A SPECIAL MEETING REVIEW EDITION

Highlights in Cytomegalovirus From the 2018 BMT Tandem Meetings

A Review of Selected Presentations From the 2018 BMT Tandem Meetings
• February 21-25, 2018 • Salt Lake City, Utah

Special Reporting on:

- Letermovir Resistance Genotyping in a Clinical Trial of Cytomegalovirus Prophylaxis for Hematopoietic Cell Transplant Recipients

- Viral Kinetic Correlates of Cytomegalovirus Disease and Death After Hematopoietic Cell Transplant

- Cost Effectiveness of Letermovir in Prevention of Clinically Significant CMV Infection in CMV Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients

- A Modified Intensive Strategy to Prevent CMV Disease in Seropositive Umbilical Cord Blood Transplant Recipients

- Functional Signatures Revealed by Deep Phenotyping of CMV-Specific CD8+ T Cells Predict Risk of Early CMV Reactivation After Allogeneic Hematopoietic Cell Transplantation

- Early HHV-6 Reactivation in CMV-Seronegative Cord Blood Transplant Recipients Is Associated With Inferior Relapse-Free and Overall Survival

- Cytomegalovirus Infection and Disease Incidence and Risk Factors Across Diverse Hematopoietic Cell Transplantation Platforms Using a Standardized Monitoring and Treatment Approach: A Comprehensive Evaluation From a Single Institution

- Clinical Impact and Burden of CMV Infection on the Use of Resources in Allogeneic Hematopoietic Cell Transplantation

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Sanjeet Singh Dadwal, MD
Associate Clinical Professor of Medicine
Division of Infectious Disease
Head, Antimicrobial Stewardship Program
Co-Lead, Infectious Disease, Transplant Disease Team
City of Hope National Medical Center
Duarte, California

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PROPHYLAX WITH *PREVYMIS* TO PROTECT HSCT PATIENTS FROM CMV

Start PREVYMIS™ (letermovir) as early as day 0 for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)

PROVEN CMV PROPHYLAXIS

In a pivotal, phase 3 clinical study (N=565), PREVYMIS demonstrated:

- Significant efficacy vs placebo in the primary endpoint: Clinically significant CMV infection at week 24 (38% vs 61%, respectively; *P*<0.0001)[a]

CMV prophylaxis was assessed in a randomized, multicenter, double-blind, placebo-controlled, pivotal, phase 3 study of adult CMV-seropositive recipients [R+] of allogeneic HSCT. Patients were randomized 2:1 to PREVYMIS or placebo and stratified by study site and high vs low risk (N=565).

[a]Clinically significant CMV infection was defined as either the occurrence of CMV end-organ disease or initiation of anti-CMV preemptive therapy, based on documented CMV viremia and the clinical condition of the patient. Viremia was determined using the Roche COBAS® AmpliPrep/COBAS TaqMan® assay; lower limit of quantification was 137 IU/mL, which is approximately 150 copies/mL.

INDICATION

- PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).
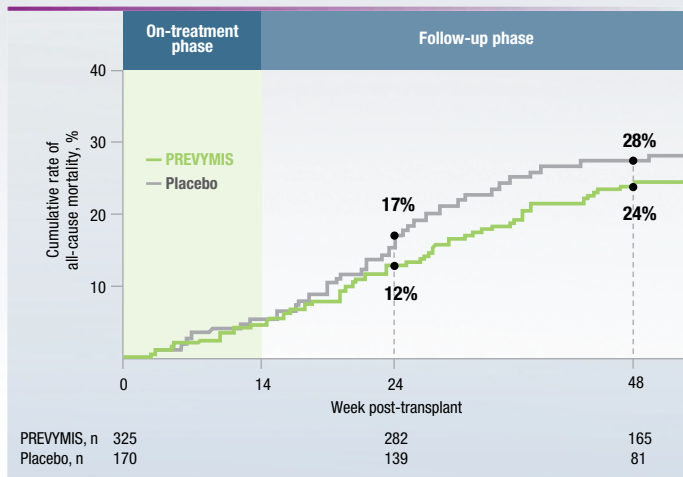
SELECTED SAFETY INFORMATION

- PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids.
  — Increased pimozide concentrations may lead to QT prolongation and torsades de pointes.
  — Increased ergot alkaloids concentrations may lead to ergotism
- PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Significantly increased pitavastatin or simvastatin concentrations may lead to myopathy or rhabdomyolysis.
- The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug. Consider the potential for drug interactions prior to and during PREVYMIS therapy; review concomitant medications during PREVYMIS therapy; and monitor for adverse reactions associated with PREVYMIS and concomitant medications.
- The cardiac adverse event rate (regardless of investigator-assessed causality) was higher in subjects receiving PREVYMIS than placebo (13% vs 6%). The most common cardiac adverse events were tachycardia (reported in 4% PREVYMIS subjects and 2% placebo subjects) and atrial fibrillation (reported in 3% PREVYMIS subjects and 1% placebo subjects). Among those subjects who experienced one or more cardiac adverse events, 85% of PREVYMIS and 92% of placebo subjects had events reported as mild or moderate in severity.
- The rate of adverse events occurring in at least 10% of PREVYMIS-treated HSCT recipients and at a frequency at least 2% greater than placebo were nausea (27% vs 23%), diarrhea (26% vs 24%), vomiting (19% vs 14%), peripheral edema (14% vs 9%), cough (14% vs 10%), headache (14% vs 9%), fatigue (13% vs 11%), and abdominal pain (12% vs 9%).
- The most frequently reported adverse event that led to study drug discontinuation was nausea (occurring in 2% of PREVYMIS subjects and 1% of placebo subjects). Hypersensitivity reaction, with associated moderate dyspnea, occurred in one subject following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.
- Co-administration of PREVYMIS with drugs that are inhibitors of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters may result in increases in letermovir plasma concentrations.
- Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations. Co-administration of PREVYMIS with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates.
- Co-administration of PREVYMIS with drugs that are substrates of OATP1B1/3 transporters may result in a clinically relevant increase in plasma concentrations of co-administered OATP1B1/3 substrates.
- The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when PREVYMIS is co-administered with cyclosporine. See the prescribing information for cyclosporine for information on drug interactions with cyclosporine.
- If dose adjustments of concomitant medications are made due to treatment with PREVYMIS, doses should be readjusted after PREVYMIS treatment is completed. Drug interactions may occur based on results from studies. Drug interactions may also occur based on predicted interactions. Potentially significant drug interactions include, but are not limited to, the following (information below applies to co-administration of PREVYMIS and the concomitant drug without cyclosporine, unless otherwise indicated):
  — Anti-arrhythmic agents
    ○ Amiodarone: increases ↑amiodarone concentration
  — Anticoagulants
    ○ Warfarin: decreases ↓warfarin concentration
  — Anticonvulsants
    ○ Phenytoin: decreases ↓phenytoin concentration
  — Antidiabetic agents
    ○ Glyburide: increases ↑glyburide concentration
    ○ Repaglinide: increases ↑repaglinide concentration
    ○ Rosiglitazone: increases ↑rosiglitazone concentration
  — Antifungals
    ○ Voriconazole: decreases ↓voriconazole concentration
  — Antimycobacterial
    ○ Rifampin: decreases ↓letermovir concentration

Not an actual patient.

Lower All-Cause Mortality for PREVYMIS vs Placebo[1]

	On-treatment phase	Follow-up phase

Cumulative rate of all-cause mortality, %

— PREVYMIS
— Placebo

17%
12%
28%
24%

	0	14	24	48

Week post-transplant

PREVYMIS, n	325	282	165
Placebo, n	170	139	81

Data through week 24 post-transplant *P*=0.0401.[1]
Data through week 48 post-transplant *P*=0.2117, not significant.[1]

PREVYMIS™
(letermovir)

240 mg, 480 mg tablets
Injection 20 mg/mL

Learn more about **PREVYMIS** for CMV prophylaxis
at **prevymis.com**

SELECTED SAFETY INFORMATION
(continued)

— Antipsychotics
  ○ Pimozide: increases ↑pimozide concentration; co-administration is contraindicated
— Ergot alkaloids
  ○ Ergotamine: increases ↑ergotamine concentration; co-administration is contraindicated
  ○ Dihydroergotamine: increases ↑dihydroergotamine concentration; co-administration is contraindicated
— HMG-CoA reductase inhibitors
  ○ Pitavastatin, simvastatin: increases ↑HMG-CoA reductase inhibitors concentration; co-administration is contraindicated when PREVYMIS is co-administered with cyclosporine
  ○ Atorvastatin: increases ↑atorvastatin concentration
  ○ Fluvastatin, lovastatin, pravastatin, rosuvastatin: increases ↑HMG-CoA reductase inhibitors concentration
— Immunosuppressants
  ○ Cyclosporine: increases ↑both cyclosporine and letermovir concentrations
  ○ Sirolimus: increases ↑sirolimus concentration
  ○ Tacrolimus: increases ↑tacrolimus concentration
— Proton pump inhibitors
  ○ Omeprazole: decreases ↓omeprazole concentration
  ○ Pantoprazole: decreases ↓pantoprazole concentration

— CYP3A substrate examples
  ○ Alfentanil, fentanyl, midazolam and quinidine: may increase ↑CYP3A substrate concentration
  ○ Pimozide and ergot alkaloids are contraindicated
• The safety and efficacy of PREVYMIS in patients below 18 years of age have not been established.
• For patients with creatinine clearance (CLcr) greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment. The safety of PREVYMIS in patients with end-stage renal disease (CLcr less than 10 mL/min), including patients on dialysis, is unknown.
• No dosage adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

Before prescribing PREVYMIS, please read the adjacent Brief Summary of the Prescribing Information. For additional copies of the Prescribing Information, please call 1-800-672-6372, visit prevymis.com, or contact your Merck representative.

Reference: 1. Data available on request from Merck Professional Services-DAP, WP1, PO Box 4, West Point, PA 19486-0004. Please specify information package AINF-1228859-0000_RD2.

MERCK

PREVYMIS™
(letermovir)
240 mg, 480 mg tablets
Injection 20 mg/mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

PREVYMIS™ is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

DOSAGE AND ADMINISTRATION

Important Dosing and Administration Information
PREVYMIS™ Tablets
- Administer with or without food.
- Swallow tablets whole.

PREVYMIS™ Injection
- Administer by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour.
- Do not administer as an intravenous bolus injection.

Recommended Dosage in Adult Patients
The recommended dosage of PREVYMIS is 480 mg administered orally or intravenously once daily. Initiate PREVYMIS between Day 0 and Day 28 post-transplantation (before or after engraftment), and continue through Day 100 post-transplantation. Dosage of PREVYMIS should be adjusted when coadministered with cyclosporine.

PREVYMIS injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. PREVYMIS tablet and injection may be used interchangeably at the discretion of the physician, and no dosage adjustment is necessary when switching formulations.

Patient Monitoring
Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation is recommended.

Dosage Adjustment When Co-administered with Cyclosporine
If oral or intravenous PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily.
- If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily.
- If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily.
- If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed.

Use in Patients with Renal Impairment
- For patients with creatinine clearance (CLcr) greater than 10 mL/min, no dosage adjustment of PREVYMIS is required based on renal impairment.
- There are insufficient data in patients with CLcr 10 mL/min or less or in patients on dialysis to make PREVYMIS dosing recommendations.
- In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, may occur. Closely monitor serum creatinine levels in these patients.

