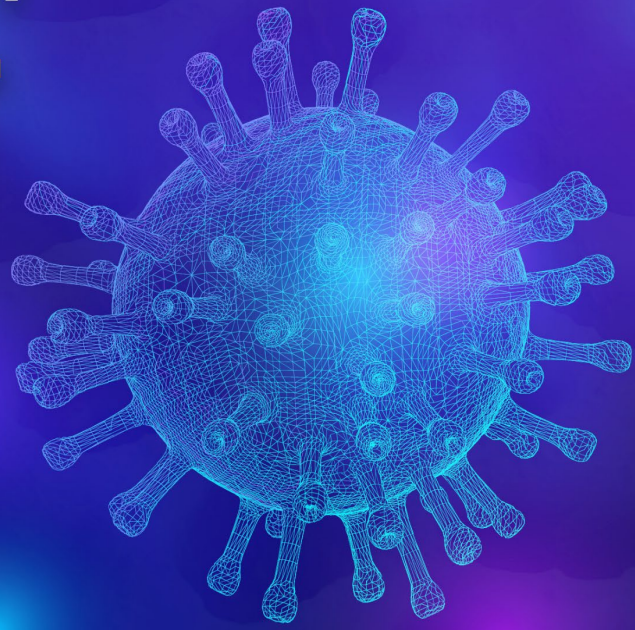
CLINICAL FORUM®

# A BALANCING ACT: Safety and Success in CMV MANAGEMENT for HCT Patients



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# Disclosures

**Genovefa Papanicolaou, MD,** has relevant financial relationship(s) with Genentech, Regeneron, Symbio *(Consultant)*; Merck *(Advisor)*; Advarra, Merck, Takeda *(Grant/Research Support)*; Advarra, Allovir, Trellis Bioscience *(Independent Contractor)*.

**Roy F. Chemaly, MD, MPH, FACP, FIDSA, CMQ,** has relevant financial relationship(s) with Adagio Therapeutics, ADMA Biologics, AiCuris, Ansun Pharmaceuticals, Astellas, InflaRX, Janssen, Karius, Merck, Moderna, Oxford Immunotec, Partner Therapeutics, Roche/Genentech, Shinogi, Takeda, Tether *(Consultant)*; AiCuris, Ansun Pharmaceuticals, Eurofins-Viracor, Genentech, Karius, Oxford Immunotec, Merck, Takeda *(Researcher)*.

All of the relevant financial relationships listed for these individuals have been mitigated according to the Medical College of Wisconsin policies.

CLINICAL FORUM

# CMV Prevention and Treatment in HCT Patients

**Genovefa Papanicolaou, MD**
*Director,* Infectious Disease Service
Memorial Sloan Kettering Cancer Center
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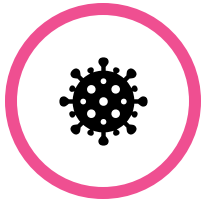
Weill Cornell Medical College, Cornell University
New York, NY

# What is Cytomegalovirus?



**Member of the beta herpesvirus group**

**Establishes life-long latency after initial infection**

**Frequently observed opportunistic pathogen in transplant recipients**

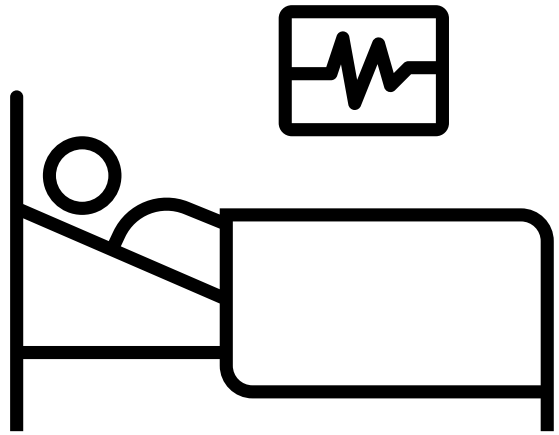
**CMV infection may be asymptomatic in transplant patients**

**Most transplant patients get prophylactic or preemptive therapy to prevent CMV disease**

CMV, cytomegalovirus

Hakki M, et al. *Transplant Cell Ther.* 2021;27(9):707-719; Boeckh M, et al. *Blood.* 2009;113(23):5711-5719; Ljungman P, et al. *Lancet Infect Dis.* 2019;19(8):e260-e272.

# Consequences of CMV in HCT



**Higher complication risk**

**Tissue invasive disease (GI tract, lungs, liver, CNS, and retina)**

**Opportunistic co-infections (viral, bacterial, and fungal)**

**Higher risk of acute GvHD in recipients of T-cell depleted grafts**

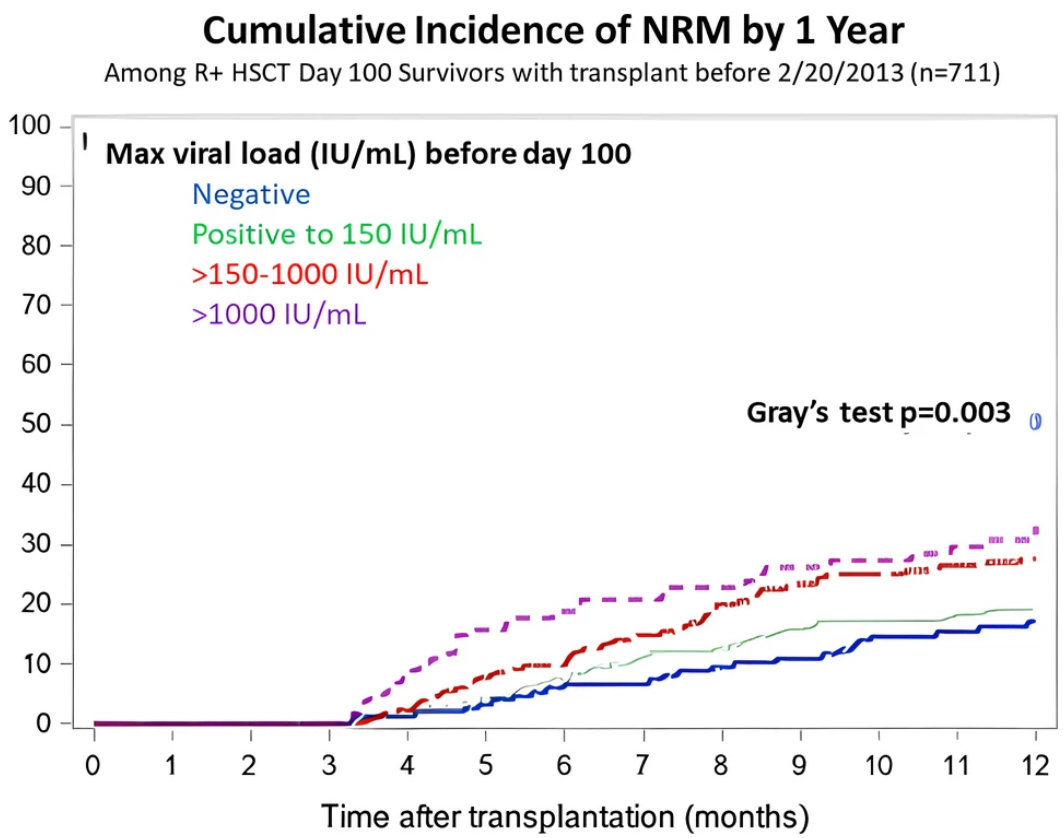
**Higher risk of chronic GvHD**

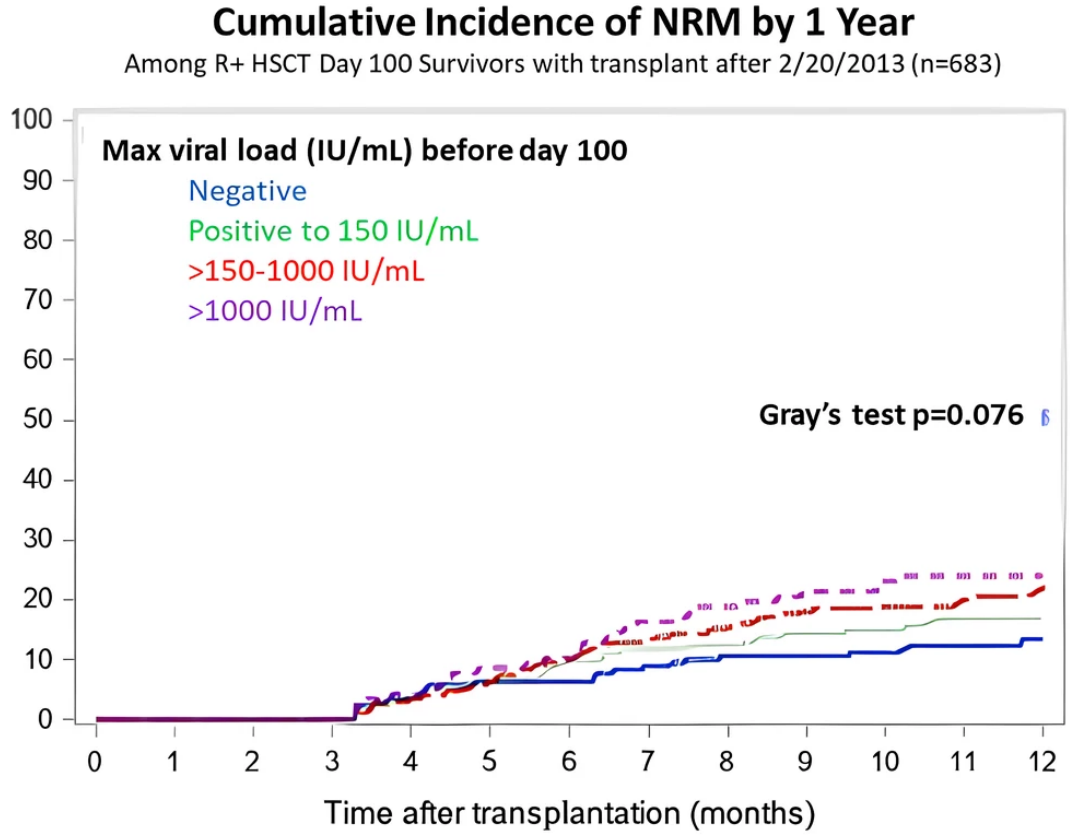
**Increased non-relapse and overall mortality**

GvHD, graft-versus-host disease; HCT, hematopoietic cell transplant

Hakki M, et al. *Transplant Cell Ther.* 2021;27(9):707-719; Boeckh M, et al. *Blood.* 2009;113(23):5711-5719; Ljungman P, et al. *Lancet Infect Dis.* 2019;19(8):e260-e272.

# CMV Viral Load Continues to be a Strong Predictor of 1-Year Non-Relapse Mortality Post-HCT




NRM, non-relapse mortality

Sadowski-Klasa A, Zamora D, Xie H, et al. Poster A161 EBMT 2024

# Risk Factors for CMV in HCT Patients

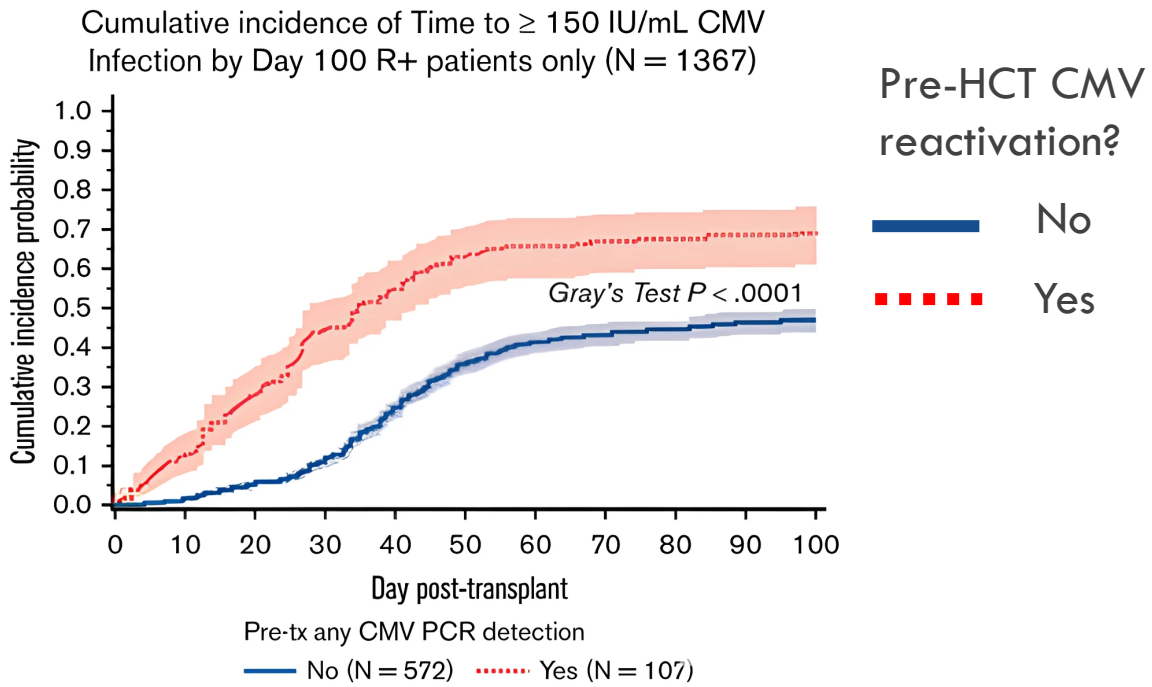
| Donor/Recipient CMV Serostatus | Transplant Type | Immuno-suppression | GvHD | Age |
|---|---|---|---|---|
| Highest risk: D-/R+ | • Mismatched, unrelated, or haploidentical<br>• Cord blood transplant<br>• T-cell depletion* | • Prednisone use ≥1 mg/kg/day<br>• Post-HCT cyclophosphamide<br>• Lymphopenia | Acute GvHD | Advanced Age |

Hakki M, et al. *Transplant Cell Ther.* 2021;27(9):707-719.

# CMV Reactivation Pre-Transplant is a Risk Factor for CMV Post-HCT

Post-Transplant

**Preemptive Antiviral Therapy (N=1367)**

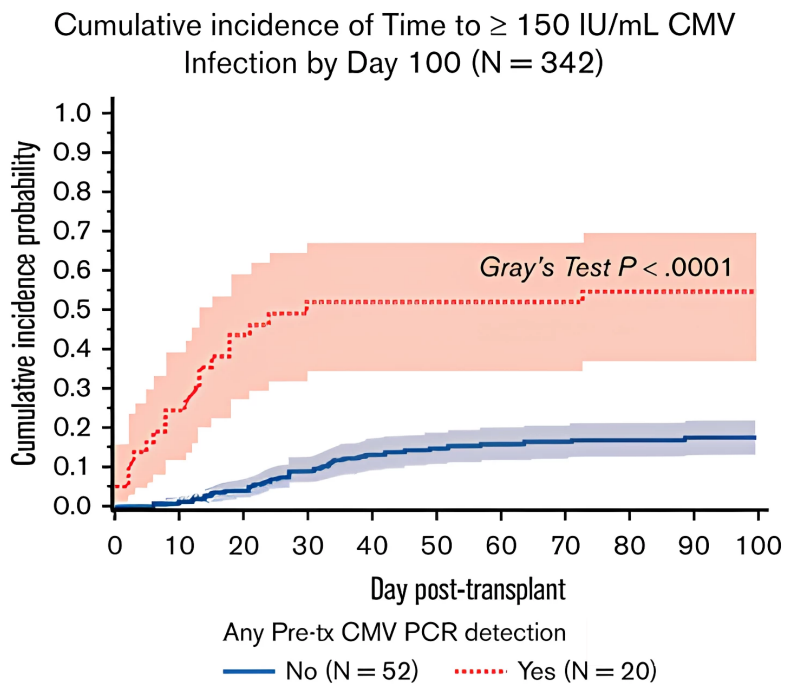



Pre-HCT CMV reactivation?

