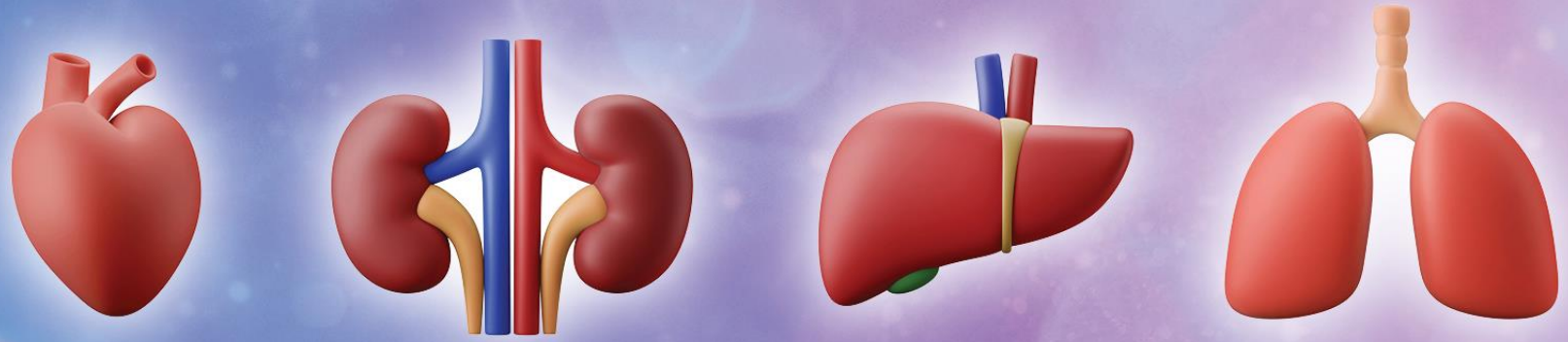
CARE TEAM FORUM

Tackling Treatment-Refractory and Drug-Resistant CMV in the Solid Organ Transplant Setting



Provided by
RMEI Medical Education, LLC

RMEI MEDICAL EDUCATION FOR BETTER OUTCOMES

Supported by an educational grant from
Takeda Pharmaceuticals U.S.A., Inc.

Disclosures

Atul Humar, MD, MSc, FRCPC, FAST, has relevant financial relationships with Astellas Pharma, Inc, Roche, Takeda *(Consultant)*; Qiagen *(Grant/Research Support)*.

Raymund R. Razonable, MD, FIDSA, FAST, has relevant financial relationships with Gilead Sciences, Inc., Regeneron, Roche *(Grant/Research Support)*; AlloVir *(Other: Data Adjudication Committee)*; Novartis *(Other: Data Safety Monitoring Board)*.

Fernanda P. Silveira, MD, MS, FIDSA, FAST, has relevant financial relationships with Eurofins Viracor, Janssen Pharmaceuticals, Takeda *(Advisor)*; Ansun Biopharma, Merck, Regeneron, Takeda *(Grant/Research Support)*.

Patient participating in this activity has no relevant financial relationship(s) with ineligible companies to disclose.

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

Navigating the Current CMV Landscape in SOT

Raymund R. Razonable, MD, FIDSA, FAST

Professor, Medicine
Program Director, Infectious Diseases Fellowship Program
Vice Chair, Division of Infectious Diseases
Mayo Clinic
Rochester, MN

CMV in SOT: Epidemiology

Onset

Occurs most commonly within 3 months after SOT (or within 3 months after stopping antiviral prophylaxis)

Disease Burden

- Common cause of morbidity and may lead to death
- Higher risk for complications
- Tissue invasive disease
- Higher risk of graft rejection

Risk Factors

- **Host factors:** Lack or inadequate immunity (D+/R-, use of T-cell depleting immunosuppression, high-doses of immunosuppression, lymphopenia, rejection)
- **Viral factors:** High viral burden (lung, intestinal organ)

SOT, solid organ transplant

Razonable RR, et al. *Clin Transplant*. 2019;33(9):e13512.

CMV Prevention

Antiviral Prophylaxis

- Valganciclovir 900 mg PO once daily (adjust for renal function)
- Start soon (and within 10 days) after transplantation
- Duration: 3 months to 1 year (depending on risk)

Preemptive Therapy

- Weekly CMV QNAT surveillance up to 3 to 4 months
- If viral load above pre-defined threshold: valganciclovir 900 mg PO BID (until viral load is no longer detected)

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Clinical Presentation

Asymptomatic Infection

Detection of CMV DNA in the blood without clinical signs and symptoms

CMV Syndrome

Fever, malaise, fatigue, leukopenia, thrombocytopenia, elevated ALT + CMV DNAemia

Tissue-invasive Disease

End-organ involvement: gastrointestinal disease, pneumonia, hepatitis, retinitis, encephalitis, allograft involvement

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Antiviral Drugs

CMV DNA Polymerase Inhibitors

Ganciclovir (IV), valganciclovir (oral)

- Standard first-line antiviral drug for prevention and treatment

Alternative

- Foscarnet (IV)
  - Cidofovir (IV)

Novel Therapeutics

Letermovir (oral)

- Viral terminase inhibitor

Maribavir (oral)

- UL97 inhibitor with multimodal effect

IV, intravenous

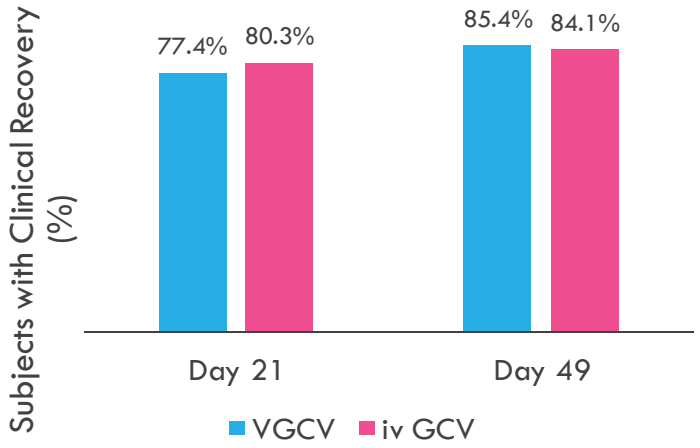
Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Treatment for Mild-to-Moderate CMV Disease

Antiviral Drugs

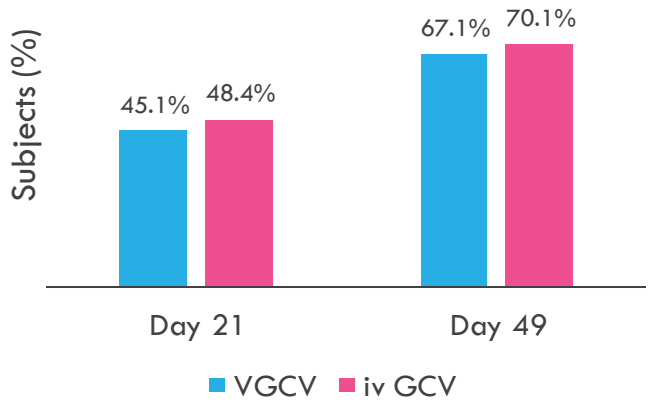
Oral valganciclovir and intravenous ganciclovir are equally effective initial therapy for mild-to-moderate CMV disease