Use in Patients with Hepatic Impairment
No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

Preparation and Administration of Intravenous Solution
PREVYMIS injection is supplied in 30 mL single-dose vials containing either 240 mg/12 mL per vial (20 mg/mL) or 480 mg/24 mL per vial (20 mg/mL). The preparation and administration instructions are the same for either dose.

PREVYMIS vials are for single use only. Discard any unused portion.

Preparation and Administration Instructions
- PREVYMIS must be diluted prior to intravenous (IV) use.
- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS injection is a clear colorless solution. Do not use the vial if the solution is discolored or contains visible particles.
- Do not shake PREVYMIS vial.
- Add one single-dose vial of PREVYMIS injection into a 250 mL pre-filled IV bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix bag

gently. Do not shake. Only 0.9% Sodium Chloride and 5% Dextrose are chemically and physically compatible with PREVYMIS injection.
- Use compatible IV bags and infusion set materials. PREVYMIS injection is compatible with the following IV bags and infusion set materials. PREVYMIS injection is not recommended with any IV bags or infusion set materials not listed below (note that PREVYMIS injection is not recommended for use with polyurethane-containing IV administration set tubing).

IV Bags Materials:
Polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and polyolefin (polypropylene and polyethylene)

Infusion Sets Materials:
PVC, polyethylene (PE), polybutadiene (PBD), silicone rubber (SR), styrene–butadiene copolymer (SBC), styrene-butadiene-styrene copolymer (SBS), polystyrene (PS)

Plasticizers:
Diethylhexyl phthalate (DEHP), tris (2-ethylhexyl) trimellitate (TOTM), benzyl butyl phthalate (BBP)

Catheters:
Radiopaque polyurethane

- Once diluted, the solution of PREVYMIS is clear, and ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.
- The diluted solution is stable for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2°C to 8°C (36°F to 46°F) (this time includes storage of the diluted solution in the intravenous bag through the duration of infusion).
- Administer the entire contents of the intravenous bag by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour.

Compatible Drug Products Used for Intravenous Administration
Compatible Drug Products
The physical compatibility of PREVYMIS injection with selected injectable drug products was evaluated in two commonly available diluents. PREVYMIS should not be co-administered through the same intravenous line (or cannula) with other drug products and diluent combinations except those listed below. Refer to the respective prescribing information of the co-administered drug(s) to confirm compatibility of simultaneous co-administration.

List of Compatible Drug Products when PREVYMIS and Drug Products are Prepared in 0.9% Sodium Chloride Injection, USP: Ampicillin sodium, ampicillin sodium/sulbactam sodium, anti-thymocyte globulin, caspofungin, daptomycin, fentanyl citrate, fluconazole, furosemide, human insulin, magnesium sulfate, methotrexate, micafungin.

List of Compatible Drug Products when PREVYMIS and Drug Products are Prepared in 5% Dextrose Injection, USP: Amphotericin B (lipid complex)*, anidulafungin, cefazolin sodium, ceftaroline, ceftriaxone sodium, doripenem, famotidine, folic acid, ganciclovir sodium, hydrocortisone sodium succinate, morphine sulfate, norepinephrine bitartrate, pantoprazole sodium, potassium chloride, potassium phosphate, tacrolimus, telavancin, tigecycline.

*Amphotericin B (lipid complex) is compatible with PREVYMIS. However, Amphotericin B (liposomal) is incompatible.

Incompatible Drug Products for Intravenous Administration
Incompatible Drug Products
PREVYMIS injection is physically incompatible with amiodarone hydrochloride, amphotericin B (liposomal), aztreonam, cefepime hydrochloride, ciprofloxacin, cyclosporine, diltiazem hydrochloride, filgrastim, gentamicin sulfate, levofloxacin, linezolid, lorazepam, midazolam HCl, mycophenolate mofetil hydrochloride, ondansetron, palonosetron.

CONTRAINDICATIONS
PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids:
- Pimozide: Concomitant administration of PREVYMIS in patients receiving pimozide may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, which may lead to QT prolongation and torsades de pointes.
- Ergot alkaloids: Concomitant administration of PREVYMIS in patients receiving ergot alkaloids may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism.
- PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Concomitant administration of PREVYMIS in combination with cyclosporine may result in significantly increased pitavastatin or simvastatin concentrations, which may lead to myopathy or rhabdomyolysis.

WARNINGS AND PRECAUTIONS
Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions
The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in practice.

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT

The safety of PREVYMIS was evaluated in one Phase 3 randomized, double-blind, placebo-controlled trial (P001) in which 565 subjects were randomized and treated with PREVYMIS (N=373) or placebo (N=192) through Week 14 post-transplant. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation. The mean time for reporting adverse events and laboratory abnormalities was approximately 22% longer in the PREVYMIS arm compared to the placebo arm.

Cardiac Adverse Events:

The cardiac adverse event rate (regardless of investigator-assessed causality) was higher in subjects receiving PREVYMIS (13%) compared to subjects receiving placebo (6%). The most common cardiac adverse events were tachycardia (reported in 4% of PREVYMIS subjects and in 2% of placebo subjects) and atrial fibrillation (reported in 3% of PREVYMIS subjects and in 1% of placebo subjects). Among those subjects who experienced one or more cardiac adverse events, 85% of PREVYMIS and 92% of placebo subjects had events reported as mild or moderate in severity.

Common Adverse Events

The rate of adverse events occurring in at least 10% of subjects in the PREVYMIS group and at a frequency at least 2% greater than placebo are outlined in Table 1.

Table 1: Trial P001 All Grade Adverse Events Reported in ≥ 10% of PREVYMIS-Treated HSCT Recipients at a Frequency at least 2% Greater than Placebo

Adverse Events	PREVYMIS (N=373)	Placebo (N=192)
nausea	27%	23%
diarrhea	26%	24%
vomiting	19%	14%
peripheral edema	14%	9%
cough	14%	10%
headache	14%	9%
fatigue	13%	11%
abdominal pain	12%	9%

Overall, similar proportions of subjects in each group discontinued study medication due to an adverse event (13% of PREVYMIS subjects vs. 12% of placebo subjects). The most frequently reported adverse event that led to study drug discontinuation was nausea, occurring in 2% of PREVYMIS subjects and 1% of placebo subjects. Hypersensitivity reaction, with associated moderate dyspnea, occurred in one subject following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

Laboratory Abnormalities

Selected laboratory abnormalities reported during treatment or within 2 weeks of stopping treatment are presented in the table below.

Table 2: Trial P001 Selected Laboratory Abnormalities

	PREVYMIS N=373	Placebo N=192
Absolute neutrophil count (cells/µL)		
< 500	19%	19%
500 – < 750	4%	7%
750 – < 1000	8%	9%
Hemoglobin (g/dL)		
< 6.5	2%	1%
6.5 – < 8.0	14%	15%
8.0 – < 9.5	41%	43%
Platelets (cells/µL)		
< 25000	27%	21%
25000 – < 50000	17%	18%
50000 – < 100000	20%	30%
Serum creatinine (mg/dL)		
> 2.5	2%	3%
> 1.5 – 2.5	17%	20%

The median time to engraftment (defined as absolute neutrophil count ≥ 500/mm^3 on 3 consecutive days after transplantation) was 19 days in the PREVYMIS group and 18 days in the placebo group.

DRUG INTERACTIONS

Potential for Other Drugs to Affect PREVYMIS

Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters. Coadministration of PREVYMIS with drugs that are inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations (Table 3).

Potential for PREVYMIS to Affect Other Drugs

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations, indicating letermovir is a moderate inhibitor of CYP3A. Co-administration of PREVYMIS with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates (Table 3).

Letermovir is an inhibitor of OATP1B1/3 transporters. Co-administration of PREVYMIS with drugs that are substrates of OATP1B1/3 transporters may result in a clinically relevant increase in plasma concentrations of co-administered OATP1B1/3 substrates (Table 3).

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when PREVYMIS is co-administered with cyclosporine. See the prescribing information for cyclosporine for information on drug interactions with cyclosporine.

Established and Other Potentially Significant Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with PREVYMIS, doses should be readjusted after treatment with PREVYMIS is completed.

Table 3 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with PREVYMIS or are predicted drug interactions that may occur with PREVYMIS.

Table 3: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions* (Information in the Table Applies to Co-administration of PREVYMIS and the Concomitant Drug without Cyclosporine, Unless Otherwise Indicated)

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration[†]	Clinical Comments
Anti-arrhythmic agents		
amiodarone	↑ amiodarone	Close clinical monitoring for adverse events related to amiodarone is recommended during co-administration. Frequently monitor amiodarone concentrations when amiodarone is co-administered with PREVYMIS.
Anticoagulants		
warfarin	↓ warfarin	When PREVYMIS is co-administered with warfarin, frequently monitor International Normalized Ratio (INR)[§].
Anticonvulsants		
phenytoin	↓ phenytoin	When PREVYMIS is co-administered with phenytoin, frequently monitor phenytoin concentrations[§].
Antidiabetic agents		
Examples: glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	When PREVYMIS is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations[§]. When PREVYMIS is co-administered with cyclosporine, use of repaglinide is not recommended.
Antifungals		
voriconazole[‡]	↓ voriconazole	If concomitant administration of voriconazole is necessary, closely monitor for reduced effectiveness of voriconazole[§].
Antimycobacterial		
rifampin	↓ letermovir	Co-administration of PREVYMIS and rifampin is not recommended.
Antipsychotics		
pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes.

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration[†]	Clinical Comments
Ergot alkaloids		
ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is contraindicated due to risk of ergotism.
HMG-CoA Reductase Inhibitors		
atorvastatin[‡]	↑atorvastatin	When PREVYMIS is co-administered with atorvastatin, do not exceed an atorvastatin dosage of 20 mg daily[§]. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of atorvastatin is not recommended.
pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of PREVYMIS and pitavastatin or simvastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, use of either pitavastatin or simvastatin is contraindicated due to significantly increased pitavastatin or simvastatin concentrations and risk of myopathy or rhabdomyolysis.
fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	When PREVYMIS is co-administered with these statins, a statin dosage reduction may be necessary[§]. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of lovastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
cyclosporine[‡]	↑ cyclosporine ↑ letermovir	Decrease the dosage of PREVYMIS to 240 mg once daily. Frequently monitor cyclosporine whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of cyclosporine accordingly[§].
sirolimus[‡]	↑ sirolimus	When PREVYMIS is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of sirolimus accordingly[§]. When PREVYMIS is co-administered with cyclosporine and sirolimus, refer to the sirolimus prescribing information for specific sirolimus dosing recommendations[§].
tacrolimus[‡]	↑ tacrolimus	Frequently monitor tacrolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of tacrolimus accordingly[§].
Proton pump inhibitors		
omeprazole	↓ omeprazole	Clinical monitoring and dose adjustment may be needed.
pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed.

CYP3A Substrates		
Examples: alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	When PREVYMIS is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor[§]. When PREVYMIS is co-administered with cyclosporine, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for dosing of the CYP3A substrate with a strong CYP3A inhibitor[§]. CYP3A substrates pimozide and ergot alkaloids are contraindicated.

[*] This table is not all inclusive.
[†] ↓ =decrease, ↑=increase
[‡] These interactions have been studied.
[§] Refer to the respective prescribing information.