No

Yes

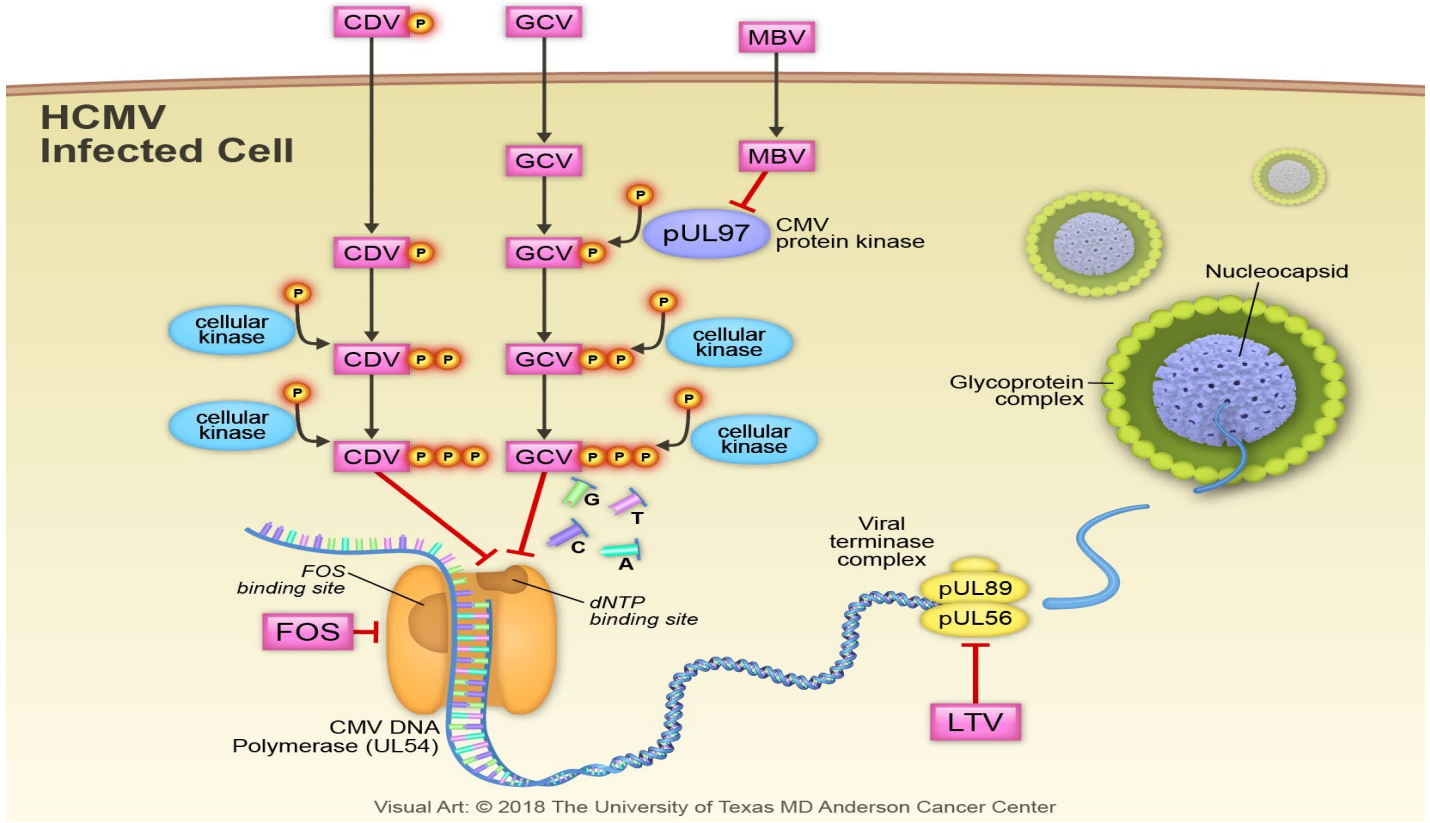
**Letermovir Prophylaxis (N=342)**




**Patients with pre-HCT CMV reactivation had an ~5-fold risk of post-HCT CMV reactivation, however, the risk was lower in patients who cleared their pre-HCT CMV before HCT.**

Zamora D, et al. *Blood Adv*. 2024;8(17):4568-4580.

# CMV Antivirals




**DNA Polymerase Inhibitors: Treatment**

- Ganciclovir/Valganciclovir (IV/PO)
- Foscarnet (IV)
- Cidofovir (IV)
- Brincidofocir (IV, in Phase 2)*

**CMV-specific pathways downstream of DNA polymerase**

- Letermovir (Prophylaxis)
- Maribavir (Treatment)

HCMV, human cytomegalovirus; CDV, cidofovir; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir

Foolad F, et al. *Expert Rev Clin Pharmacol.* 2018;11(10):931-941.

*NCT04706923

# Prophylaxis versus Preemptive Therapy

| | PROPHYLAXIS | PRE-EMPTIVE THERAPY |
|---|---|---|
| **Description** | ▪ Antivirals for all patients at risk prior to the onset of CMV infection | ▪ Routine monitoring for CMV infection<br>▪ Treatment upon detection of asymptomatic CMV infection |
| **Pros** | ▪ Can prevent direct and indirect effects<br>▪ Viral load (VL) monitoring not required (if agent is effective)<br>▪ CMV disease may occur without detectable CMV DNA<br>▪ **Potential impact on all-cause mortality** | ▪ Targets patients at highest risk<br>▪ Minimizes overtreatment and toxicity<br>▪ May improve CMV-specific immune reconstitution |
| **Cons** | ▪ Potential for overtreatment/added cost<br>▪ Potential for unnecessary exposure to drug toxicity (reduced with letermovir; GCV: hematologic; foscarnet: renal)<br>▪ **May delay CMV-specific immune reconstitution** | ▪ Potential to miss cases of CMV disease not preceded by DNAemia or antigenemia<br>▪ Relies on availability of CMV testing<br>▪ Concern for drug resistance<br>▪ **Concern for survival disadvantage** |

Yahav D, et al. *Eur J Cancer*. 2009;45(18):3131-3148; Milano F, et al. *Blood*. 2011;118(20):5689-5696; Ljungman P, et al. *Hematol Oncol Clin North Am*. 2011;25(1):151-169.

# Resistance to CMV Antivirals

| | Maribavir | Valganciclovir |
|---|---|---|
| **Preemptive Therapy** (First line) | 10% Median 56 days | (2.5%) Median 90 days |
| **Refractory** | 26% Median 56 days | |

Rebound CMV DNAemia during maribavir treatment is usually due to resistance.

Chou S, et al. *J Infect Dis.* 2024:jiae469. https://doi.org/10.1093/infdis/jiae469; Chou S, et al. *J Infect Dis*. 2024;229(2):413-421.

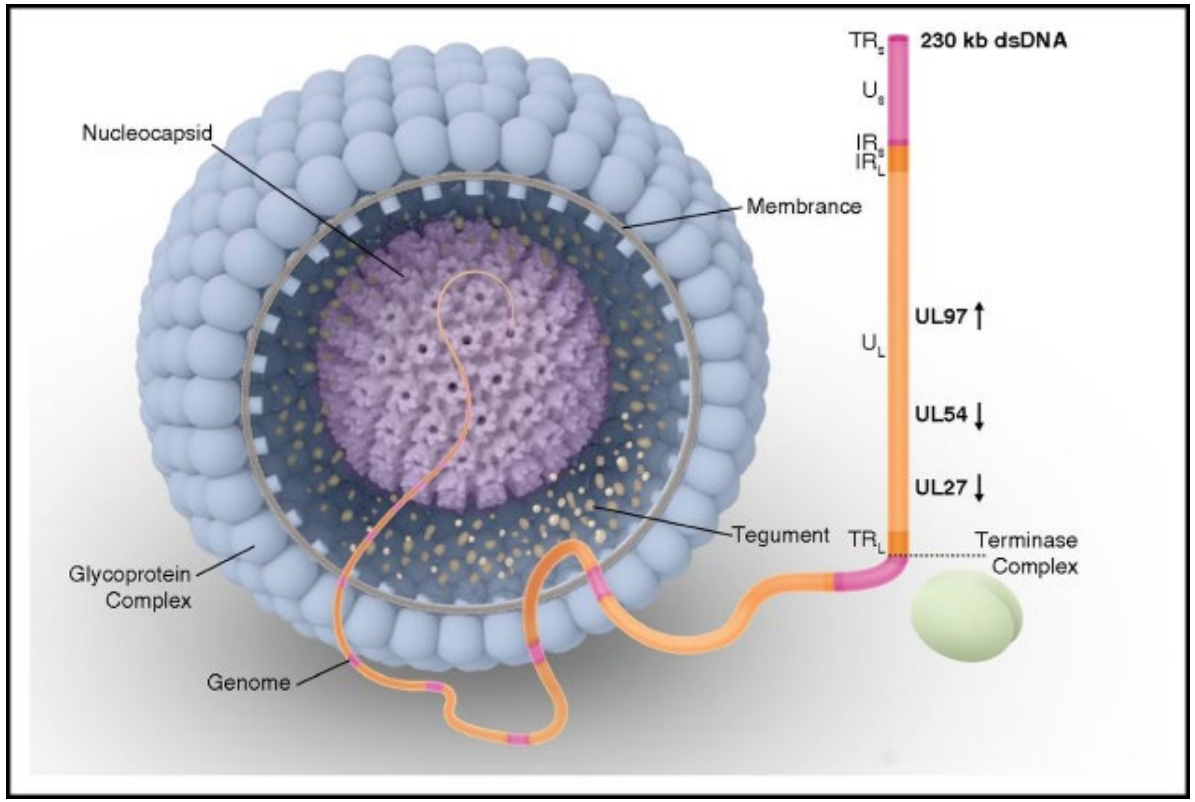
# Letermovir

## Mechanism of Action

- CMV replication involves cleaving of concatemeric genomic DNA and packaging of each genome into preformed virus capsids by the CMV terminase complex (UL56, UL89)
- Letermovir inhibits the terminase complex by binding to UL56

## Use

- Approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic HCT
- Approved for prophylaxis in high-risk kidney transplant recipients (Donor+/Recipient-)
- Not myelosuppressive or nephrotoxic

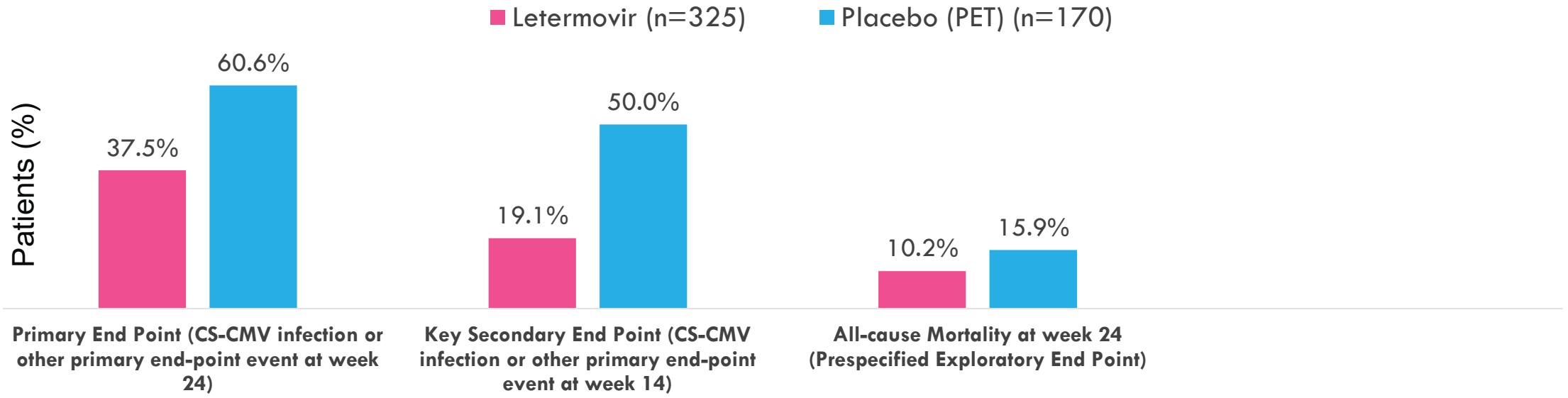



El Chaer F, et al. *Blood*. 2016;128(23):2624-2636.

## Protocol 01

# Phase 3: Letermovir Prophylaxis for CMV in R+ HSCT

- Randomized, placebo controlled, double-blind, multi-center superiority study of adult CMV R+ HSCT
- 67 centers, 20 countries
- Randomized 2:1 to letermovir or placebo, PO or IV, through week 14 (day 100) after transplantation




**CS-CMV Infection** (clinically significant CMV infection) = CMV disease or CMV viremia leading to preemptive treatment

**Primary End Point** = Proportion of patients with CS-CMV infection through week 24 after transplantation among patients without detectable CMV DNA at randomization (primary efficacy population); patients who discontinued the trial for any reason before week 24 (day 168) after transplantation or who had missing data at week 24 were imputed as having a primary end-point event

**Key Secondary Endpoint** = Proportion of patients with CS-CMV infection through week 14 after transplantation

**Prespecified Exploratory Endpoint** = All cause mortality

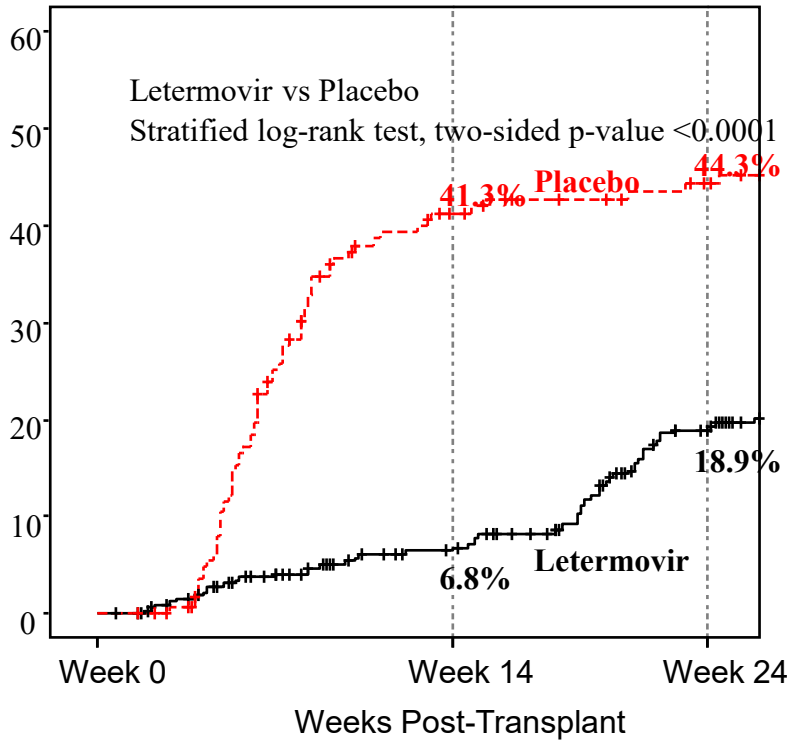
Marty FM, et al. *N Engl J Med.* 2017;377:2433-2444.

# Background: Risk of CMV Reactivation After Completion of 100 Days of Letermovir Prophylaxis

**Rational for Protocol 40**

- LET was superior to placebo in preventing CS-CMVi through week 24 (~200 days) post-transplant when administered until week 14 (~100 days) post-transplant in Protocol 001.
- There was an increased incidence of CS-CMVi after treatment ended between weeks 14 and 24 post-transplant.
- Post-hoc analyses indicated that GvHD after randomization, concomitant steroid use, and baseline high-risk stratum (as defined in Protocol 001) were associated with developing CS-CMVi following completion of 100 days of LET.

