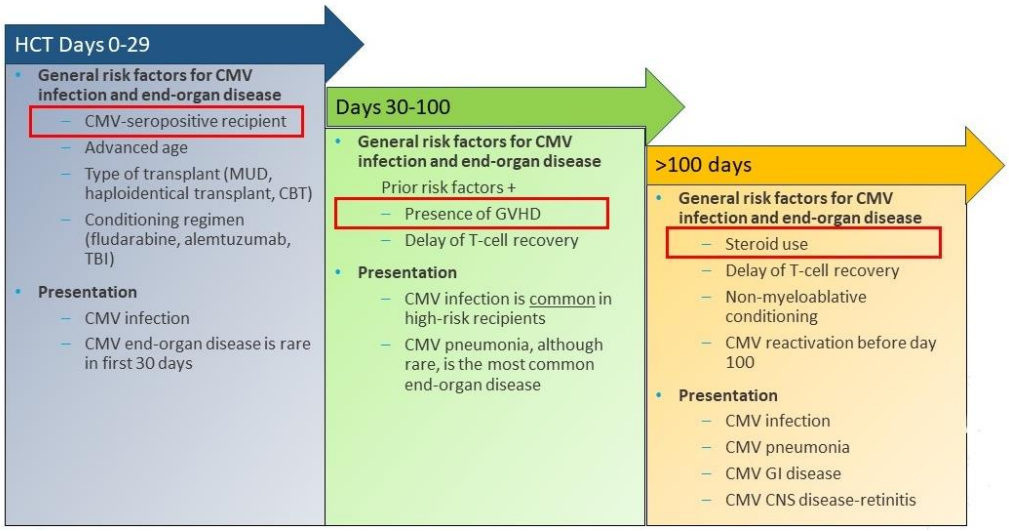
Treating HCT Patients with CMV: A New Era of Therapy

CMV Reactivation in HCT Recipients

After allogeneic HCT, in the absence of prophylaxis against CMV, up to 80% of patients may develop CMV infection or reactivation. The most important risk factor for CMV reactivation is whether the HCT recipient is seropositive for CMV. Other baseline risk factors include whether the donor is seropositive, the type of transplant (matched donor vs haploidentical), and the source of the transplanted stem cells (cord blood). The risk of CMV reactivation is dynamic and may change over time, with different risk factors in the short-term vs. in the longer term (after engraftment or day 30 posttransplant). In particular, in the longer term, patients who develop graft-versus-host disease (GVHD) are at increased risk, in part because GVHD and related complications are treated with low-dose or high-dose steroids depending on the site and extent of GVHD (Figure 1).

Figure 1: Risk Factors for CMV Infection in HCT Recipients



MUD: matched unrelated donor; CBT: cord blood transplantation; TBI: total body irradiation; GI: gastrointestinal; CNS: central nervous system.

Anti-CMV Agents in Clinical Trials or Approved

Several agents have been investigated in clinical trials for the prevention of CMV reactivation or infection after allogeneic HCT, as well as for treatment of infection. These include brincidofovir, maribavir, and letermovir. Brincidofovir did not produce positive results for CMV prevention.[1]

Maribavir

Maribavir demonstrated promising results for prevention of CMV infection in an early trial but failed in a phase 3 trial. However, a phase 2 trial of maribavir in patients with refractory or resistant CMV infections showed response rates of up to 67%.[2] Maribavir is also being developed as a preemptive therapy for patients with early reactivation.[3] Two phase 3 trials of maribavir are underway, one comparing maribavir with valganciclovir and one evaluating maribavir in the treatment of refractory or resistant CMV infections[4,5]; results are expected in 2020 or 2021.

