be prioritized for a third dose.

a) **Solid tumor malignancies:** We recommend a third dose for patients who received cancer therapy within 1 year of the initial vaccine administration. Realizing that specific therapies have different effects on the immune system, this recommendation applies to all cancer therapies, including but not limited to chemotherapy, targeted therapy, immunotherapy, hormonal therapy, surgery, radiation, and investigational agents. These criteria do not apply to non-melanoma skin cancers or superficial mucosal lesions treated solely with local therapy. In addition, patients with newly diagnosed cancer or recurrent cancer who will receive cancer therapy are included among patients prioritized for a third dose.

b) **Hematologic malignancies:** We recommend that all patients with active hematologic malignancies receive a third dose regardless of whether they are receiving cancer therapy. The reason for this recommendation is that patients with hematologic malignancies are at high risk for poor serologic responses to vaccination both as a result of immunodeficiency due to the malignancy and their associated cancer therapies (eg, B-cell–depleting agents such as anti-CD20 antibodies and Bruton tyrosine kinase inhibitors).2-10 As examples, patients with Hodgkin and Non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, myelodysplastic syndrome, or chronic myeloproliferative neoplasms should be prioritized for a third dose even if not on active therapy for these malignancies.

c) **Hematopoietic cell transplant and cellular therapy:** We recommend a third dose in HCT recipients and those who received engineered cellular therapy (eg, CAR T cells), prioritizing those who are ≤2 years post-procedure. A third dose is recommended for all allogeneic HCT recipients who are actively receiving immunosuppressive therapy or with a history of GVHD regardless of the time post-transplant.
d) **Cancer and other immunosuppressive conditions that do not meet other criteria:** We recommend a third dose for patients with cancer who have other concurrent immunocompromising conditions, such as HIV infection or autoimmune diseases. In addition, patients with cancer treated with systemic corticosteroids and other immunosuppressive agents separate from cancer therapy should be prioritized for a third dose.

**Timing of Administration of Third Dose:**
The CDC recommends the additional dose of an mRNA COVID-19 vaccine be administered at least 4 weeks after a second dose of the Pfizer-BioNTech or Moderna vaccine. For people who received the Pfizer-BioNTech or Moderna COVID-19 vaccine series, a third dose of the same mRNA vaccine should be used if possible. If the same mRNA vaccine isn’t available for the third dose administration or if the prior vaccine is unknown, either mRNA COVID-19 vaccine may be used. The NCCN Committee recommends a second dose for those who received the Janssen/Johnson & Johnson vaccine at 2 months post the first dose; an mRNA vaccine is preferred over a Janssen/Johnson & Johnson second dose. Although national guidance recommends a single additional dose (for those who received one Janssen/Johnson & Johnson dose), two additional doses are recommended by the NCCN Committee for these high-risk patients (at least 28 days apart) and a booster at 6 months post the third dose.

a) We do not recommend (outside of a research study) the use of antibody titers to determine if patients should receive additional doses of vaccine.

b) Selection of patients with cancer to receive a third dose and additional booster should be made based on the underlying cancer, therapy, and other immunocompromising conditions.

c) Patients who have a history of COVID-19 following their initial vaccine series should also receive a third dose (delayed >28 days post completed vaccine series and documented clearance of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] virus).

**Mix and Match Dosing:**
Data from studies indicate that vaccine doses can be given to patients who have received other platforms (mRNA vs. AdV vector vaccines) or who received vaccines by different manufacturers (eg, Pfizer or Moderna). The preference is for patients to receive additional mRNA vaccine doses with the same vaccine (third dose or booster) or the alternate mRNA vaccine can be given. Patients who have received the Janssen/Johnson & Johnson vaccine can receive either mRNA vaccine as a second dose (preferred) or a second Janssen/Johnson & Johnson vaccine. Patients receiving mRNA vaccines can also be boosted with AdV vector vaccines, although mRNA vaccine boosting is currently recommended.

Patients who have completed a full series of any of the COVID-19 vaccines listed for emergency use by WHO (eg, Astra-Zeneca, Sinovac, Covaxin) are considered fully vaccinated. However, patients with cancer and other patients who are immunocompromised should receive a third dose of mRNA vaccine at least 28 days after receiving the second vaccine dose (all ≥12 years of age), and those ≥12 years of age should receive an additional booster at least 6 months after completing their initial three doses.52-53

**Third Dose Vaccine for Immunocompromised Persons Versus Booster Vaccines for the General Public:**
The recommendation on third dose vaccine administration for immunocompromised patients (full dose for both mRNA vaccines – 100 ug mRNA-1273 and 30 ug BNT162b2) was soon followed by a recommendation for booster vaccines for the general public, ages 16 years and older. Boost dosing is 50 ug for mRNA-1273 and 30 ug for BNT162b2. Boosters are administered at least 6 months after completion of the primary vaccination series. The rationale for a booster is the waning of vaccine effectiveness over time that is likely Due to waning immunity and the greater infectiousness of the Delta variant and more recently the Omicron variant. In the case of the Moderna COVID-19 vaccine booster shot, the booster is half the dose of that given for the primary series. Booster with BNT162b2 vaccine (Pfizer) reduced COVID-19 incidence and
Among patients with a history of cancer, those who do not meet the criteria for the third vaccine dose given to immunocompromised persons should be offered a booster similar to the general population. Those patients with cancer who received a two-dose primary series should be offered a booster dose at 6 months after completion of their primary series.

