CMEO Snack

Novel Approaches to Treating CMV Infection in People Receiving Solid Organ or Hematopoietic Stem Cell Transplantations

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

Roy F. Chemaly, MD, MPH, FIDSA, FACP
Professor of Medicine
Chief, Infection Control Officer
Director, Clinical Virology Research
Department of Infectious Diseases, Infection Control, and Employee Health
The University of Texas MD Anderson Cancer Center
Houston, TX

Genovefa Papanicolaou, MD, FIDSA
Attending Physician, Infectious Disease Service
Memorial Sloan Kettering Cancer Center
Professor, Weill Cornell Medical College
Cornell University
New York, NY

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Learning Objective 1

Identify factors that increase the risk of CMV infection.

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Learning Objective 2

Recognize the impact of CMV infection on treatment outcomes for transplant recipients.

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Learning Objective 3

Develop balanced treatment plans for patients with CMV disease.

CMV Background

- CMV infection remains among the most significant and common complications after HCT and SOT
- Cumulative incidence of CMV reactivation
  - 36% among all allo-HCT
  - Up to 80% Cord Blood Transplant
  - Up to 80% SOT
- CMV end-organ-disease: The incidence of CMV pneumonia ranges from 1% to 6% in low-risk HCT recipients and 10% to 30% in high-risk HCT recipients (e.g., haploidentical and T-cell depleted HCT)

Allo-HCT = allogeneic hematopoietic stem cell transplant; CMV = cytomegalovirus; HCT = hematopoietic stem cell transplant; SOT = solid organ transplantation

Haidar G, et al. J Infect Dis. 2020;221(Suppl 1):S23-S31. Hajjar SA, et. al. *Hematol Oncol Stem Cell Ther*. 2011;4(2):68-69.
Kotloff RM, et al. *Am J Respir Crit Care Med*. 2004;170:22-48. Ariza E, et al. *Cancer Letters*. 2014 Jan 1;342(1):1-8.
Yong MK, et al. Transplant Cell Ther. 2021;27(12):957-967.

Burden of CMV Infection After HCT or SOT

- CMV infection damages multiple organs and tissues leading to increased the risk of morbidity, mortality, and graft failure.[1]
  - Organ rejection
  - Venous thrombosis
  - Pneumonitis
  - Hepatitis
  - Myocarditis
  - Retinitis
  - Bone marrow suppression and infections
  - Pancreatitis
  - Colitis, gastritis, esophagitis, and enteritis
  - Meningitis or encephalitis
- Frequent concomitant gastrointestinal CMV disease and graft versus host disease (GVHD) in patients receiving HCT[2]
- Increased risk of vascular disease and atherosclerosis after heart transplant[3]
- Increased the risk of developing diabetes after renal transplant[4]
- Increased hospitalizations, costs[5]

1. Haidar G, et al. *J Infect Dis*. 2020;221(Suppl 1):S23-S31. 2. Ljungman P, et al. *Hematol Oncol Clin North Am*. 2011;25(1):151-169.
3. Sambiase NV, et al. *Modern Pathology*. 2000;13(2):173-179. 4. Hjelmesaeth J, et al. *Diabetologia*. 2004;47(9):1550-1556.
5. Cheng WY, et al. *Journal of Medical Economics*. 2022;25(1):367-380.

Risk Factors for CMV Infection in HCT

HCT Days 0-29

CMV DNAemia; end-organ disease is rare in first 30 days

Risk factors for CMV infection and end-organ disease

- CMV-seropositive recipient
- Advanced age
- Type of transplant (MUD, haploidentical transplant, CBT)
- Conditioning regimen (fludarabine, alemtuzumab, total body irradiation)
- Immunosuppression (antithymocyte globulin, steroids)

Days 30-100

CMV infection is common in high-risk recipients (pneumonia is most common)

Risk factors for CMV infection and end-organ disease

Prior risk factors +

- Presence of acute GVHD
- Delay of T-cell recovery

> 100 Days

CMV end-organ disease: pneumonia, GI, CNS, retinitis

Risk factors for CMV infection and end-organ disease

- Steroids use, GVHD
- Delay of T-cell recovery
- Non-myeloablative conditioning
- CMV reactivation before day 100

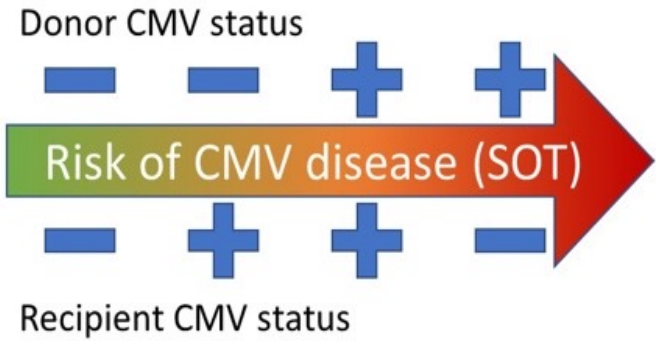
50% - 70% of CMV R+ patients develop CMV viremia after HCT

CBT = cord blood transplant; CNS = central nervous system; GI = gastrointestinal; MUD = matched unrelated donor

Ariza-Heredia EJ, et al. *Cancer Lett.* 2014;342:1-8.