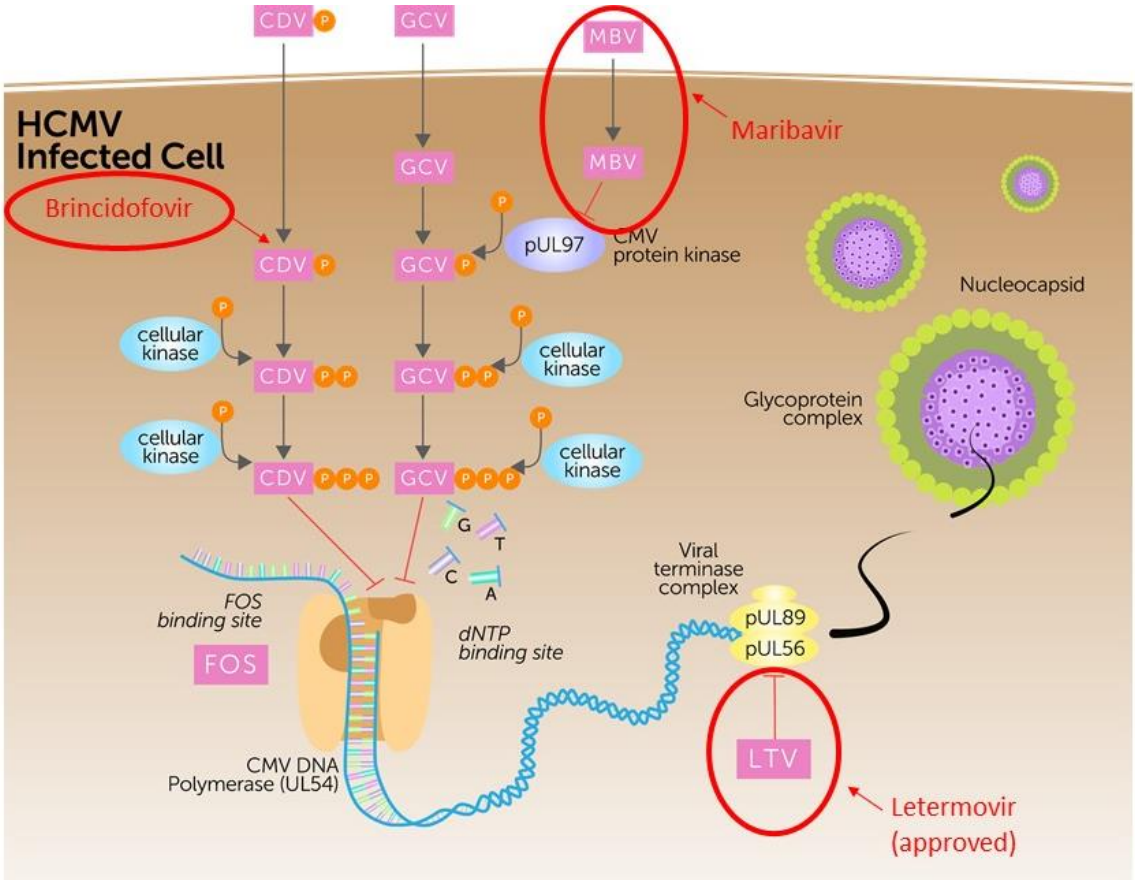
Letermovir

Letermovir was strongly recommended for the prevention of CMV in adults undergoing HCT by the 2017 European Conference on Infections in Leukaemia (ECIL-7).[6] This is the first medication to show efficacy and a good safety profile in the prevention of CMV reactivation in adults who are seropositive for CMV after allogeneic HCT. The A1 recommendation given in the ECIL-7 guidelines was based on data from recently published phase 2 and phase 3 trials.[6-8] Although the European guidelines were the first to make such recommendations, the American Society for Transplantation and Cellular Therapy (ASTCT) is expected to update the corresponding North American guidelines soon.

The Importance of Mechanism of Action

Letermovir has a different mechanism of action than many other agents for treating or preventing CMV infection. Letermovir is a virally directed agent that inhibits the terminase complex of CMV (the UL89, UL56, and UL51 coding sequences) and interferes with the elongation and the packaging of DNA into procapsids, capsids, virions, and virus.[9] By contrast, ganciclovir impacts the UL97 coding sequence, leading to inhibition of DNA polymerase, while foscarnet acts directly on DNA polymerase. The implication is that when resistance to other anti-CMV agents occurs, there is less likelihood for cross-resistance to letermovir. Figure 2 depicts the inhibitory pathways for various anti-CMV agents, providing insight into why letermovir may be less likely to be affected by cross-resistance.

