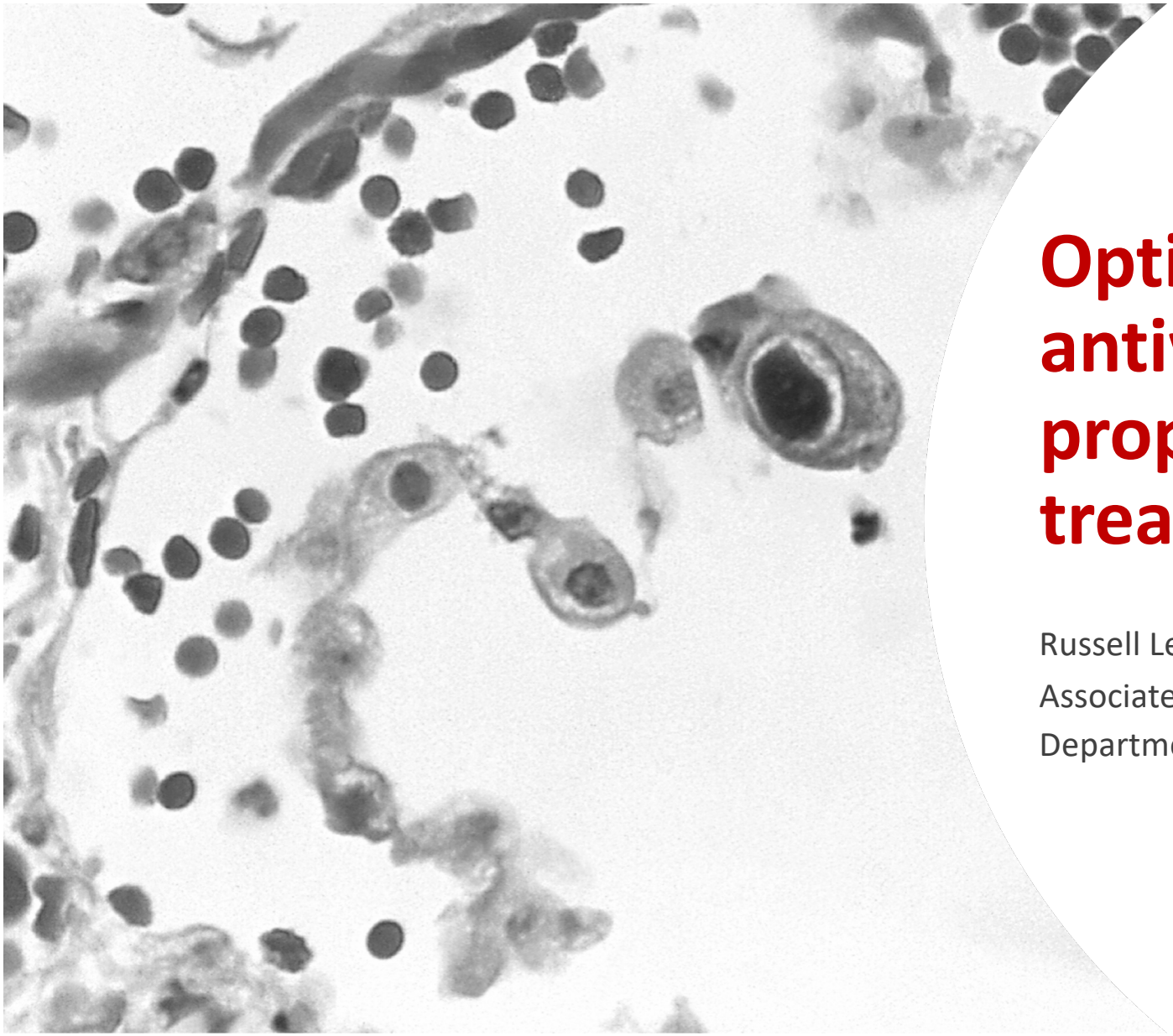
Ottimizzazione delle nuovo opzioni per la profilassi ed il trattamento dell'infezione da CMV post-triapanto