Risk Factors for CMV Infection in SOT

- Patients receiving lung, heart, and multi-organ transplants have the highest risk,
  - Kidney and stem cell transplants have the lowest risk
- Biggest risk factor for CMV disease in SOT is serological mismatch between the donor and recipient
  - Recipient is CMV seronegative (R-) and donor is seropositive (D+)
  - CMV D+/R+ and CMV D-/R+ transplantations are intermediate risk
  - CMV D-/R- transplantation is low risk



- Late onset CMV infection develops in third of seropositive recipients

Kumar D, et al. *Am J Transplant*. 2019;19(9):2505-2516. Azevedo LS, et al. *Clinics (Sao Paulo)*. 2015;70(7):515-523.

Additional Risk Factors for CMV Infection in SOT

- Intense immunosuppression (low white blood counts due to conditioning, post-transplant corticosteroids)
- Use of lymphocyte-depleting antibodies (e.g., antithymocyte globulin)
- Acute rejection/GvHD
- Advanced age in the donor and/or recipient, low renal function, high BMI
- HLA mismatch
- Other concurrent infections (e.g., herpes virus 6 or 7)
- Genetic polymorphisms

BMI = body mass index; HLA = human leukocyte antigen

Kumar D, et al. *Am J Transplant*. 2019;19(9):2505-2516. Azevedo LS, et al. *Clinics (Sao Paulo)*. 2015;70(7):515-523.

CMV Diagnosis

- PCR testing and assays including sensitivity, tests over time, and result interpretation
- IgG seropositivity – assessing donors and recipients
- CMV-specific T-cell immunity

IgG = immunoglobulin G; PCR = polymerase chain reaction

CMV Prevention Strategies HCT: Prophylaxis vs. Preemptive Therapy

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

Preemptive therapy has been the preferred strategy

GCV = ganciclovir

Haidar G, et al. *J Infect Dis*. 2020;221(Suppl 1):S23-S31. Yahav D, et al. *Eur J Cancer*. 2009;45:3131-3148. Milano F, et al. *Blood*. 2011;118:5689-5696. Ljungman P, et al. *Hematol Oncol Clin North Am*. 2011;25:151-169.

CMV Prevention Strategies SOT: Prophylaxis vs. Preemptive Therapy vs. Hybrid

	Prophylaxis	Preemptive Therapy
Description	▪ Antivirals for all patients at risk prior to the onset of CMV infection	▪ Routine monitoring for CMV infection ▪ Treatment upon detection of asymptomatic CMV infection
Pros	▪ Large evidence base ▪ Ease of coordination ▪ Prevents CMV infection/disease ▪ Prevents indirect effects of CMV (graft loss, opportunistic infections)	▪ Simulates natural CMV immunity ▪ Prevents delayed-onset CMV ▪ Less neutropenia ▪ Possibly more cost-effective
Cons	▪ Postprophylaxis disease ▪ High cost ▪ Neutropenia ▪ Use of antivirals in some patients who will not develop CMV infection	▪ Logistical difficulties ▪ Small evidence base ▪ Unknown impact on indirect effects of CMV ▪ Viral thresholds not defined ▪ Unknown frequency of testing ▪ Rapid doubling time of CMV viral loads in some patients

Prophylaxis has been the preferred strategy

Haidar G, et al. *J Infect Dis.* 2020;221(Suppl 1):S23-S31.

CMV Infection Treatment

Agent	MoA	Dosing	Considerations
Letermovir	CMV UL56/98-binding agent	Oral	Approved for CMV prophylaxis; significant drug interactions
Ganciclovir	Target CMV polymerase	IV	Recommended for first-line preemptive therapy; leukopenia
Valganciclovir		Oral	
Val/acyclovir		IV/oral	Limited activity against CMV infection; HCT and kidney transplants only; neurologic adverse effects
Foscarnet		IV	Recommended when ganciclovir/valganciclovir resistance/intolerance; highly nephrotoxic
Cidofovir		IV	
Maribavir	CMV UL97-binding agent	Oral	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)

Limitations of CMV Treatments

- Toxicity
  - Myelosuppression, neutropenia
  - Nephrotoxicity
- Multiple CMV treatment courses needed
  - 42% of patients receiving allo-HCT, approximately 28 days/course
  - 53% of patients receiving SOT, approximately 60 days/course
- Drug interactions
- Lack of response, development of refractory/resistant CMV infection

Cheng WY, et al. *J Med Econ*. 2022;25(1):367-380.