Drugs without Clinically Significant Interactions with PREVYMIS

No clinically significant interactions were observed in clinical drug-drug interaction studies of letermovir and acyclovir, digoxin, mycophenolate mofetil, posaconazole, ethinyl estradiol, and levonorgestrel.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

No adequate human data are available to establish whether PREVYMIS poses a risk to pregnancy outcomes. In animal reproduction studies, embryo-fetal developmental toxicity (including fetal malformations) was observed in rats during the period of organogenesis at letermovir exposures (AUC) 11 times higher than human exposure at the recommended human dose (RHD). In rabbits, no embryofetal developmental toxicity was noted at exposures that were not maternally toxic (up to letermovir exposures 2 times higher than human exposure at the RHD). In a rat pre/post-natal development study, total litter loss was observed at maternal letermovir exposures approximately 2 times higher than human exposure at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Letermovir was administered orally to pregnant rats at 0, 10, 50 or 250 mg/kg/day from gestation days 6 to 17. Developmental toxicities, including skeletal malformations and umbilical cord shortening, were observed at 250 mg/kg/day (approximately 11 times higher than human exposure at the RHD). In addition, decreased fetal body weight and skeletal variations (due to maternal toxicity) were observed at this dose. No embryo-fetal toxicities were observed at 50 mg/kg/day (approximately 3 times higher than human exposure at the RHD).

Letermovir was administered orally to pregnant rabbits at 0, 25, 75 or 225 mg/kg/day from gestation days 6 to 20. Developmental toxicities, including spontaneous abortion, increased post-implantation loss, and skeletal variations, were observed at a maternally toxic dose (225 mg/kg/day; approximately 2 times higher than human exposure at the RHD). No embryo-fetal toxicities were observed at 75 mg/kg/day (less than human exposure at the RHD).

In the pre/post-natal development study, letermovir was administered orally to pregnant rats at 0, 10, 45 or 180 mg/kg/day from gestation day 6 to lactation day 22. At 180 mg/kg/day (approximately 2 times higher than human exposure at the RHD), total litter loss due to stillbirth or possible maternal neglect was observed in 5 of 23 pregnant females by post-partum/lactation day 4. In surviving offspring, slight developmental delays in vaginal opening and pinna unfolding were accompanied by reduced body weight gain at this dose. No toxicities were observed at 45 mg/kg/day (similar to human exposure at the RHD).

Lactation

Risk Summary

It is not known whether letermovir is present in human breast milk, affects human milk production, or has effects on the breastfed child.

When administered to lactating rats, letermovir was present in the milk of lactating rats as well as the blood of nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREVYMIS and any potential adverse effects on the breastfed child from PREVYMIS or from the underlying maternal condition.

Females and Males of Reproductive Potential

Infertility

There are no data on the effect of letermovir on human fertility. Decreased fertility due to testicular toxicity was observed in male rats.

Pediatric Use

Safety and efficacy of PREVYMIS in patients below 18 years of age have not been established.

Geriatric Use

Of the 373 subjects treated with PREVYMIS in Trial P001, 56 (15%) subjects were 65 years of age or older. Safety and efficacy were similar across older and younger subjects. No dosage adjustment of PREVYMIS is required based on age.

Renal Impairment

For patients with CLcr greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment. The safety of PREVYMIS in patients with end-stage renal disease (CLcr less than 10 mL/min), including patients on dialysis, is unknown.

In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur. Closely monitor serum creatinine levels in these patients.

Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

OVERDOSAGE

There is no specific antidote for overdose with PREVYMIS. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment be instituted.

It is unknown whether dialysis will result in meaningful removal of PREVYMIS from systemic circulation.

For more detailed information, please read the Prescribing Information.
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Letermovir Resistance Genotyping in a Clinical Trial of Cytomegalovirus Prophylaxis for Hematopoietic Cell Transplant Recipients

Most adults who undergo hematopoietic stem cell transplant (HSCT) have evidence of prior infection with cytomegalovirus (CMV) and are at risk for CMV reactivation after transplant. In November 2017, letermovir was approved by the US Food and Drug Administration (FDA) for the prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic HSCT.[1] Letermovir is an antiviral compound with a novel mechanism of action: It targets the CMV DNA terminase complex, which is required for viral DNA processing and the assembly of infectious virions. With a median EC_{50} of 2.1 nM against clinical CMV isolates, letermovir is a potent inhibitor of CMV. Moreover, letermovir has demonstrated activity against CMV strains that are resistant to DNA polymerase inhibitors, such as cidofovir and ganciclovir. The CMV terminase complex consists of 2 pro-tein subunits, pUL89 and pUL56.[2] The function of the terminase complex is to cleave CMV DNA concatemers into single units prior to packaging in the capsid. DNA sequencing revealed mutations in the *UL56* gene among mutant CMV variants that were resistant to letermovir in vitro. Although *UL56* mutations that confer resistance to letermovir have occasionally been observed in the clinic, the most common *UL56* polymorphisms do not affect susceptibility to letermovir.

Letermovir was evaluated in the phase 3 MK-8228-001 study (P001; Letermovir [MK-8228] Versus Placebo in the Prevention of Clinically-Significant Cytomegalovirus [CMV] Infection in Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients) of CMV-seropositive patients who underwent allogeneic HSCT.[3,4] The double-blind study randomly assigned 565 patients in 20 countries in a 2:1 ratio to receive letermovir at 480 mg or placebo. The letermovir dose was reduced to 240 mg in patients receiving cyclosporine. The study medication was initiated within 28 days after transplant and continued through week 14. Preemptive therapy was administered to patients who exhibited clinically significant CMV infection. CMV genotyping was assessed by next-generation sequencing.

Among the 495 patients in the primary efficacy population, 128 developed clinically significant CMV infection during the first 24 weeks after HSCT. The study randomly assigned 57 patients to the letermovir arm and 71 patients to the placebo arm. CMV DNA samples for sequencing were available for 34 patients in the letermovir arm and 50 patients in the placebo arm. To increase the number of samples available for genotyping, plasma samples that had been collected for viral load testing were repurposed and analyzed for CMV genotyping. This step increased the number of samples available for genotyping to 40 in the letermovir arm and 42 in the placebo arm. Plasma samples were drawn only from patients who experienced clinically significant CMV infection. Baseline plasma samples were not collected from any of the patients.

Next-generation sequencing is extremely sensitive, but the results can be confounded by polymerase chain reaction (PCR) artifacts resulting from the presence of very low numbers of the starting template. In the P001 trial, the median viral load at failure was approximately 400 copies/mL in the letermovir arm vs 700 copies/mL in the placebo arm. Two strategies were used to reduce sequencing artifacts. First, to be considered a true variant, the sequence had to be present in at least 5% of the sample sequence data.

ABSTRACT SUMMARY Outcomes of Resistant or Refractory CMV Infection in Recipients of Allogeneic Hematopoietic Cell Transplant

A retrospective chart review aimed to characterize the genetic basis of CMV resistance in allogeneic HSCT patients at a single center (Abstract 560). Patients were treated from January 2010 through November 2016 and had undergone CMV genotypic testing for suspected resistance. CMV was categorized as refractory or resistant. Refractory CMV strains did not contain known genetic resistance mutations, whereas resistant strains had known antiviral resistance mutations in the *UL97* and/or *UL*54 genes. CMV genotype results were available for 81 patients. Sixty patients had refractory CMV strains, and 21 had strains that were genetically resistant to ganciclovir (n=14), foscarnet (n=3), or both (n=4). Patients infected with resistant CMV strains had more prior infections and a longer time from transplant to suspicion of resistance compared with the refractory cohort (*P*<.01 for each). The incidence of CMV disease was 57% in resistant patients and 47% in refractory patients. All-cause mortality was approximately 64% in both cohorts (*P*=.85). CMV was fatal in 6 patients (10%) with refractory infection and in 1 patient (7%) with resistant infection.

Table 1. Letermovir-Susceptible CMV *UL56* Variants in Patients Who Failed Prophylaxis With Letermovir

CMV Variant	Number Identified From 40 Samples
T189M	1
V425A	32
S435A	1
M442T	1
S445N	3
N446 deletion	7
T452I	2
S454N	1
A464T	9
A471V	8
A476V	12
E485G	3
N586D	31
S749N	3
V778A	1
A793V	9
P800L	4

Data from Douglas CM et al. BMT Tandem Meetings abstract 72. *Biol Blood Marrow Transplant.* 2018;24(3)(suppl 1).[3]

Figure 1. In a phase 2b trial of letermovir, 1 patient had the cytomegalovirus V236M mutation. EOTM, end of trial medication; HCMV, human cytomegalovirus; LLQ, lower limit of quantification; M, mutation; WT, wild type. Adapted from Douglas CM et al. BMT Tandem Meetings abstract 72. *Biol Blood Marrow Transplant.* 2018;24(3)(suppl 1)[3] and Lischka P et al. *J Infect Dis.* 2016;213(1):23-30.[6]

Second, replicate testing was used to detect true variants. Replicate testing was performed on samples with novel substitutions that were present in 5% to 98% of sequence reads at a single nucleotide position. The protocol for replicate testing was to repeat the DNA isolation, amplification, and sequencing for the sample in question. If any of the replicate tests confirmed the original mutation, then the mutation was considered correct. Among the 21 substitutions evaluated by replicate testing, 13 were in the *UL89* gene and 8 were in the *UL56* gene. Eighteen of these samples failed replicate testing and were therefore considered sequencing artifacts. Numerous known *UL56* variants were identified (Table 1). The analysis also identified common variants that had not been characterized for letermovir resistance,
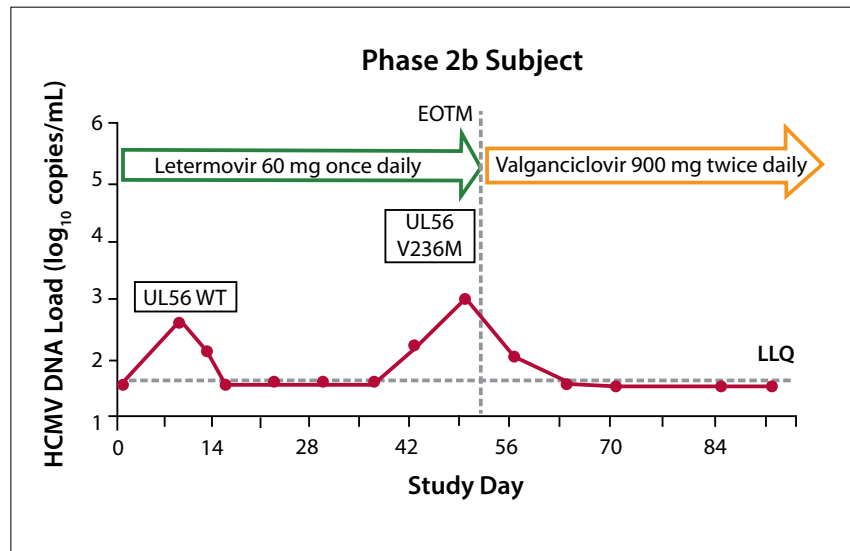
many of which were observed among patients in the placebo arm. These common variants were unlikely to have emerged under selection pressure associated with letermovir. They included R246C (n=1), N446S (n=7), SNS445-447 deletion (n=3), S484G (n=1), and A779V (n=4).