Clinical Success*



*Clinical resolution of CMV as assessed by investigators

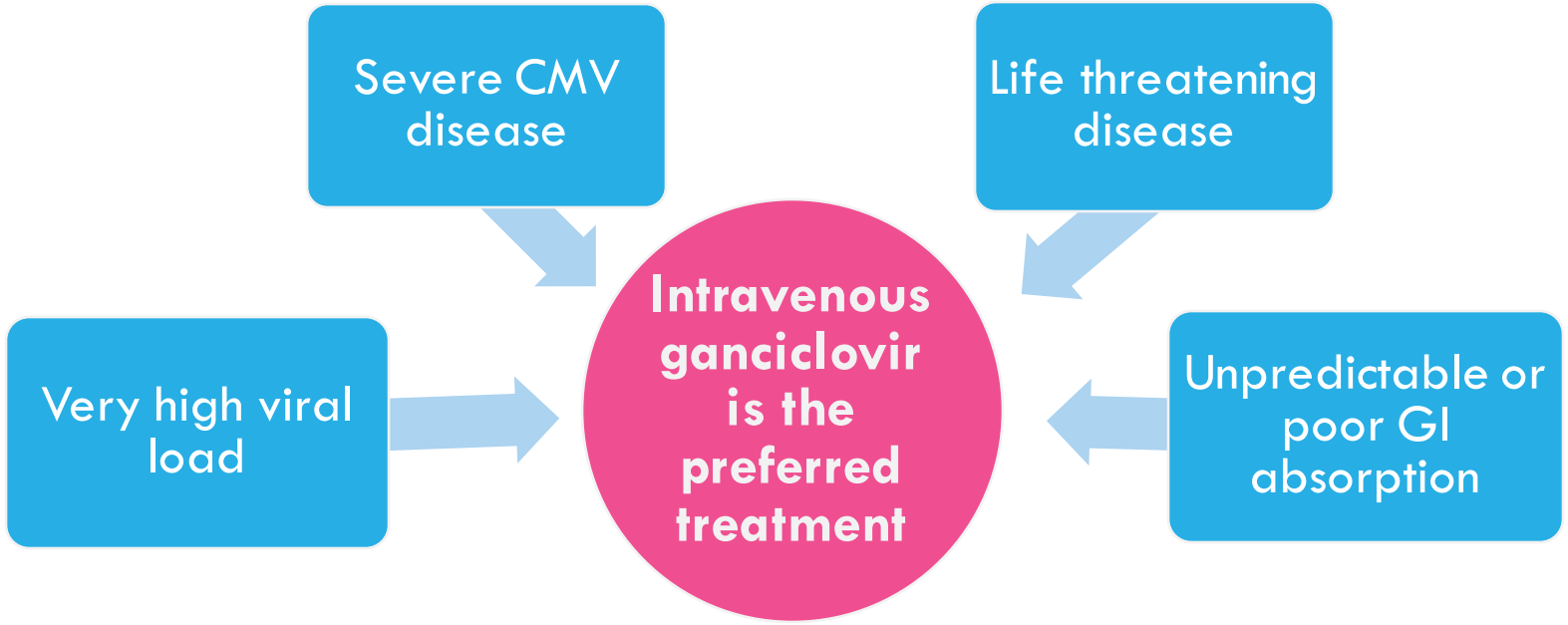
Viral Eradication**



**<600 copies/mL plasma

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.
Asberg A, et al. *Am J Transplant.* 2007;7(9):2106-2113.

Treatment Recommendations



- ✓ Initial treatment with intravenous ganciclovir may be switched to oral valganciclovir once there is adequate clinical and virologic control, as assessed by the provider

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Additional Treatment Recommendations

Foscarnet and cidofovir are second-line treatment	• Increased risk of nephrotoxicity and electrolyte disturbance
Letermovir	• Low genetic barrier of resistance • Not approved for treatment of CMV disease
Maribavir	• Not approved as initial treatment of CMV disease

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Treatment Side Effects

SAFETY Toxicities often lead to premature discontinuation, predisposition to resistance development, and subsequent virologic failure

Antiviral Agent	Bone Marrow	Kidney	Altered Taste
Ganciclovir	✓		
Valganciclovir	✓		
Foscarnet		✓	
Cidofovir		✓	
Maribavir			✓

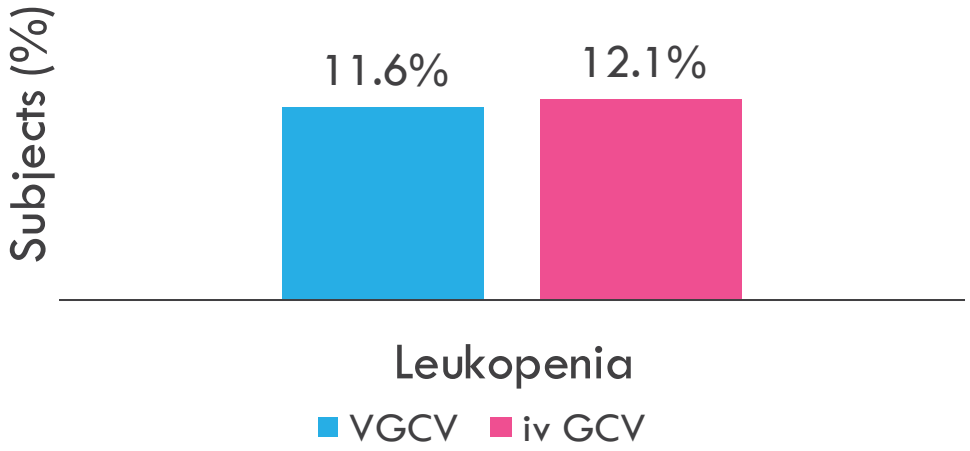
Treatment Monitoring

Laboratory Monitoring[1,2]

- Weekly CBC differential count (assess for leukopenia)
- Serum creatinine (adjust dose)
- CMV load (virologic response)

➢ Routine ganciclovir therapeutic drug monitoring not recommended

Rates of Leukopenia During Treatment[3]



VGCV, valganciclovir; iv, intravenous; GCV, ganciclovir

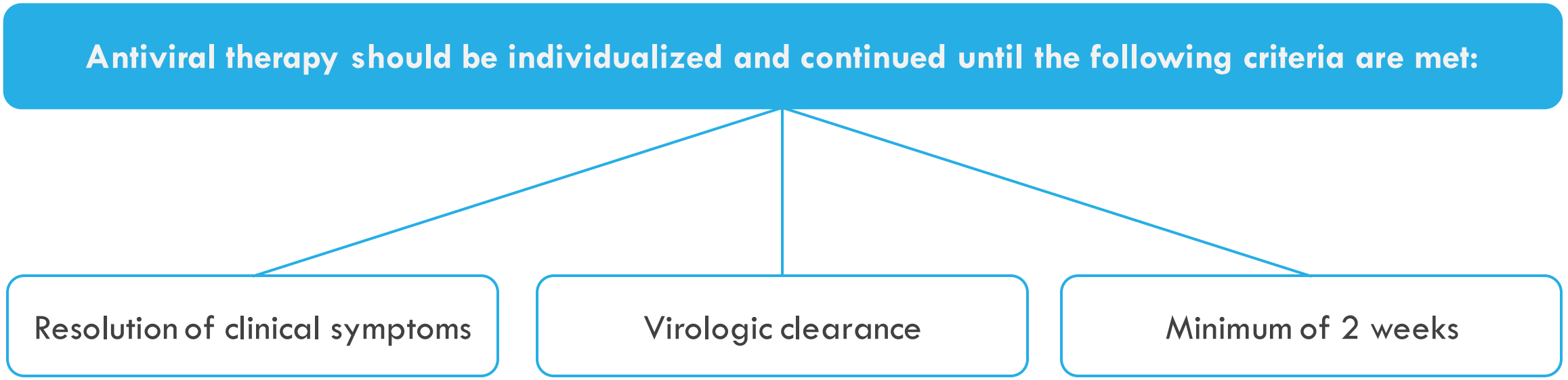
1.Razonable RR, et al. Clin Transplant. 2019;33(9):e13512.
2.Ritchie BM, et al. Antimicrob Agents Chemother. 2019:e01855.
3. Asberg A, et al. Am J Transplant. 2007;7(9): 2106-2113.