Refractory and Resistant (R/R) CMV Infection

Term	Definition
Refractory CMV infection	CMV viremia that increases* after at least 2 week of appropriately dosed antiviral therapy
Probable refractory CMV infection	Persistent viral load** after at least 2 week of appropriately dosed antiviral therapy
Refractory CMV end-organ disease	Worsening signs and symptoms or progression into end-organ disease after > 2 week of appropriately dosed antiviral therapy
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after at least 2 week of appropriately dosed antiviral drugs
Antiviral drug resistance	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs

* > 1 log10 increase in CMV DNA levels in blood or serum and determined by log10 change between the peak viral load in week 1 vs ≥ 2 weeks as measured in the same laboratory with the same assay.

** ≥ peak viral load within 1 week but < 1 log10 increase in CMV DNA titers done in the same laboratory and with the same assay.

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

Risk Factors for CMV Therapy Resistance

HOST FACTORS

- Profound immune depression
- Suboptimal doses of antiviral dose-limiting toxicities
- Poor compliance to PET antiviral
- Poor absorption of PET oral drug

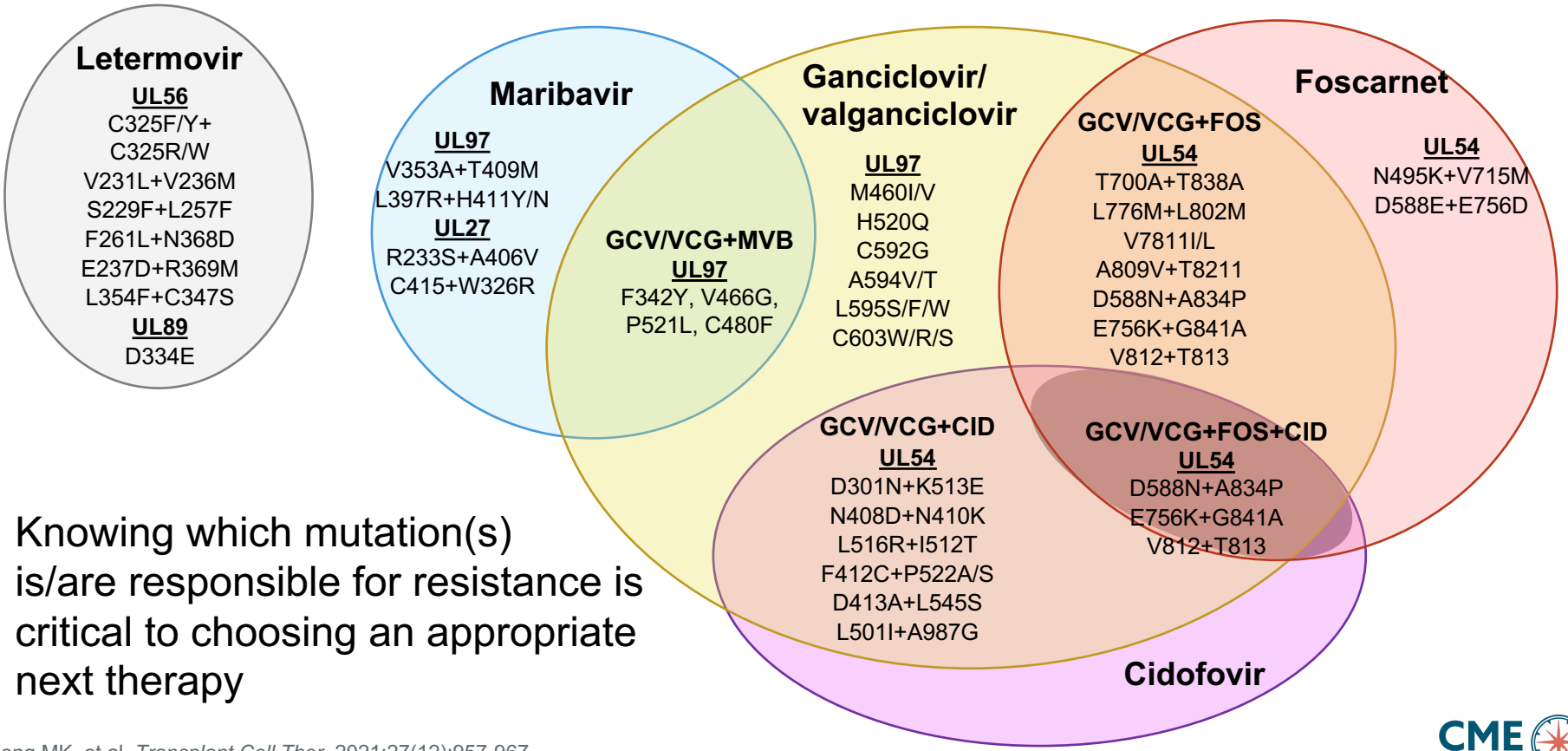
VIRAL FACTORS

- Initial high viral load
- Viral replication kinetics
- Genotypic resistance (6%-25%) of refractory infections

- Rate of resistance is higher in SOT than HCT
- Mortality rate is higher in HCT than SOT
  - Up to 42% mortality in T-cell depleted HCT with resistant CMV disease

Lurain NS, Chou S. *Clin Microbiol Rev*. 2010;23(4):689-712.