**P001: Time to CS-CMVi through week 24 post-transplant**




Number of Subjects at Risk (FAS)

| | | | |
|---|---|---|---|
| Letermovir | 325 | 270 | 212 |
| Placebo | 170 | 85 | 70 |

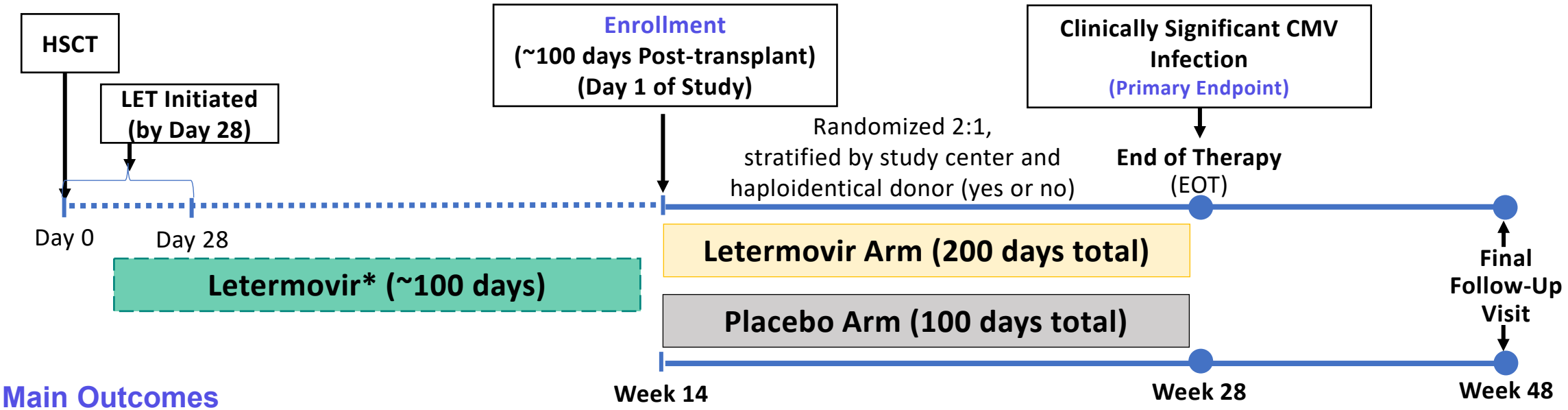
Russo D, et al. *Lancet Haematol.* 2024;11(2):e127-e135.
Marty FM, et al. *N Engl J Med.* 2017:377(25):2433-2444.

## Protocol 40

# Phase 3 Study of Extended Duration LET in High-Risk HSCT

## R+ HSCT at Risk of CMV Infection and/or Disease Beyond Day 100

- Randomized, placebo-controlled, double-blinded, superiority trial of adult CMV R+ HSCT
- 32 participating sites, 6 countries (France, Germany, Italy, Japan, UK, USA); June 21, 2019 and March 16, 2022
- 220 R+ HSCT patients randomized; 181 completed treatment (efficacy population); 218 received ≥1 dose (safety population)




### Main Outcomes

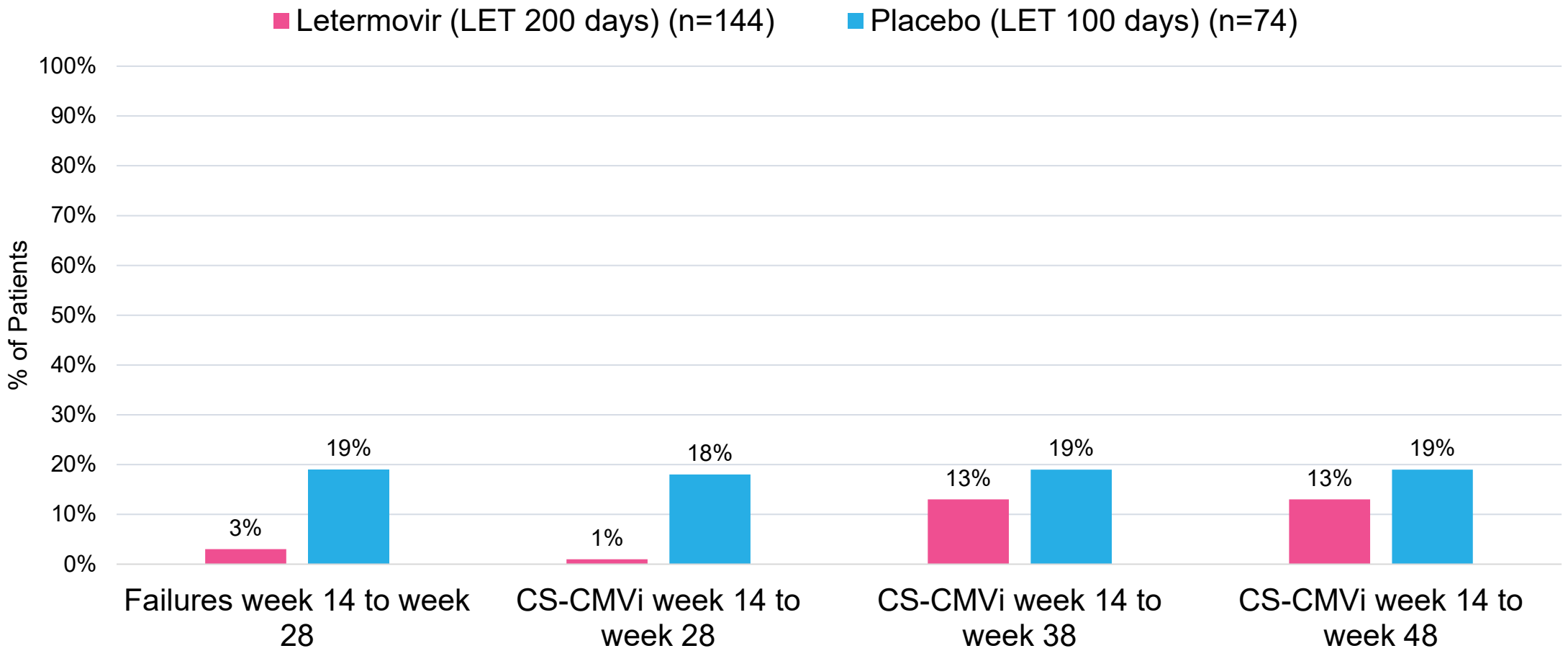
- **Primary endpoint**: Proportion with CS-CMV infection from randomization (week 14) to end of prophylaxis at week 28
- **Secondary endpoints included:** Proportion with CS-CMV infection from randomization to week 38 and to week 48; time to onset of CS-CMV infection; proportion with PET; proportion with all-cause mortality
- **Safety and tolerability**: Adverse events (AEs) and discontinuations due to AEs

Russo D, et al. *Lancet Haematol.* 2024;11(2):e127-e135.

## Protocol 40

# Phase 3 Study of Extended Duration LET in High-Risk HSCT

## R+ HSCT at Risk of CMV Infection and/or Disease Beyond Day 100

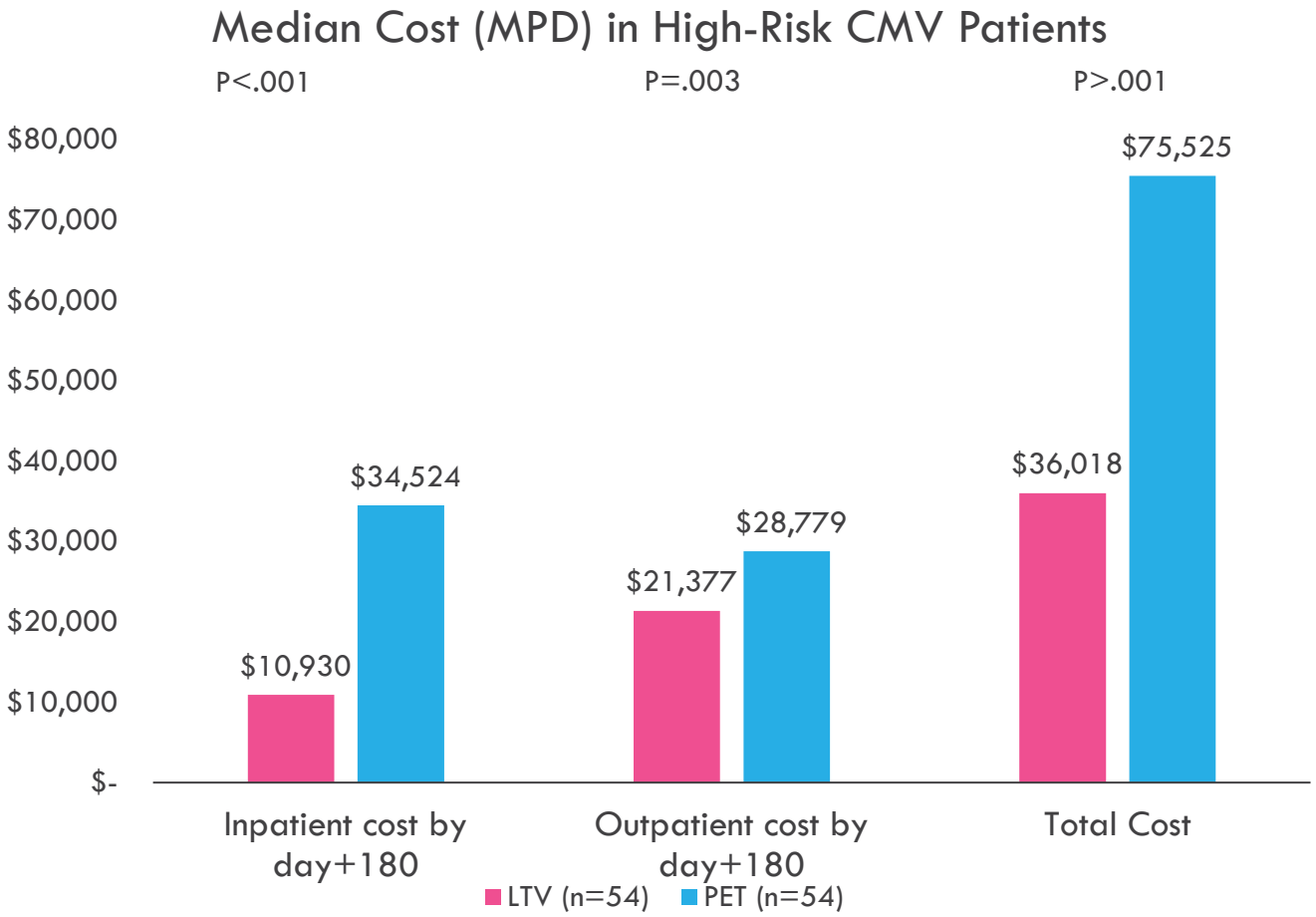



LET, letermovir; PBO, placebo; PET, pre-emptive therapy

For the primary endpoint, an observed failure approach was used to handle missing data values, in which failure was defined as all participants who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viremia. The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

Russo D, et al. *Lancet Haematol.* 2024;11(2):e127-e135.

# Impact of Letermovir Extended Prophylaxis on Total Cost by Day 180




| | LTV N=54 | PET N=54 | *P* Value |
|---|---|---|---|
| **LTV duration, days, median (IQR)** | 157 (110, 174) | | |
| **CS-CMV infection, N (%)** | 11 (20.4) | 38 (70.4) | < .001 |
| **Patients with ≥1 CMV-related readmissions (%)** | 3 (5.6) | 18 (33.3) | < .001 |
| **Total outpatient visits by day+180** | 36 (25, 44) | 42 (29, 54) | .032 |

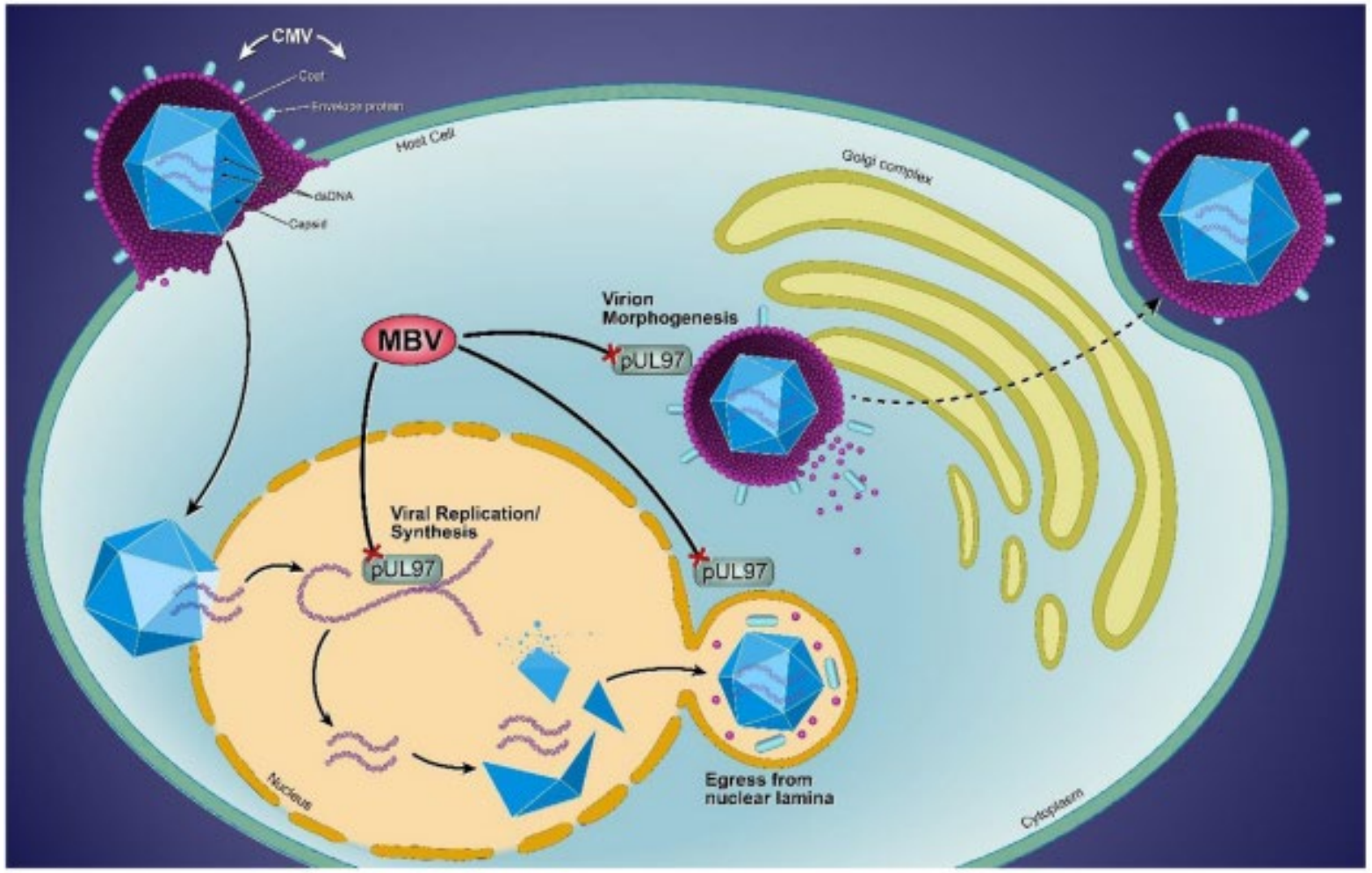
MPD, Medicare Proportional Dollars; LTV, letermovir; PET, pre-emptive therapy

Tan CA, et al. *Transplant Cell Ther.* 2024;30(8):792.