Figure 2: Mechanisms of Action of Approved and Investigational Anti-CMV Agents[9]



Results From the Letermovir Phase 3 Trial[7]

The phase 3 trial of letermovir investigated prevention of CMV reactivation or clinically significant CMV infection after allogeneic HCT in adults seropositive for CMV. Patients could be randomized before engraftment, as prior studies did not identify any letermovir-associated signals of myelosuppression, delayed engraftment, or other impacts on engraftment. Patients were randomized to receive letermovir or placebo for 14 weeks after transplantation, and the dosage was dependent on the patient's immunosuppressive regimen: letermovir doses of 480 mg/day for patients receiving tacrolimus and 240 mg/day for patients receiving cyclosporine. The primary endpoint was the rate of clinically significant CMV infection at week 24. Letermovir prevented more clinically significant CMV infections than placebo at 14 weeks and at 24 weeks, which was 10 weeks after discontinuation of letermovir therapy (Figure 3). The trial also investigated all-cause mortality at week 24 as an exploratory endpoint and found a significant survival advantage at week 24 for patients receiving letermovir; by 48 weeks a nonsignificant numerical advantage for letermovir remained (Figure 4).

Key Outcomes:

Figure 3: Primary Endpoint: Rate of Clinically Significant CMV Infection

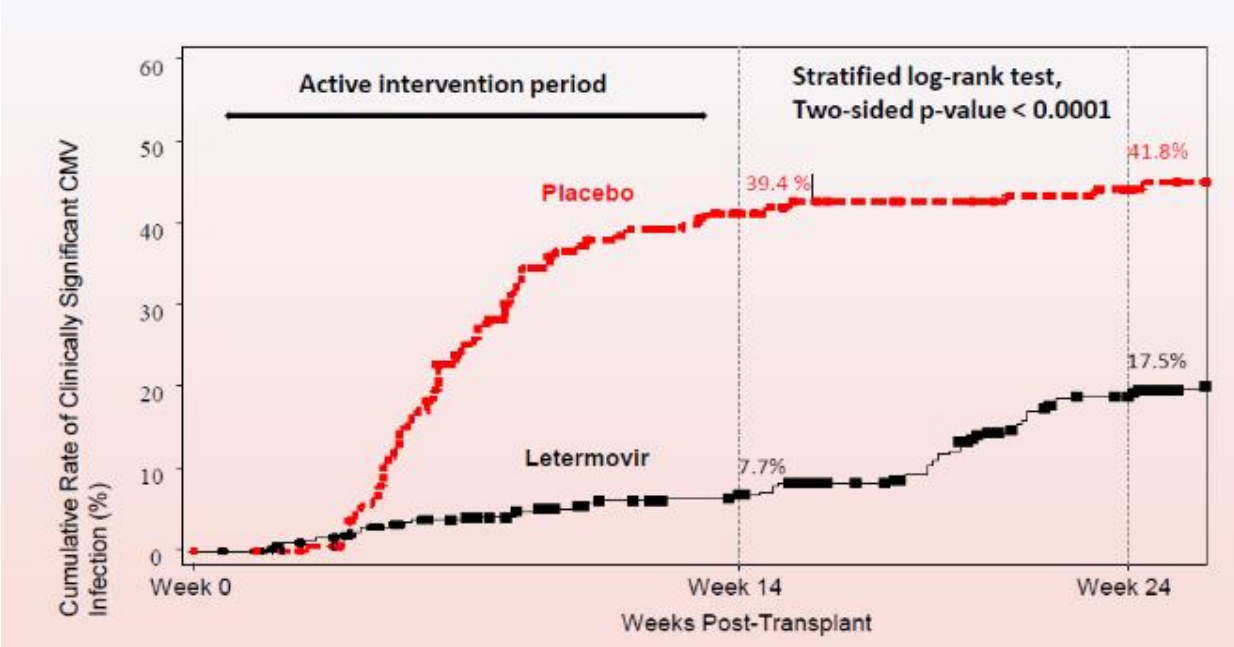
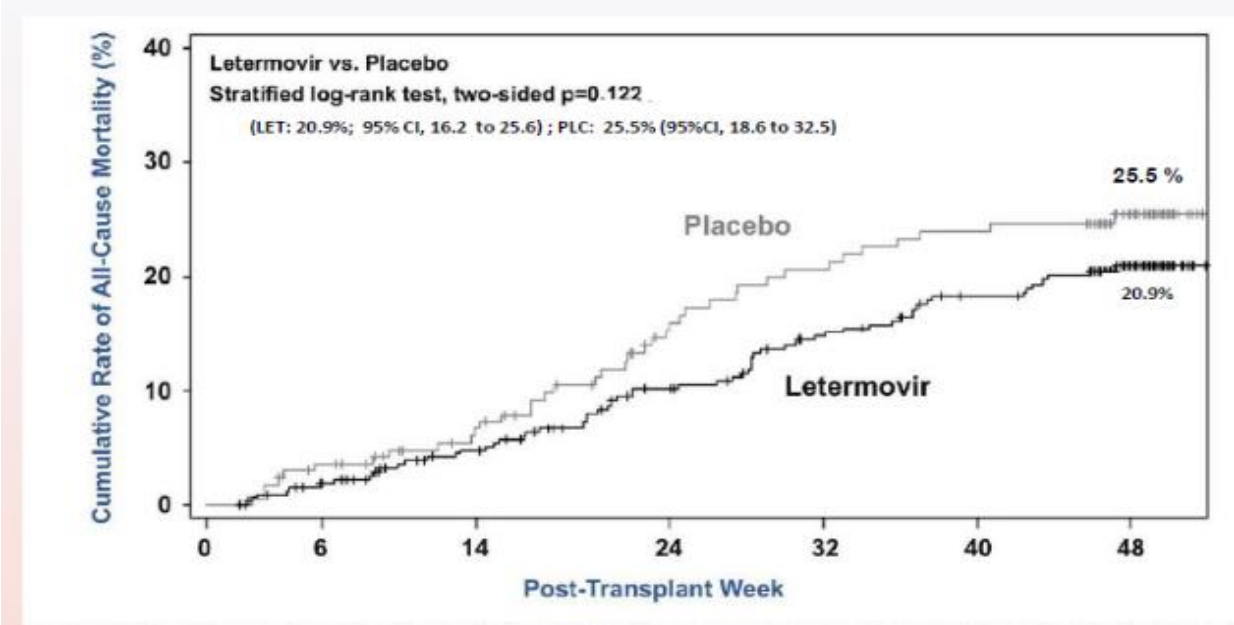