Polling Question

Antiviral treatment for CMV disease in patients with SOT should be given for a minimum of:

A. 1 week
B. 2 weeks
C. 3 weeks
D. 4 weeks

Treatment Individualization



Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Treatment Individualization (cont'd)

Cautious reduction in immunosuppression

- If feasible, to allow for immunologic recovery
- Severe lymphopenia or deficient T-cell function

Emerging role of immunity

- To predict relapse and guide treatment strategies
  - Low absolute lymphocyte count
  - Absent CMV-specific T-cell immune response

Role of secondary antiviral prophylaxis is debated

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

Panel Discussion

- What are the CMV treatment challenges that clinicians face when managing SOT patients?
- How do you manage CMV treatment side effects?

Recognizing Treatment-Refractory and Drug-Resistant CMV

Atul Humar, MD, FRCPC, FAST

Professor, Department of Medicine
University of Toronto
R. Fraser Elliott Chair, Transplantation
University Health Network
Director, University of Toronto Transplant Institute
Toronto, ON, Canada

Definition: What is Refractory/Resistant CMV?

R/R CMV Infection or Disease

Refractory*

- Increasing or persistent viral load after at least 2 weeks of adequate antiviral therapy
- Worsening or failure to improve signs and symptoms after at least 2 weeks of adequate antiviral therapy

Resistant

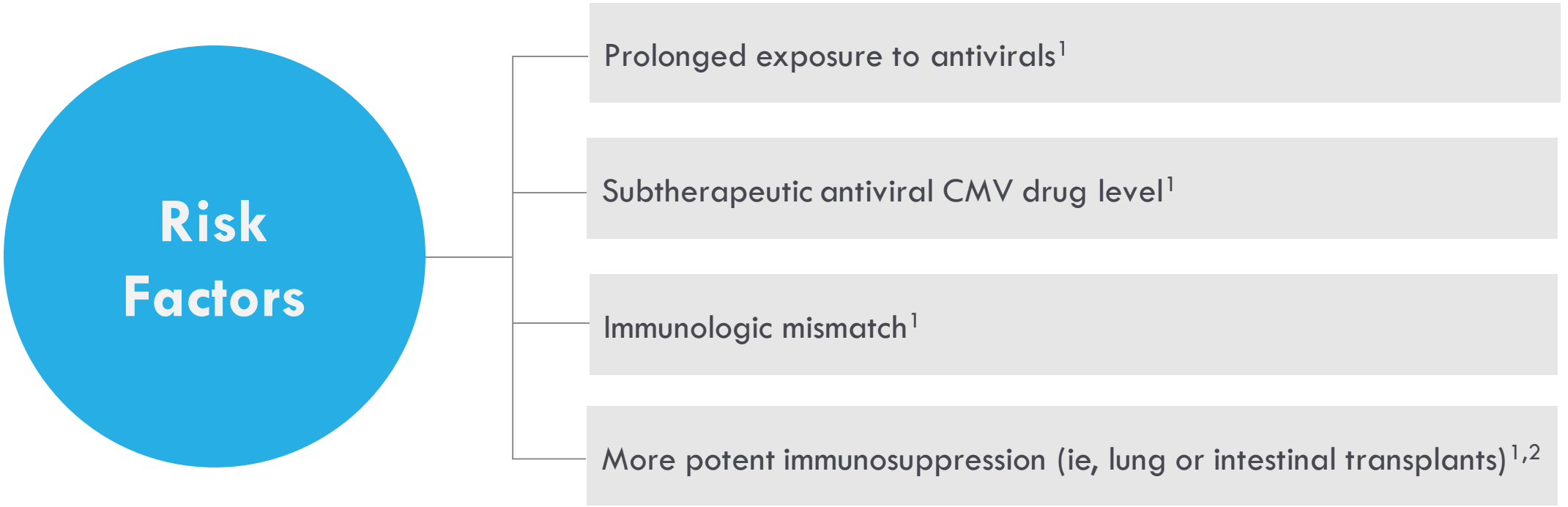
- Viral genetic alteration that decreases susceptibility to one or more drugs

*Not all patients with refractory CMV have resistant virus

CMV, cytomegalovirus; R/R, refractory/resistant

Chemaly RF, et al. *Clin Infect Dis.* 2019;68(8):1420-1426.

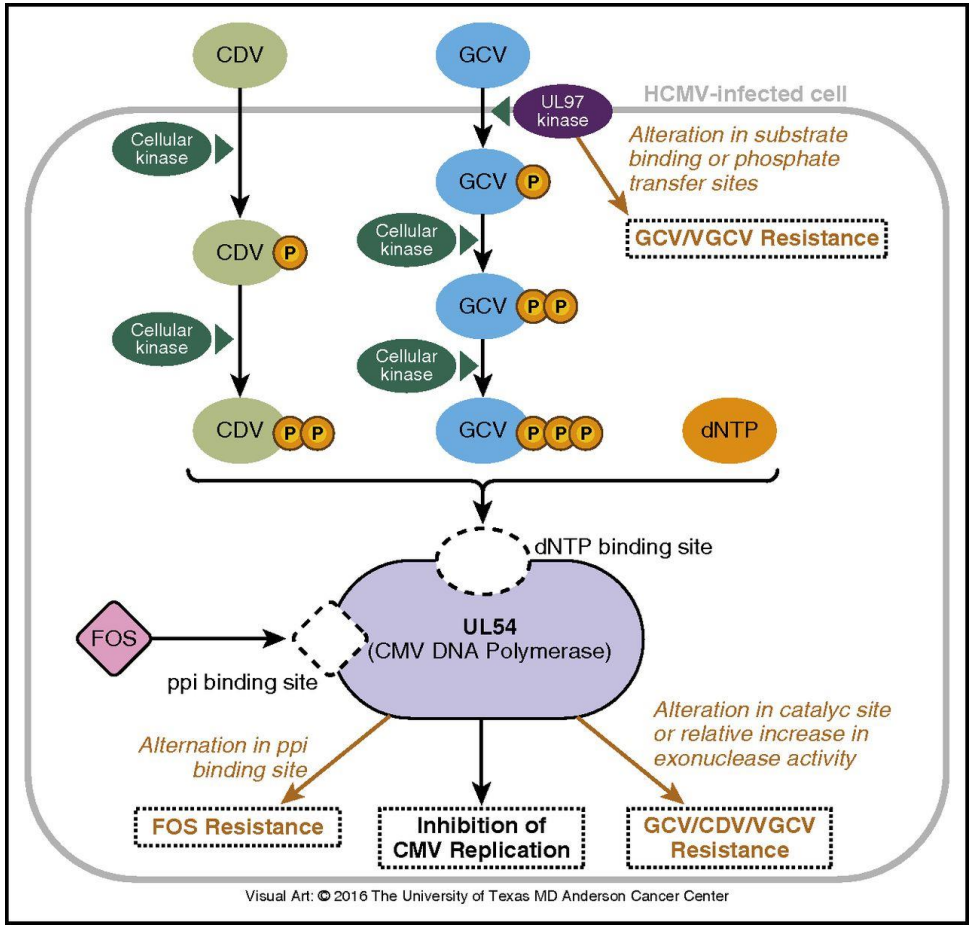
What are the Risk Factors for R/R CMV Infection?