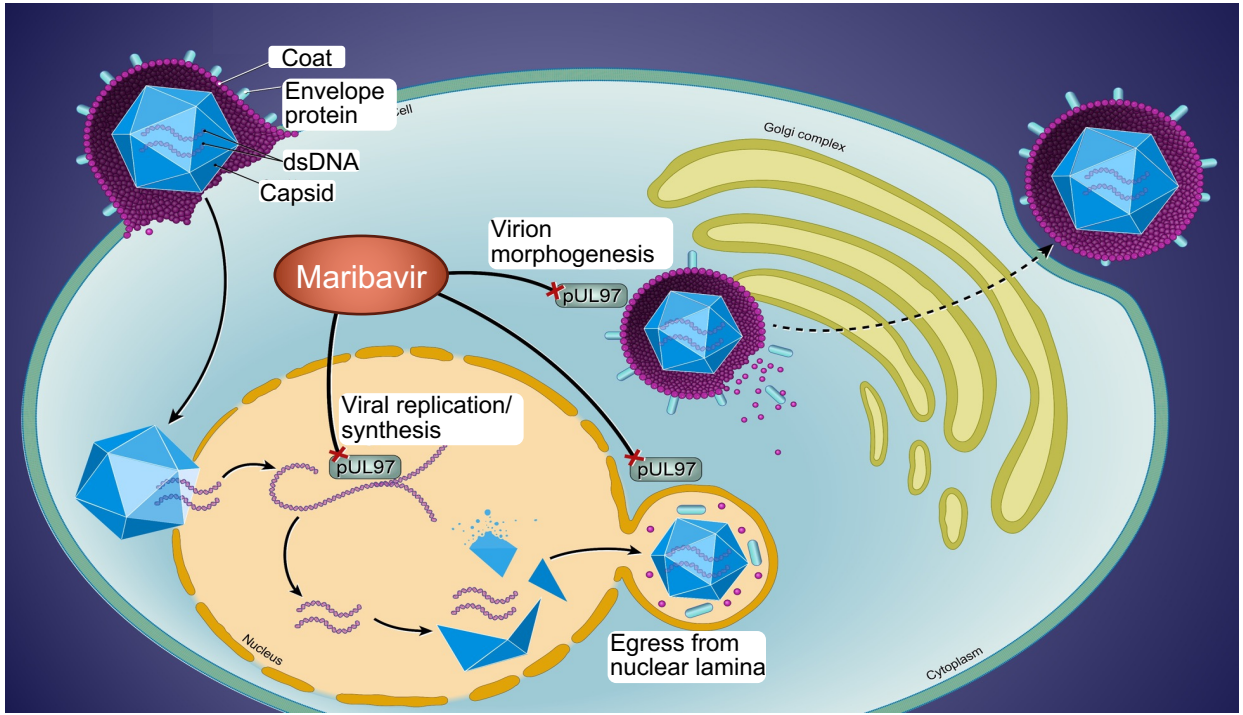
Most Common Known Mutations Conferring CMV Therapy Resistance in Patients Receiving HCT



Knowing which mutation(s) is/are responsible for resistance is critical to choosing an appropriate next therapy

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

Maribavir for Treatment of CMV



- Orally bioavailable
- No myelotoxicity
- No nephrotoxicity
- Targets pUL97
  - Active against 3 points in viral lifecycle