Figure 4: Exploratory Endpoint: All-Cause Mortality Through Week 48



Real-World Experience with Letermovir

Dr. Chemaly serves as a Professor of Medicine at MD Anderson Cancer Center in Houston, TX as well as faculty on this CME activity. His center is probably one of the first to use letermovir to prevent CMV reactivation after allogeneic HCT. Letermovir is started at day +5 following transplant in patients who are CMV-seropositive. This strategy was initiated in March 2018.

Data were reviewed for a total of 129 HCT recipients, most of whom had received letermovir. Findings were consistent with those observed in the phase 3 trial: less CMV reactivation, fewer CMV-related complications, and reduced emergence of refractory/resistant CMV. A final point of emphasis is the importance of familiarity with the letermovir safety profile as elucidated in the phase 3 trial, including slightly increased rates of tachycardia and atrial fibrillation among patients receiving letermovir.

References

1. Marty FM, Winston DJ, Chemaly RF, et al; SUPPRESS Trial Clinical Study Group. A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2019;25:369-381.

2. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for refractory or resistant cytomegalovirus infections in hematopoietic-cell or solid-organ transplant recipients: a randomized, dose-ranging, couble-blind, phase 2 study. *Clin Infect Dis.* 2019;68:1255-1264.

3. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for preemptive treatment of cytomegalovirus reactivation. *N Engl J Med.* 2019;381(12):1136-1147.

4. Clinicaltrials.gov. NCT02931539. Efficacy and Safety Study of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients With Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment With Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir. 2019;. https://clinicaltrials.gov/ct2/show/NCT02931539. Updated July 23, 2019. Accessed February 4, 2020.

5. Clinicaltrials.gov. NCT02927067. Efficacy and Safety Study of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients. 2019; Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02927067. Updated March 11, 2019. Accessed February 4, 2020.

6. Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis.* 2019;19:e260-e272.

7. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med.* 2017;377:2433-2444.

8. Chemaly RF, Ullmann AJ, Stoelben S, et al; AIC246 Study Team. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. *N Engl J Med.* 2014;370:1781-1789.

9. Foolad F, Aitken SL, Chemaly RF. Letermovir for the prevention of cytomegalovirus infection in adult cytomegalovirus-seropositive hematopoietic stem cell transplant recipients. *Expert Rev Clin Pharmacol.* 2018;11:931-941.