Russell Lewis
Università di Bologna

Disclosures of Russell Lewis

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Merck	X						
F2G			X			X	
Scynexis			X				
Pfizer					X		
Avir					X		
Gilead	X		X		X		



Optimizing new antivirals for prophylaxis and treatment of CMV

Russell Lewis, Pharm.D., FCCP
Associate Professor, Infectious Diseases
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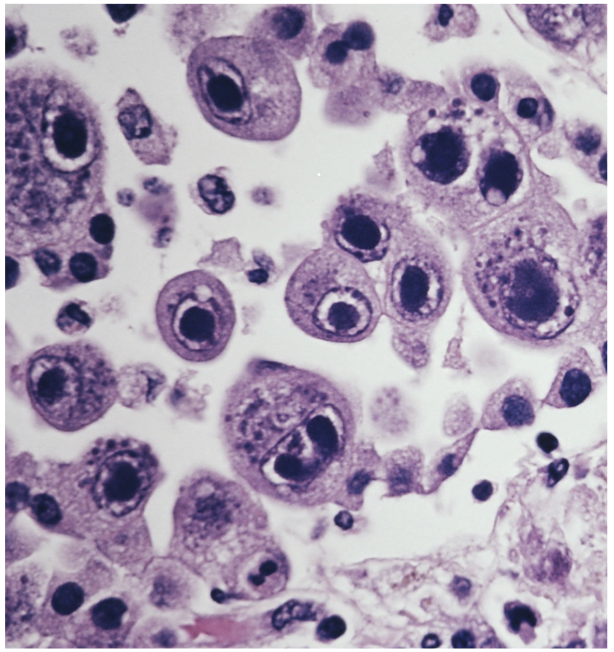
Agenda

- **Brief review CMV management strategies**
- **How has letermovir transformed CMV management?**
- **What will be the future role for maribavir?**

…will defer discussion of CMI monitoring (and potential role of adoptive immunotherapy) to the subsequent speaker

CMV in HSCT: Background

- **CMV infection is prevalent following HSCT with a high cumulative incidence of reactivation:[1,2]**
  - Without prophylaxis, between 30-70% in CMV seropositive HSCT recipients develop CMV infection
- **Any CMV reactivation is associated with higher all-cause mortality[2]**
- **Considerable improvements in CMV end-organ disease over the last 20 years[3]**
  - (1990s) 18-27%
  - (2000s) 1.5-10%
- **Moderate improvements in CMV-attributable mortality in patients with end-organ disease[3,4]**
  - CMV pneumonia 30d mortality: 45 → 30%[3]



[1]Dziedzic M et al. Anticancer Res. 2017 37:6551-6
[2]Teira P et al. Blood. 2016 127:2427-2438
[3]Erard V et al. Clin Infect Dis. 2015 61:31-39
[4]Limaye AP et al. Clin Microbiol Rev. 2020 34:e00043-19

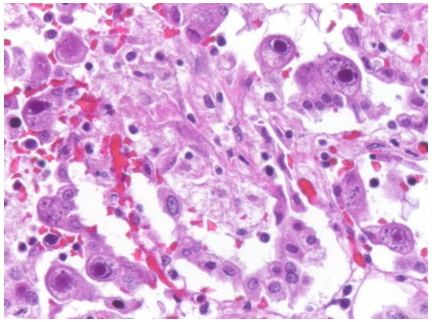
Direct and indirect effects of CMV infection

Direct effects
(tissue invasion and damage)