Active in vitro against CMV strains resistant to standard agents

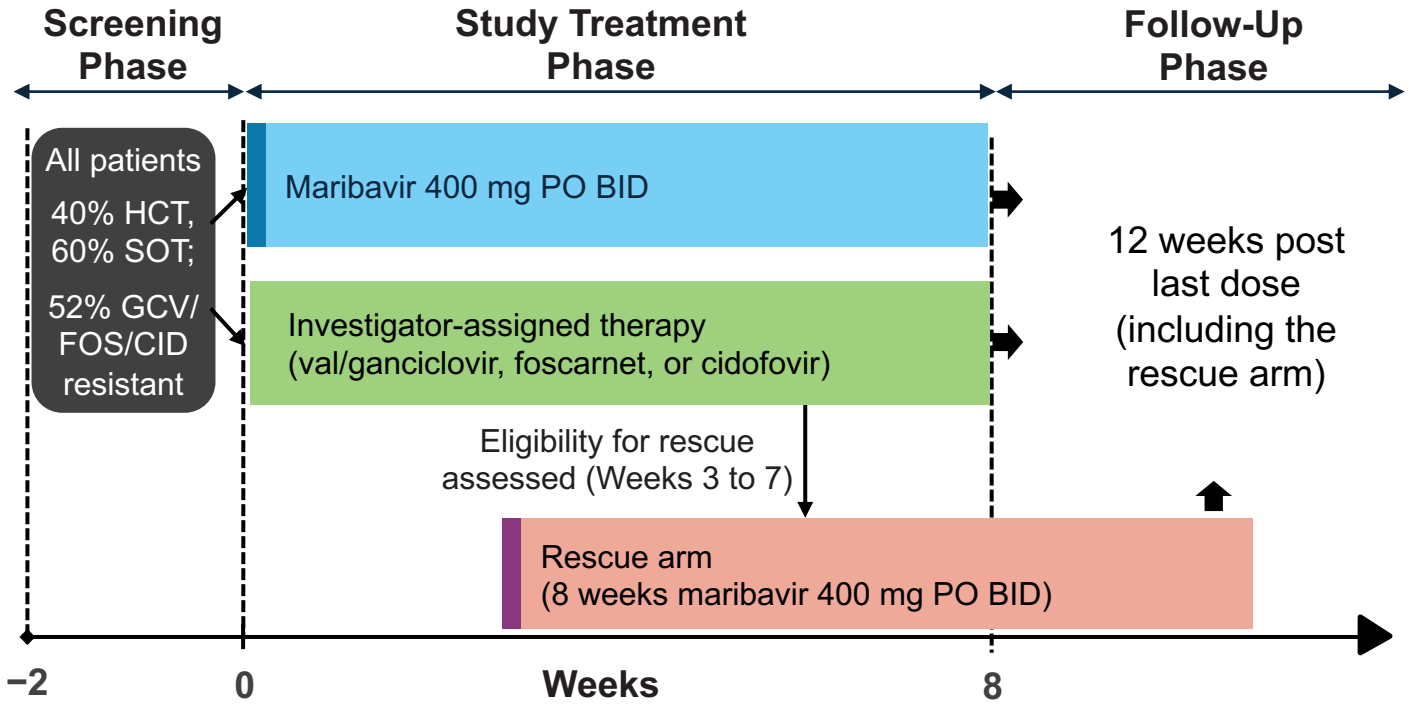
Khawaja F, et al. *submitted to CMI* 2022

Maribavir

- Multimodal anti-CMV activity
- Inhibits UL97 protein kinase
  - CMV DNA replication, encapsidation, and nuclear export of viral capsids
- In the phase II study
  - 67% of patients with R/R CMV infection achieved undetectable CMV DNA plasma levels within 6 weeks across all three doses (400, 800, 1200 mg oral BID)
  - On-treatment recurrence occurred in 21% of patients
    - Of these, 52% developed mutations conferring maribavir resistance
  - Maribavir discontinued in 34% patients
    - Of these, 41% due to CMV infection

Papanicolaou GA, et al. *Clin Infect Dis*. 2019;68(8):1255-1264.

SOLSTICE: Trial Design



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

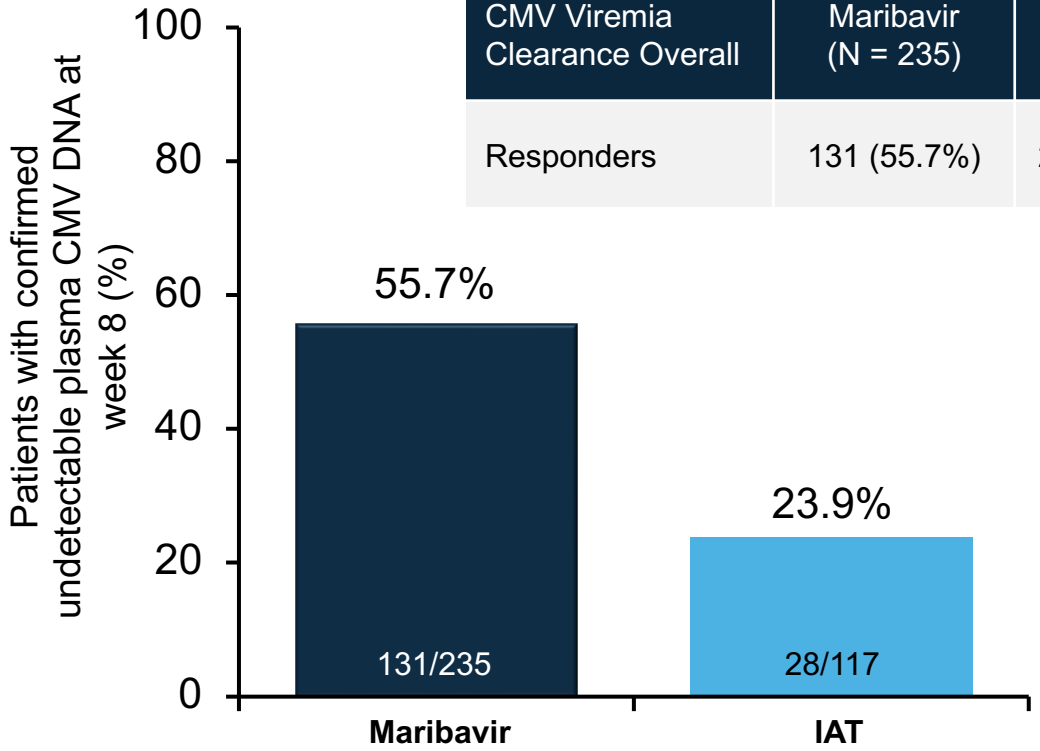
Key secondary endpoint
Achievement of CMV clearance and symptom control at end of week 8 and maintained through week 16