Important Note: Patients may be refractory to antiviral treatment but not have detectable resistance

1. Chemaly RF, et al. *Clin Infect Dis.* 2019;68(8):1420-1426.
2. Lumbreras C, et al. *Clin Microbiol Infect.* 2014;20(suppl 7):19-26.

Mechanism of Action of Antiviral Drugs for CMV

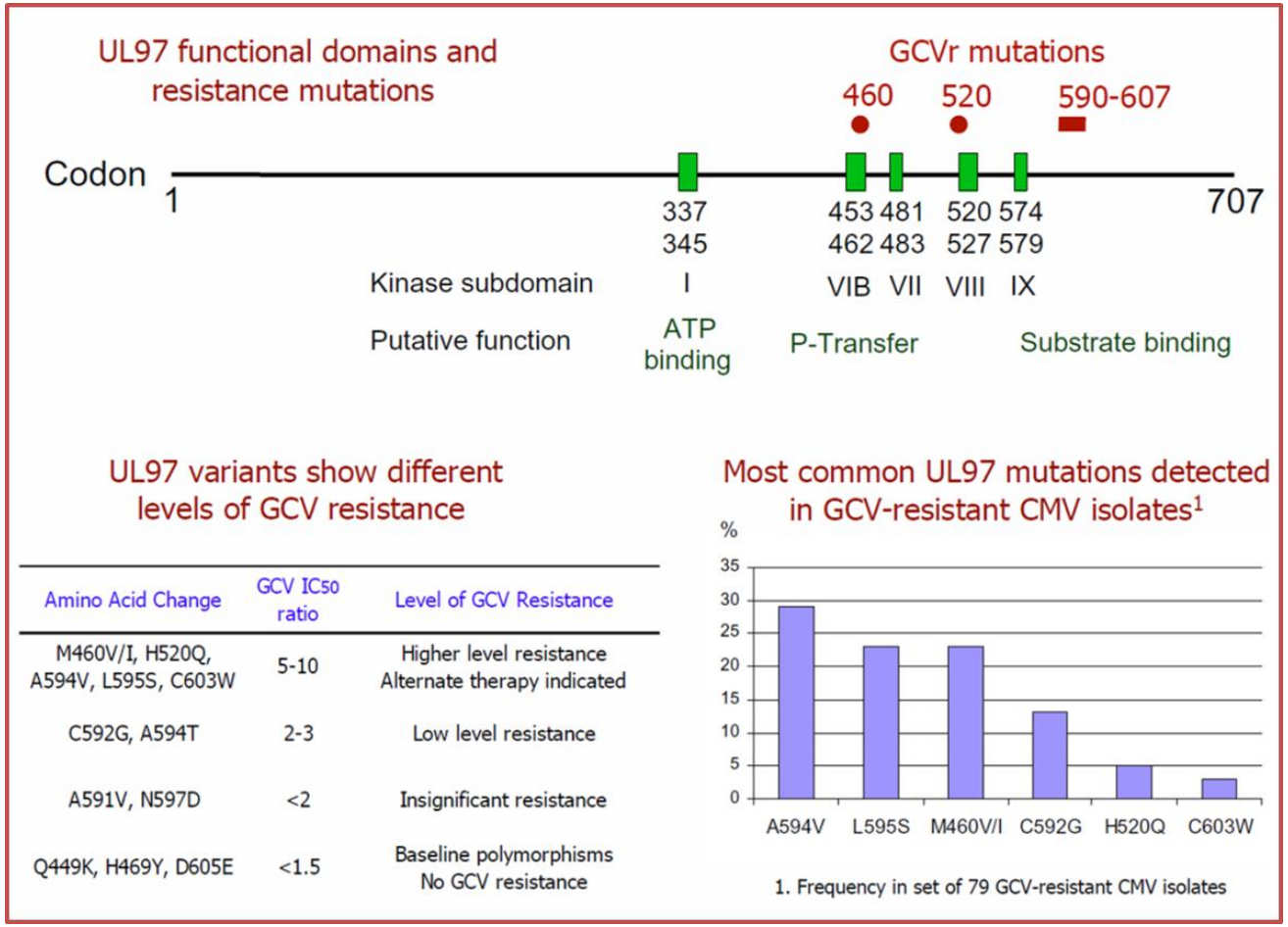


GCV, ganciclovir; CDV, cidofovir; FOS, foscarnet

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

How Do You Confirm Resistant CMV

- Genotypic resistance testing involves sequencing of relevant portions of the CMV genome and is the preferred method
- Phenotypic resistance testing involves culturing the virus in the presence of different drug concentrations and is more labor intensive



Courtesy S. Chou

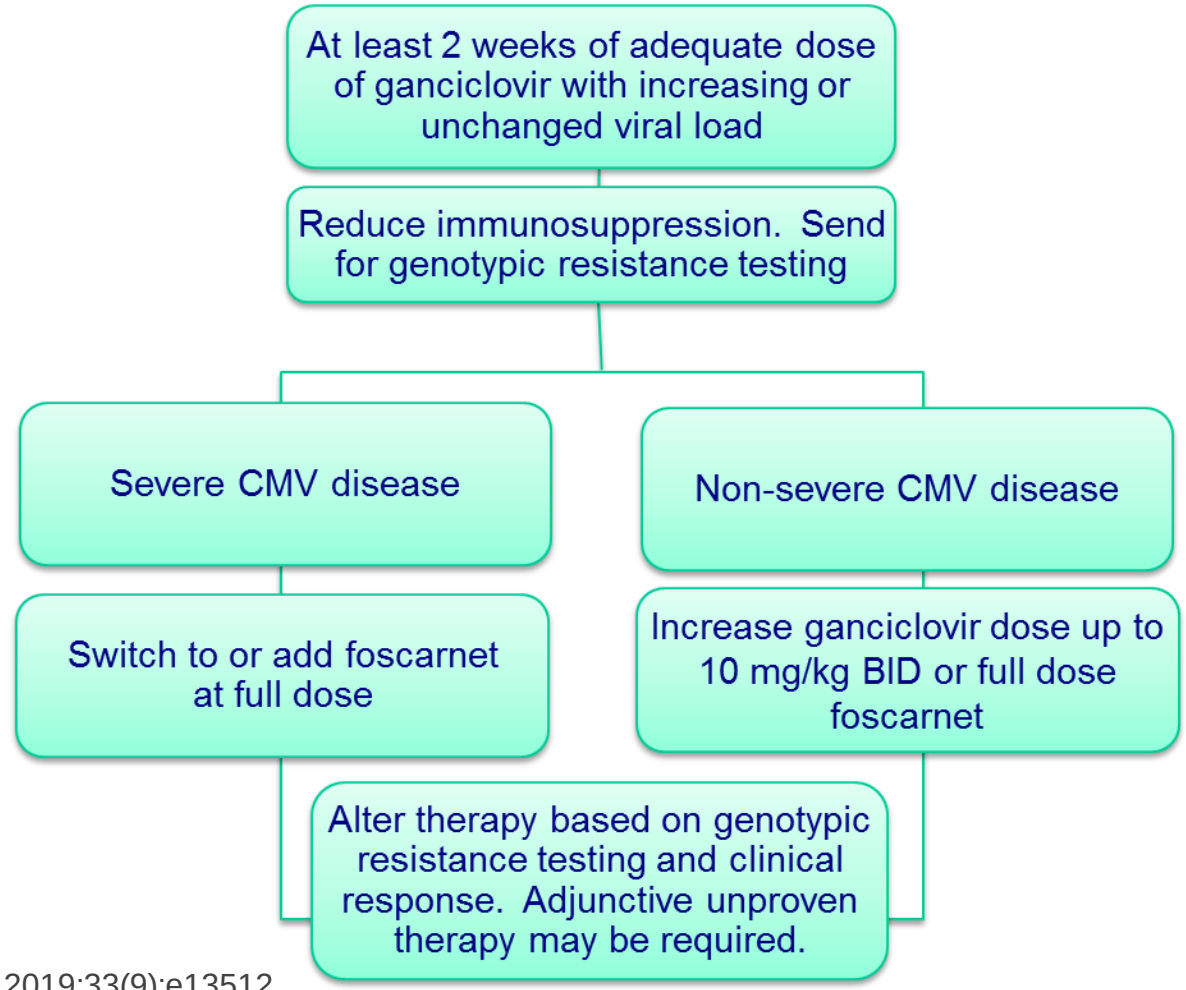
Lurain NS, Chou S. *Clin Microbiol Rev.* 2010;23(4):689-712.
Chou S. *Curr Opin Infect Dis.* 2015;28(4):293-299.