Another group included 14 novel variants that had not been characterized for letermovir resistance. Most identified mutations occurred in 2 known variable regions (VR1 and VR2) of the *UL56* gene and were therefore unlikely to have evolved from selection pressure associated with letermovir. Variant V236M was identified in this group. The change from valine to methionine was associated with a reduction in letermovir affinity for CMV, as represented by a 30- to 50-fold increase in the EC_{50} in a cell-culture model of CMV infection. However, the mutation did not affect the affinity of other antiviral agents, including cidofovir, foscarnet, and ganciclovir.[5] The V236M mutation was not observed in any of the patients in the placebo arm of trial P001, nor

was it observed among CMV pUL56 sequences in public databases. One patient in a phase 2b trial of letermovir (60 mg daily) had the CMV V236M mutation (Figure 1).[6] Both this patient and the patient with the CMV V236M mutation in the P001 trial were successfully treated with ganciclovir or valganciclovir preemptive therapy.

In the phase 3 trial, all-cause mortality was 20.9% in the letermovir arm vs 25.5% in the placebo arm at week 48 after transplant.[4] The frequency and severity of adverse events were similar in the letermovir and placebo groups. Most adverse events were of low grade. Vomiting was reported in 18.5% of the patients in the letermovir arm vs 13.5% in the placebo arm. Edema was observed in 14.5% vs 9.4%, respectively, and atrial fibrillation or flutter occurred in 4.6% vs 1.0%. Rates of myelotoxicity and nephrotoxicity were similar in the 2 groups.

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Viral Kinetic Correlates of Cytomegalovirus Disease and Death After Hematopoietic Cell Transplant

Preemptive treatment of CMV with ganciclovir and foscarnet has been the standard of care for nearly 20 years.[1] The development of preemptive therapy in response to PCR-based detection of viral DNA has led to a low incidence of CMV after HSCT, with rates of 3% to 5% in the first 100 days after the procedure.[2,3] Toxicities associated with standard preemptive therapy remain high. However, the low rates of CMV infection have made it more challenging to develop new antiviral agents. Although detection of CMV DNA is commonly used as the clinical finding that signals the need for preemptive therapy, it has not been established as a surrogate endpoint for clinically significant CMV disease in a randomized, placebo-controlled clinical trial.

The safety and efficacy of ganciclovir as preemptive treatment for CMV were assessed in a randomized, placebo-controlled, phase 3 trial. This study also extended the data from an early landmark trial to establish the long-term impact of early treatment for CMV.[4] In addition, the trial established virologic, kinetic, PCR-based correlates of the risk for CMV disease and death after HSCT, with the goal of establishing surrogate endpoints defined by viral load. A double-blind study published in 1991 established the value of early treatment of CMV infection in reducing the incidence of CMV disease and improving survival after allogeneic bone marrow transplant.[5] This study evaluated 72 bone

marrow transplant recipients who were seropositive for CMV based on viral culture. After transplant, surveillance cultures of the blood, urine, and throat were performed weekly on all patients. CMV disease developed in 3% of patients treated with prophylactic ganciclovir vs 43% of patients in the placebo arm (*P*<.00001). By day 100 after transplant, 6 patients in the placebo group had died (all from CMV-related complications), and 1 patient in the ganciclovir group had died (from leukemic relapse). The difference in overall survival was significant at 100 days (*P*=.04) and 180 days (*P*=.03) after HSCT.

Frozen plasma samples for the 72 patients in the trial were used in the current study.[4] The new analysis included retrospective specimen testing, reanalysis of the existing data, and extension of the chart review. Viral kinetic calculations were performed, and correlations were evaluated by means of the Cox proportional hazards model. Mathematical extension of the results to 3 years showed a significant reduction in CMV disease (*P*=.02) and improvement in overall survival (*P*=.04), even though ganciclovir had been administered only through day 100 after HSCT. Extension of the results to 20 years continued to show a reduced incidence of CMV disease among patients treated with preemptive ganciclovir (*P*=.01). Differences in overall survival data were significant through 3 years (*P*=.04; Figure 2), and the survival curves remained well-separated through year 20.

The concept of using viral load as a surrogate endpoint was established in the field of AIDS research. In 1997, the FDA accepted viral load as an endpoint for disease-related mortality in trials of AIDS and HIV. Several criteria must be met to establish a surrogate endpoint, including use in a randomized controlled trial that demonstrated effective intervention and incorporated measurement of a biomarker, along with other clinical endpoints. The biomarker must reflect the effect of the intervention on the clinical endpoint.

For the 72 patients from the 1991 study, superimposition of plots reflecting viral load showed a visible reduction in viral load after randomization and administration of ganciclovir, but not placebo. The CMV viral load diverged in the ganciclovir and placebo arms at approximately 6 to 8 weeks after HSCT and immediately after randomization.

Viral kinetic parameters were calculated from CMV DNA PCR values as continuous, time-dependent variables. Cox proportional hazard models were used to assess associations between viral kinetic markers and time to CMV disease or death. Models were adjusted for the presence of acute graft-versus-host disease and donor CMV serostatus. Events were counted through day 100 or day 180. With events counted through day 100 after transplant, variables associated with CMV disease included most recent viral load (*P*<.001), highest viral load (*P*<.001), and duration of
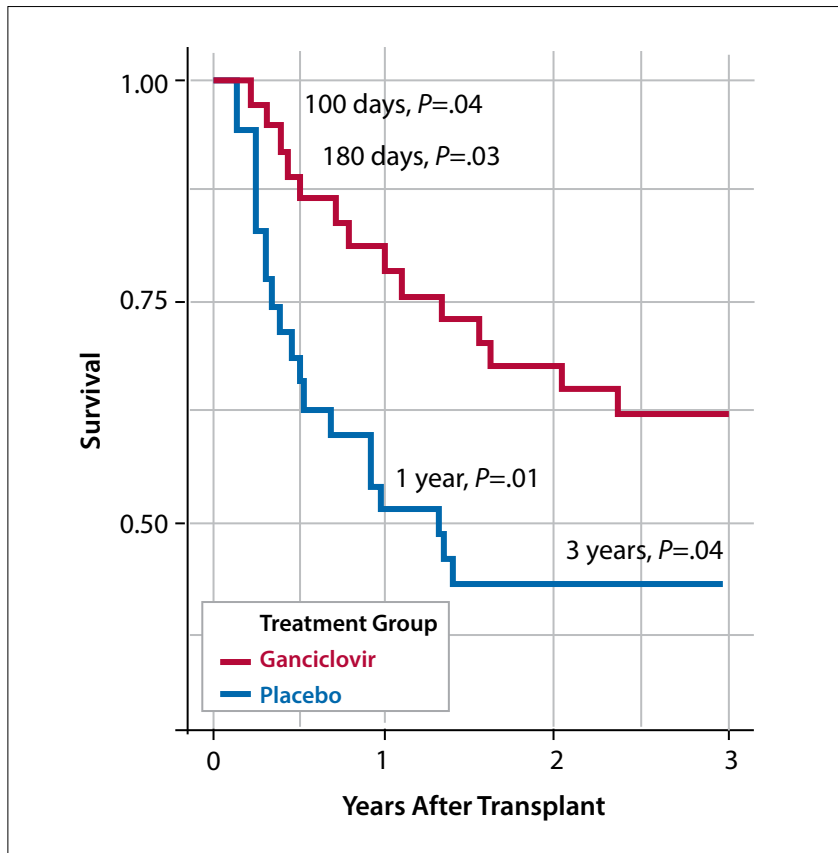
Figure 2. Overall survival after 3 years in an analysis that extended results seen in a 1991 study of ganciclovir as preemptive treatment for cytomegalovirus. Adapted from Duke ER et al. BMT Tandem Meetings abstract 1. *Biol Blood Marrow Transplant*. 2018;24(3)(suppl 1).[4]

viremia (P=.01). The same variables were significantly associated with CMV disease or death. With events counted through day 180 after transplant, variables associated with CMV disease included most recent viral load (P<.001), highest viral load (P<.001), and duration of viremia (P=.004), and the same variables were significantly associated with CMV disease or death.

The study authors concluded that 3 markers—viral load, highest viral load, and duration of viremia—warrant further investigation as surrogate endpoints for the relevant clinical endpoints. CMV viral load kinetics correlated with the risk for CMV disease and mortality. However, to establish viral load as a valid surrogate endpoint, further work must show whether the biomarker captures the entire effect of treatment. The option to use viral load as a surrogate endpoint for CMV disease and/or mortality would be of value in optimizing clinical trial design, speeding evaluation of new antiviral agents, and informing clinical management of CMV after bone marrow transplant.

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ABSTRACT SUMMARY Donor Anti-CMV Immunity Is Associated With Fewer Reactivations After Allogeneic Hematopoietic Cell Transplant

After a patient undergoes allogeneic HSCT, CMV-specific T cells are necessary to control CMV reactivation and infection. The effect of donor and recipient anti-CMV immunity on posttransplant CMV reactivation was retrospectively evaluated in 81 consecutive allogeneic HSCT recipients (Abstract 572). All patients underwent their first allogeneic HSCT between May 2008 and October 2016. Levels of anti-CMV T cells were quantified in recipients before transplant and again at 30 days and 100 days afterward. The patients' median age was 53 years (range, 21-72 years). Most patients were diagnosed with acute myelogenous leukemia (41%) or myelodysplastic syndrome (20%). Fifty-one transplant pairs included a CMV-seropositive donor and/or recipient. The average number of CMV reactivations was 1.24 for seronegative donor pairs vs 0.36 for seropositive donor pairs. The median time to first reactivation was 40 days vs 47.5 days, respectively. In pairs that included a donor with detectable levels of anti-CMV T cells, the average number of reactivations was lower (0.42 vs 1.03), and the median time to the first reactivation was longer (46 vs 40 days).

Cost Effectiveness of Letermovir in Prevention of Clinically Significant CMV Infection in CMV Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients

HSCT is associated with a high risk for CMV infection. The phase 3 MK-8228-001/P001 study demonstrated the efficacy of prophylactic letermovir in adult CMV-seropositive patients undergoing allogeneic HSCT.[1] The trial showed a significant reduction in the risk for clinically significant CMV infection at 24 weeks posttransplant in patients treated with letermovir vs placebo (18.9% vs 44.3%; *P*=.0005). The trial also showed a significant reduction in all-cause mortality with letermovir at 24 weeks posttransplant (10.2% vs 15.9%; *P*=.0327), thus

meeting the primary endpoint. Using patient data from the MK-8228-001 trial, a retrospective study evaluated the cost-effectiveness of letermovir vs preemptive treatment from the perspective of a third-party payer. In the MK-8228-001 study, patients were randomly assigned 2:1 to receive letermovir or placebo.[2] The total cost of treatment, including letermovir, and lifetime quality-adjusted life years (QALYs) were estimated by a decision-analytic model. Outcomes with letermovir treatment were compared with those in the placebo arm, in which patients received preemptive

treatment based on each institution's standard of care. Efficacy data from the MK-8228-001 clinical trial were available through 24 weeks after transplant and included rates of CMV infection, CMV disease, rehospitalization, mortality, and quality of life. Cost information was obtained from published literature. Life-years during the first 24 weeks were estimated from the clinical trial mortality data. To estimate life-years 24 weeks after transplant, a relative risk for death from HSCT was applied to the general mortality risk calculated from US life expectancy data. Sensitivity analysis explored the impact of including data from the extended follow-up period through 48 weeks posttransplant. The model used an annual discount rate of 3% for costs and benefits. To calculate quality of life, responses from the EQ-5D questionnaire administered in the MK-8228-001 clinical trial were translated into utility values using a time trade-off value set from a population in the United Kingdom.