Revaccination Following HCT or CAR T-Cell Therapy:

In patients who received COVID-19 vaccination prior to HCT or engineered cellular therapy, there is major concern for loss of immunity. Loss of vaccine-induced immunity following these therapies is observed in several childhood vaccines (e.g., measles, mumps, and rubella vaccine), necessitating re-vaccination post-therapy. The same depletion of immunity is expected for COVID-19 vaccines. These patients are expected to have attenuated responses to COVID-19 vaccination post-transplant, particularly in the setting of GVHD. In addition, lymphodepletion prior to CAR T-cell and other cellular therapy regimens is expected to attenuate post-therapy immune responses to vaccination. Recognizing these limitations, the CDC, American Society for Transplantation and Cellular Therapy (ASTCT), and American Society of Hematology (ASH) recommend that patients completing these therapies should receive a repeat vaccination series starting at 3 months post-treatment. We support these recommendations. As we learn more about vaccine-induced immunity in these settings, these recommendations may be modified (e.g., the inclusion of a booster at 6 months post third dose).

Prioritization if Local Supply Issues Occur:

The above recommendations for a third dose and booster are based on adequate vaccine supply, which is the case in the vast majority of regions in the United States. With adequate supply, we strongly endorse that patients with cancer who meet these eligibility criteria obtain the third dose and booster where available and most convenient, including at local pharmacies, but would also prioritize allocation to cancer centers to assure ease of distribution to high-risk patients. In situations of limited vaccine availability, individual cancer centers and oncologists may need to prioritize a third dose to those patients who are least likely to respond to the standard two-dose series, such as:

a) HCT/cellular therapy recipients
b) Patients with hematologic malignancies on active therapy
c) Patients with solid tumor malignancies receiving active intravenous chemotherapy

OVERVIEW:

Large cohort studies have demonstrated that patients with cancer are at high risk for COVID-19–associated complications. As an at-risk population, there is a clear need for vaccinating these patients to avoid excess morbidity and mortality during the SARS-CoV-2 pandemic. In addition, since immunosuppressed patients may be sources of prolonged viral shedding and development of variants, 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 EUA by the FDA [Pfizer/BioNTech vaccine (Comirnaty®) is now fully FDA approved for those ≥16 years of age]. This document, while focusing on approved vaccines in the United States, can also be used to support vaccination approaches in patients with cancer using vaccines approved in other parts of the world.

The NCCN Committee recommends that COVID-19 vaccines should be given to all patients with cancer, as well as household contacts and caregivers, when they are eligible to receive the vaccine; the committee believes that mRNA vaccines should be offered as the preferred vaccine(s). 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 patients with cancer, 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. The key principles are as follows:

1. 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. Vaccines should be offered to patients with cancer 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 strongly recommended for all eligible patients with cancer.
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.
8. The committee strongly supports vaccine mandates for health care workers.

Vaccine Safety and Efficacy in Patients with Cancer:
Patients with cancer 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 are emerging. The data on COVID-19 vaccine immunogenicity are mostly limited to measurement of post-vaccine antibody titers to the viral spike protein. Still, early data have demonstrated blunted antibody responses in patients with solid tumors and hematologic malignancies, particularly patients on active treatment; data among other immunosuppressed populations also indicate more limited antibody responses. 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, 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 patients with cancer are not available. All patients with cancer should receive education regarding the importance of following all current prevention guidance post-vaccination.
Eligible caregivers and household/close contacts should be strongly encouraged to get vaccinated. The committee strongly supports vaccination mandates for health care workers (see statement).

There are no safety signals that suggest adverse events specifically among patients with cancer receiving currently available COVID-19 vaccines, although rare case reports have been reported in cancer populations.41 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.21 Although other vaccines are currently available in other parts of the world (eg, Astra-Zeneca COVID-19 vaccine, Sputnik [AdV-type 26, AdV-type 5 vaccine], Covaxin [killed whole virus vaccine with adjuvant], Sinovac [killed whole virus vaccine]), they are not currently available for use in the United States.