# Maribavir

**Mechanism of Action**

- Inhibits UL97 viral protein kinase
  - Inhibits viral encapsidation
  - Inhibits nuclear egress of viral particles
- Maribavir does not affect the UL54 CMV DNA polymerase




Sun K, et al. *Clin Transl Sci*. 2024;17(1):e13696.
Khawaja F, et al. *Clin Microbiol Infect*. 2023;29(1):44-50.

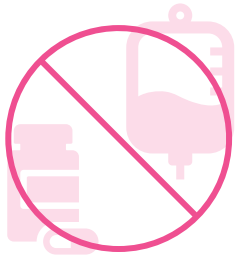
# Treatment: Maribavir

Approved for the treatment of post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet

**Orally bioavailable**

**Not myelosuppressive or nephrotoxic**

**Main side effect is taste disturbance**



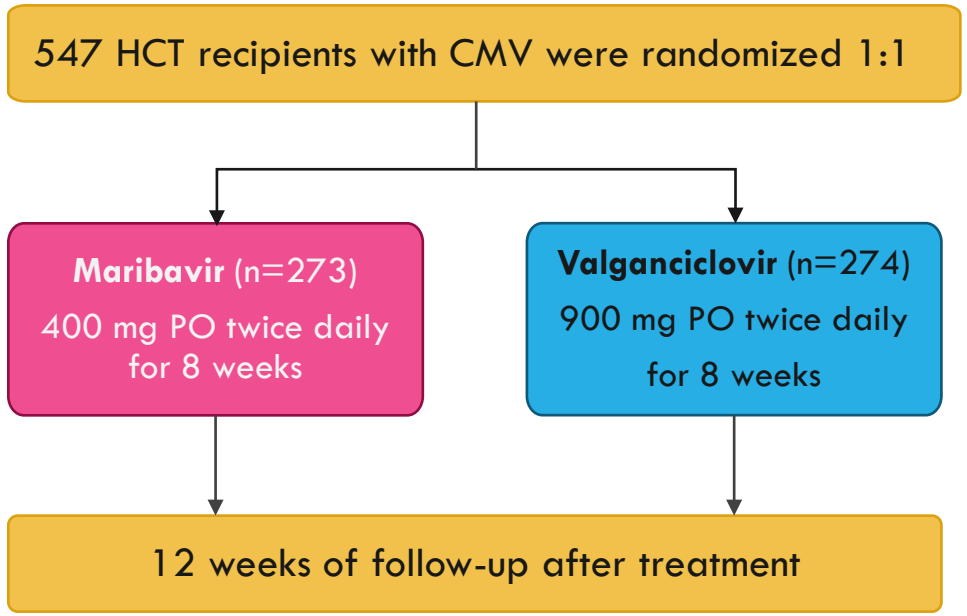
**Should not be used in combination with ganciclovir or valganciclovir**

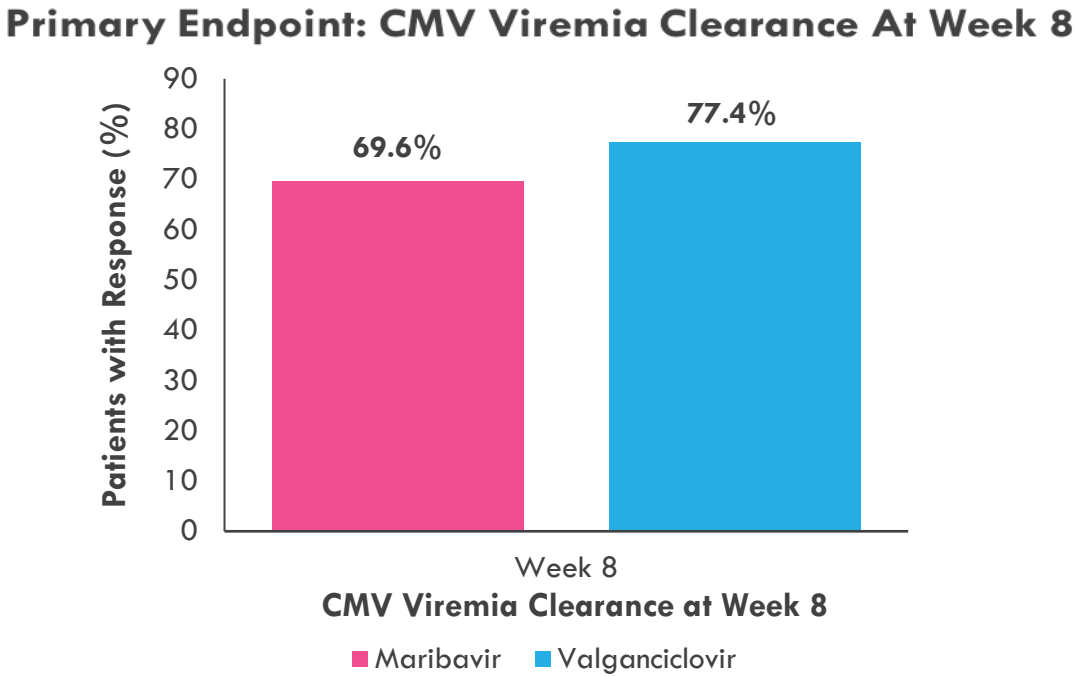
**Should not be used in case of encephalitis or retinitis**

**Inhibits CYP3A4: tacrolimus dose may need to be lowered**

Sun K, et al. *Clin Transl Sci*. 2024;17(1):e13696.

# Phase 3 AURORA Trial for Maribavir Preemptive Treatment of CMV in HCT




Maribavir did not meet its primary endpoint of non-inferiority versus valganciclovir based on a prespecified non-inferiority margin of 7% (maribavir 69.6% versus valganciclovir 77.4%; adjusted difference, -7.7%; 95% CI: -14.98, -0.36)

HCT, hematopoietic cell transplant

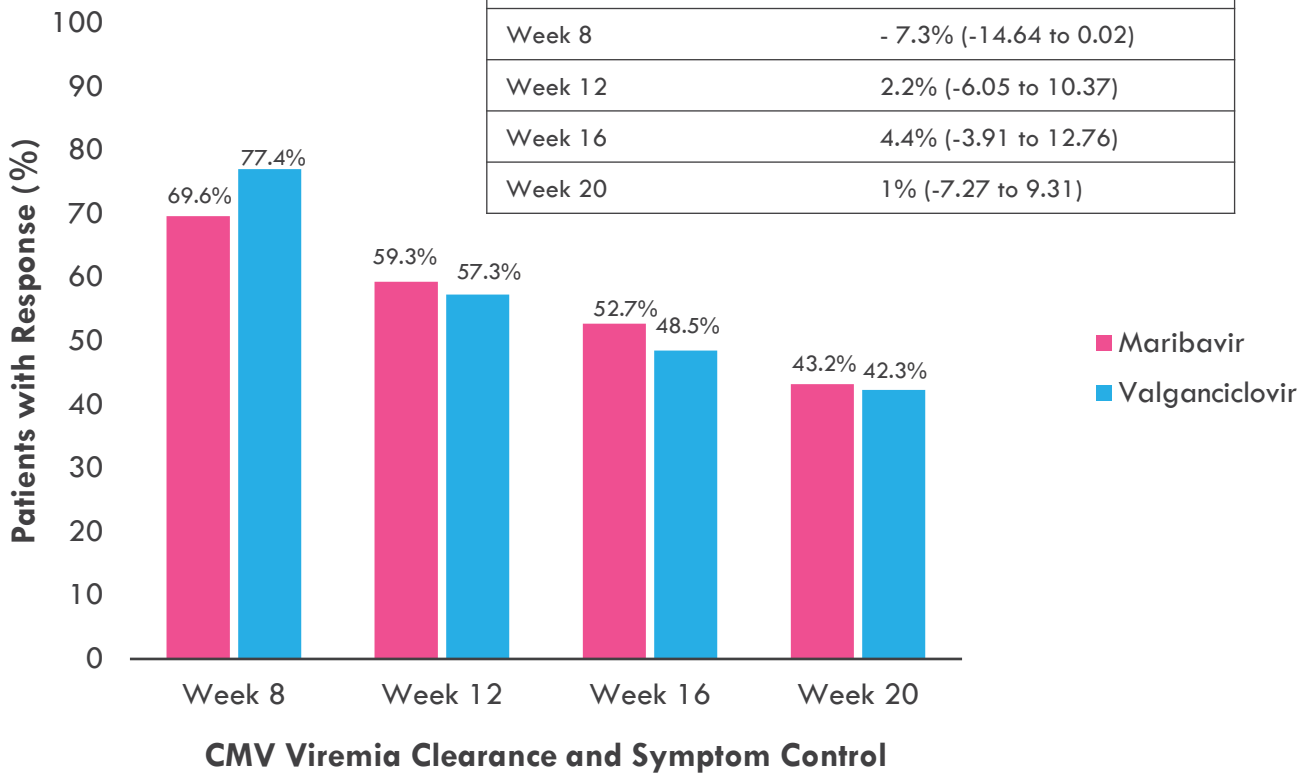
Papanicolaou GA, et al. *Clin Infect Dis*. 2024;78(3):562-572.

# Phase 3 AURORA Trial for Maribavir Preemptive Treatment of CMV in HCT

- A sustained maintenance effect was observed with maribavir during post-treatment evaluations at week 12 and week 20.
- Reaffirmed maribavir's favorable safety profile compared to valganciclovir.
  - Treatment-emergent neutropenia was 21.2% for maribavir versus 63.5% for valganciclovir.
  - Rate of premature discontinuation of therapy due to neutropenia was 4% for maribavir versus 17.5% for valganciclovir.

## Secondary Endpoint: Confirmed Viremia Clearance and Symptom Control

| | Adjusted difference (95% CI) |
|---|---|
| Week 8 | - 7.3% (-14.64 to 0.02) |
| Week 12 | 2.2% (-6.05 to 10.37) |
| Week 16 | 4.4% (-3.91 to 12.76) |
| Week 20 | 1% (-7.27 to 9.31) |




Papanicolaou GA, et al. *Clin Infect Dis*. 2024;78(3):562-572.

# CMV Treatment and Prophylaxis in HCT: ASTCT Guideline Recommendations

| Agent | CMV target | Route of Administration | Dose per Indication* | | | Major Toxicities†,§ | Significant Drug Interactions | CMV genes involved in resistance | Activity against other herpes viruses |
|---|---|---|---|---|---|---|---|---|---|
| | | | Treatment† | | | | | | |
| | | | Prophylaxis | Induction | Maintenance‖ | | | | |
| Ganciclovir | DNA polymerase (UL54) | IV | NA¶ | 5 mg/kg bid | 5 mg/kg/day | Cytopenias | None | kinase (UL97), UL54 | HSV1&2, VZV, HHV-6 |
| Valganciclovir | UL54 | Oral | NA¶ | 900 mg bid# 7 × BSA × GFR bid** | 900 mg/day# 7 × BSA × GFR/day** | Same as ganciclovir | None | UL97, UL54 | HSV1&2, VZV, HHV-6 |
| Foscarnet | UL54 | IV | NA¶ | 90 mg/kg q 12 hrs or 60 mg/kg q 8 hours | 90 mg/kg/day | Nephrotoxicity, electrolyte wasting, gastrointestinal | None | UL54 | HSV1&2, VZV, HHV-6 |
| Cidofovir | UL54 | IV | NA¶ | 5 mg/kg/week | 5 mg/kg every other week | Nephrotoxicity, neutropenia, headache, uveitis/iritis, diarrhea, ocular hypotony | None | UL54 | HSV1&2, VZV, HHV-6 |
| Letermovir | Terminase complex (UL 56,51,89) | IV, oral | 480 mg/day††,‡‡,§§ | NA¶ | NA¶ | Nausea | Cyclosporine, voriconazole, tacrolimus, sirolimus, statins, ergot alkaloids | UL56‖‖ | No |

BSA, body surface area; GFR, glomerular filtration rate; BID, twice daily; q, every; NA, not applicable; mg, milligram; kg, kilogram

* All agents require dose adjustment in the setting of renal dysfunction. Loading doses of ganciclovir and valganciclovir should be administered even in patients with renal impairment.

† Preemptive therapy or therapy for disease.

‖ Dosing may also be used for secondary prophylaxis.

¶ NA = the agent is not approved for, or typically used for, the indication.

†† Approved only for primary prophylaxis in adult CMV seropositive HCT recipients; not approved for pediatric patients.‡‡Reduce dose to 240 mg/day if coadministered with cyclosporine.

§§ Dose is same for primary and secondary prophylaxis.

Hakki M, et al. *Transplant Cell Ther*. 2021;27(9):707-719.

# ASTCT Guideline Recommendation Update on CMV Treatment and Prophylaxis in HCT

**ID-SIG Track**

**Date:** Thursday, February 13, 2025
**Location:** Room 312 (HCC)
**Time:** 10:48 AM to 11:06 AM

## Topics

- **Optimizing Duration of Prophylaxis**
- **Pediatric Dosing for Letermovir**
- **New Treatment Options**

# CMV Challenges: Refractory and Resistant Disease

**Roy F. Chemaly, MD, MPH, FACP, FIDSA, CMQ**
*Professor* and *Chair*
*G. P. Bodey, Sr. Distinguished Professorship,* Infectious Diseases
*Director*, Clinical Virology Research
Department of ID/IC/EH
UT MD Anderson Cancer Center
Houston, TX

# Revised Definitions of Refractoriness

**We consolidated the 2 definitions of refractory and probable refractory CMV infection into one category:**

**Refractory CMV Infection:** CMV viremia (DNAemia or antigenemia) that increases (ie, **>1 $\log_{10}$ increase in CMV DNA levels in the same blood compartment from the peak viral load** as measured in the same laboratory and/or with the same commercial assay) **OR** persists (≤1 $\log_{10}$ increase or decrease in CMV DNA levels) after at least 2 weeks of appropriate antiviral therapy

**Refractory CMV End-organ Disease:** Worsening in signs and symptoms or progression into end-organ disease **OR** lack of improvement in signs and symptoms after at least 2 weeks of appropriately dosed antiviral therapy

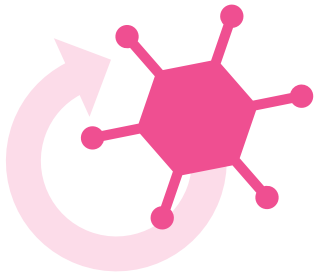
**Resistant CMV Infection:** Refractory CMV infection ***in addition to*** viral genetic alteration that decreases susceptibility to one or more antiviral drugs

Ljungman P, et al. *Clin Infect Dis.* 2024;79(3):787-794.

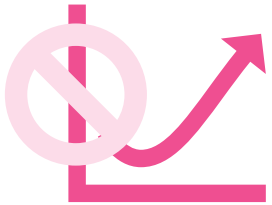
# R/R CMV Risk Factors

**Prolonged antiviral therapy**

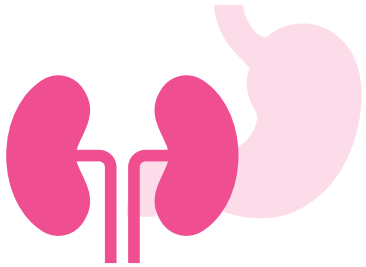
**Previous antiviral drug exposure**



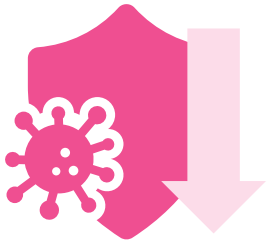
**Recurrent infection**



**Inadequate antiviral absorption or drug conversion**



**Type of transplant**



**Immunosuppressive therapy**

**Independent Predictors of R/R CMVi**

Type of Transplant
- MRD
- MUD/MMUD
- Haploidentical
- Cord

Donor CMV+ Status

Letermovir Primary Prophylaxis

Chemaly RF, et al. *Clin Infect Dis*. 2019;68(8):1420-1426; Yong MK, et al. *Transplant Cell Ther*. 2021;27(12):957-967; Hakki M, et al. *Transplant Cell Ther.* 2021;27(9):707-719.