The base-case analysis showed that the use of letermovir would be cost-effective compared with no use if the incremental cost-effectiveness ratio threshold was at or below $50,000 per QALY gained. Sensitivity analysis incorporating data from 48 weeks posttransplant did not significantly impact the results. The analysis showed that HSCT patients who received treatment with letermovir could be expected to have a prolonged life, with improved health-related quality of life and fewer adverse outcomes (Figure 3). Cost-effectiveness analysis showed that each life-year gained with letermovir treatment had an associated cost of $23,270, and each QALY gained had an associated cost of $25,222. Although the use of letermovir as prophylaxis is associated
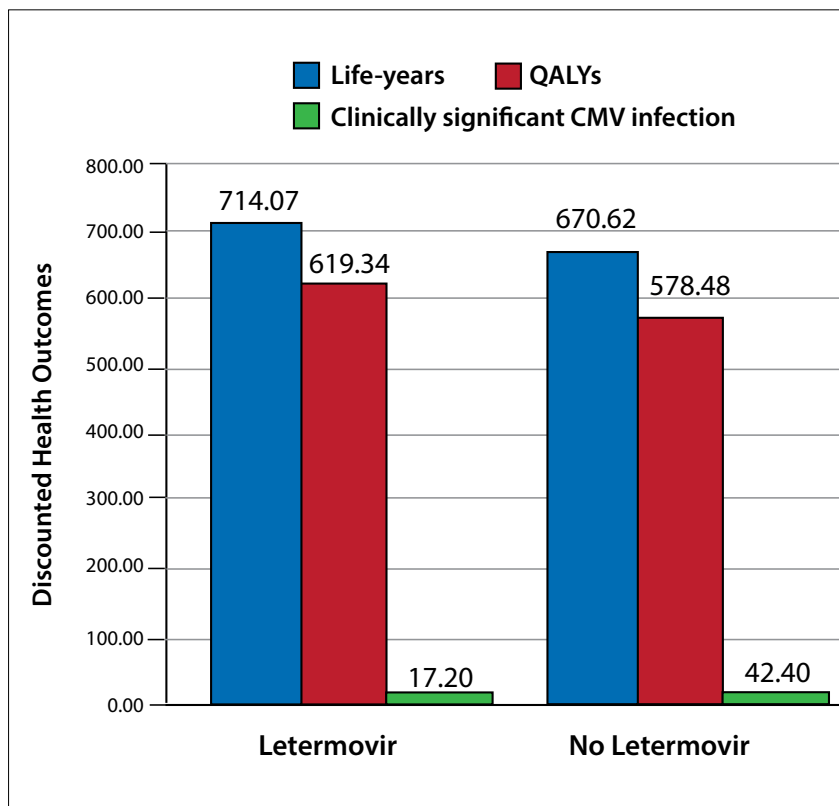

Figure 3. A retrospective cost-effectiveness analysis of patients who underwent HSCT showed that letermovir prolonged life, improved health-related quality of life, and reduced cases of clinically significant CMV infection. CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; QALYs, quality-adjusted life years. Adapted from Schelfhout J et al. BMT Tandem Meetings abstract 557. *Biol Blood Marrow Transplant*. 2018;24(3)(suppl 1).[2]
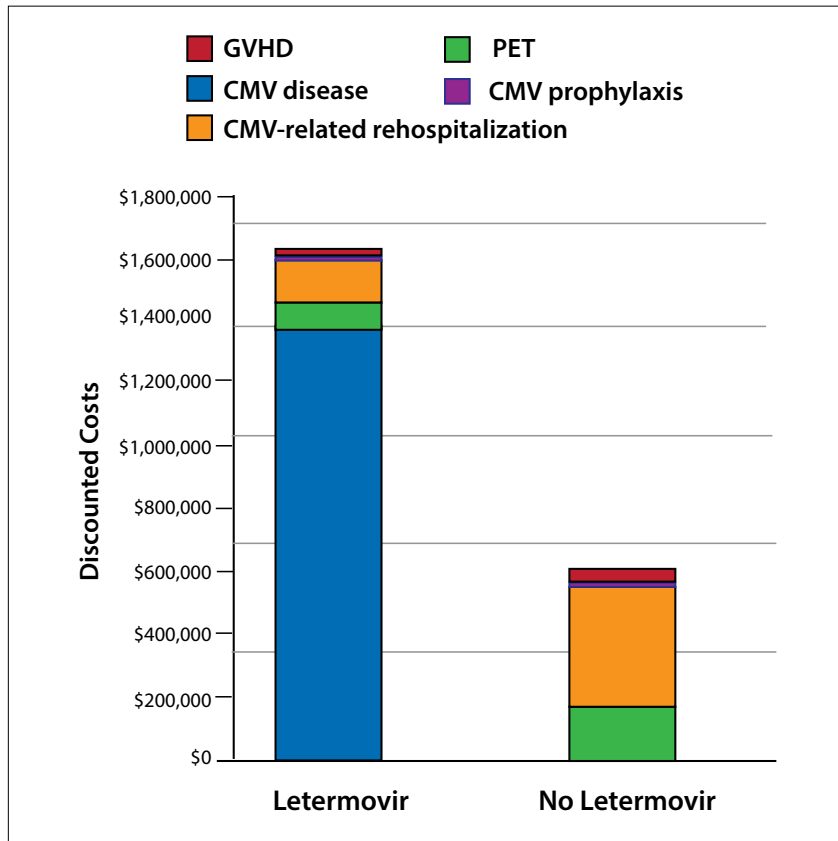
Figure 4. Differences in costs between patients who did or did not receive letermovir after HSCT, as shown in a retrospective analysis. CMV, cytomegalovirus; GVHD, graft-versus-host disease; PET, positron emission tomography; HSCT, hematopoietic stem cell transplant. Adapted from Schelfhout J et al. BMT Tandem Meetings abstract 557. *Biol Blood Marrow Transplant.* 2018;24(3)(suppl 1).[2]

with an increase in treatment cost relative to the standard of care, the letermovir costs are partially offset by decreases in costs associated with preemptive therapy, CMV-related rehospitalization, CMV disease, and graft-versus-host disease (Figure 4). In probabilistic sensitivity analysis, the majority of incremental cost-effectiveness ratios fell below the willingness-to-pay threshold of $50,000 per QALY gained. The model inputs with the greatest impact were a reduction in the rates of mortality and rehospitalization, and the increased cost of letermovir treatment. The analysis is limited by the paucity of cost data for CMV treatment. In addition, many costs of treatment for CMV infection, disease, and mortality are not routinely captured.

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A Modified Intensive Strategy to Prevent CMV Disease in Seropositive Umbilical Cord Blood Transplant Recipients

Umbilical cord blood transplant is associated with a nearly universal risk of CMV reactivation.[1,2] The procedure also confers a risk for CMV disease of up to 28% and an attributable mortality of up to 11% by 1 year posttransplant. Early cord transplant procedures used prophylactic anti-CMV regimens that had been developed for other types of transplant. The standard treatment consists of acyclovir (800 mg twice daily) or valacyclovir (500 mg twice daily). With this regimen, weekly

PCR tests are administered to assess viral load, and treatment is initiated at 125 IU/mL. An alternative to standard treatment is an intensive regimen consisting of ganciclovir (5 mg/kg daily) on days –8 through –2 prior to transplant, plus valacyclovir (2 g 3 times daily) after transplant. With this regimen, CMV viral loads are assessed twice weekly, and preemptive therapy is implemented after any positive test. In a comparison of the treatments, the intensive regimen decreased the incidence of CMV disease by 4.7% at 1

year posttransplant, and it was associated with no CMV-related mortality.[2]

A study conducted at a single institution evaluated the intensive prophylactic treatment vs a modified intensive prophylactic treatment in patients who underwent umbilical cord transplant.[3] Data from a separate study of standard prophylactic treatment at the same institution were used for comparison.[2] The modified intensive treatment regimen omitted the administration of ganciclovir prior to cord transplant, partly to reduce costs

ABSTRACT SUMMARY Clinical and Economic Burden of Pre-Emptive Therapy of Cytomegalovirus Infection in Hospitalized Allogeneic Hematopoietic Cell Transplant Recipients: The MD Anderson Cancer Center Experience

A retrospective, descriptive, cohort study evaluated the economic and clinical burden of CMV preemptive therapy (Abstract 542). The study included 100 consecutive allogeneic HSCT recipients with CMV reactivation who were treated between January 2012 and December 2015 at a single US institution. The patients' median age was 56 years (range, 20-76 years), and 55% were male. The most common underlying malignancy was leukemia, reported in 73%. The HSCT procedure consisted of a matched, unrelated donor transplant in 59% of patients. Within the first year after transplant, patients had received 192 preemptive treatments, which included ganciclovir (41%), foscarnet (40%), and valganciclovir (38%). Intravenous immunoglobulin was administered in 20% of preemptive regimens. CMV disease occurred in 4 patients (4%). The average direct cost per patient admitted for preemptive therapy was $126,038 (range, $7866-$641,841). The mean cost of antiviral therapy per hospitalization was $6096 for intravenous immunoglobulin, $2410 for foscarnet, $836 for ganciclovir, and $780 for valganciclovir. Among 53 patients treated with foscarnet, the mean costs increased significantly for those who developed nephrotoxicity ($284,006 vs $112,195; *P*=.021).

Number of Patients at Risk

Standard	29	22	12	4	2	2	1	0	0	0	0
Intensive	43	39	31	27	22	16	15	13	13	13	11
Modified Intensive	40	34	26	22	19	16	16	15	14	14	14

Figure 5. The incidence of CMV in a study evaluating prophylactic regimens in seropositive umbilical cord blood transplant recipients. The incidence for the standard treatment was taken from historical data. CMV, cytomegalovirus. Adapted from Hill JA et al. BMT Tandem Meetings abstract 96. *Biol Blood Marrow Transplant*. 2018;24(3)(suppl 1).[3]

and associated toxicities, but also to address the logistical barrier of treating patients who are not yet hospitalized. The study evaluated the risk for CMV reactivation, rate of CMV disease, and duration of anti-CMV therapy by day 100 posttransplant.

Data were available for 43 patients treated with the intensive regimen from 2008 to 2010. The modified-intensive regimen was used in 40 consecutive CMV-seropositive patients from 2014 to 2017. In the intensive-treatment cohort, fewer patients had received myeloablative conditioning (79% vs 98%), and the median total nucleated cell dose was lower (4.9×10^7/kg vs 7.2×10^7/kg). Both the intensive and modified-intensive regimens showed a significantly reduced incidence of CMV infection compared with the historical data for the standard treatment (*P*<.001; Figure 5). Moreover, the incidence of CMV infection was similar for the intensive and modified-intensive prophylactic regimens after approximately 60 days posttransplant. Compared with intensive treatment, the modified-intensive regimen had a similar reduction in CMV reactivation (hazard ratio, 1.1; 95% CI, 0.6-1.9; *P*=.77) and early reactivation (hazard ratio, 1.1; 95% CI, 0.6-2.2; *P*=.76). The median duration of CMV detection within 100 days posttransplant was 17 days (range, 8-29 days) with intensive treatment vs 36 days (range, 26-47 days) with modified-intensive treatment, representing a mean difference of 9 more days for the modified regimen (range, 0.2-18 days; *P*=.05). The duration of CMV therapy was also longer in the modified-intensive treatment cohort (mean difference, 9 days [range, −3 to 21 days]; *P*=.15). However, inclusion of the 7 days of ganciclovir administration in the intensive treatment cohort eliminated this difference.