Randomization 2:1 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]).

Avery RK, et al. *Clin Infect Dis*. 2021:ciab988.

SOLSTICE: CMV Clearance vs. IAT at Week 8

CMV Viremia Clearance Overall	Maribavir (N = 235)	IAT (N = 117)	Adjusted Difference % (95% CI)	*P*-value
Responders	131 (55.7%)	28 (23.9%)	32.8 (22.8 - 42.7)	< 0.001

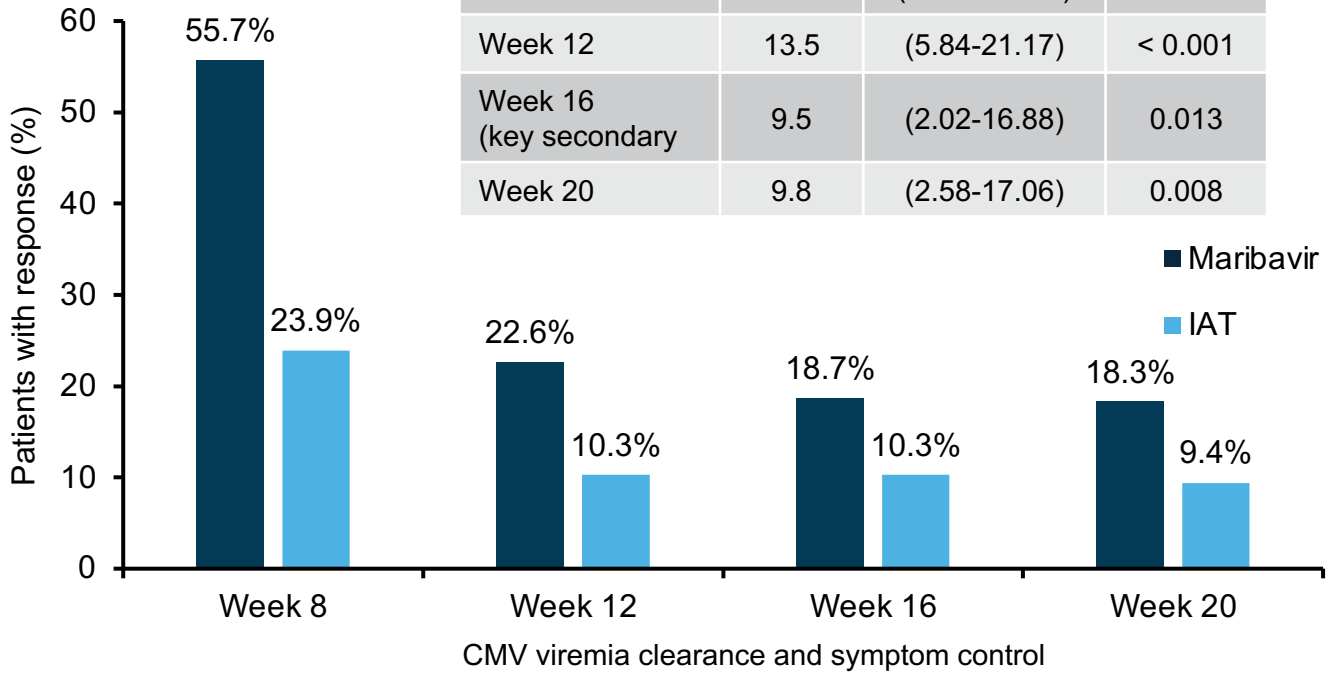


IAT = investigator assigned therapy

Avery RK, et al. *Clin Infect Dis.* 2021:ciab988.