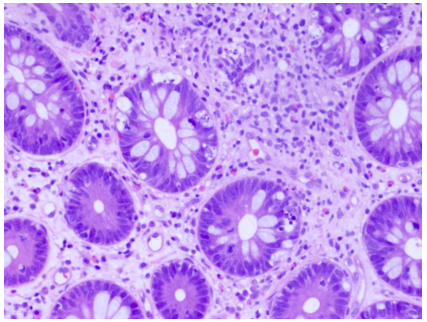
- Pneumonia
- Colitis
- Encephalitis
- Hepatitis
- Bone marrow suppression

Indirect effects
(altered immunosuppression/inflammation)

- Increased incidence/severity of GVHD
- Increased mortality from bacterial and fungal infection
- Increased thrombotic/cardiovascular events



H&E stain demonstrating CMV in lung biopsy

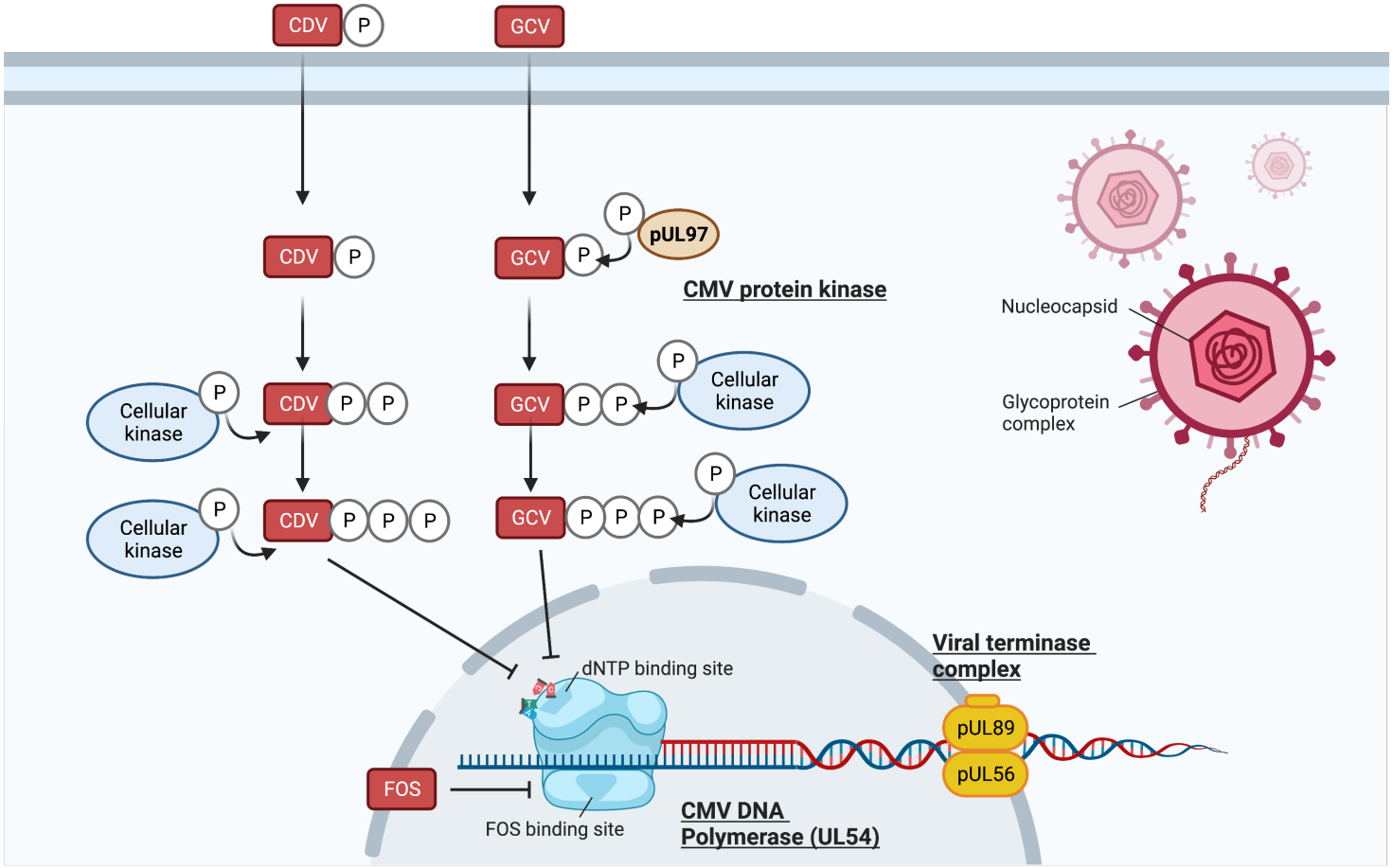