Polling Question

Which of the following do you use most often to treat refractory or drug-resistant CMV in patients with SOT?

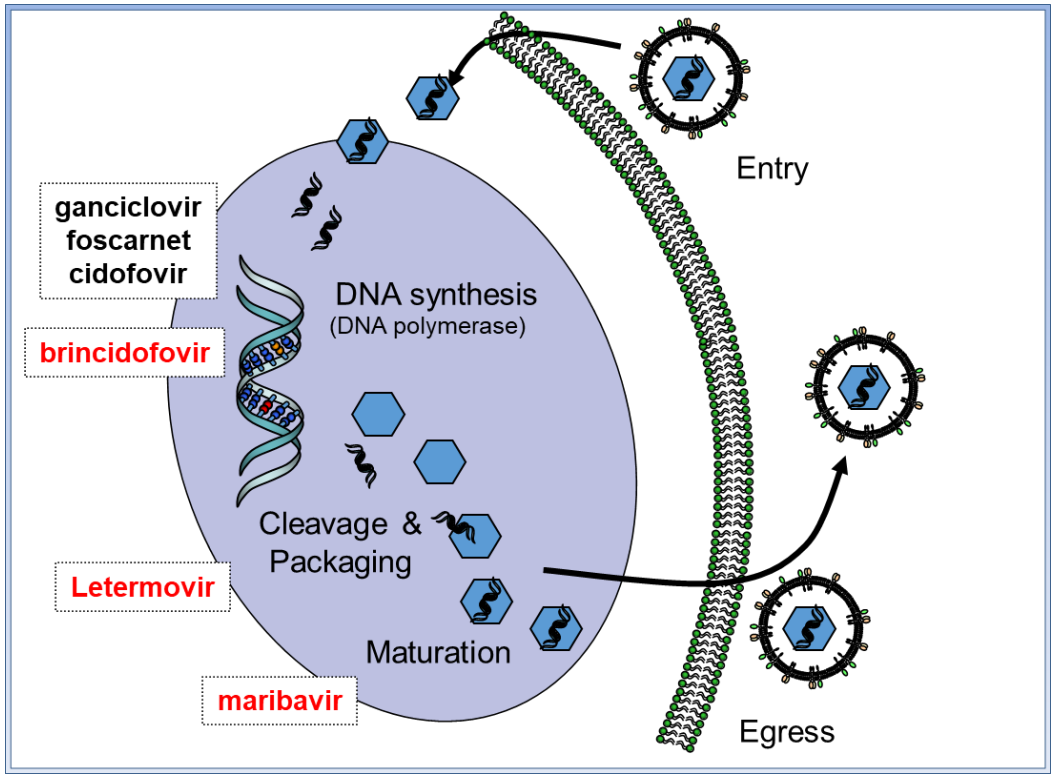
A. Foscarnet
B. Cidofovir
C. Maribavir
D. High-dose ganciclovir

Traditional Approach to GCV R/R Typically Involves Foscarnet or High-dose GCV

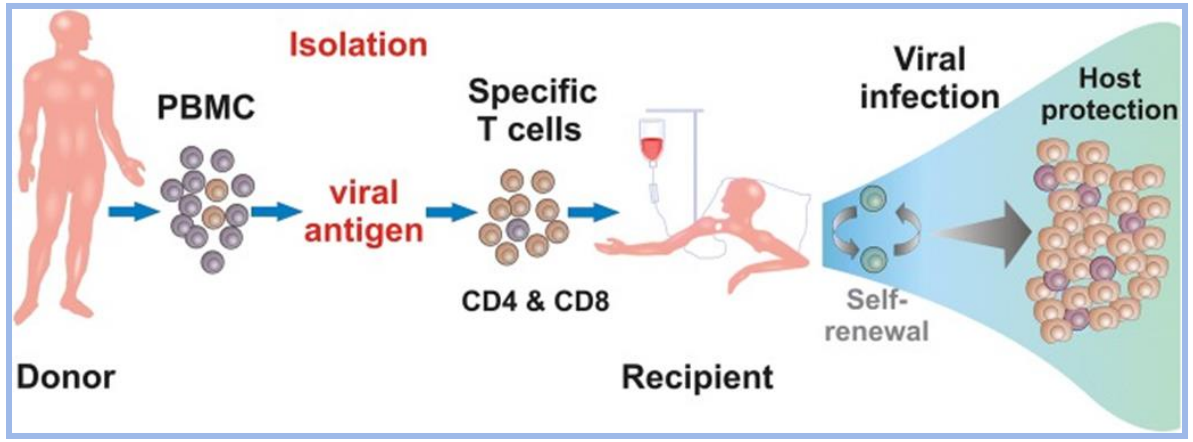


Razonable RR, Humar A. Clin Transplant. 2019;33(9):e13512.

New Approaches for R/R CMV Available or in Development



New Small Molecules



Adoptive T-cell Therapy

Courtesy of Karl S. Peggs

Kaeuferle T, et al. *J Hematol Oncol*. 2019;12(1):13.

