DUKE Vaccination Protocol for Adult patients with Hematological Malignancy receiving Chimeric Antigen Receptor (CAR) T-cell and/or Bispecific T-cell Engager (BiTE) Therapy

Preamble

- This protocol is intended as guidance for patients receiving chimeric antigen receptor (CAR) T-cell or bispecific T-cell engager (BiTE) therapy for treatment of hematological malignancy.
- Patients receiving BCMA-directed CAR T-cell therapy should be revaccinated with a primary immunization series due to anticipated impairment to vaccine-induced humoral immunity.
- Patients receiving BiTE or CD19-directed CAR T-cell therapy should receive age- and risk-appropriate vaccinations starting ≥3 months after CAR T-cell infusion or end of BiTE therapy. These patients do not require revaccination with a primary immunization series.
- Patients who have undergone hematopoietic stem cell transplantation (HSCT) following BiTE, CD19-directed, or BCMA-directed CAR T-cell therapy should be revaccinated according to the HSCT revaccination protocol.
- Patients who undergo BCMA-directed CAR T-cell therapy following HSCT will need to repeat a primary immunization series as directed below if they have already received part or all of their post-HSCT vaccinations.

- Transplant ID should be consulted to guide vaccination strategies for **patients with primary immune deficiencies**.
- Screening for vaccination eligibility should occur **6 months** following BCMA-directed CAR T-cell therapy.
- Vaccines that may be considered before 6 months include:
    - **Annual COVID-19 vaccine**: Irrespective of prior vaccinations, all BCMA-directed CAR T-cell therapy recipients should receive the most recent COVID-19 vaccine 3 months post-infusion, preferentially with either Moderna (mNEXSPIKE) or Pfizer-BioNTech. Novavax is an alternative for those who are intolerant to mRNA vaccines.
    - **RSV vaccine**: Can be given as early as 3 months following BCMA-directed CAR T-cell and ideally before the fall/winter RSV season (see glossary for further details).
    - **Influenza vaccine**: Can be given as early as 3 months following BCMA-directed CAR T-cell therapy and annually thereafter (see glossary for further details).

Criteria for vaccine eligibility

1. Minimum 6 months post BCMA-directed CAR T-cell therapy*
2. CD4 > 200 cells/uL†
3. Not receiving maintenance chemotherapy post BCMA-directed CAR T-cell therapy (apart from single agent bortezomib, lenalidomide, pomalidomide)
4. No exposure to B-cell depleting agents (ie. rituximab) in the previous 6 months

*If patients remain ineligible for vaccination at 6 months (based on criteria above) then regularly reassess eligibility every 3 months thereafter.
†CD19 > 20 cells/uL may be used in addition to CD4 > 200 cells/uL as an indicator of a patient's capacity to mount a protective vaccine response, but is not required.

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Vaccination Schedule

Table 1a: Vaccine schedule

Time of initiation post-therapy	Recommended vaccines	Optional vaccines
≥ 6 months	PCV-20	MCV4[A], MBV[A]
≥ 9 months	PCV-20, RZV[B], Pentacel®	MCV4[A], MBV[A]
≥ 12 months	PCV-20, RZV[B], Pentacel®, HBV[C]	MBV[A], HPV
≥ 18 months	PCV-20, Pentacel®, HBV[C]	HAV, HPV
≥ 24 months	HBV[C], MMR[D]	HPV, HAV, Varivax®[D]
≥ 26 months		Varivax®[D]
Annual	IIV	

HAV, hepatitis A virus vaccine; *HBV*, hepatitis B virus vaccine; *HPV*, human papilloma virus vaccine; IIV, Inactive influenza virus vaccine; *MBV*, meningococcal B vaccine; *MCV4*, quadrivalent meningococcal vaccine; *MMR*, measles, mumps and rubella vaccine; *PCV,* pneumococcal conjugate vaccine; RZV, recombinant zoster vaccine (Shingrix®)

[A]In at risk sub-populations (e.g., persons with anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use, college students, especially those who live in on-campus housing, or participate in sororities and fraternities), MCV4 and MBV should be administered according to the schedule indicated above

[B]Commencement of the RZV series can be modified to earlier or later time points based on the planned duration of ACV prophylaxis. Patients should receive the full 2-dose RZV series prior to cessation of ACV prophylaxis. Current recommendations are to continue ACV prophylaxis at least 4 weeks post administration of RZV dose 2.

[C]2-doses only if Heplisav-B is used. All other formulations require a 3rd dose.

[D]This is a live vaccine and should only be administered in patients ≥ 24-months post CAR-T, off all immunosuppression, and with CD4 cell count ≥200cells/uL. Live vaccines should also be delayed ≥ 8 months after receipt of IVIg whenever feasible. Criteria for early administration of MMR in local outbreaks are detailed in Table 2.