aGVHD of colon with crypt apoptosis

Kotton CN. Et al. A report from the International CMV Symposium 2021. Transpl Infect Dis 2022 In press

Antiviral therapies for CMV

Ganciclovir (GCV), Foscarnet (FOS), Cidofovir (CDV)



Antiviral therapies for CMV

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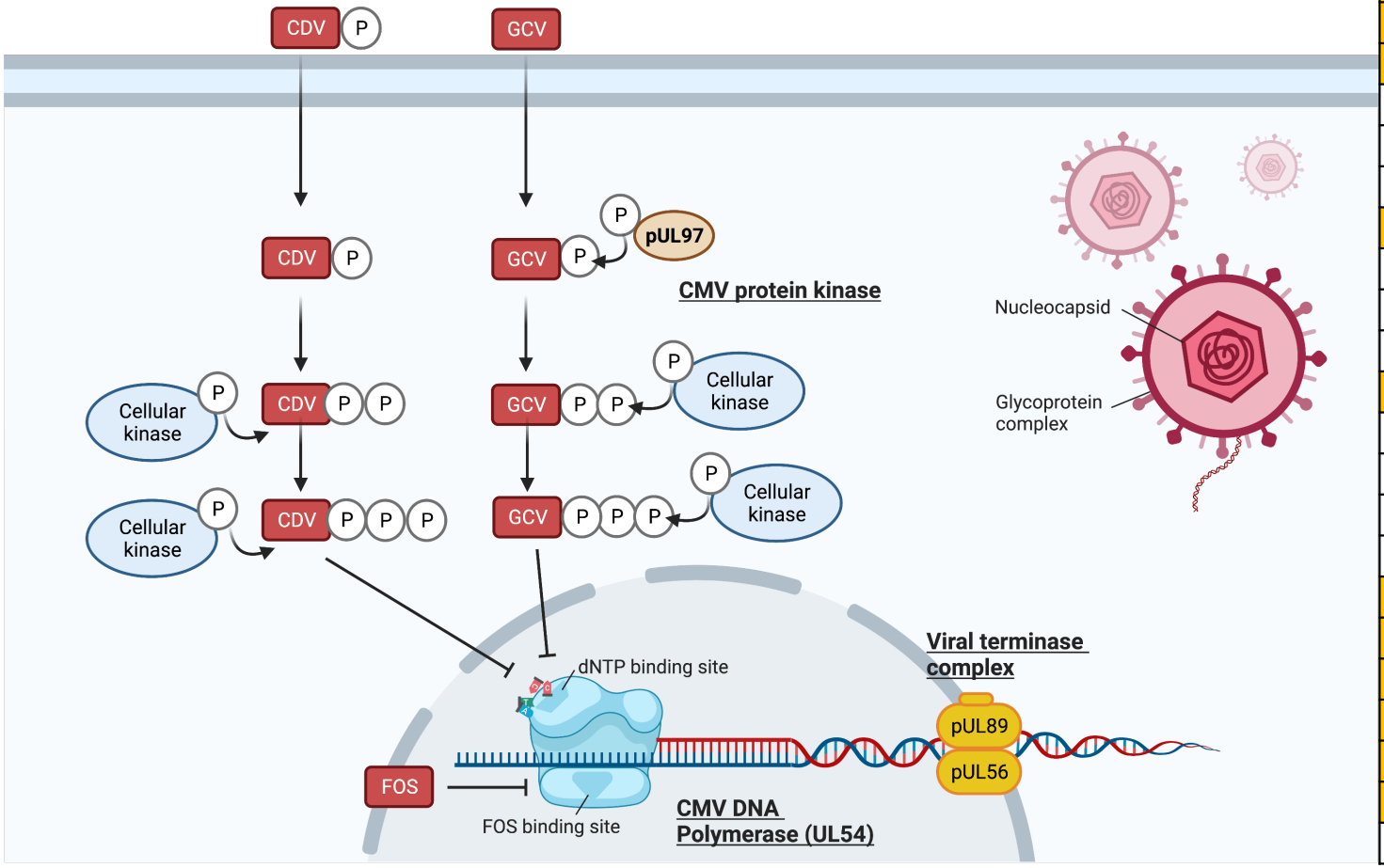
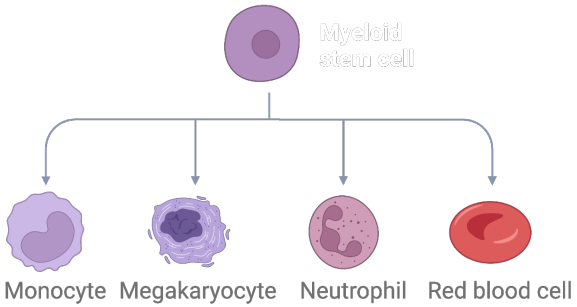