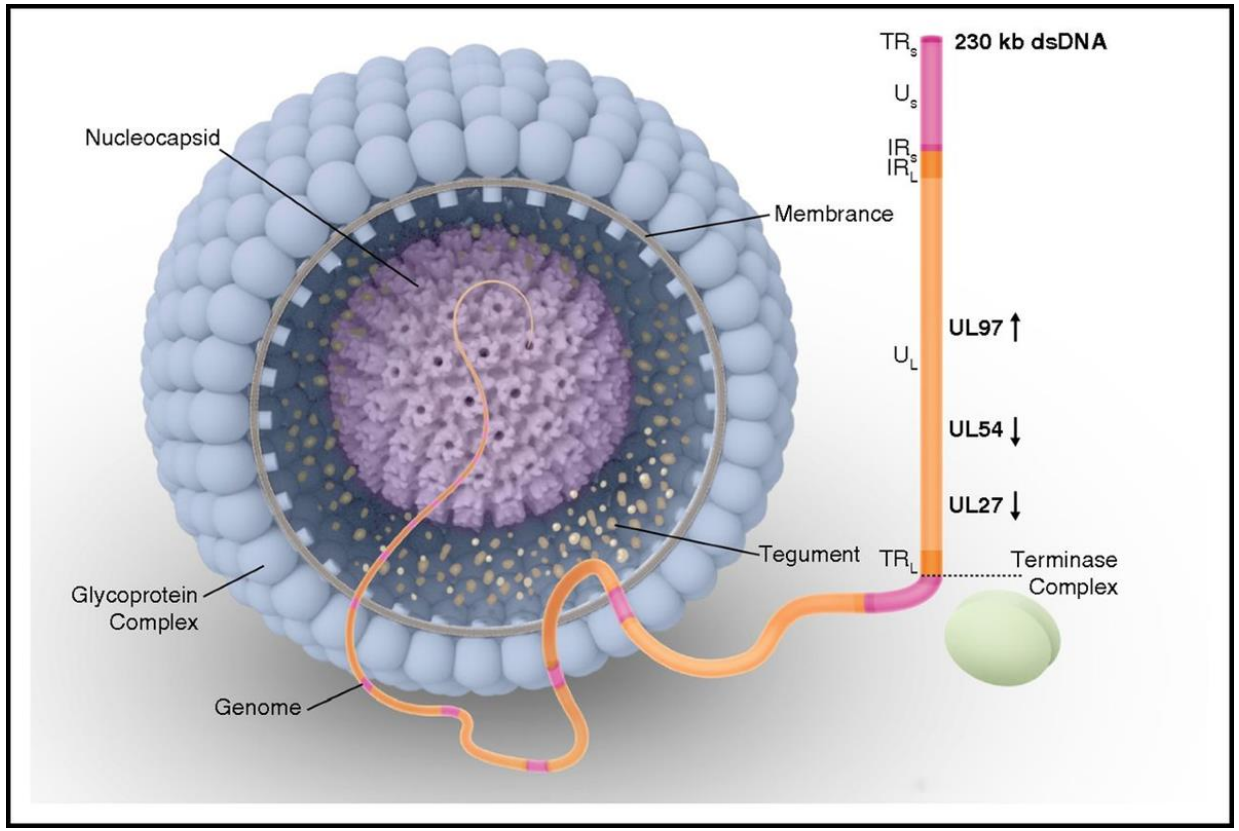
Letermovir

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

- FDA approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogenic HCT
- Recently shown to be non-inferior to valganciclovir for CMV prophylaxis in D+/R- kidney transplant recipients[1]



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

HCT, hematopoietic cell transplant

1. Limaye AP, et al. Presented at IDWeek; October 19-23, 2022; Abstract LB2307.

Letermovir in Transplant Patients and R/R CMV Infection

- Limited clinical studies with R/R CMV infection – off-label, unproven indication
  - Multicenter study of 47 SOT and HCT patients with CMV treated with letermovir[1]
    - 37 patients with low VL (<1000 IU/mL) had good response
    - Only 2 patients had VL increase >1 log by 12 weeks
    - 10 patients with higher VL had mixed response (~60 % response to <1000 IU/mL)
  - Study of 28 lung transplant patients with R/R CMV treated with letermovir[2]
    - 14 patients with VL >10,000 IU/mL
    - 82.1% response with VL decline >1 $\log_{10}$
    - 3 patients developed letermovir resistance mutations (UL56, C325Y)
- Uncertainty about optimal dosing[3] and possible low barrier to resistance[4]
- More studies are needed before letermovir can be recommended for treatment

R/R, refractory/resistant; SOT, solid organ transplant; HCT, hematopoietic cell transplant; VL, viral load

Linder KA, et al. *Transpl Infect Dis*. 2021;23(4):e13687.
Veit T, et al. *Am J Transplant*. 2021;21(10):3449-3455.
Hakki M. *Curr Hematol Malig Rep*. 2020;15(2):90-102.
Shigle TL, et al. *Ther Adv Hematol*. 2020;11:2040620720937150.