All three available vaccines (in the United States) 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.17-19 To date, only Pfizer/BioNTech mRNA vaccine (Comirnaty®) is fully approved by the FDA. Short-term safety of the Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors has been reported.33 Anaphylaxis has been reported with both mRNA vaccines, although incidence is very low, ranging from 2.5 to 4.9 cases per million doses administered22; 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.42 The mechanism that causes TTS is not fully understood. To date there have been no associations between TTS and patients with cancer, 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 patients with cancer: Reactive lymphadenopathy has been reported in up to 16% of 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).23-25 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 to 6 weeks following the completion of the COVID-19 vaccination, when possible.26 Unilateral lymphadenopathy noted on chest CT may likely be reactive following the vaccine unless it persists beyond 6 weeks following the second dose of the vaccine27; abnormal FDG uptake with PET scanning has also been reported.28 With the currently available data, we recommend delay of imaging studies by 4 to 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:**

Available vaccines have not been systematically evaluated in patients with active cancer or recipients of cellular therapy (HCT/CAR T cell), as these populations were mostly excluded from clinical trials; however, both the Pfizer/BioNTech and Janssen/Johnson & Johnson vaccine clinical trials did include patients with cancer. 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 limited, so utility of such post-vaccine testing is unclear. There is clear need for future vaccine trials to include patients with cancer.

The correlation between specific levels of circulating antibodies against the spike protein and protection from COVID-19 is not known at this time. Additionally, 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, including 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 if sent should target the spike protein (marker of vaccine response) and not the SARS-CoV-2 nucleocapsid protein (marker of acute infection). Importantly, antibody testing should not be used to determine if patients should receive the recommended third dose of mRNA vaccines.

**IMPORTANCE OF COVID-19 VACCINATION AMONG PATIENTS WITH CANCER, THEIR HOUSEHOLD MEMBERS, AND THE GENERAL POPULATION:**

In prior versions of this guidance, 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 from of completion of therapy (excluding those receiving only hormonal therapy). The guidance also recommended consideration of older age and comorbidities that increase the risk of COVID-19–related morbidity and mortality (eg, chronic lung, cardiovascular, or renal disease) and social and demographic factors such as poverty, limited access to health care, and underrepresented minorities. Although barriers to vaccine access still exist, the need for prioritization of patients with cancer has been largely obviated 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 (eg, 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 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 eligible household members and other close contacts of patients with cancer to be immunized.

**Vaccination of patients with cancer 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-19
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.44

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.20 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-19.30 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.31 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:
The committee strongly recommends continued vigilance for patients with cancer after completion of COVID-19 vaccination. As patients with cancer 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. 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.45

PRIORITIZATION AMONG PATIENTS WITH CANCER IN SETTINGS OF LIMITED VACCINE AVAILABILITY:
Vaccine supply is currently not an issue in the United States. COVID-19 vaccine availability varies in different regions of the world, and limitations exist in 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 as evidence-based but also as value-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 only receiving hormonal therapy should 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 HCT 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

PRE-EXPOSURE PROPHYLAXIS

COVID-19 vaccination is a form of pre-exposure prophylaxis; the vaccination is designed to induce immune responses to prevent or diminish the severity of COVID-19 following a subsequent exposure to SARS-CoV-2. With the predominance of variant strains, vaccination remains the most effective approach to avert serious COVID-19 complications, including hospitalization and mortality. However, a major gap in vaccination is that many immunocompromised persons develop inadequate immune responses to available COVID-19 vaccines. This gap in protection is addressed by a combination of vaccination that induces host responses directed against the spike protein (both humeral and cellular) and passive immunotherapy that confers protection independently of host immune responses.

Tixagevimab co-packaged with cilgavimab (Evusheld) is a long-acting monoclonal antibody combination directed against the spike protein. Tixagevimab plus cilgavimab was effective as prophylaxis in patients at risk for COVID-19 complications. In the PROVENT trials, 3,441 people received tixagevimab plus cilgavimab and 1,731 received placebo. Of the 5,197 subjects, 78% had baseline comorbidities or characteristics associated with an increased risk for severe COVID-19 (eg, obesity, diabetes, cardiovascular disease); a limitation in applying results to patients with cancer is that only 7% had active cancer or a history of cancer, and only 3% received immunosuppressive medications. Tixagevimab plus cilgavimab recipients had a 77% reduction in risk of developing COVID-19, and this risk reduction was maintained through 6 months post dosing. The safety and effectiveness of tixagevimab plus cilgavimab continue to be evaluated. In the era of Omicron spread, early data suggest tixagevimab plus cilgavimab maintains at least partial efficacy against the Omicron variant and could provide additional protection for high-risk patients.