Razonable RR. Curr Opin Organ Transplant. 2018 23:388-394.

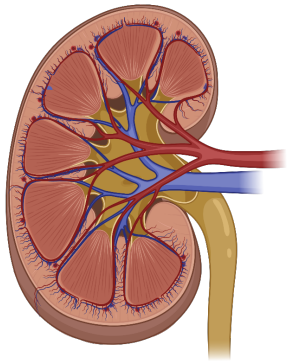
Ganciclovir	Cidofovir	Foscarnet
D301N	D301N	S290R
N408D/K/S	E303D/G	N495K
F412C/L/S	N408D/K	Q578
D413A/F	N410K	D588E/N
L501F/1	F412C/V	T700A
T503/I	D413A/E/Y	V715M
K513E/N/R	L501I	E756D/N/Q
I521T	P522A	V7811
P522A/S	D542E	V787L
del524	L545S	L802M
L545S/W	D588N	A809V
Q578H	E756K	V812L
D588N	K805Q	T813S
E756K	V812L	T821I
V7811	Y813S	A834
V787L	G841A	T838A
L802M	Del 981-982	G841A
A809V	A987G	E951D
T813S		Del 981-982
T8211		
A834P		
G841A		
Del 981-982		
A9898G		

Dose-limiting toxicities of nucleoside analogues



Ganciclovir, valganciclovir

Myelosuppression → direct cytotoxicity to myeloid stem cells →neutropenia, thrombocytopenia up to 50% of patients



Foscarnet, cidofovir

Acute kidney injury → foscarnet: tubular interstitial nephritis, electrolyte disturbances in 25%, neurologic toxicity, cutaneous toxicities (ulceration)

Acute kidney injury → cidofovir: proximal tubular damage in up to 25% of patients, myelosuppression

Boeckh M et al. Biol Blood Marrow Transplant. 2015 21:24-29.