Optional vaccines:

- **Human papilloma virus** (HPV) vaccine: Should be considered in males and non-pregnant females up to age 50 at the providers' discretion.
- **Varivax®:** Varicella zoster vaccine to be used frontline prior to RZV if fulfilling all 3 criteria: recipient seronegative to VZV, varicella zoster naïve (ie. no history of chickenpox), and no previous vaccination with Varivax. Patient must also meet criteria for receipt of live vaccines.
- **Hepatitis A virus vaccine**: A 2-dose hepatitis A virus (HAV) vaccination series should be considered in high-risk individuals (see criteria under vaccine glossary).

Vaccine Glossary (Alphabetical)

1. Hepatitis A vaccine (HAV): Havrix® or VAQTA® (1 mL IM), 2-dose series, *minimum 6-month interval between doses*; Vaccine indicated in the following "increased risk" groups:
    - Men who have sex with men, persons with chronic liver disease, persons with liver GVHD, concurrent infection with other hepatitis viruses, persons who use injection or non-injection illicit drugs
    - Persons working with HAV-infected primates or with HAV in a research laboratory setting
    - Persons who receive clotting factor concentrates

- Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A

2. Hepatitis B virus vaccine (HBV): Heplisav-B® or Engerix-B®, *dosing and intervals brand specific as below*
   - Preferred: **Heplisav-B** (0.5mL IM), 2-dose series, *minimum 1-month interval between doses*
   - Alternative: Engerix-B® (2mL IM), 3-dose series, *minimum 1-month interval between dose 1-2, and 5-month interval between dose 2-3*
   - Check hepatitis B surface antibody (anti-HBs) one month after completion of full vaccination series. If anti-HBs negative, repeat vaccination series

   In patients on hemodialysis, HBV vaccination should be coordinated with and performed by dialysis centers due to possible false positive hepatitis B surface antigen testing early post receipt of HBV vaccine.

3. Human papilloma virus vaccine (HPV): Gardasil-9® Nonavalent vaccine (0.5 mL IM), 3-dose series, minimum *2-month interval between dose 1-2, and 4-month interval between dose 2-3*. Primarily indicated in non-pregnant females and males up to age 26 but series can be initiated in non-pregnant individuals up to age 50 at providers' discretion.

4. Inactivated influenza virus vaccine (IIV): IIV should be administered ≥6 months post-therapy. In epidemics/community outbreaks, IIV can be administered early (e.g., ≥3 months post-therapy) and can be repeated 4-6 weeks later. Recommended formulations for immunocompromised patients and/or those ≥65 years of age include the adjuvanted quadrivalent (Fluad® Quadrivalent, 0.5 mL IM), quadrivalent high dose vaccine (Fluzone® High-Dose Quadrivalent, 0.7 mL IM), or quadrivalent recombinant vaccine (Flublok® quadrivalent, 0.5 mL IM). Patients with accessibility or cost barriers to any of these formulations should receive any available IIV as an alternative.

5. Measles, mumps, and rubella vaccine (MMR): M-M-R II® (0.5 mL subQ), 1-dose. This is a live vaccine and should only be administered when all the following criteria are met: 1. ≥ 24 months post-therapy, 2. No active GVHD, 3. Off of all immunosuppressive therapy for ≥ 12 months, and 4. CD4 cell counts ≥ 200/mm^3. Use of MMR vaccine is permissible if IVIG has been administered but should be delayed by 8-months whenever feasible. Other live vaccines can be administered on the same day (e.g. Varivax®), but if not performed on same day, the second live vaccine should be given ≥ 28 days later. Use of MMR vaccine is permissible in patients on maintenance lenalidomide, pomalidomide, or bortezimib. Early administration of MMR may be recommended in event of local outbreak (see Table 2).

6. Mpox vaccine: Use of Mpox vaccine is permissible in immunocompromised hosts ≥ 18 years of age at high risk for infection. Further details on eligibility and vaccination be found on Duke Custom ID (Mpox).

7. Pentacel® vaccine: Combination vaccine containing diphtheria, tetanus and acellular pertussis (DTaP), *Haemophilus influenzae* B (Hib) and inactivated polio virus (IPV). Pentacel® (0.5 mL IM), 3-dose series, *minimum 2-month interval between doses*. If this combination vaccine cannot be given then individual components can be administered separately (3-dose series): (1) DTaP (0.5 mL IM) – Daptacel® or Infanrix® [alternative Tdap (0.5 mL IM) – Adacel® or Boostrix®], (2) Hib (0.5 mL IM) - ActHIB® or Hiberix®, (c) IPV (0.5 mL IM, subQ) – IPOL®.