# Overcoming Limitations of Current Therapies

## Summary of Existing CMV Antivirals

- Existing CMV antivirals include ganciclovir, valganciclovir, foscarnet, or cidofovir
- Each pose potential serious toxicities that may lead to treatment failure/discontinuation
- Common MOA may predispose them to cross-resistance
- Ganciclovir, foscarnet, and cidofovir require IV administration

**There is an urgent need for efficacious and safer therapeutic option with different MOAs than existing antivirals**

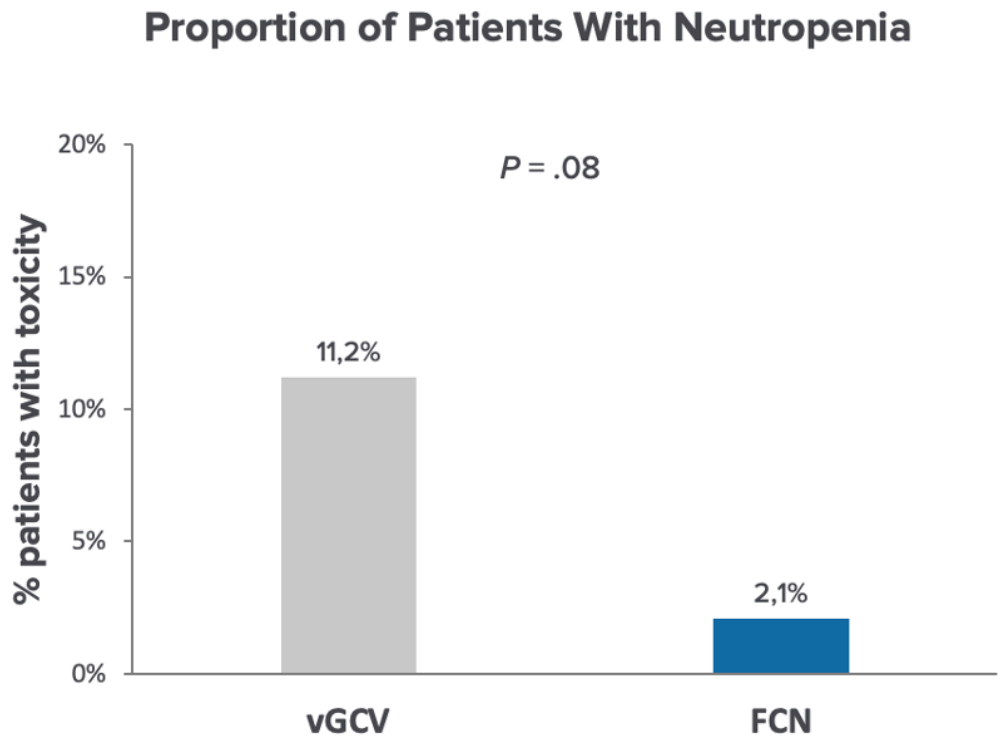
CMV, cytomegalovirus; FDA, Food and Drug Administration; MOA, mechanism of action

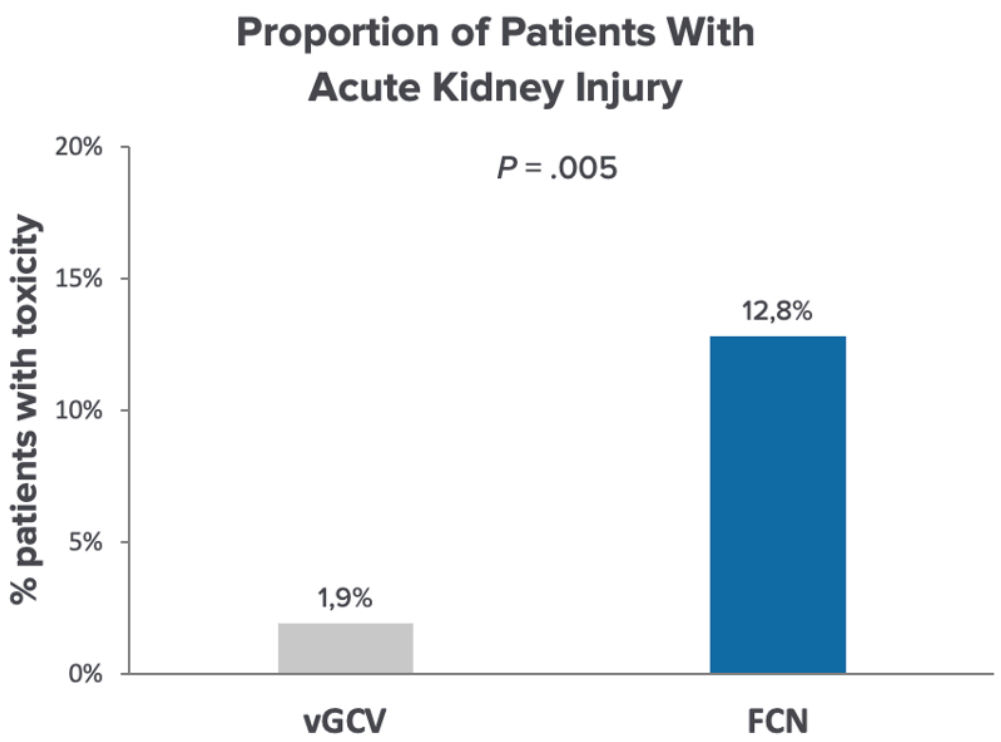
Azevedo LS, et al. *Clinics (Sao Paulo)*. 2015;70(7):515-523; Avery RK, et al. *Transplantation*. 2016;100(10):e74-e80.
Razonable RR, et al. *Minerva Med.* 2009;100(6):479-501. PMID: 20010483; Styczynski J. *Infect Dis Ther.* 2018;7(1):1-16; WHO, 2018.

# Common Adverse Effects of CMV Antiviral Therapy

| Antiviral Agent | Bone Marrow | Kidney | Eyes | Changes in Electrolytes | GI Symptoms | Altered Taste |
|---|---|---|---|---|---|---|
| Ganciclovir | ✓ | | | | | |
| Valganciclovir | ✓ | | | | | |
| Foscarnet | | ✓ | | ✓ | | |
| Cidofovir | | ✓ | ✓ | | | |
| Letermovir | | | | | ✓ | |
| Maribavir | | | | | | ✓ |

# Cytopenias and Renal Dysfunction are the Hallmark of Traditional CMV Drug Toxicity




FCN, foscarnet; vGCV, valganciclovir.

Zavras P, et al. *Biol Blood Marrow Transplant.* 2020;26(8):1482-1491.

# Mutations Associated With Resistance

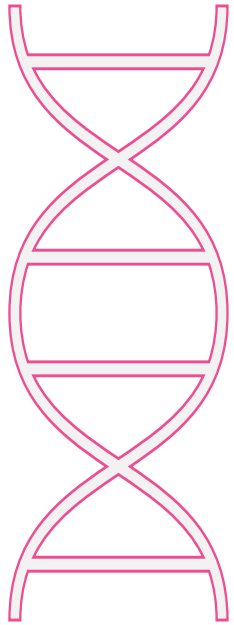
## Genotypic resistance testing detects mutations in UL97, UL54, and UL56 genes

**UL97**

Mutations common conferring resistance to ganciclovir

**UL97: Specific mutations (T409M, H411Y)**

Confer resistance to maribavir



**UL54**

Mutations may confer resistance to foscarnet, ganciclovir, or cidofovir

**UL56**

Mutations may confer resistance to letermovir only. No cross resistance with ganciclovir, foscarnet, or cidofovir

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

# Genotypic Assays are Preferred for Resistance Testing

## Genotypic Assays

Performed on viral sequences amplified from blood (whole blood, plasma, or leukocytes), fluids (urine, cerebrospinal, lung, eye) or tissue specimens

Results are more reliable if the CMV copy number in the specimen is at least 1000 IU/mL

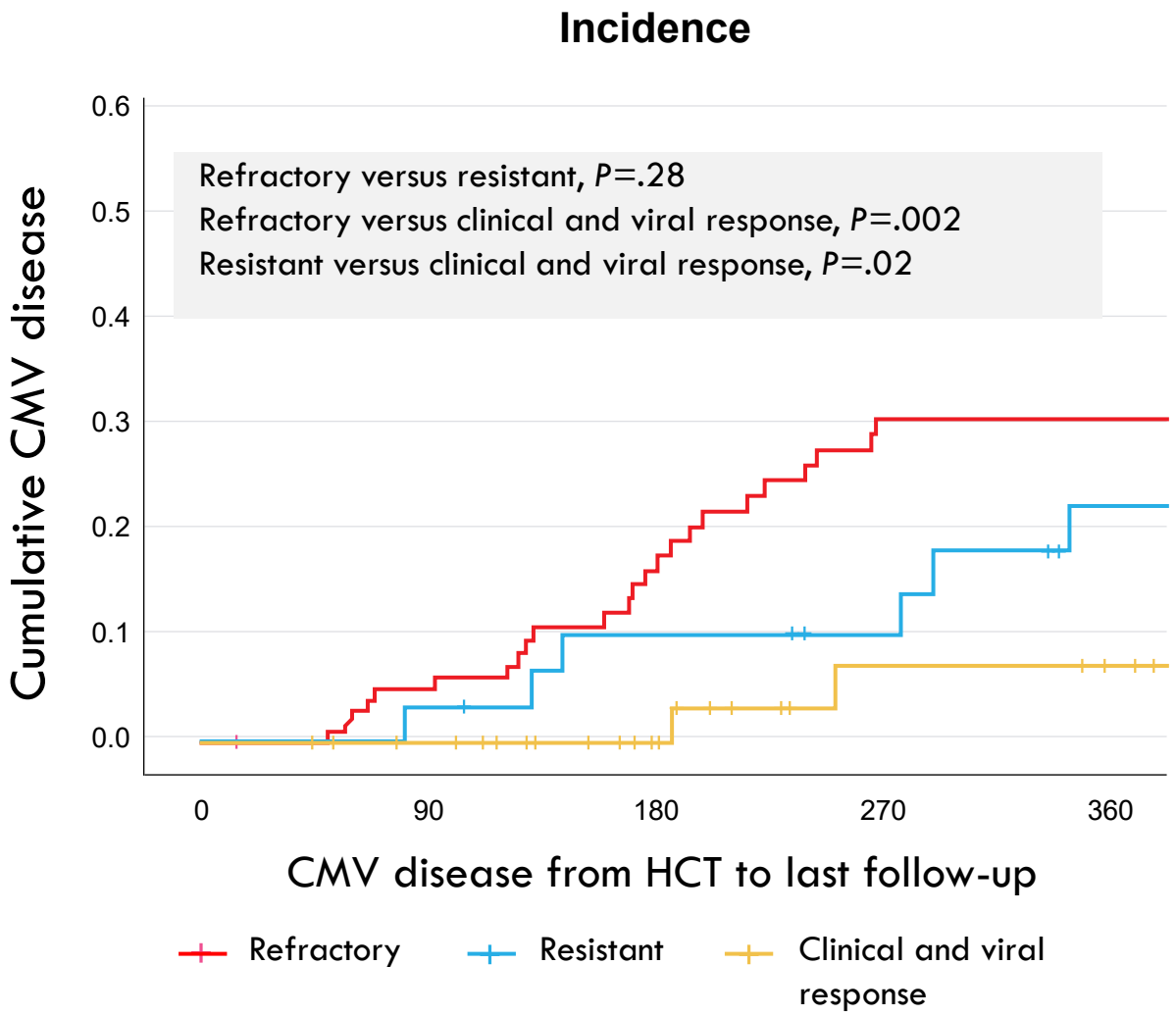
## Quality Control Concerns

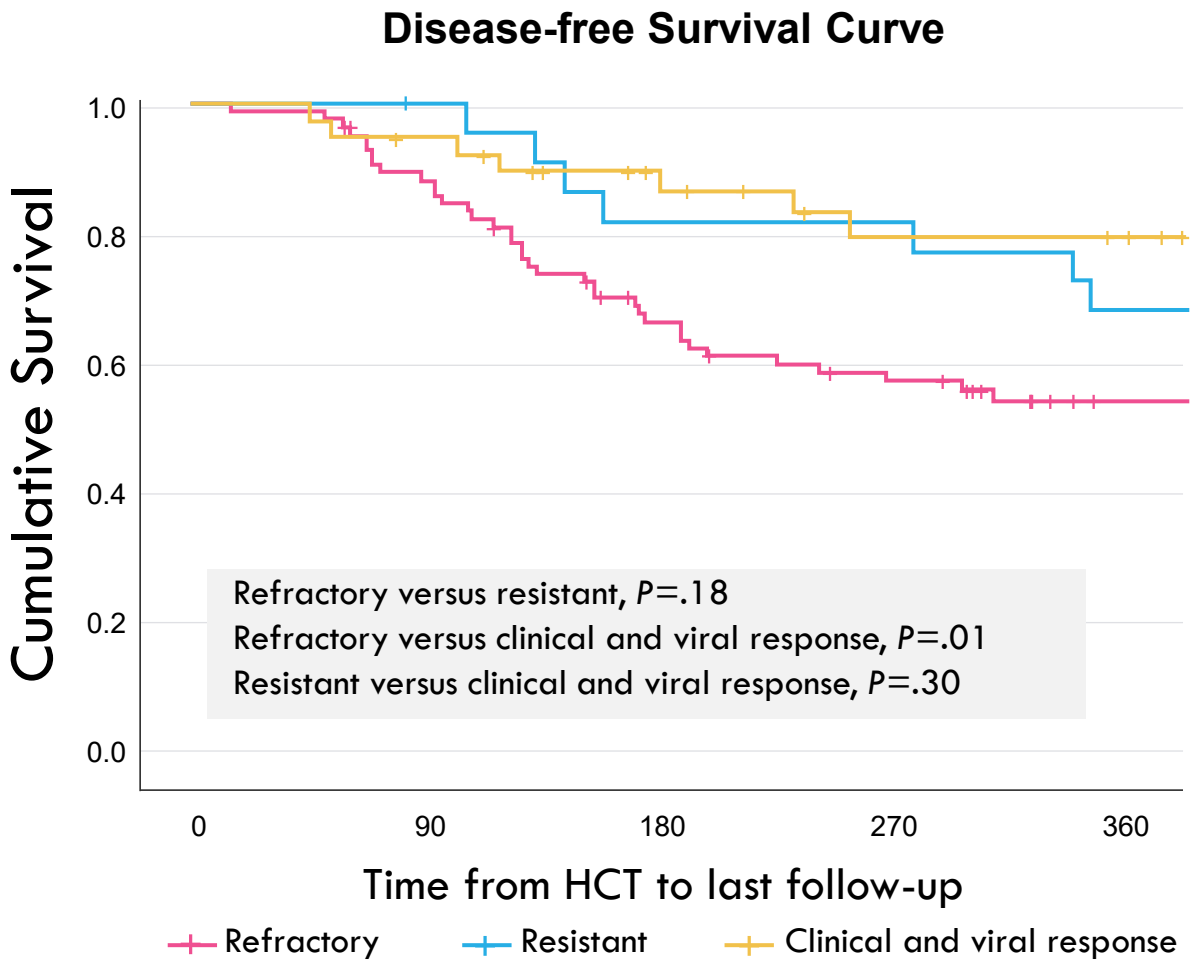
- (+) False positives due to mixed populations from low viral-load specimens
- (−) False negatives due to insensitivity in detecting mutant subpopulations comprising less than 20% to 30% of the total

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931. Razonable RR, Humar A. *Clin Transplant*. 2019;33(9):e13512.