Management of CMV post allo-HSCT

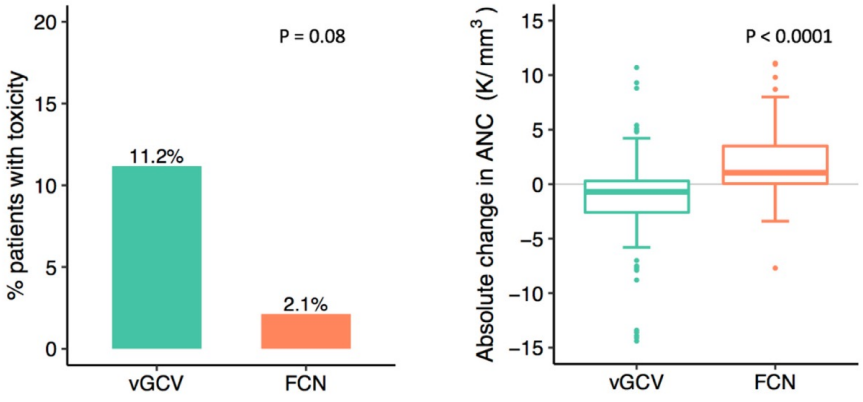
Prophylaxis vs. preemptive therapy

	Prophylaxis	Preemptive therapy
Description	• Antivirals administered to all patients prior to onset of CMV infection	• Routine monitoring for CMV infection (DNAemia) • Treatment started after detection of asymptomatic CMV infection
Pros	• Can prevent direct and indirect CMV effects • Viral load monitoring not required if antiviral is effective • Covers CMV disease without detectable CMV DNA • Reduce all-cause mortality?	• Targets patients at highest risk • Minimizes over-treatment and toxicity • Improved CMV-specific immunoreconsititution
Cons	• Potential over treatment/ added cost • Concerns for drug resistance • Delays CMV-specific immune-reconstitution • Increased risk for myelotoxicity, acute kidney injury	• Potential missed cases of CMV disease if not proceeded by DNAemia • Relies on availability of timely CMV testing • Concern for survival disadvantage

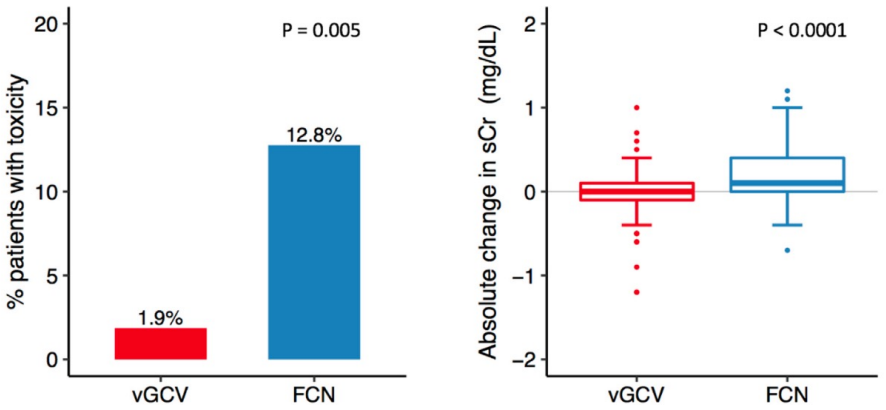
Preemptive therapy has been the standard of care for last 20 years

Impact of preemptive therapy approaches on ganciclovir/ foscarnet toxicity

Neutropenia



Nephrotoxicity



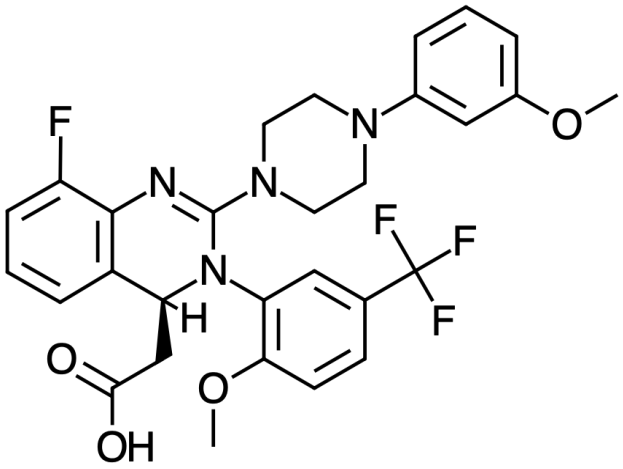
Preemptive therapy for CMV increased the risk of neutropenia and AKI in the first 100 days post-HCT by 1.8-fold and 2.8-fold, respectively.