The median time to engraftment was slightly longer for the patients who received ganciclovir prior to cord blood transplant (20 days vs 17 days). The reduced time to engraftment among patients who received the modified
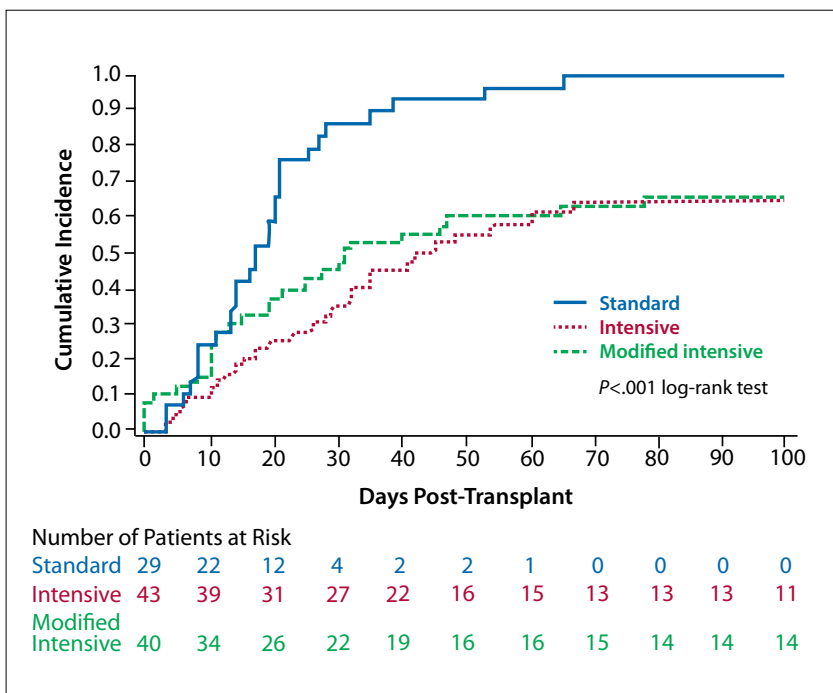
treatment may reflect the fact that these patients also received a higher median dose of nucleated cells (7.2 × 10^7/kg vs 4.9 × 10^7/kg). Rates of neutropenia were similar in both cohorts. The rate of acute kidney injury was higher in the intensive therapy cohort (26% vs 4%), whereas the rates of foscarnet use were similar (40% vs 49%, respectively). The modified-intensive regimen was significantly associated with an increase in the proportion of days that patients were alive and not hospitalized.

In summary, outcomes in patients treated with the modified-intensive anti-CMV regimen, which excluded pretransplant ganciclovir, were generally similar to those in patients who received the intensive regimen. Further studies are needed to establish whether pretransplant ganciclovir can be eliminated from prophylactic anti-CMV treatment without a loss of efficacy.

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Functional Signatures Revealed by Deep Phenotyping of CMV-Specific CD8+ T Cells Predict Risk of Early CMV Reactivation After Allogeneic Hematopoietic Cell Transplantation

CMV reactivation occurs in most seropositive patients after HSCT and is associated with transplant-related mortality, as well as considerable treatment costs.[1-3] However, the pivotal phase 3 trial of letermovir vs placebo showed that 39% of patients did not need anti-CMV prophylaxis.[4] Therefore, many patients are needlessly receiving preemptive treatment. CMV reactivation after HSCT is controlled by T cells.[5] The most immunodominant antigens that CMV-directed T cells recognize include IE1, IE2, and pp65.

In an effort to derive biomarker signatures that might predict the risk for CMV reactivation, CD8-positive T-cell responses to IE1 and pp65 were evaluated in cryopreserved peripheral blood mononuclear cells collected on day 30 after HSCT.[6] Samples were categorized into 3 clinically distinct subgroups. Elite controllers (n=19) were CMV-seropositive but never experienced CMV reactivation (based on weekly surveillance testing). Spontaneous controllers (n=16) were CMV-seropositive patients in whom low-grade viremia resolved without antiviral therapy. Noncontrollers (n=21) were CMV-seropositive patients who experienced high-grade CMV viremia (defined as a viral load >1000 IU/mL) and required antiviral therapy. The study's hypothesis was that the 3 clinically distinct groups of patients would exhibit immunologically distinct cytokine signature profiles within the population of CMV-specific CD8-positive cells.

In comparison with the noncontrollers, spontaneous controllers demonstrated a significantly higher median absolute lymphocyte count,

ABSTRACT SUMMARY Analysis of Cytomegalovirus Infections in the First 180 Days in Adult Sero-Positive Cord Blood Transplantation Recipients Reveals High Infection Rates and Treatment Burden

Cord blood donation from an unrelated donor commonly causes CMV infection in seropositive recipients. A study was conducted to investigate the incidence and treatment burden associated with CMV infection in adult CMV-seropositive recipients within 180 days after cord blood transplant (Abstract 549). Treatment included ganciclovir prophylaxis on days –7 to –2. Foscarnet, ganciclovir, or valganciclovir was administered for induction or maintenance treatment based on the patient's viremia level and infection assessment vs the risk of toxicity. The 55 patients had a median age of 52 years (range, 23-66 years). The most common diagnosis was acute myeloid leukemia or lymphoblastic leukemia (75%). The cumulative incidence of CMV infection was 84% (95% CI, 70%-91%). The median onset to viremia was 35 days (range, 5-74 days), and the median time from detection to therapy was 3 days (range, 0-39 days). The median total therapy time was 58 days (range, 4-92 days) during days 1 to 100 posttransplant and 57 days (range, 0-80 days) during days 101 to 180 posttransplant. Among the 55 patients, 6 (11%) developed CMV-related disease. One patient died of graft-versus-host disease, and 2 died of acute respiratory failure with viremia.
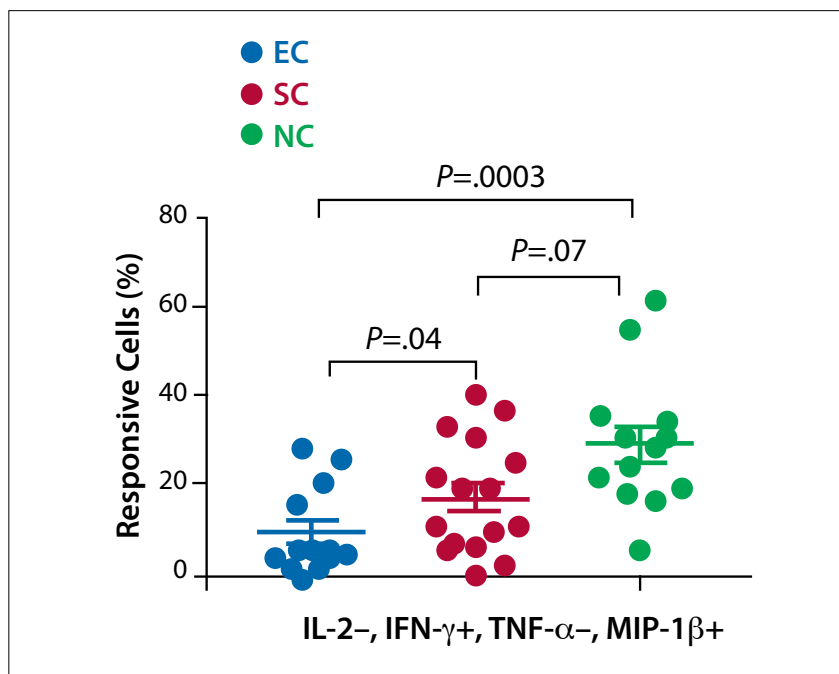
Figure 6. Functional signatures were shown to correlate with response in a study that evaluated deep phenotyping of CMV-specific CD8-positive T cells. EC, elite controllers; IFN, interferon; IL, interleukin; NC, noncontrollers; SC, spontaneous controllers; TNF, tumor necrosis factor. Adapted from Camargo JF et al. BMT Tandem Meetings abstract 93. *Biol Blood Marrow Transplant*. 2018;24(3)(suppl 1).[6]

higher numbers of CMV-responsive CD4-positive T cells, and higher numbers of CMV-responsive CD8-positive T cells. The level of CMV-responsive CD4-positive T cells was significantly higher in the elite controllers vs the noncontrollers. Six patients did not respond to therapy. These patients had a significantly lower median absolute lymphocyte count, as well as reduced median levels of CMV-responsive CD4-positive and CD8-positive T cells compared with the cohort of noncontrollers. Interferon γ (IFN-γ) levels alone were not associated with the cumulative incidence of CMV viremia requiring therapy. CMV viremia that required therapy was reported in 31% of patients with high IFN-γ levels vs 21% of those with low levels, a nonsignificant difference.

Functional signatures were shown to correlate with response (Figure 6). The study identified 2 CMV-specific, CD8-positive T-cell cytokine signatures measured at day 30 posttransplant. The CD8-positive T-cell nonprotective signature (interleukin 2 [IL-2]^{neg}, IFN-γ^{pos}, tumor necrosis factor α [TNF-α]^{neg}, and macrophage inflammatory protein 1β [MIP-1β]^{pos}) was positively associated with CMV reactivation. CD8-positive T cells with the nonprotective signature were present at higher levels in the combined cohort of spontaneous controllers and noncontrollers compared with the elite controllers (19.4% vs 4.9%; *P*=.002). Cells with the nonprotective signature were more common in the separate cohorts of spontaneous controllers and noncontrollers compared with the elite controllers. Similar trends were observed for cells stimulated with IE1 or pp65.

Cells with the protective signature produced all 4 cytokines (IL-2^{pos}, IFN-γ^{pos}, TNF-α^{pos}, and MIP-1β^{pos}). After stimulation with IE1 or pp65, the proportion of CD8-positive cells

with the protective signature was lower among noncontrollers compared with the spontaneous controllers, but the difference did not reach statistical significance. In a multivariate analysis, the presence of the nonprotective cytokine signature was associated with CMV reactivation (*P*=.02). Patients with more than 5.7% of cells with the nonprotective signature were significantly more likely to experience CMV reactivation compared with patients who had a lower level of cells with the nonprotective signature (71% vs 11%; *P*=.006). Similarly, using a cutoff value of 16%, patients with a higher level of CD8-positive cells with the nonprotective signature were more likely to experience CMV viremia requiring therapy compared with patients who had lower levels of CD8-positive cells with the nonprotective signature (35% vs 5%; *P*=.02).

Limitations of the study included the small numbers of patients in each cohort, and the lack of samples available prior to 30 days posttransplant. The mechanisms underlying the associations between CMV status and cytokine signatures remain to be elucidated.