SOLSTICE: Maribavir Symptom Control

	Adjusted difference (95% CI)		*P* value
Week 8	32.8	(22.80-42.74)	< 0.001
Week 12	13.5	(5.84-21.17)	< 0.001
Week 16 (key secondary	9.5	(2.02-16.88)	0.013
Week 20	9.8	(2.58-17.06)	0.008



CMV viremia clearance and symptom control

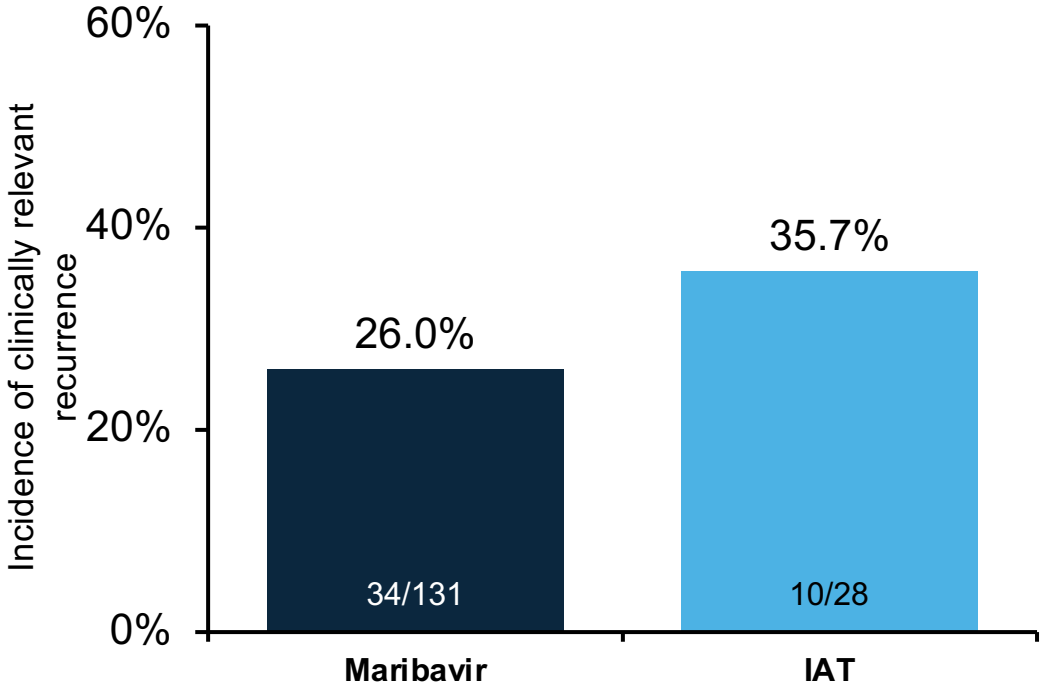
Composite endpoint of CMV DNA level < LLOQ and CMV infection symptom control at Week 8, with maintenance through Week 16

- CMV infection symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no symptoms for patients who were asymptomatic at baseline.
- In both treatment arms, the percentage of patients achieving this composite endpoint was lower than the primary endpoint in:
  - Virologic relapse
  - Reactivation of CMV during periods of immunosuppression

IAT = investigator assigned therapy

Avery RK, et al. *Clin Infect Dis*. 2021:ciab988.

SOLSTICE: Clinically Relevant Recurrence of CMV During Follow-Up



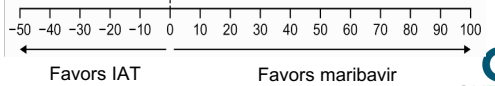
Clinically relevant CMV viremia recurrence was defined as recurrence after achieving the primary endpoint of CMV viremia clearance at the end of Study Week 8, which required alternative anti-CMV treatment.

Avery RK, et al. *Clin Infect Dis*. 2021:ciab988.

SOLSTICE: Viremia Clearance in Subgroups

- Results generally consistent across subgroups including
  - IAT agent
  - Transplant type
  - Baseline viral load
  - Baseline resistance to other CMV antivirals

Characteristic	n/N (%) of responders: Maribavir	IAT	Adjusted difference in proportion of responders (95% CI)
Age group			
18-44 years	28/55 (50.9)	8/32 (25.0)	26.4 (6.1-46.7)
45-64 years	71/126 (56.3)	19/69 (27.5)	29.9 (16.243.6)
≥ 65 years	32/54 (59.3)	1/16 (6.3)	53.9 (36.81-71.08)
Transplant type			
SOT	79/142 (55.6)	18/69 (26.1)	30.5 (17.3-43.6)
HCT	52/93 (55.9)	10/48 (20.8)	36.1 (20.9-51.4)
IAT			
Valganciclovir/ganciclovir	NA	15/56 (26.8)	31.7 (18.6-44.8)
Foscarnet	NA	9/47 (19.1)	36.4 (13.4-40.4)
> 1 IAT	NA	4/7 (57.1)	-3.2 (-40.3-34.0)
Baseline CMV viral load			
LOW	95/153 (62.1)	21/85 (24.7)	37.4 (25.4-49.4)
Intermediate/high	36/82 (43.9)	7/32 (21.9)	21.8 (3.9-39.7)
Presence of IAT resistance mutation			
Yes	76/121 (62.8)	14/69 (20.3)	44.1 (31.3-56.9)
No	42/96 (43.8)	11/34 (32.4)	12.6 (-6.2-31.4)
Anti-lymphocyte globulin use			
Yes	53/100 (53.0)	12/49 (24.5)	29.9 (14.3-45.5)
No	78/135 (57.8)	16/68 (23.5)	35.0 (21.9-48.0)
Symptomatic CMV infection by EAC			
Yes	10/21 (47.6)	1/8 (12.5)	30.6 (-7.5-68.6)
No	121/214 (56.5)	27/109 (24.8)	32.5 (22.1-43.0)



Avery RK, et al. *Clin Infect Dis*. 2021:ciab988.