# Incidence and Outcomes of CMV Episodes

## Unmet Need With Traditional Antiviral Therapies

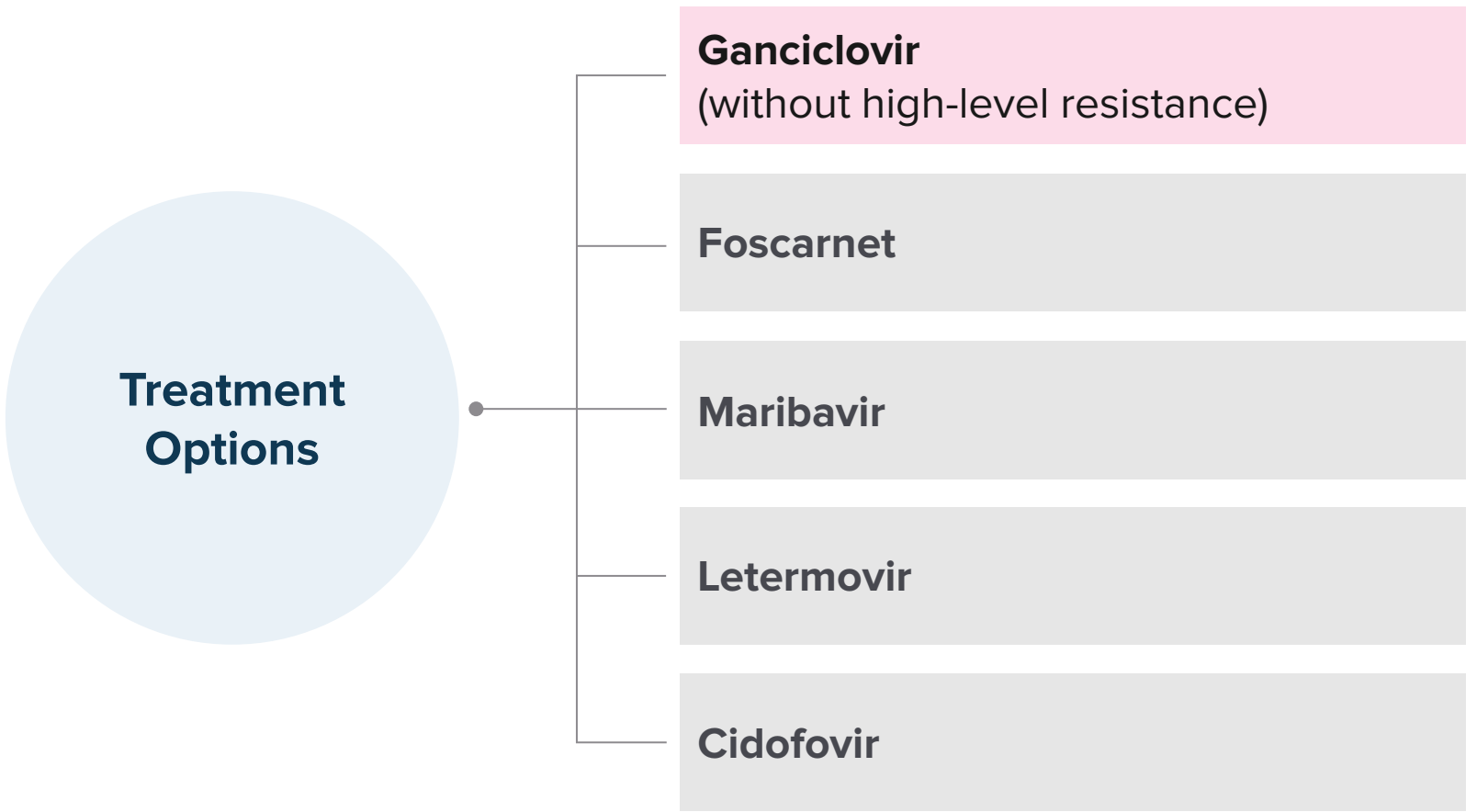



Batista M/Chemaly RF, et al. Presented at: ASBMT/TCT 2018.

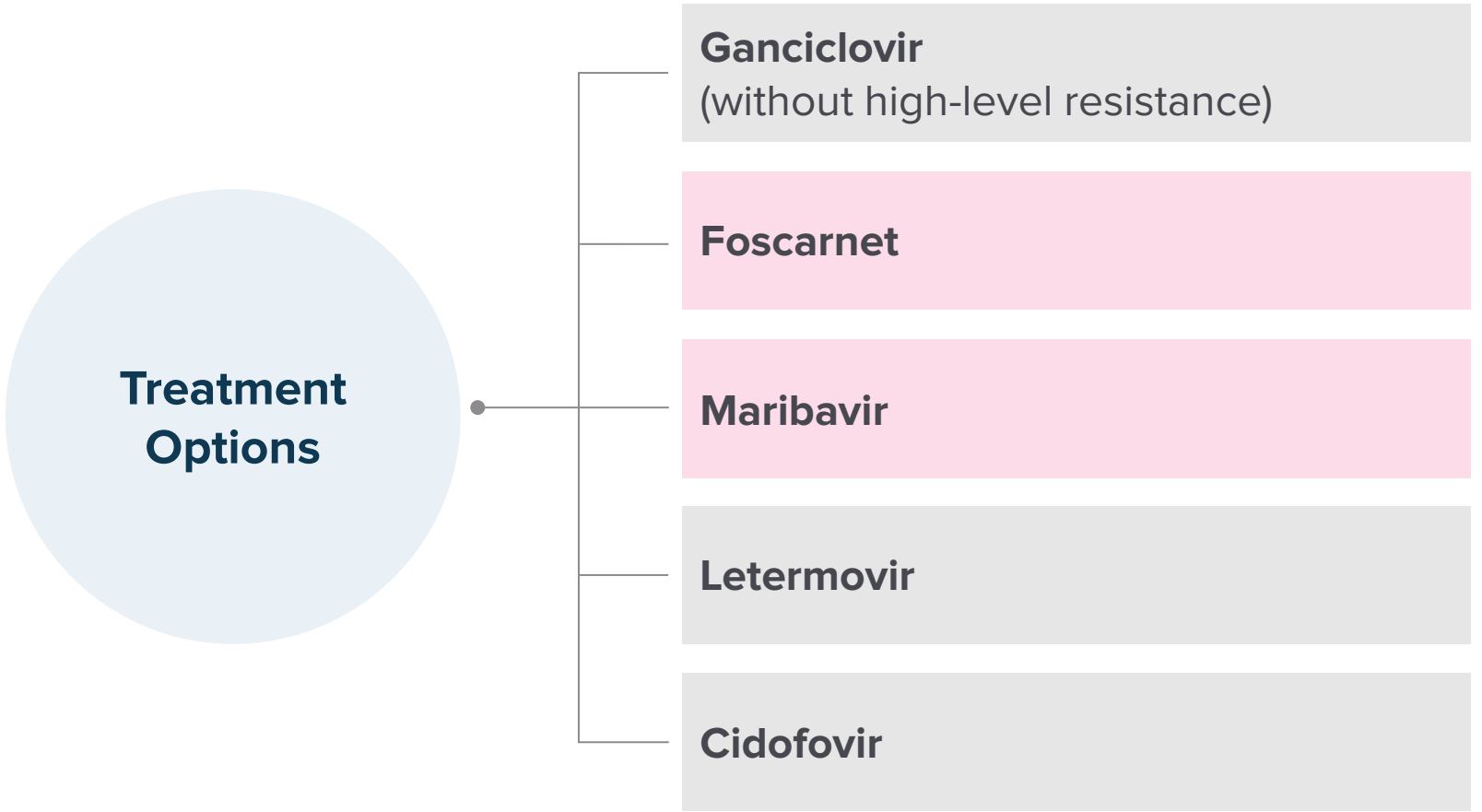
# Managing Refractory and/or Resistant CMV Infections

# Treatment of Ganciclovir-Resistant CMV Disease




Razonable RR, Humar A. *Clin Transplant.* 2019;33(9):e13512.

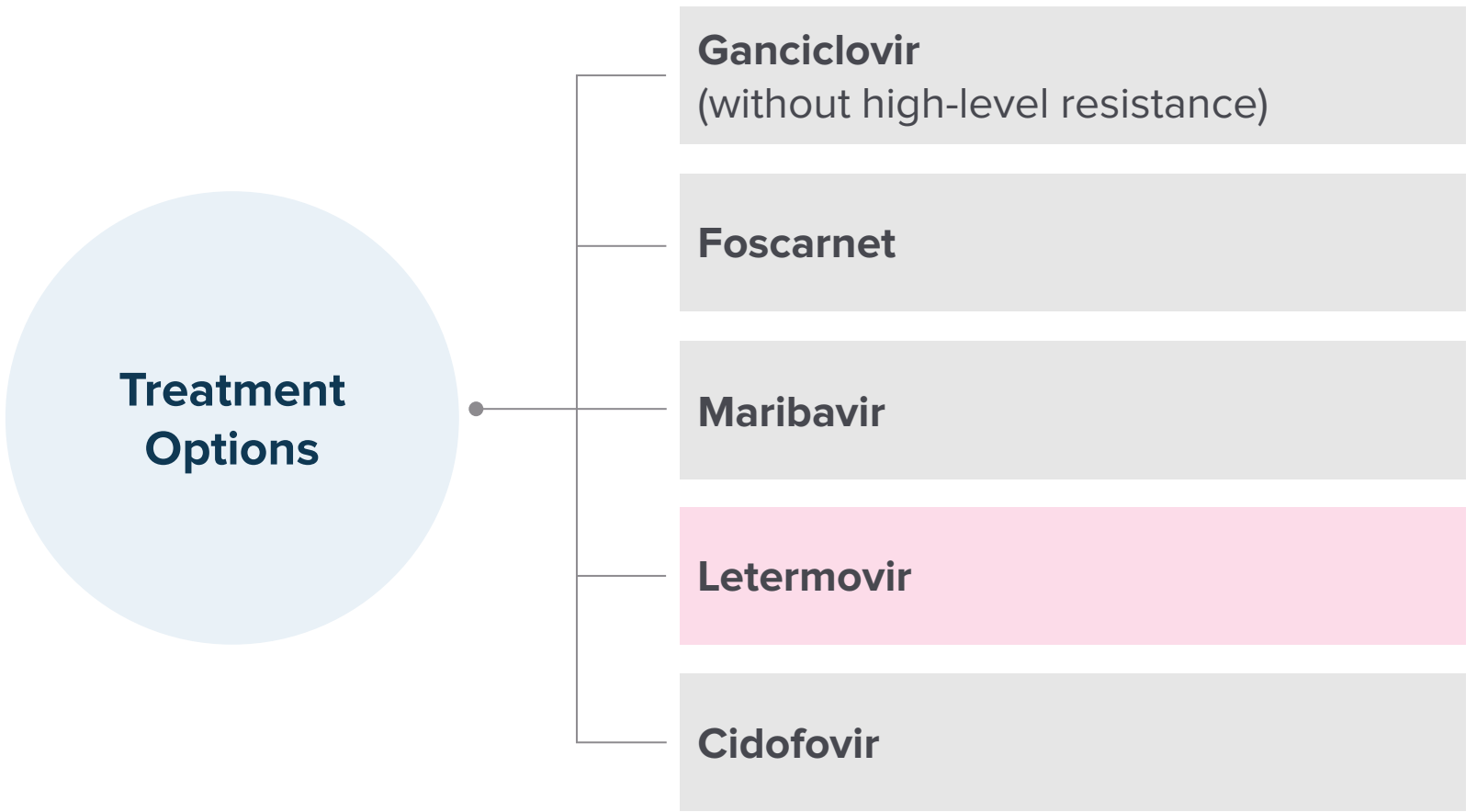
# Treatment of Ganciclovir-Resistant CMV Disease




**Typically choosing between these 2 options, but maribavir could be the first option**

Razonable RR, Humar A. *Clin Transplant.* 2019;33(9):e13512.

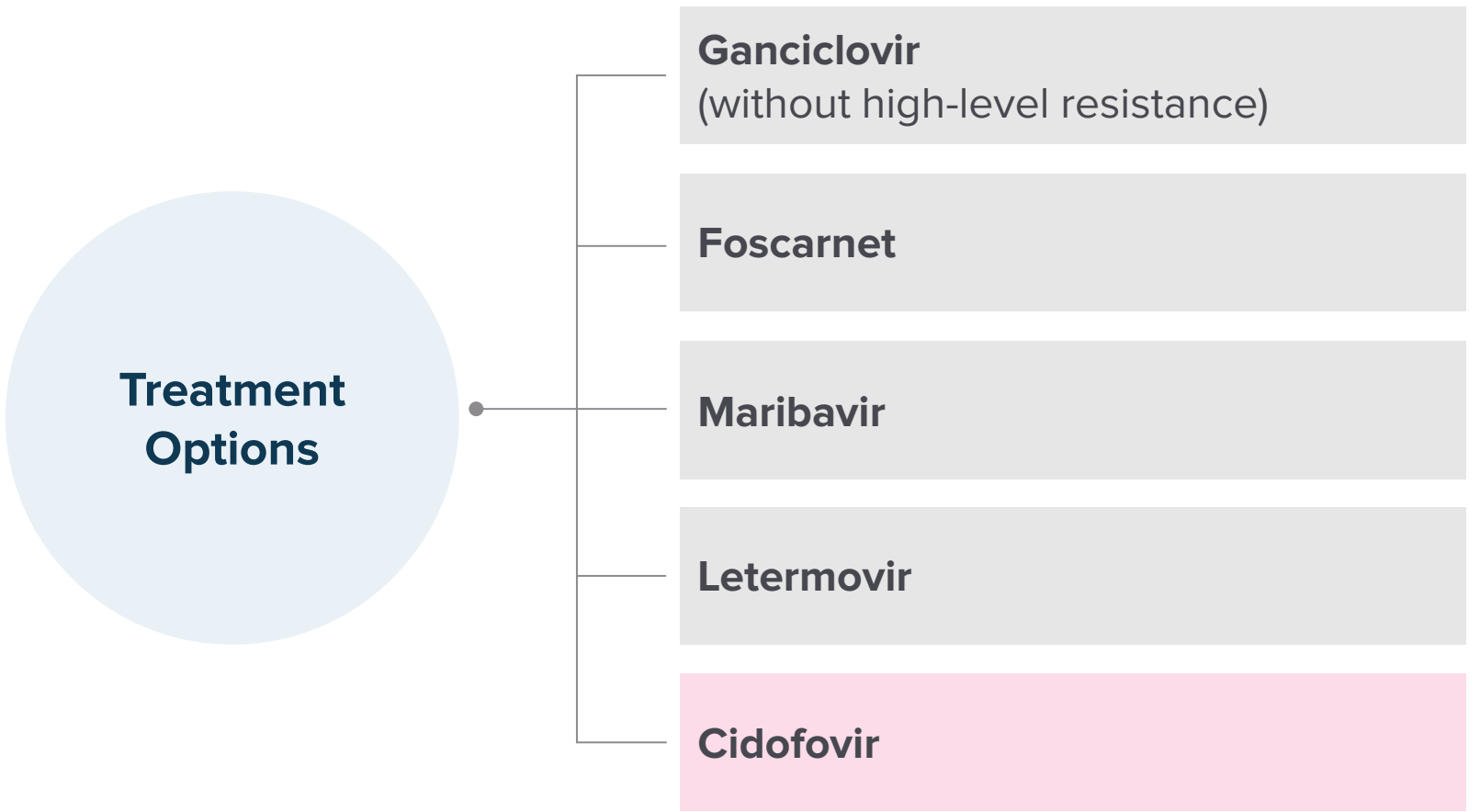
# Treatment of Ganciclovir-Resistant CMV Disease




**Concerns for lower barrier to resistance when used for treatment**

Razonable RR, Humar A. *Clin Transplant.* 2019;33(9):e13512.