The FDA issued an EUA for tixagevimab plus cilgavimab for the pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (≥12 years of age weighing at least 40 kg) who have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination. Importantly, pre-exposure prevention with tixagevimab plus cilgavimab, however, is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended, so efforts to assure vaccination remain important.54 Per the EUA, medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include but are not limited to55-56:
   - Active treatment for solid tumor and hematologic malignancies
   - Receipt of solid-organ transplant and taking immunosuppressive therapy
   - Receipt of CAR T-cell therapy or HCT (within 2 years of transplantation or taking immunosuppression therapy)
   - Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome)
   - Advanced or untreated HIV infection
The supply of tixagevimab plus cilgavimab is extremely limited nationwide at this time. The U.S. Department of Health and Human Services is allocating product as it becomes available from the manufacturer, and individual states are distributing based on supplies and needs. Similar to the time when COVID-19 vaccine availability was limited, cancer centers must make difficult decisions about prioritizing which patients should be offered tixagevimab plus cilgavimab first. Patients with hematologic malignancies (including HCT and those receiving engineered cellular therapy) are more likely to have inadequate responses to COVID-19 vaccination and are at highest risk of major COVID-19 complications. The committee agreed that a reasonable option is to prioritize these patients for tixagevimab plus cilgavimab. In addition, centers should make efforts to assure equitable distribution of the drug when delivering their allocation. Some centers may choose to use vaccination or antibody status to help determine allocation, targeting those with poor responses first. The committee remained agnostic on the use of antibody levels to determine priority, and such decisions should be determined at the local level until additional data become available.

By contrast, most patients with solid tumors are likely to respond to COVID-19 vaccination. These patients should be strongly recommended to receive third doses and boosters as the primary mode of prevention and those on active therapy should be offered tixagevimab plus cilgavimab when supply is available. Since tixagevimab plus cilgavimab is administered by deep intramuscular injection, center-based policies regarding dosing in patients with thrombocytopenia or on anticoagulation should be followed.

To avoid interference with vaccine-induced immunity, tixagevimab plus cilgavimab should be administered at least 2 weeks after COVID-19 vaccination. In the specific case of HCT and cellular therapy recipients, the prior administration of tixagevimab plus cilgavimab has the potential to reduce the efficacy of post-transplant/cellular therapy re-vaccination. The timing of post-transplant/cellular therapy vaccinations (both primary series and boosters) in patients who previously received tixagevimab plus cilgavimab warrants evaluation. Knowing these limitations, the committee recommends the use of tixagevimab plus cilgavimab in these high-risk patients as soon as supply is available.

*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 shown to be attenuated in immunocompromised patients with cancer.
REFERENCES:


##

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 31 leading cancer centers devoted to patient care, research, and education. NCCN is dedicated to improving and facilitating quality, effective, equitable, and accessible cancer care so all patients can live better lives. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. By defining and advancing high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers around the world.

NCCN resources are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches. Any clinician seeking to apply or consult NCCN resources is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. NCCN makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
NCCN Advisory Committee on Covid-19 Vaccination and Pre-exposure Prophylaxis

*Steven Pergam, MD, MPH (Co-Leader)
Infectious Disease
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

*Lindsey Robert Baden, MD (Co-Leader)
Infectious Disease
Dana-Farber/Brigham and Women’s
Cancer Center

*Brahm Segal, MD (Co-Leader)
Infectious Disease
Roswell Park Comprehensive Cancer Center

*Gregory Abel, MD, MPH
Medical Oncology, Ethics
Dana-Farber/Brigham and Women’s
Cancer Center

Kerin Adelson, MD
Medical Oncology
Yale Cancer Center/Smilow Cancer Hospital

*Craig Bunnell, MD, MPH, MBA
Medical Oncology
Dana-Farber/Brigham and Women’s
Cancer Center

*Natalie Callander, MD
Hematology Oncology
University of Wisconsin
Carbone Cancer Center

*Sanjeet Dadwal, MD
Infectious Disease
City of Hope National Medical Center

John Glaspy, MD
Hematology Oncology
UCLA Jonsson Comprehensive Cancer Center

*Ayad Hamdan, MD
Hematology
UC San Diego Moores Cancer Center

Aparna Hegde, MD
Hematology Oncology
O’Neal Comprehensive Cancer Center at UAB

James Helstrom, MD, MBA
Surgical Oncology
Fox Chase Cancer Center

Paul Hendrie, MD, PhD
Hematology
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Ephraim Hochberg, MD
Hematology Oncology
Massachusetts General Hospital
Cancer Center

Carol Ann Huff, MD
Hematology Oncology
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Michael Hurwitz, MD, PhD
Medical Oncology
Yale Cancer Center/Smilow Cancer Hospital

Matt Kalaycio, MD
Hematology Oncology
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Robert Keenan, MD, MMM
Surgical Oncology
Moffitt Cancer Center