SOLSTICE: Maribavir Safety

- Median (range) duration of exposure was 57 days with maribavir and 34 days with IAT
- At least 1 treatment emergent adverse event (TEAE) was reported in 97.4% maribavir and 91.4% IAT groups
- Fewer patients discontinued due to TEAEs: 13.2% maribavir, 31.9% IAT
  - Dysgeusia resulted in discontinuation in 2 patients (0.9%) in the maribavir arm

TRAEs (≥ 5%)	Maribavir (n = 234)	IAT (n = 116)
Dysgeusia	**37.2%**	3.4% overall
Neutropenia	9.4%	22.4% overall **33.9%** valganciclovir/ganciclovir 14.9% foscarnet
Leukopenia	3.0%	6.9% overall **12.5%** valganciclovir/ganciclovir 2.1% foscarnet
Hypokalemia	3.4%	9.5% overall 1.8% valganciclovir/ganciclovir **19.1%** foscarnet 1/6 cidofovir
Acute kidney injury	8.5%	9.5% overall 1.8% valganciclovir/ganciclovir **21.3%** foscarnet

* % expressed as a function of that portion of the IAT group receiving specified therapy (n = 56, valganciclovir/ganciclovir; n = 47, foscarnet; n = 6, cidofovir)
TRAEs = treatment-related adverse events

Avery RK, et al. *Clin Infect Dis*. 2021:ciab988

Summary for the Treatment Options for Resistant/Refractory CMV

Resistance genotype	Recommendations
1. UL97 mutations with HIGH level resistance to ganciclovir	• Switch to foscarnet as first-line option • Switch to cidofovir as second-line option
2. UL97 mutations with LOW Level resistance to ganciclovir (M460I, C592G, L595W)	• High-dose ganciclovir dosing 7.5mg-10mg/kg q12h as tolerated if CMV disease not present • Switch to foscarnet or cidofovir as next option
3. UL54 mutations conferring resistance to foscarnet and ganciclovir (± UL97 mutations)	• Switch to cidofovir as first-line option • Consider adding alternative agents such as leflunomide, artesunate • Seek access or trial participation for investigational agents including 3rd party CMV T-cells
4. UL54 mutations conferring resistance to ganciclovir and cidofovir only	• Continue foscarnet as first-line option • May consider adding adjunct agents such as leflunomide, artesunate • Seek access or trial participation for investigational agents* including 3rd party CMV T-cells
5. UL54 mutations conferring resistance to foscarnet only	• Stop foscarnet and start ganciclovir standard dose 5mg/kg q12h • May consider adding adjunct agents such as leflunomide, artesunate
6. UL54 mutations conferring resistance to ganciclovir, foscarnet and cidofovir	• Continue foscarnet and ADD high-dose ganciclovir 7.5-10mg/kg q12h • Consider G-CSF support with high-dose ganciclovir use • Consider adding alternative agents such as leflunomide or artesunate • Maribavir through early access or trial participation including 3rd party CMV T-cells
7. UL56, UL89, UL51 conferring resistance to letermovir	• Switch to ganciclovir or foscarnet as first-line option
8. Refractory CMV without known resistant mutations	• Optimize dosing of current ganciclovir as appropriate • Switch to foscarnet as next-line option • Maribavir through early access or trial participation

Institutional Differences in CMV Infection Treatment

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Summary

- CMV infection remains a significant problem after HCT and SOT
  - Seropositivity is the greatest predictor (highest risk with R+ in HCT and D+ in SOT)
- Prophylaxis, preemptive therapy, and hybrid approaches to CMV infection prevention are effective, but CMV infection/reactivation remains common
- Resistance to CMV therapy remains a challenge?
  - Knowing which mutation(s) is/are responsible for resistance is critical to choosing an appropriate next therapy
- The risks and benefits of various drugs for CMV disease treatment
- Maribavir is a new, safe and efficacious agent for CMV therapy resistant/refractory infection or disease

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Review patient and transplant characteristics, in order to identify patients at higher risk of CMV reactivation/infection
- Request genotyping when you suspect resistant/refractory CMV infection
- Consider
  - Letermovir for CMV prophylaxis in patients receiving HCT
  - Maribavir for treatment of resistant/refractory CMV infection or disease in patients receiving HCT or SOT

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