A phase II randomized, placebo-controlled, multicenter trial to evaluate the efficacy of cytomegalovirus PepVax vaccine in preventing cytomegalovirus reactivation and disease after allogeneic hematopoietic stem cell transplant

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https://doi.org/10.3324/haematol.2023.284544
A phase 2 randomized, placebo-controlled, multicenter trial to evaluate the efficacy of cytomegalovirus PepVax vaccine in preventing cytomegalovirus reactivation and disease after allogeneic hematopoietic stem cell transplant

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Supplementary data

Supplementary Figure legends

**Figure 1S: Enrollment and randomization of HCT recipients.** The flow diagram shows the trial profile including enrollment, intervention allocation, follow-up, and data analysis. *Denotes day of primary efficacy endpoint; HCT = hematopoietic stem cell transplant; COH = City of Hope; UMN = University of Minnesota; FHCC = Fred Hutchinson Cancer Center; OSUMC = The Ohio State University Wexner Medical Center; GVHD = graft-versus-host disease; AE = adverse event.

**Figure 2S: Time-to-event curves for CMV events.** Kaplan–Meier estimates are shown, with censoring times indicated. The analysis was conducted by comparing cumulative incidence of CMV event rate by day 100 between PepVax and placebo arm, using Gray’s test for competing-risk events. (A) Bar indicates the cumulative incidence of CMV events at day 100 post-HCT (primary efficacy endpoint). (B) CMV events according to the treatment assignment, in the subgroup of HCT recipients who received a transplant from a CMV seropositive donor (left plot) and that one of HCT recipients who received a transplant from CMV seronegative donor (right plot).

**Figure 3S: Frequency of pp65495–503-specific CD8 T-cells by HCT donor CMV serostatus.** Longitudinal levels (T cells/µl) of pp65<sub>495–503</sub>-specific CD<sup>3</sup><sup>+</sup> CD<sup>8</sup><sup>+</sup> T-cells are shown by HCT donor CMV serostatus. Levels were computed using the loess scatterplot smoother providing the marginal geometric mean concentrations through time for each arm (as specified in the color legend). A 95% confidence band is shown in gray, and individual measurement trajectories are shown for each participant up to 7 days before the protocol-defined cytomegalovirus event. Logarithmic spacing of both scales is used to aid visualization. Distribution of pp65<sub>495–503</sub> specific CD8 T cells levels were approximately normal after log 10-transformation. Generalized estimating equations models were used to assess the vaccine effect on immunological responses All analyses were performed using SAS version 9.4 (SAS institute). The syringe symbol indicates post-HCT day of injections. D<sup>+</sup> = HCT CMV seropositive donor; D<sup>−</sup> = HCT CMV seronegative donor.
Figure 1S.

76 Patients met inclusion criteria pre-HCT:
50 eligible patients were enrolled at COH, 11 at UMN, 8 at FHCRC and 7 at OSUMC

15 Were excluded from randomization on day 28 post-HCT
14 Met exclusion criteria
5 (33%) Had GVHD ≥ grade 3 and/or received ≥1mg/kg/day corticosteroids
3 (20%) Had ≥ grade 3 AE
2 (13%) Had CMV reactivation
1 (7%) Had disease relapsed
1 (7%) Did not engraft
2 (13%) Received flu vaccine
1 (7%) Died

61 Underwent randomization

32 Were assigned to PepVax arm and received 1st injection
29 Were assigned to placebo arm and received 1st injection

5 Did not receive 2nd injection
- 3 Met exclusion criteria
  1 (20%) Had CMV event
  2 (40%) Had ≥ grade 3 AE
- 2 Were not approached
  1 (20%) Declined
  1 (20%) At physician request

27 Received 2nd injection
lost to follow-up after day 100: 2
32 were included in primary analysis

26 Received 2nd injection
lost to follow-up by day 100*: 1
after day 100: 5
29 were included in primary analysis
Figure 2S.

A

CMV events

HR: 2.28 (95% CI, 0.70-7.42)  
$p = 0.15$

B

CMV events

HR: 1.72 (95% CI, 0.32-8.34)  
$p = 0.53$

HR: 2.88 (95% CI, 0.57-14.57)  
$p = 0.17$
Figure 3S.
Protocol experimental design schema

CMV adults about to undergo 8/8 high resolution HLA donor allele matching hematopoietic stem cell transplant (HCT) for the treatment of a hematologic malignancy

Projected enrollment of **106-115** participants to meet Target: N=98* randomized/vaccinated within 4 years

Informed Consent, Screening Procedures, Eligibility Review

HCT (Day 0)

- Allocation to study arm based on CMV donor status
- CMVPeppVax: N=48
- Placebo: N=48

Randomization
- Allocation communicated to pharmacy “Day 21”
- Pharmacists, biostatistics staff, and monitors will know the randomization status. Remaining study team members and participants will be blinded.

Day 28 Evaluation for Vaccination
- Participants who do not meet the Day 28 vaccine criteria are removed from the study and replaced:
  - Primary engraftment without secondary graft failure
  - Absence of CMV disease and CMV viremia (gPCR ≤ 500 copies/mL)
  - Disease has not relapsed
  - No ongoing ≥ Grade 3 AE
  - Virodansine or equivalent must be ≤1 mg/kg/day for 7 days
- Only participants who receive a Day 28 vaccine are considered "randomized”.

Vaccine Administration
- Vaccine must be administered within 90 minutes of preparation start time.
- 1 ml subcutaneous injection to upper arm

Disease Relapse
- Participants who experience disease relapse are followed for survival only through Day 365

Clinical Care During Trial
- Clinical care will be per SOC except:
  - Vaccines are prohibited to Day 70 post-HCT
  - Prophylactic use of anti-viral therapy is prohibited
  - Prophylactic use of CMV IgG prohibited
  - In vivo T-cell depleting agents are prohibited
  - Virodansine or equivalent must be ≤1 mg/kg/day for 7 days prior to Day 28 and Day 56 vaccine to meet vaccine administration criteria

**Interim analysis for futility when 48 participants reach Day 100; study will continue if CMV reactivation is greater in the Placebo arm vs. the CMVPepVax arm

**Safety review for severe acute GVHD and non-relapse mortality will occur at the 12th, 24th, and 36th participant on the CMVPepVax arm reach Day 100

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