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Early HHV-6 Reactivation in CMV-Seronegative Cord Blood Transplant Recipients Is Associated With Inferior Relapse-Free and Overall Survival

Reactivation of the human herpesvirus 6 (HHV-6) is seen in most cord-blood transplant recipients. Reactivation is associated with delayed engraftment, encephalitis, graft-versus-host disease, and CMV.[1-3] The mechanisms that lead to these events have not been fully described. Immunosuppression of transplant recipients enables reactivation of not only HHV-6, but other viruses as well, making it difficult to determine the specific effects of HHV-6 reactivation.

A retrospective study of patients treated at a single institution between July 2010 and May 2017 evaluated the impact of HHV-6, including its immunosuppressive activity, after cord blood transplant.[4] To avoid the confounding influence of CMV, samples were restricted to consecutive CMV-seronegative recipients of cord blood. The study excluded patients with reactivation of CMV, adenovirus, Epstein-Barr virus, or BK virus. Early HHV-6 reactivation was defined as 1 or more positive quantitative DNA PCR tests on whole blood within 30 days after cord blood transplant. The absence of HHV-6 reactivation was defined as 1 or more negative PCR tests in the first 2 weeks and 1 or more negative PCR tests in the second 2 weeks after transplant. Research blood samples to evaluate T-cell populations by flow cytometry were collected on day 30 in a subset of patients. The primary endpoint was the rate of relapse.

Among the 152 patients, 120 (79%) tested positive for HHV-6. Patient characteristics such as age, sex, diagnosis, conditioning regimen,
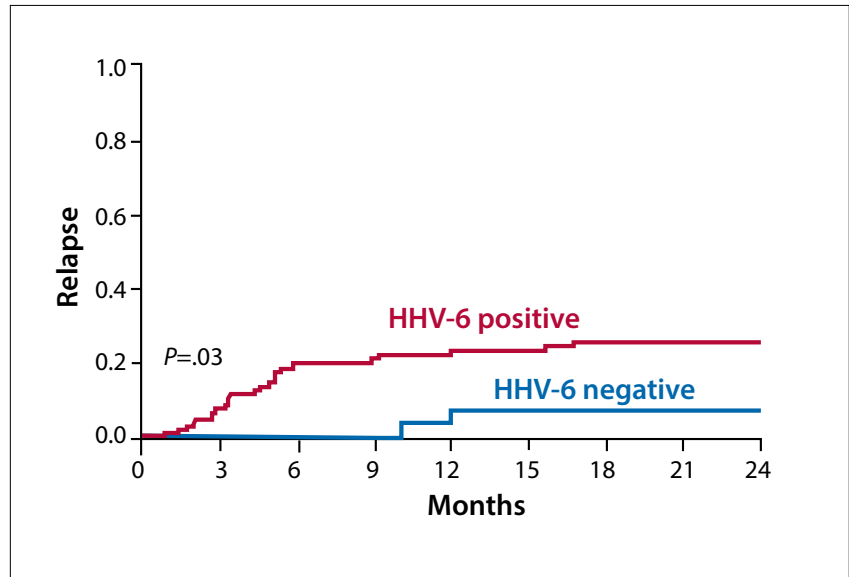

Figure 7. In a retrospective analysis, CMV-seronegative cord blood transplant recipients with HHV-6 reactivation by day 28 were significantly more likely to relapse. CMV, cytomegalovirus; HHV-6, human herpesvirus 6. Adapted from Rashidi A et al. BMT Tandem Meetings abstract 534. *Biol Blood Marrow Transplant*. 2018;24(3)(suppl 1).[4]

and CMV reactivation were generally well-balanced between the cohorts of patients who did relapse vs those who did not. Patients with HHV-6 reactivation by day 28 were significantly more likely to relapse (P=.03; Figure 7). HHV-6 relapse was not associated with conditioning intensity or CMV reactivation by day 30. The HHV-6–negative and HHV-6–positive cohorts showed similar rates of overall survival, relapse-free survival, and nonrelapse mortality. There was a nonsignificant trend toward a higher rate of acute graft-versus-host disease in the HHV-6–positive cohort. Rates of chronic graft-versus-host disease, however, were similar between the 2 groups. Flow cytometry indicated

that natural killer cells did not appear to be involved in HHV-6 reactivation.

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Cytomegalovirus Infection and Disease Incidence and Risk Factors Across Diverse Hematopoietic Cell Transplantation Platforms Using a Standardized Monitoring and Treatment Approach: A Comprehensive Evaluation From a Single Institution

Allogeneic HSCT is potentially curative for numerous hematologic disorders. However, the procedure requires suppression or ablation of the host immune system to facilitate engraftment of donor cells. Donor T cells must be removed, reduced, or suppressed to prevent graft-versus-host disease. As a result, the graft recipient is susceptible to viral infections after transplant. More than 40% of at-risk recipients (defined as those who were seropositive or whose donor was seropositive) experience infection within the first 100 days after transplant.

A retrospective study was conducted to characterize posttransplant CMV infection and disease across all HSCT protocols.[1] The study evaluated the incidence, associated risk factors, and virus-associated nonrelapse mortality. Enrolled patients had undergone their first transplant and had follow-up data available through 1 year after the procedure, with at least 64% of weekly PCR results available through day 100 posttransplant. CMV infection was defined as 2 quantitative PCR results between 3.08 to 4.11 $\log_{10}$ IU/mL within a single week, 1 quantitative PCR value of greater than 4.11 $\log_{10}$ IU/mL, or sufficient clinical suspicion of CMV disease to prompt therapy. The duration of CMV infection was determined from weekly quantitative PCR values and length of treatment. Recurrent infection referred to patients who had previous evidence of CMV infection but in whom CMV was not detected for at least 4 weeks prior to the new infection.[2]

Among at-risk recipients, the cumulative incidence of CMV infection at 100 days posttransplant was 46%. The cumulative incidence of CMV infection varied mainly by recipient CMV serostatus (P<.0001). The estimates of infection at day 100 were 2% for patients who were donor- and recipient-negative, 6% for those who were donor-positive and recipient-negative, 38% for those who were donor-negative and recipient-positive, and 40% for those who were donor- and recipient-positive. In keeping with results from a separate study, donor and/or recipient serostatus appeared to be the main determinant of CMV infection.[3] The 100-day cumulative incidence of CMV infection associated with cord blood was 64%, which was higher than that of bone marrow (39%) or peripheral blood stem cells (30%; P=.016). This result was expected based on the cord unit's immature immune system and general lack of antiviral immunity.

The cumulative incidence of CMV infection at 100 days posttransplant was highest with cord-based T-cell manipulation (67%; P=.043) and lowest with calcineurin inhibitors and T-cell manipulation based on the mammalian target of rapamycin (mTOR; 41%; P<.001). The incidence of CMV infection was 61% in patients who received calcineurin inhibitors only vs 20% in those treated with a calcineurin inhibitor and an mTOR
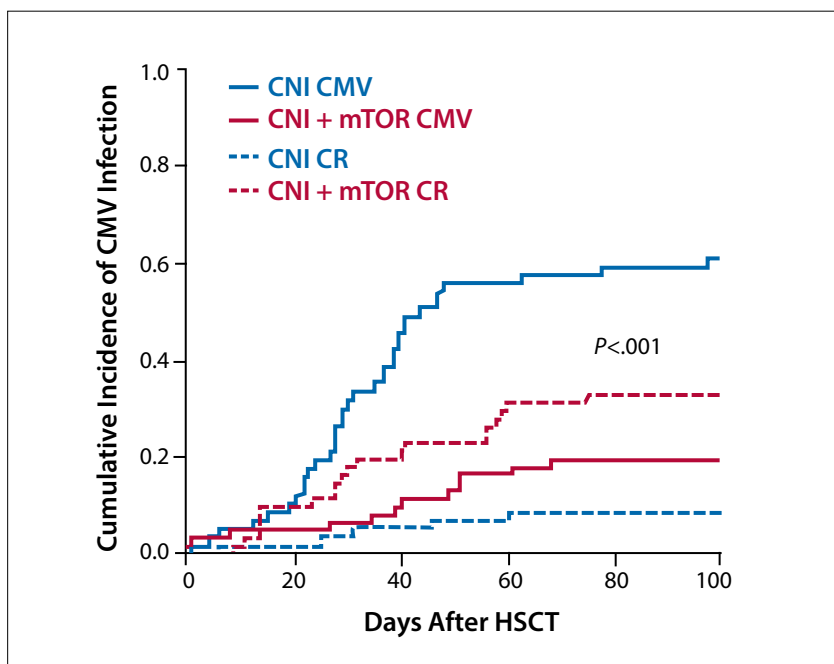

Figure 8. Incidence of CMV infection in the first 100 days after HSCT, according to the use of CNI/mTOR inhibitor–based T-cell manipulation. CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, competing risk; HSCT, hematopoietic stem cell transplant; mTOR, mammalian target of rapamycin. Adapted from Marchalik R et al. BMT Tandem Meetings abstract 546. *Biol Blood Marrow Transplant*. 2018;24(3)(suppl 1).[1]

inhibitor (*P*<.001; Figure 8). The median duration of CMV therapy was longer for patients who had undergone HSCT with cord blood (36 days) compared with transplants using peripheral blood stem cells (21 days) or bone marrow (28.5 days; *P*=.03).

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Clinical Impact and Burden of CMV Infection on the Use of Resources in Allogeneic Hematopoietic Cell Transplantation

Despite the standard use of preemptive therapy, CMV infection continues to be a major complication after allogeneic HSCT and is associated with increased transplant-related mortality.[1] Novel anti-CMV therapies are in development to reduce the rates of CMV reactivation, infection, and disease. In addition to offering a clinically effective alternative to current antiviral agents, improved therapies could decrease the overall costs associated with CMV-related morbidity and mortality. The impact of CMV infection on cost and resource use has not been extensively examined. A retrospective study evaluated the impact of CMV infection on clinical outcomes and the use of resources.[2] The study included all allogeneic HSCT recipients at a single center between 2009 and 2016. The median age of the 183 patients was 44 years (range, 16-68 years), and 59% were male. For nearly all of the patients, the transplant procedure was their first. It was the second transplant in 9 and the third in 2. The HSCT procedure used materials from an identical sibling donor in 45% of cases, cord blood in 30%, and an unrelated donor in 20%. The procedure was a haploidentical stem cell transplant in 5%. In 88% of cases, CMV serology indicated an at-risk transplant. The severity of graft-versus-host disease was low (grade 0 to 1) in 67% and high (grade 2 to 4) in the remainder (based on criteria from the Mount Sinai Acute GVHD International Consortium).