8. Pneumococcal conjugate vaccine (PCV-20): Prevnar-20® (0.5 mL IM or subQ), 4-dose series, *minimum interval between doses 1-3 is 1 month, followed by a fourth PCV-20 dose at least 6 months after the 3rd PCV-20 dose, or at least 12 months after therapy, whichever is later.* BCMA recipients who have started their pneumococcal vaccine series with another pneumococcal conjugate vaccine (e.g., Prevnar-13 or Prevnar-15) may complete their 4-dose pneumococcal vaccine series with PCV-20.

9. Recombinant zoster vaccine (RZV): Shingrix® (0.5mL IM), 2-dose series, *2-6 month interval between doses*. Used in patients with a previous history of primary varicella infection (chickenpox), pre-therapy seropositivity to VZV and/or documented receipt of Varivax® vaccine prior to cellular therapy. In all other cases, RZV should be deferred and Varivax® series administered ≥ 24 months post-therapy if meeting criteria for live vaccines. Acyclovir prophylaxis should continue until at least 4-weeks following completion of the RZV vaccine series and off all immunosuppression.

10. Respiratory Syncytial virus vaccine (RSV): Abrysvo® (Pfizer: 0.5mL IM), Arexvy® (GSK: 0.5mL IM), or MResvia (Moderna: 0.5mL IM). Recommended in patients aged ≥ 75 or 50-74 with high risk for severe infection (e.g. severe heart or lung disease). Vaccination may be considered in high-risk patients <50 years of age but patients may incur out-of-pocket costs and vaccination in this age group should be based on shared clinical decision making. Abrysvo® is available on formulary at DUHS.

11. Varicella virus vaccine: Varivax® (0.5 mL subQ), 2-dose series (separated by ≥ 4–8 weeks) is given to patients not meeting criteria for RZV (Shingrix®). Consult therapy infectious diseases team for guidance in all VZV seronegative recipients. Varivax® is a live vaccine and should only be administered in patients ≥ 24-months post-therapy and off all immunosuppressive therapy for ≥ 12-months with CD4 cell counts ≥ 200/mm^3. Delay administration of Varivax® for at least 8-months after the receipt of IVIG whenever feasible. LIVE vaccines can be administered on the same day (e.g., MMR and Varivax®) but if unable to administer the same day the second live vaccine should be given ≥ 28 days later.

Table 2: Criteria recommended for MMR vaccination during local outbreak

- MMR vaccination may be recommended in the case of a local outbreak of measles. Criteria for early administration as below (adapted from reference 10):

Timing	> 1-year post-CAR T-cell therapy
Immunosuppressive Therapy	No post-therapy chemotherapy, unless lenalidomide, pomalidomide or bortezomib for maintenance therapy
Steroid Use	≤ 5mg prednisone daily (for secondary adrenal insufficiency
Cell Counts	Total lymphocyte count of ≥ 1 x 10^3 μL or CD4 > 200 cells/mm^3 and CD19 > 20 cells/mm^3
Immunoglobulin Level	Unsupported IgG > 400mg/dL and measurable IgA > 6mg/dL

If administered early, patients should receive 2 doses of MMR due to reduced rates of seroconversion. Dose 2 to be given no less than 1 month after first dose and at least > 15 months post-therapy.

REFERENCES

1. Bhoj VG, Arhontoulis D, Wertheim G, et al. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. *Blood*. Jul 21 2016;128(3):360-70. doi:10.1182/blood-2016-01-694356
2. Gonzalez MA, Bhatti AM, Fitzpatrick K, et al. Humoral and cellular responses to SARS-CoV-2 vaccines before and after chimeric antigen receptor-modified T-cell therapy. *Blood Adv*. May 9 2023;7(9):1849-1853. doi:10.1182/bloodadvances.2022008338
3. Hill JA, Krantz EM, Hay KA, et al. Durable preservation of antiviral antibodies after CD19-directed chimeric antigen receptor T-cell immunotherapy. *Blood Adv*. Nov 26 2019;3(22):3590-3601. doi:10.1182/bloodadvances.2019000717
4. Josyula S, Pont MJ, Dasgupta S, et al. Pathogen-Specific Humoral Immunity and Infections in B Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy Recipients with Multiple Myeloma. *Transplant Cell Ther*. Jun 2022;28(6):304.e1-304.e9. doi:10.1016/j.jtct.2022.03.005
5. Lee D, Jordan AI, Menges MA, et al. Pneumococcal Conjugate Vaccine Does Not Induce Humoral Response When Administrated Within the Six Months After CD19 CAR T-Cell Therapy. *Transplant Cell Ther*. Apr 2023;29(4):277.e1-277.e9. doi:10.1016/j.jtct.2022.08.011
6. Walti CS, Krantz EM, Maalouf J, et al. Antibodies against vaccine-preventable infections after CAR-T cell therapy for B cell malignancies. *JCI Insight*. Jun 8 2021;6(11)doi:10.1172/jci.insight.146743