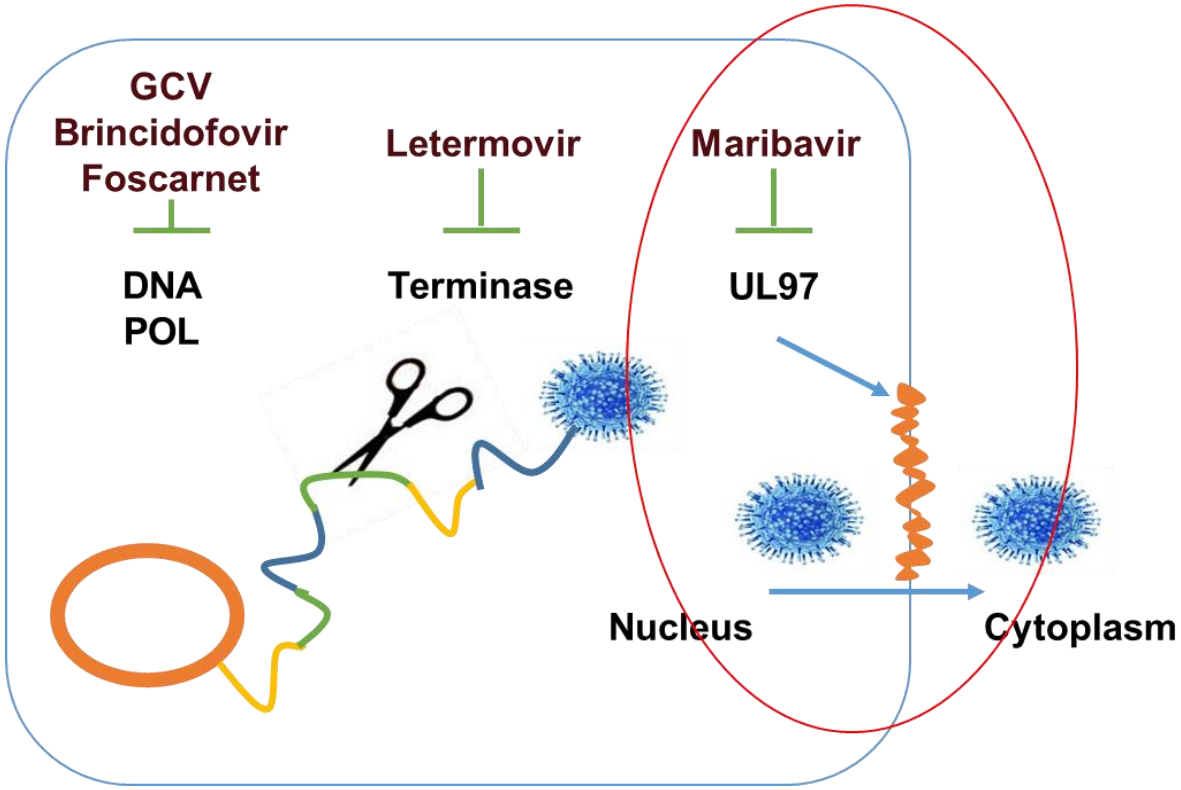
Maribavir

Mechanism of Action

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

Use

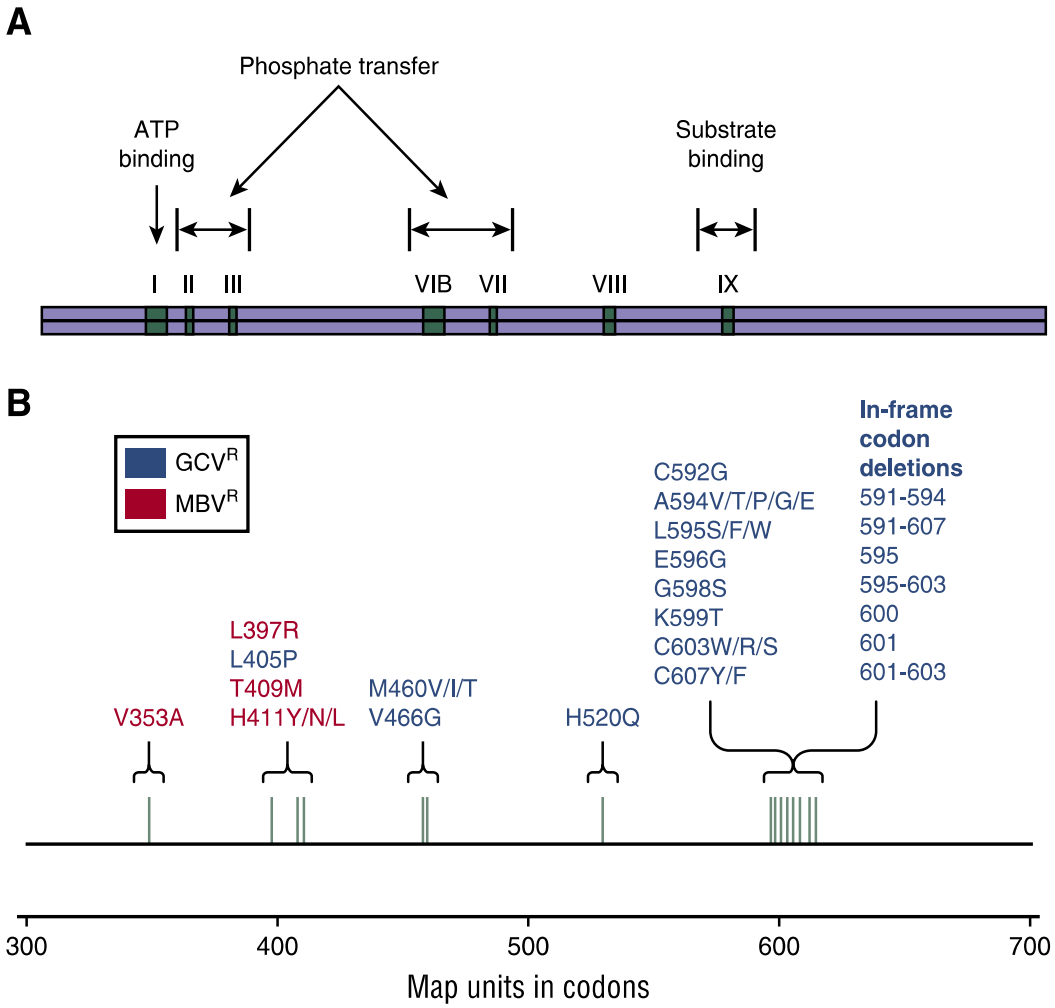
- FDA approved for the treatment of adults and pediatric patients with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet
- Orally bioavailable
- Not myelosuppressive or nephrotoxic—main side effect is taste disturbance
- Should not be used in case of encephalitis or retinitis



Maribavir Resistance Generally Maps to Different Parts of UL97 Compared to GCV Resistance

A. Map of the CMV UL97 Gene: Functional Regions of the UL97 Kinase

B. UL97 Mutations With Corresponding Antiviral Resistance Profiles



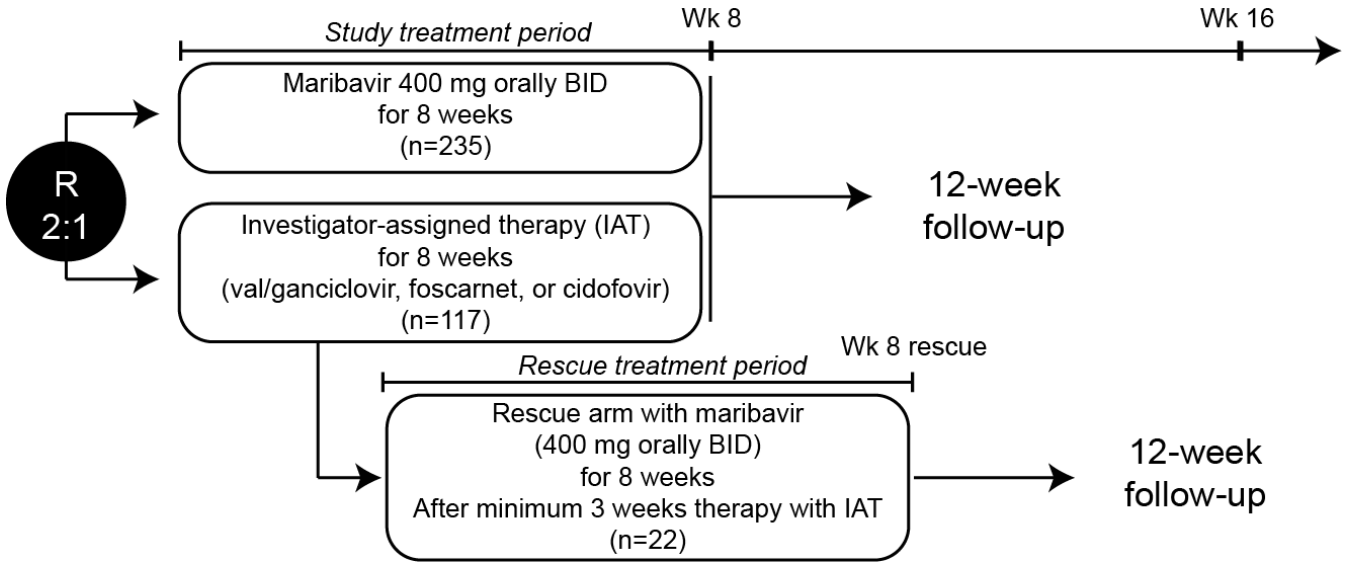
El Chaer F, et al. Blood. 2016;128(23):2624-2636.

Maribavir Phase 3 SOLSTICE Trial: Study Design

CARE TEAM FORUM®

Key Study Inclusion Criteria

- SOT/HCT recipients
- CMV infection (plasma CMV DNA ≥910 IU/mL)
- Refractory to most recent therapy (failure to achieve >1 $\log_{10}$ decrease in CMV DNA after 14 days)