# Treatment of Ganciclovir-Resistant CMV Disease



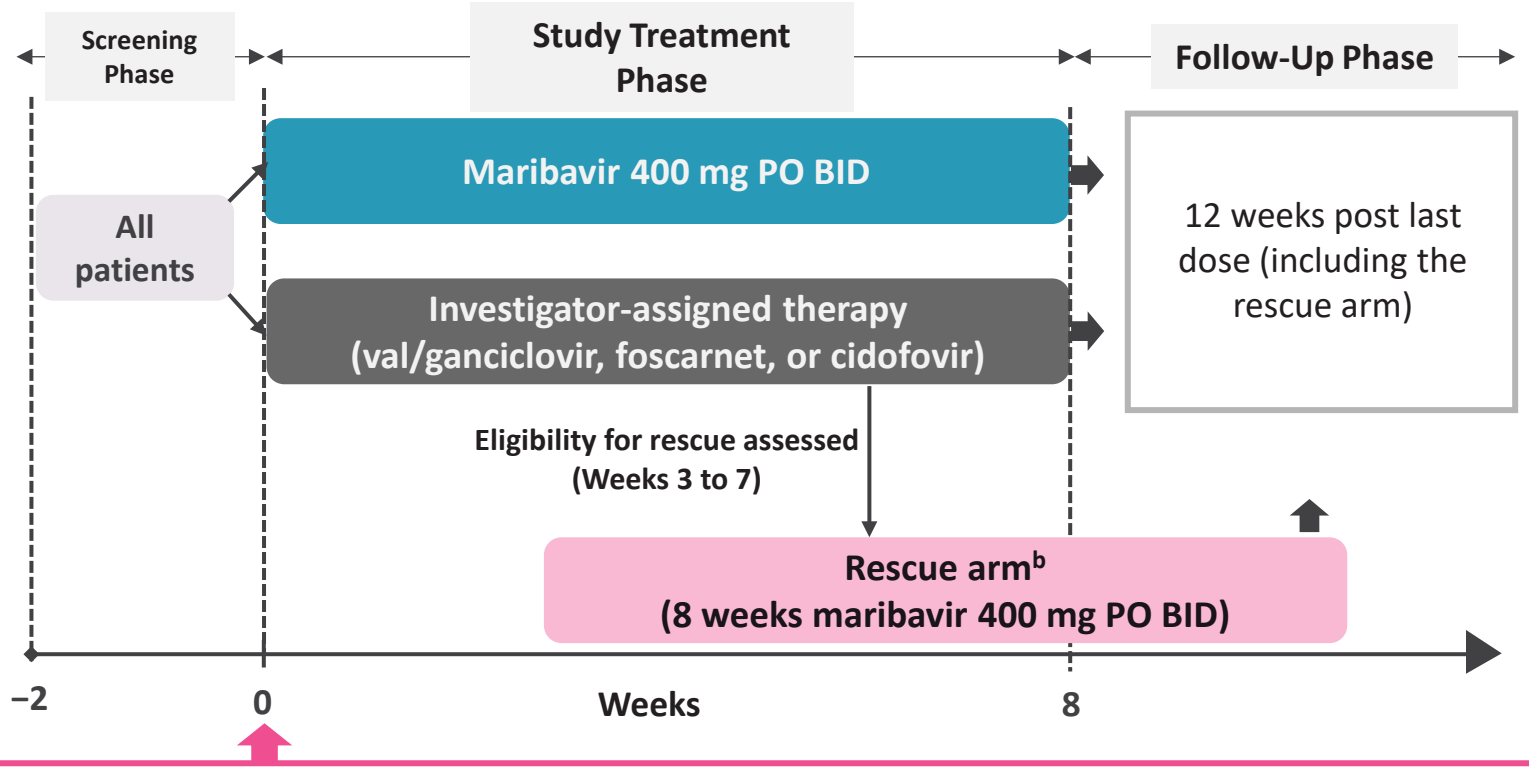

**High risk for nephrotoxicity, myelosuppression, uveitis, etc.**

Razonable RR, Humar A. *Clin Transplant.* 2019;33(9):e13512.

# Maribavir versus Investigator-assigned Therapy (IAT) for the Treatment of Transplant Recipients with R/R CMV Infection

A Phase 3, Randomized, Open-label, Multicenter, Active-controlled Study

## STUDY DESIGN




**Randomization 2:1**[a] stratified by **transplant type** (SOT or HCT) and **screening CMV DNA level** (high: ≥273,000 IU/mL [whole blood] or 91,000 IU/mL [plasma]; intermediate: ≥27,300 and <273,000 IU/mL [whole blood] or ≥9100 and <91,000 IU/mL [plasma]; low: <27,300 and ≥2730 IU/mL [whole blood] or <9100 and ≥910 IU/mL [plasma])

## ENDPOINTS

### Primary Endpoint

Confirmed CMV clearance (plasma CMV DNA <137 IU/mL in 2 consecutive tests ≥5 days apart at central laboratory) at end of week 8

### Key Secondary Endpoint

Achievement of CMV clearance and symptom control at end of week 8 and maintained through week 16

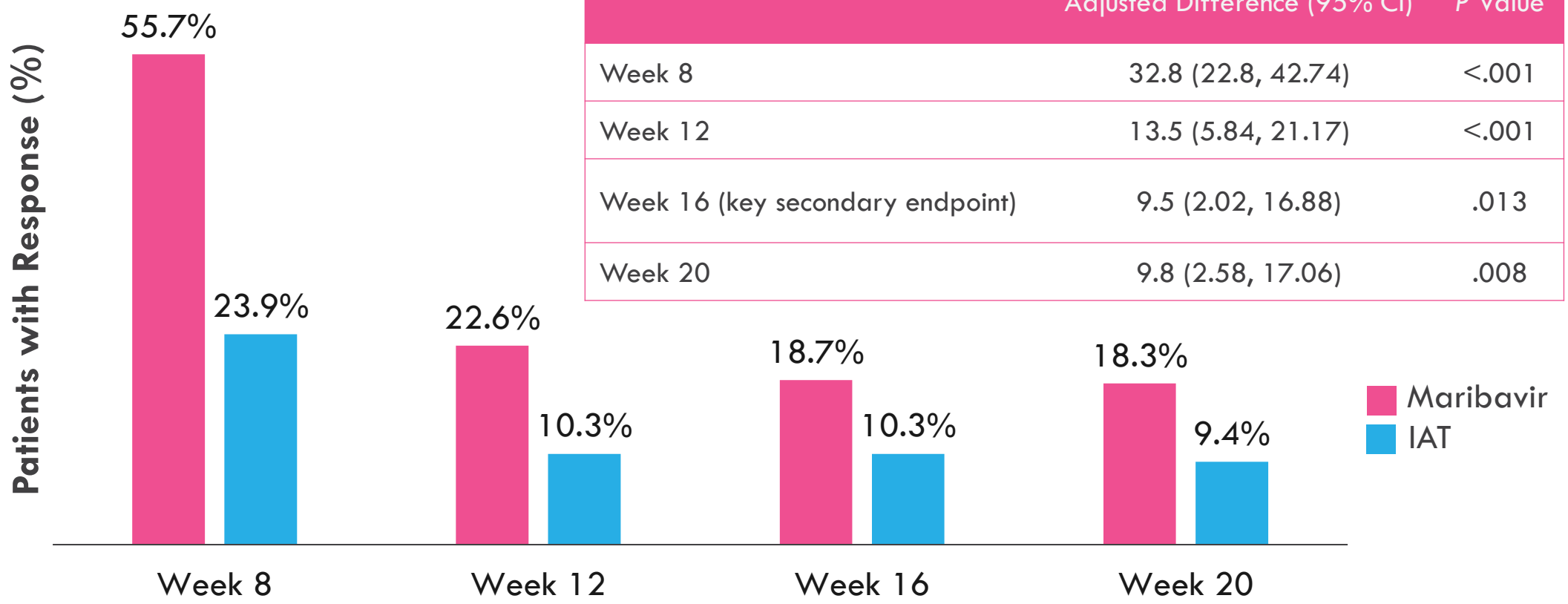
[a] Maribavir: IAT using Interactive Response Technology; [b] Rescue arm data not presented here

Duarte RF, et al. 47th Annual Meeting of the EBMT. https://ebmt2021.abstractserver.com/program/#/details/presentations/2943.

# SOLSTICE: Primary and Secondary Endpoint Results

## Confirmed Viremia Clearance and Symptom Control

| | Adjusted Difference (95% CI) | *P* Value |
|---|---|---|
| Week 8 | 32.8 (22.8, 42.74) | <.001 |
| Week 12 | 13.5 (5.84, 21.17) | <.001 |
| Week 16 (key secondary endpoint) | 9.5 (2.02, 16.88) | .013 |
| Week 20 | 9.8 (2.58, 17.06) | .008 |




Avery RK, et al. *Clin Infect Dis*. 2022;75(4):690-701.

# Treatment Emergent Adverse Events Reported by >10% of Patients

| Preferred Term | Maribavir (n=234) | IAT (n=116) | By Drug (IAT arm)[a] | | |
|---|---|---|---|---|---|
| | | | Val/ganciclovir (n=56) | Foscarnet (n=47) | Cidofovir (n=6) |
| Dysgeusia | 84 (35.9) | 1 (0.9) | 1 (1.8) | 0 | 0 |
| Nausea | 20 (8.5) | 11 (9.5) | 1 (1.8) | 8 (17.0) | 1 (16.7) |
| Vomiting | 18 (7.7) | 5 (4.3) | 0 | 4 (8.5) | 1 (16.7) |
| Diarrhea | 9 (3.8) | 6 (5.2) | 1 (1.8) | 4 (8.5) | 1 (16.7) |
| Neutropenia | 4 (1.7) | 16 (13.8) | 14 (25.0) | 2 (4.3) | 0 |
| Acute kidney injury | 4 (1.7) | 9 (7.8) | 0 | 9 (19.1) | 0 |
| Anemia | 3 (1.3) | 9 (7.8) | 3 (5.4) | 6 (12.8) | 0 |
| Hypokalemia | 1 (0.4) | 5 (4.3) | 0 | 4 (8.5) | 1 (16.7) |
| Proteinuria | 1 (0.4) | 2 (1.7) | 0 | 1 (2.1) | 1 (16.7) |
| Renal failure | 0 | 2 (1.7) | 0 | 0 | 1 (16.7) |

Dysgeusia rarely resulted in discontinuation (2 [0.9%] patients in the maribavir arm)

Data are for the safety set and show n (%) of patients experiencing a TEAE during the on-treatment period, which included treatment period plus 7 days after last dose of treatment or 21 days for cidofovir

IAT, investigator-assigned therapy; TEAE, treatment emergent adverse events

Duarte RF, et al. 47th Annual Meeting of the EBMT. https://ebmt2021.abstractserver.com/program/#/details/presentations/2943.

# MD Anderson R/R CMV Infection Management Approach

If patient has been receiving (val)ganciclovir ▶ Can be switched to maribavir **OR** foscarnet

If patient has been receiving foscarnet ▶ Can be switched to ganciclovir **OR** maribavir*

**Maribavir cannot be given with ganciclovir, and needs HSV/VZV ppx while on maribavir*

## Combination Therapy

Optional strategy for R/R CMV DNAemia or end-organ disease or severe cases (not usually recommended because of the increase risks for myelosuppression and nephrotoxicity):

**Foscarnet + Maribavir** **OR** **Foscarnet + Ganciclovir** **OR** **Ganciclovir + Foscarnet†**

**†Ganciclovir + Foscarnet (Discouraged)**

Utilizes one drug at full dose and one drug at reduced dose:

| | | |
|---|---|---|
| Ganciclovir 5 mg/kg IVPB q12h + Foscarnet 60 mg/kg IVPB q24h | **OR** | Ganciclovir 5 mg/kg IVPB q24h + Foscarnet 60 mg/kg IVPB q8h |

# Additional Treatment Strategies

- mTOR based immunosuppression
  - Conversion of calcineurin to mTOR inhibitor immunosuppression may provide anti-CMV activity based on observations in SOT, but has not been studied in HCT
- CMV-specific adjunct intravenous immunoglobulin (IVIG) is not recommended due to a lack of clinical benefit
- Leflunomide or artesunate are considered optional adjunctive therapies for R/R CMV if access to a clinical trial or early access program is not possible
- Secondary prophylaxis should be commenced when VLs are undetectable, or when quantifiable but below the predefined LLOD, and when risk factors for recurrent CMV remain (eg, inadequate CMV-specific immune responses, concurrent infection, and/or GvHD requiring immunosuppression)

Yong MK, et al. *Transplant Cell Ther*. 2021;27(12):957-967.

# ASTCT Practice Guideline Update

## American Society for Transplantation and Cellular Therapy Series: #4 - Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation

*Michelle K Yong, Terri Lynn Shigle, Yae-Jean Kim, Paul A Carpenter, Roy F Chemaly, Genovefa A Papanicolaou*

The ASTCT Practice Guidelines Committee partnered with its Transplant Infectious Diseases Special Interest Group (TID-SIG) to update its 2009 ID guidelines for HCT, employing an FAQ format.

The 4th topic in the series covers R/R CMV infection including:

- Diagnosis
- Definitions of Resistant and Refractory CMV
- Risk Factors
- Virologic Genotypes
- Treatment Algorithms

Yong MK, et al. *Transplant Cell Ther.* 2021;27(12):957-967.

# Summary for the Treatment Options for Resistant/Refractory CMV

| Resistance Genotype | Recommendation |
|---|---|
| **UL97 mutations with HIGH level resistance to ganciclovir** | • Switch to foscarnet as first-line option<br>• Switch to cidofovir as second-line option<br>• Maribavir* |
| **UL97 mutations with LOW level resistance to ganciclovir (M460I, C592G, L595W)** | • High-dose ganciclovir dosing from 7.5 mg to10 mg/kg q12h as tolerated if CMV disease not present<br>• Switch to foscarnet or cidofovir as next option |
| **UL54 mutations conferring resistance to foscarnet only** | • Stop foscarnet and start ganciclovir standard dose<br>• Maribavir* |
| **UL54 mutations conferring resistance to foscarnet and ganciclovir (± UL97 mutations)** | • Switch to cidofovir as first-line option<br>• Maribavir* |
| **UL97 mutations conferring resistance to Maribavir (T409M, H411Y)**<br>**C480** | • Stop maribavir and start ganciclovir standard dose 5 mg/kg q12h or foscarnet<br>• Some cross-resistance to ganciclovir |
| **UL56, UL89, UL51 conferring resistance to letermovir** | • Switch to ganciclovir or foscarnet as first-line option |

Modified from Yong MK, et al. *Transplant Cell Ther.* 2021;27(12):957-967.