The median time to the first CMV reactivation was 35 days (range, 15-58 days). CMV reactivation was observed in 60% of at-risk patients, and the rate of CMV infection was 3.4 per 100 patient-months. At 2 years, overall survival was 59.9% in patients without CMV infection vs 44.4% in patients with CMV infection (*P*=.027; Figure 9). Pooled analysis showed a higher incidence of CMV infection in recipients of cord blood or haploidentical transplants vs patients who underwent matched related or unrelated transplants (68% vs 49%; *P*=.009). The cumulative incidence of CMV infection was significantly increased among the patients with high-grade acute graft-versus-host disease vs low-grade disease (87.2% vs 42.8%; *P*<.001). Patients who were older than the median age of 44 years at the time of the HSCT were more likely to develop CMV infection compared with younger patients (65.2% vs 48%; *P*=.005). Among the patients who developed a CMV infection,

ABSTRACT SUMMARY CMV Reactivation Post CD34+ Selected Allo-HCT Has Adverse Outcomes on Blood Count Recovery

A study evaluated the effect of CD34-positive allogeneic HSCT on CMV reactivation and blood counts (Abstract 540). The analysis included 317 allogeneic HSCT recipients who were treated between April 2012 and May 2016 and had follow-up data available through 1 year after transplant. Grafts selected for CD34-positive cells were used in 205 patients, and 112 received unmodified grafts. CMV seropositivity was reported in 58% of patients in the unmodified graft cohort and 62.4% in the CD34-selected cohort. CMV reactivation was observed in 38.4% of patients who received unmodified grafts vs 71% of the CD34-selected graft recipients. The time to CMV reactivation was 40 days (range, 7-82 days) in the unmodified graft cohort and 28 days (range, 15-51 days) in the CD34-selected cohort. Among the patients who received CD34-selected grafts, those with CMV reactivation had significantly lower absolute neutrophil counts (*P*=.0001) and lower hemoglobin levels (*P*=.023), with a trend toward reduced platelet counts (*P*=.07). In contrast, in the group of patients who received unmodified grafts, blood counts were not affected by CMV serostatus or reactivation.
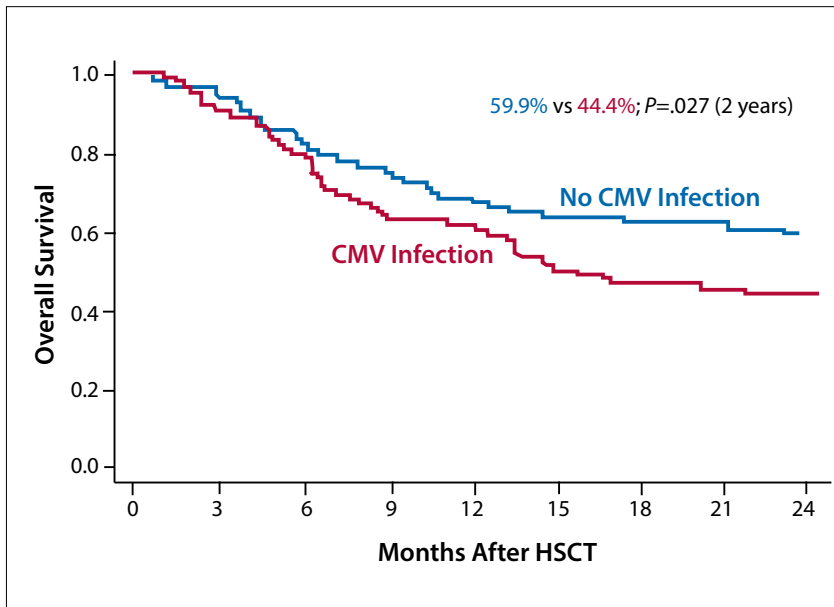
Figure 9. Overall survival at 2 years in a retrospective study that evaluated the impact of CMV infection on clinical outcomes and the use of resources. CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant. Adapted from de Miguel C et al. BMT Tandem Meetings abstract 565. *Biol Blood Marrow Transplant.* 2018;24(3)(suppl 1).[2]

57% had 2 or more infections and 20% had 4 or more. A CMV infection prolonged the duration of hospitalization by 30 days throughout the first year after transplant (*P*<.001). The length of stay in a hospital increased to more than 40 additional days in patients with 2 or more CMV infections (*P*<.001). Clinically significant adverse events associated with pre-emptive therapy were common after first-line treatment. The frequency of these events increased with second and subsequent lines of therapy.

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Highlights in Cytomegalovirus From the 2018 BMT Tandem Meetings: Commentary

Sanjeet Singh Dadwal, MD
Associate Clinical Professor of Medicine
Division of Infectious Disease
Head, Antimicrobial Stewardship Program
Co-Lead, Infectious Disease, Transplant Disease Team
City of Hope National Medical Center
Duarte, California

Several abstracts at the 2018 BMT Tandem Meetings provided important data in the management of cytomegalovirus (CMV) infection among patients undergoing hematopoietic cell transplant (HCT). The presentations reported on the burden of CMV reactivation in various HCT populations, evaluated prophylactic regimens, calculated cost and clinical burden related to reactivation, and explored the potential of biomarker signatures to determine CMV immunity.

CMV Infection (Reactivation)

Multiple abstracts presented at the 2018 BMT Tandem Meetings continued to confirm a high cumulative incidence of CMV infection (defined as detectable virus with no evidence of end-organ disease) in the first 100 days after allogeneic HCT. Dr Rachel Marchalik and colleagues evaluated the effect of T-cell manipulation on the cumulative incidence of CMV infection in the first 100 days after the procedure.[1] The overall incidence of CMV infection was 46%. The incidence was highest with cord-based T-cell manipulation (67%) and lowest with manipulation based on calcineurin and mammalian target of rapamycin (mTOR) inhibition (41%).

Dr Roni Tamari and coworkers examined CMV infection in patients who underwent CD34-selected allogeneic HCT.[2] Patients with CD34-selected grafts had a higher risk of CMV infection compared with those who received unmanipulated grafts, and this risk manifested earlier in the post-HCT period. Among patients with CD34-selected grafts and CMV infection, the absolute neutrophil count was lower, suggesting that active infection impacts allografts, with resultant cytopenia. This abstract highlights the burden of CMV, and the authors concluded that there is the need for an effective nonmyelosuppressive prophylactic agent to prevent CMV infection to avoid the downstream effects of CMV infection and its treatment.

An important area of research is the measurement of CMV immunity, with the objective of identifying patients in whom CMV is likely to reactivate vs patients who are likely to successfully clear the viremia. Dr Jose Camargo and colleagues evaluated cytokine signatures of CD8 T-cell response to pp65 and IE1 CMV peptide stimulation.[3] They identified a protective signature and a nonprotective signature, which can help distinguish between patients at higher risk for CMV infection and those who can spontaneously control infection. These findings are interesting, but the clinical applications will require further study. Perhaps a targeted approach to prophylaxis against CMV infection could employ such intervention in the future.

CMV Infection Prophylaxis

CMV infection has a significant impact on clinical outcome and is associated with high cost. High rates of morbidity and all-cause mortality are seen in patients who develop resistant or refractory infection. Without a safe and effective prophylactic agent, preemptive therapy has been the standard of care in the management of CMV infection. This approach is highly efficacious, but not without side effects. Rates of CMV infection after allogeneic HCT are highest in recipients who are seropositive.[4] Preemptive treatment for CMV infection is indicated when levels of viral load measured by polymerase chain reaction testing hit a certain threshold. The traditional approaches for preemptive treatment have been ganciclovir or foscarnet. However, both of these therapies are associated with toxicities ranging from myelosuppression with ganciclovir to nephrotoxicity with foscarnet.[5,6]

In the absence of an effective anti-CMV prophylaxis agent, various centers have used combinations of ganciclovir and acyclovir for prevention of CMV reactivation.

High-Intensity Prophylactic Regimens

One common high-intensity prophylactic regimen consists of ganciclovir given before transplant followed by high-dose acyclovir given after the procedure. In 2011, a study evaluated the use of ganciclovir administered before umbilical cord blood transplant (5 mg/kg intravenously daily from day –8 to day –2) and high-dose acyclovir (2 g, 3 times daily) after the procedure in high-risk, CMV-seropositive patients.[7] The study showed that this intensive prevention regimen significantly decreased CMV infection and disease. Recently, Dr Joshua Hill and colleagues from the same center evaluated a modified high-dose strategy that eliminated pretransplant use of ganciclovir.[8] The authors found no difference in outcomes as compared with the regimen that included pretransplant ganciclovir. A similar study, presented by Dr Carmen Lau and colleagues, also showed no benefit with the use of ganciclovir prior to transplant.[9]

Letermovir

Previously, the quest for a safe and effective prophylactic agent had been elusive. Clinical trials evaluating maribavir and CMX001 (brincidofovir) failed to meet their primary endpoints of preventing CMV infection.[10,11] In November 2017, the US Food and Drug Administration (FDA) approved letermovir for the prophylaxis of CMV infection in adult CMV-seropositive recipients undergoing HCT.[12] Letermovir is an inhibitor of the enzyme "terminase," and it is nonmyelosuppressive and nonnephrotoxic. A presentation by Dr Cameron Douglas and colleagues at the BMT Tandem Meetings showed that although polymorphisms in the *UL56* gene exist, they do not appear to impact sensitivity to letermovir.[13] In the pivotal study, only 1 patient in the full analysis set had a V236M mutation that conferred resistance to letermovir.[14] Also, there was no cross resistance to ganciclovir or foscarnet. Letermovir may play a significant role in the prevention of CMV infection, when used as suggested according to the FDA indication.

Morbidity and Mortality

From an epidemiologic standpoint, resistant or refractory CMV infection can lead to significant morbidity. Dr Annette Artau and coworkers evaluated outcomes after resistant or refractory CMV infection among patients who underwent allogeneic HCT.[15] There was a high burden of CMV disease among the 81 patients, with an incidence of 49%. All-cause mortality was also high, at 64%. Patients developed resistance to ganciclovir at a median of 153 days post-HCT and to foscarnet at a median of 98 days post-HCT. Refractory CMV infection developed at a median of 64 days after transplant. Whether prophylaxis with letermovir can prevent such reactivation early on and have an impact on the disease after day 100 remains to be seen.

Economic Burden

Several abstracts presented at the meeting evaluated the clinical and economic burden of CMV reactivation. Dr Shashank Ghantoji and colleagues showed that significant costs are associated with the preemptive use of ganciclovir or foscarnet to treat CMV infection among hospitalized patients.[16] The per episode cost was $6096 for intravenous immune globulin, $2410 for foscarnet, $836 for ganciclovir, and $780 for valganciclovir. Serious side effects were seen in 35% of patients treated with ganciclovir and 12% of patients treated with foscarnet. Dr Carlos de Miguel and coworkers evaluated clinical outcomes and resource use associated with CMV infection.[17] They also found that reactivation is associated with a substantial use of resources. Both of these studies suggest that new strategies are needed.

Additionally, Dr Jonathan Schelfhout and colleagues presented results from a study using a model evaluating the cost effectiveness of letermovir as prophylaxis among patients who underwent allogeneic HCT.[18] The cost was $23,270 for each life-year gained and $25,222 for each quality-adjusted life-year gained. The model suggested that letermovir may be associated with longer life, improved health-related quality of life, and fewer adverse outcomes. The authors noted that the costs of letermovir were partially offset by decreases in costs associated with preemptive therapy, CMV-related rehospitalization, and graft-versus-host disease.

Conclusion

The abstracts on CMV infection presented at the 2018 BMT Tandem Meetings highlighted the continued burdens—both clinical and economic—that arise from early CMV reactivation in allogeneic HCT recipients. The field is showing rapid progress in several areas, with continued epidemiologic investigations, studies of novel means of CMV immune monitoring, and updates on high-intensity prophylaxis. Researchers at MD Anderson Cancer Center generated robust data on the economic burden of early CMV infection,[16] and others are devising health care economic models based on the use of letermovir for the prevention of CMV infection.[18] With the FDA approval of letermovir for the prevention of CMV infection, as well as vaccines and other advances, the field of CMV infection is on the verge of a major transformation.

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