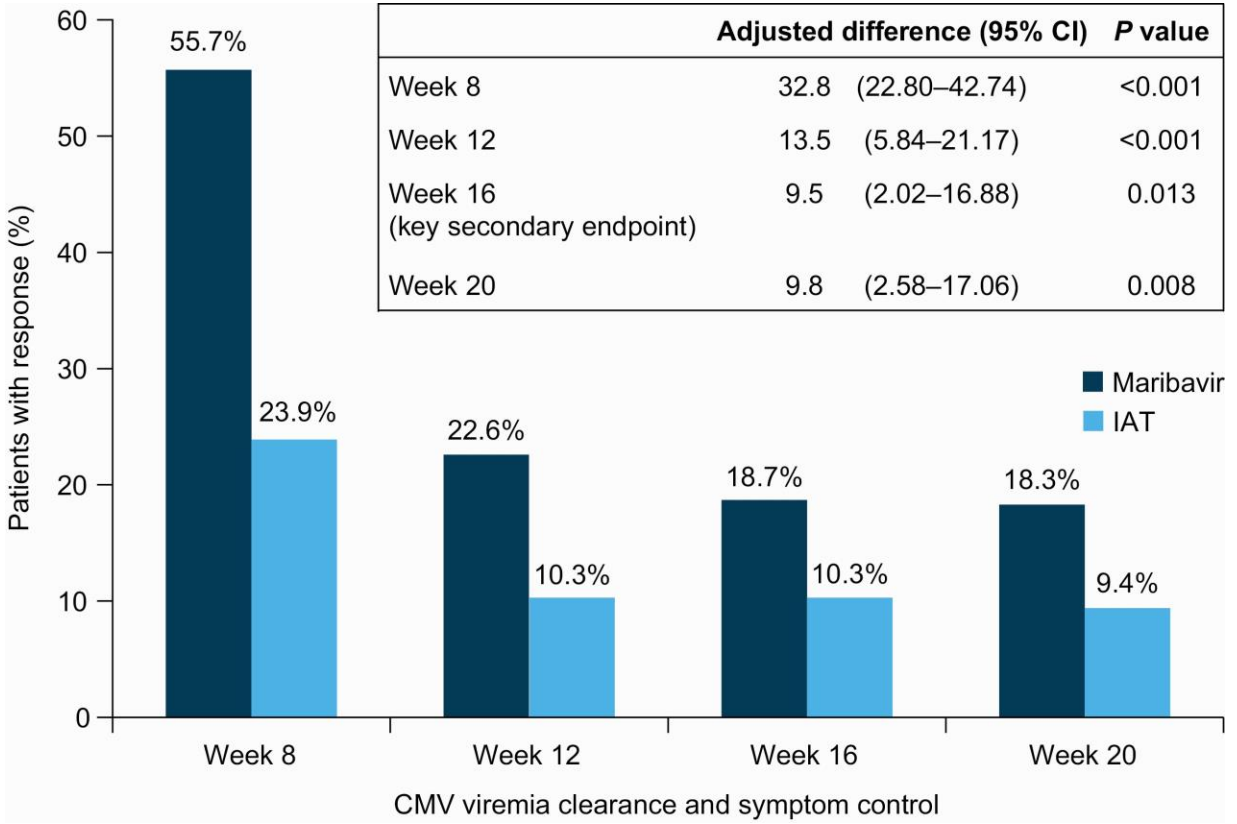
End Points		
Primary	**Key Secondary**	**Other Secondary**
Confirmed CMV viremia clearance (plasma CMV DNA <LLOQ in 2 consecutive tests ≥5 days apart at central laboratory) at end of Week 8	Composite of CMV viremia clearance and symptom control at end of Week 8 and maintained through Week 16	Assess the efficacy (including symptom control) and safety of maribavir as rescue treatment

SOT, solid organ transplant; HCT, hematopoietic cell transplant; BID, twice daily; LLOQ, lower limit of quantification

Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-671.

Maribavir Phase 3 SOLSTICE Trial: Primary and Secondary Endpoint Results

Confirmed Viremia Clearance and Symptom Control



Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-671.

Conclusions and Summary

- Exciting and interesting data in ongoing studies
- New treatment for R/R CMV infection:
  - MBV: FDA approved effective oral option with minimal serious side effects
- Potential further considerations
  - Cost / coverage for medications an important consideration
  - Inpatient versus outpatient
  - Combination therapy for GCV R/R:
    - Eg, FOS/MBV or FOS/LET or MBV/LET: no data currently
    - Avoid MBV/GCV combination (MBV inhibits UL97 which is needed for GCV phosphorylation)

R/R, refractory/resistant; MBV, maribavir; GCV, ganciclovir; FOS, foscarnet; LET, letermovir

Panel Discussion

- What are the most common risk factors for refractory and drug-resistant CMV in transplant recipients?
- What are some clinical pearls for interpreting viral load and drug-resistance testing results?

Considerations for New CMV Therapy: The Patient Voice

Fernanda P. Silveira, MD, MS, FIDSA, FAST

Professor, Medicine
Director, Clinical Operations, Transplant Infectious Diseases
University of Pittsburgh
University of Pittsburgh Medical Center
Pittsburgh, PA

Patient Case – Bret

- A 60-year-old male underwent double lung transplant for cystic fibrosis in September 2014
- Basiliximab induction + tacrolimus/mycophenolate mofetil 1000 mg BID/prednisone 5 mg/day
- Methylprednisolone pulse 2 months post-transplant for ACR; CKD from CNI toxicity, CrCl ~30 mL/min, listed for kidney transplant
- CMV donor seropositive/recipient seronegative (D+/R-); received 2 years of valganciclovir prophylaxis, renally adjusted
- Approximately 1.5 months later, presents with CMV syndrome, possible GI disease, CMV DNAemia 580,000 IU/mL (whole blood), started on IV ganciclovir
- Resolution of symptoms but persistently positive CMV DNAemia (500 to 1600 IU/mL); received CMV IgG; progressive increase of CMV DNAemia to 21,000 IU/mL
- CMV resistance testing: ganciclovir resistance, UL97 mutation (L595S)
- Evaluated for maribavir clinical trial – not eligible due to GFR 29 mL/min

BID, twice per day; ACR, acute cellular rejection; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CrCl, creatinine clearance; CMV, cytomegalovirus; GI, gastrointestinal; IV, intravenous; GFR, glomerular filtration rate

Patient Case – Bret (cont'd)

- Started on foscarnet with IV hydration and labs thrice weekly
- After 2 weeks: no significant change in CMV PCR, GFR 31 mL/min
- Enrolled in Phase 3 trial of maribavir for refractory/resistant CMV, randomized to maribavir 400 mg PO BID
- Mild dysgeusia, CMV PCR not detected on week 2
- Received 8 weeks of maribavir per trial protocol
- Episode of CMV reactivation about a year later, responded to VGCV but had neutropenia
- Intermittent, asymptomatic, low level CMV DNAemia (250 to 350 IU/mL)
- Renal function stable, excellent lung function, no need for kidney transplant!

IV, intravenous; CMV, cytomegalovirus; PCR, polymerase chain reaction; GFR, glomerular filtration rate; PO; by mouth, BID, twice per day; VGCV, valganciclovir

What Bret's Case Teaches Us

- High risk for CMV due to lung transplantation and CMV D+/R- status
- Had prolonged exposure to VGCV, a risk factor for development of antiviral resistance
- Renal insufficiency required antiviral dose adjustment
- At increased risk of nephrotoxicity with foscarnet and experienced neutropenia with VGCV
- Did well with maribavir, which allowed him to avoid further foscarnet treatment and maintain stable renal function. He does not need a kidney transplant now!
- Will be able to receive maribavir again, if necessary

CMV, cytomegalovirus; VGCV, valganciclovir

CMV From a Patient's Perspective

- What was your reaction when you were told that you had cytomegalovirus (CMV)?
- Did you know what CMV was?
- What was your experience with therapies used to treat your CMV?
- What did you think when you were offered a CMV therapy that you could take by mouth and not have to be in the hospital?
- What advice do you have for healthcare professionals in the audience who treat patients with CMV?

Panel Discussion

- How should maribavir be used in the care of SOT patients with refractory or drug-resistant CMV?
- When should clinicians seek a consult from an infectious disease clinician for SOT patients with CMV?

Audience Q&A

Thank You for Participating

To receive credit for this activity,
please click the **"Earn Credit"** icon,
Or visit:
www.medscape.org/cmelive/cmv-credit