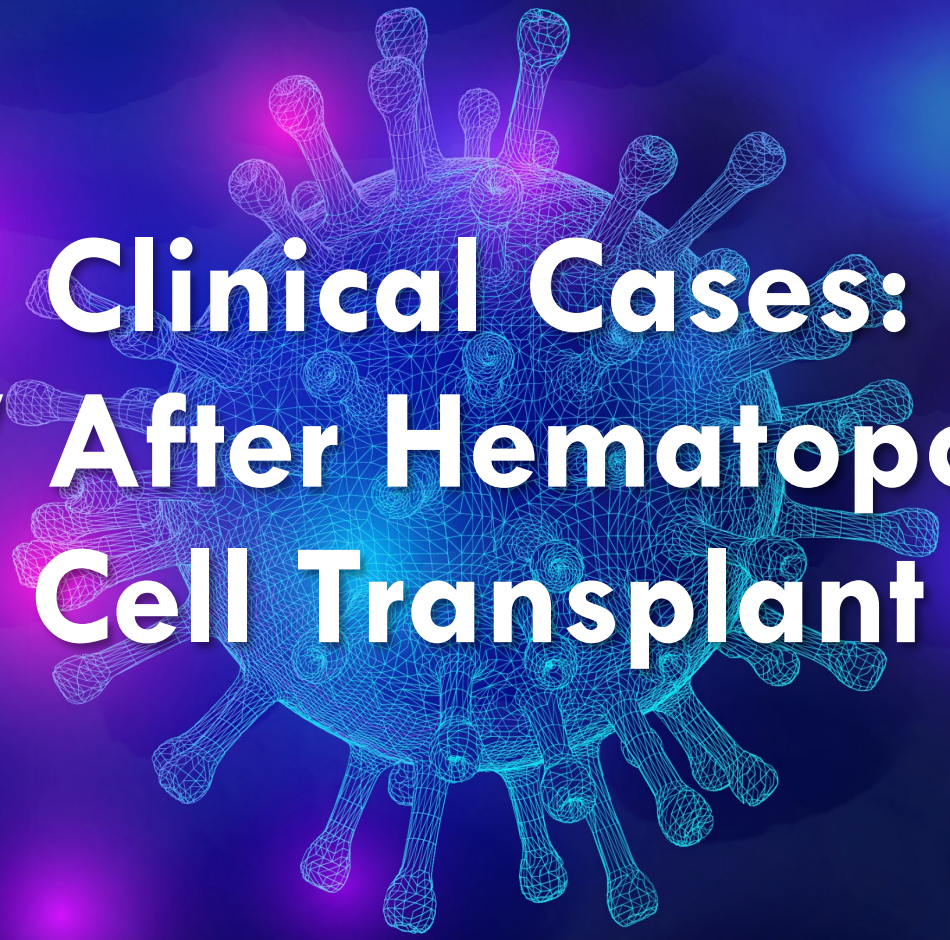
* New option since 11/21

# Conclusions

- **R/R CMV infections are associated with high incidence of CMV disease and high all-cause mortality**
- **Maribavir is an alternative option as a therapeutic agent to mitigate the impact of resistant and refractory CMV infections**

Khawaja FK, et al. *Clin Microbiol Infect.* 2023;29(1):44-50.

CLINICAL FORUM



# Clinical Cases: CMV After Hematopoietic Cell Transplant

Case 1

Case 2

Case 3

# Case 1

***Before the Era of Maribavir***

A 57-year-old man with h/o AML, underwent MUD HCT (R+/D-) after conditioning with fludarabine, busulfan, melphalan, and ATG

**Day +30:** Patient developed CMV reactivation with a VL by PCR at 600 IU/mL

Started on valganciclovir (VGV) at 900 mg PO twice a day and transitioned to maintenance VGV at 900 mg PO daily 2 weeks later after CMV viral load (VL) became undetectable

**Day +65:** Patient developed grade 3 skin GvHD and was started on methylprednisolone at 2 mg/kg/day

AML, acute myeloid leukemia; ATG, antithymocyte globulin; GvHD, graft-vs-host disease; HCT, hematopoietic cell transplant; PCR, polymerase chain reaction; PO, oral

# Case 1

***Before the Era of Maribavir***

He subsequently had recurrent CMV infection at 5500 IU/mL while off VGV and he was restarted on the latter, treatment dose at 900 mg PO BID

He was switched to foscarnet at 60 mg/kg IV q 12 hours (renally adjusted) with decline in his VL to 950 IU/mL, 10 days later

His CMV VL continued to rise 14 days later to 38,000 IU/mL and a genotypic assay was submitted

Because of worsening renal function (creatinine at 3.2) and severe nausea while on foscarnet, he was switched to VGV renally adjusted (450 mg oral BID) and his CMV VL remained around 1200 IU/mL for 2 weeks

BID, twice daily; PO, oral; VGV, oral valganciclovir; VL, viral load

# CMV Genotype Assay Results

| | |
|---|---|
| **UL97 Mutation** | Detected |
| **Ganciclovir** | Resistance Predicted |
| | UL97 Mutations: **A594T** |
| **Foscarnet** | Resistance Not Predicted |
| | Mutations: None |
| **Cidofovir** | Resistance Not Predicted |
| | Mutations: None |

# What Would You Do at This Point?

A. Increase VGV dose to 900 mg PO BID
   (Not really, as patient is nauseous and there is concern about absorption)
B. Foscarnet monotherapy
   (Creatinine of 3.2)
C. IV letermovir
   (Maybe in combination, but how to monitor response?)
D. Cidofovir
   (Suboptimal option and serious toxicities)
E. Consult ID as I am not sure what to do
   (ID should be consulted!)

# Case 1

***Before the Era of Maribavir***

Patient was started on high-dose ganciclovir. His CMV VL decreased, lingered around 950 IU/mL

Patient developed severe neutropenia and thrombocytopenia despite G-CSF support and platelets transfusions

**Day +110:** Patient died with septic shock from *E. coli* and multiple organ failure

Case 1

Case 2

Case 3

# Case 2

***Real-Life Experience with Maribavir***

1. A 47-year-old woman with AML s/p haploidentical HCT and 1 year later, MUD HCT (CMV serostatus: D-/R+), after AML relapse

2. Conditioning with reduced fludarabine, melphalan, and ATG was given prior to the second HCT

3. She had refractory CMV viremia treated with valganciclovir followed by foscarnet, 10 weeks post-HCT, with subsequent AKI. She was changed to letermovir for secondary prophylaxis

4. At 6 months post-HCT, she developed severe skin GvHD requiring treatment with high-dose steroids

# Case 2

***Real-Life Experience with Maribavir***

## Viral Load

CMV VL increased to 10,000 IU/mL

## CMV Genotypic Testing

Both wild-type and C325FW-mutated UL56, conferring letermovir resistance

## Treatment

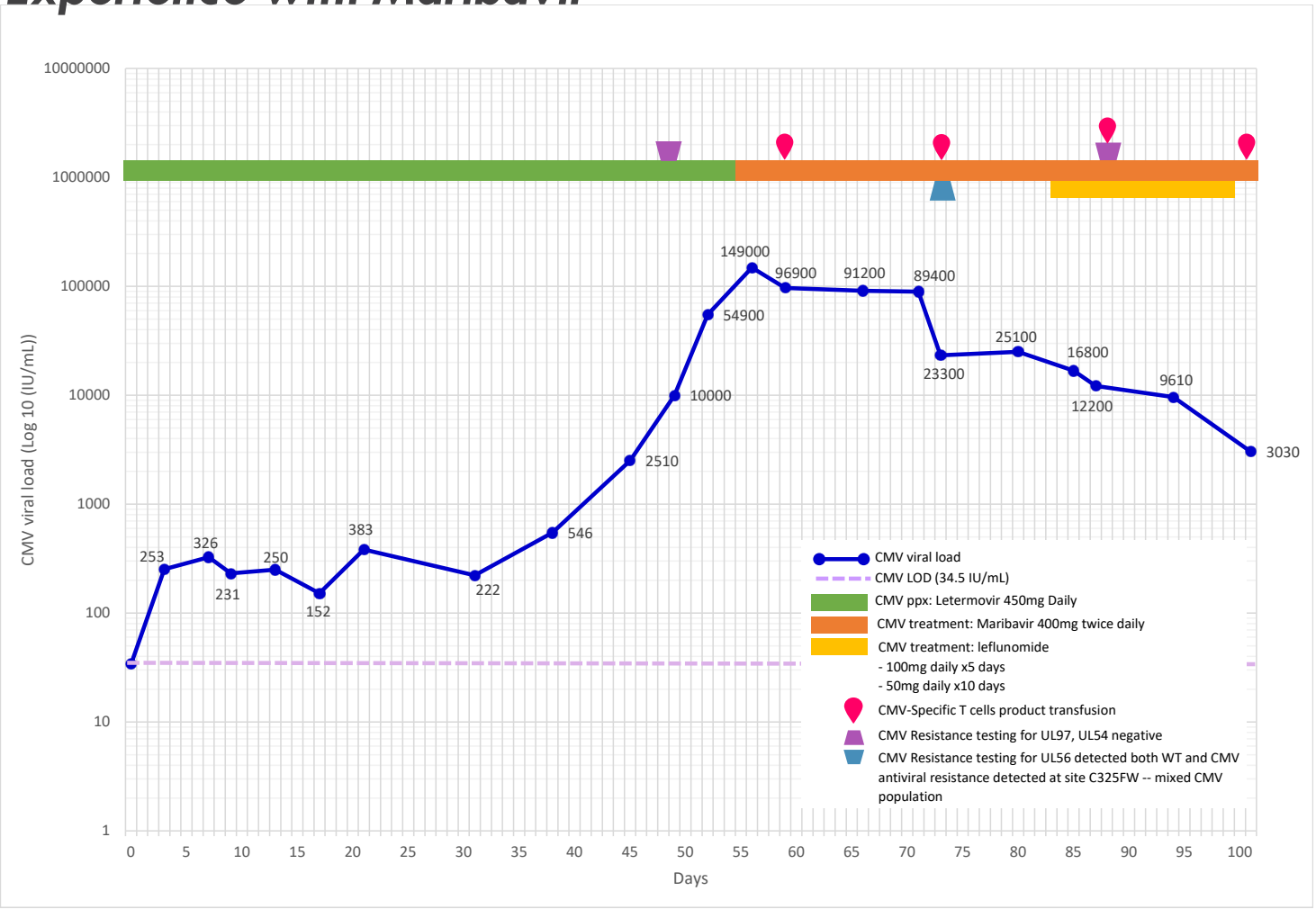
Maribavir initiated at 400 mg twice daily

# Case 2

## *Real-Life Experience with Maribavir*

After 50 days of maribavir and adjunctive therapies, the patient's CMV VL decreased to 2,530 IU/mL

During her last f/u at 2½ years, she remained on maribavir with VL ranging from 300 IU/mL to 50 IU/mL



Case 1

Case 2

Case 3

# Case 3

***Real-Life Experience with Maribavir***

A 34-year-old man with AML s/p CBT (CMV serostatus: D+/ R+) after conditioning with fludarabine, clofarabine, busulfan, ATG, and TBI

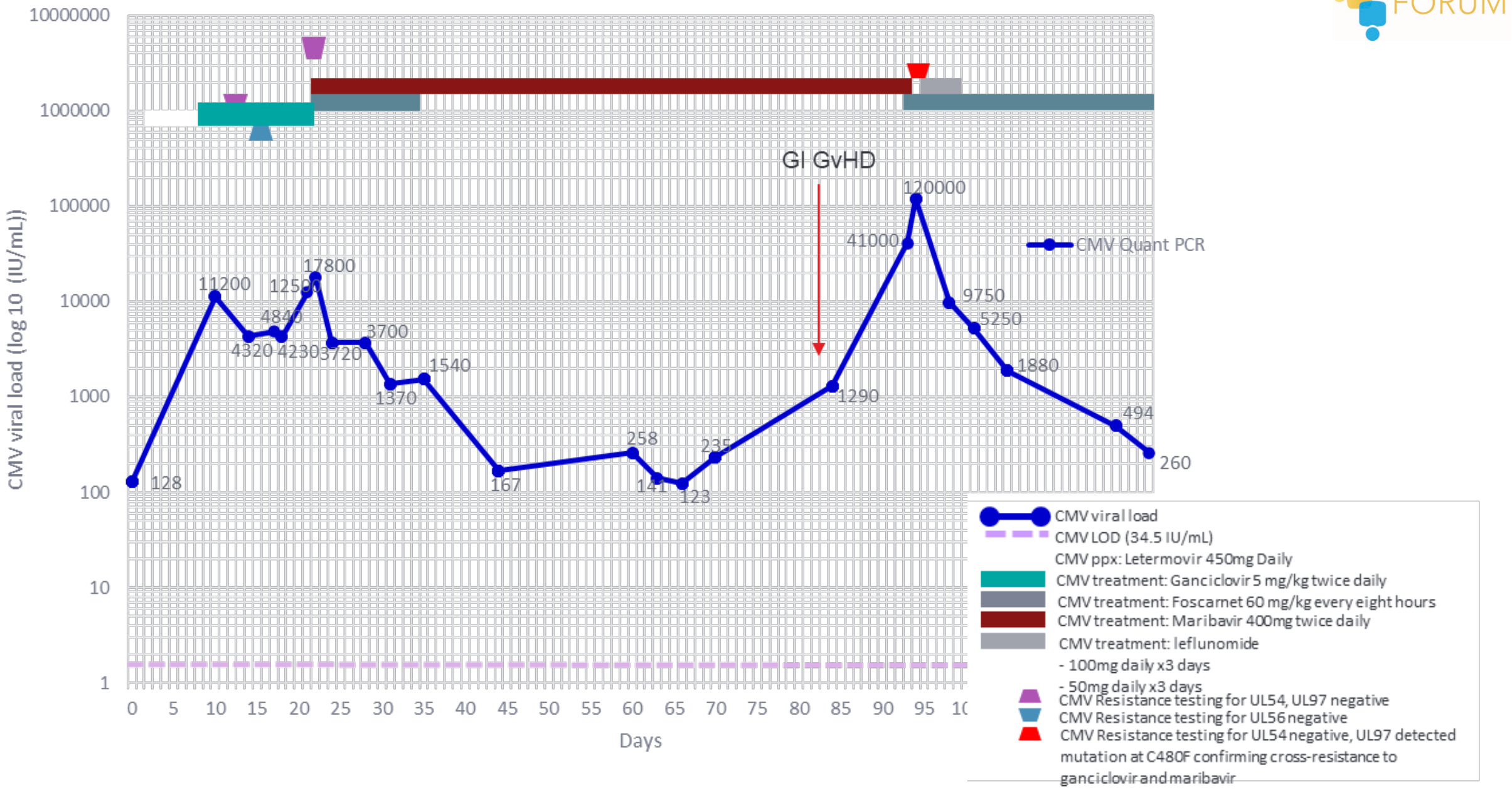
He had early HHV-6 DNAemia during the first month post-HCT treated with foscarnet, and he had skin GvHD requiring high-dose steroids

After 5 months post-HCT, he developed CMV viremia that was treated initially with ganciclovir and foscarnet, but due to concerns for refractory CMV, he was switched to maribavir

# Case 3

***Real-Life Experience with Maribavir***

- CMV genotypic testing did not identify mutations at UL97, UL54, or UL56 at that time
- CMV VL decreased from 17,800 IU/mL to a nadir of 123 IU/mL at 4 weeks from starting maribavir
- While on maribavir for 63 days, CMV VL rose to 120,000 IU/mL in the setting of worsening GI GvHD and possible malabsorption


CLINICAL FORUM
CMV viral load (log 10 (IU/mL))
10000000
1000000
100000
10000
1000
100
10
1
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 10
Days
GI GvHD
CMV Quant PCR
128
11200
4320
4840
4230
17800
12500
3720
3700
1370
1540
167
258
141
123
235
1290
41000
120000
9750
5250
1880
494
260
CMV viral load
CMV LOD (34.5 IU/mL)
CMV ppx: Letermovir 450mg Daily
CMV treatment: Ganciclovir 5 mg/kg twice daily
CMV treatment: Foscarnet 60 mg/kg every eight hours
CMV treatment: Maribavir 400mg twice daily
CMV treatment: leflunomide
- 100mg daily x3 days
- 50mg daily x3 days
CMV Resistance testing for UL54, UL97 negative
CMV Resistance testing for UL56 negative
CMV Resistance testing for UL54 negative, UL97 detected mutation at C480F confirming cross-resistance to ganciclovir and maribavir

# Case 3

***Real-Life Experience with Maribavir***

Genotypic testing detected a mutation on UL97 (C480F), conferring resistance to maribavir and cross-resistance to ganciclovir

No CMV end-organ disease was noted on workup, and the patient responded well to foscarnet therapy

Despite responding to CMV therapy, the patient subsequently died of a GI bleed due to GI GvHD

# Audience Q&A

Please complete the Evaluation to receive CME credit.