Zavras P et al. Biol Blood Marrow Transplant 2020;26:1482-1491.

Key medical need:
Less toxic antivirals

- Negative impact of CMV reactivation independent of end-organ disease
- Cross-resistance among all nucleoside analogues
- Dose-limiting toxicities of current antivirals

Letermovir

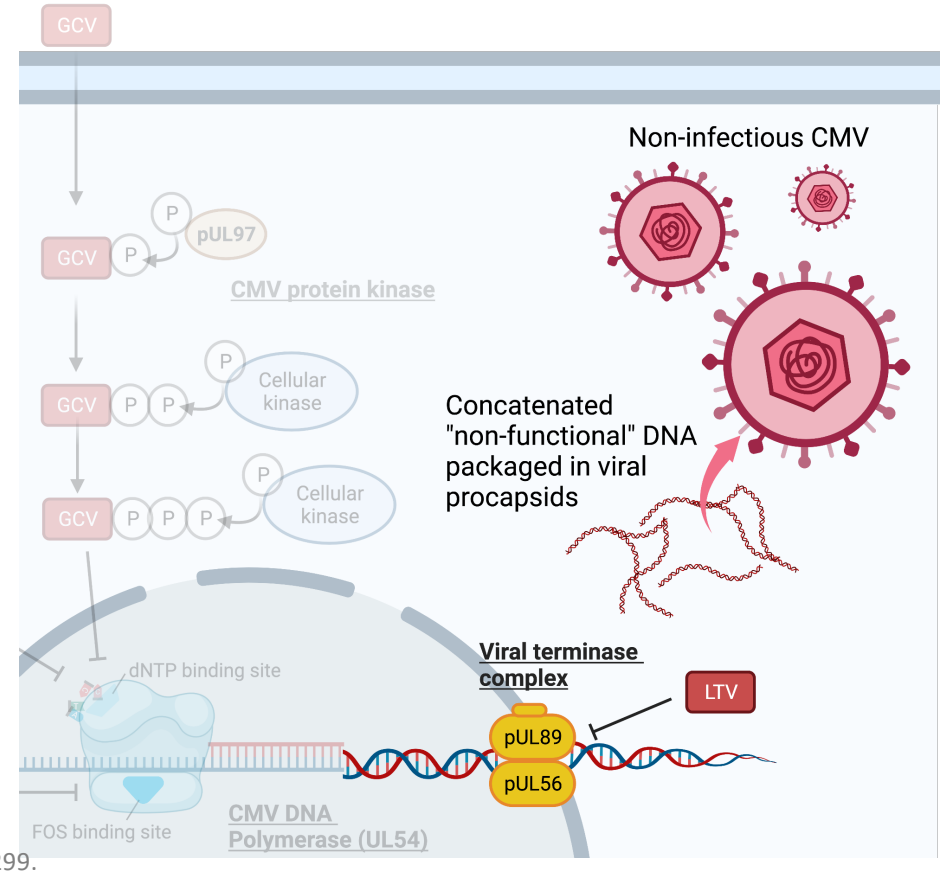


- **Indicated for prophylaxis of CMV infection and disease in seropositive allo-HCT**
- **Inhibitor of CMV terminase complex:**
  - Function → cleaves long DNA into single functional CMV DNA units → encapsulation into viral procapsid
- **Activity only against hCMV, no other herpesviruses**
- **Little cross-resistance with other anti-CMV nucleoside inhibitors**
- **Available IV, oral (bioavailability 35-94%)**
  - Bioavailability impacted by CsA (OATP transporters) reduce letermovir oral dose by 50%)
- **Multiple drug interactions (letermovir is a substrate and inhibitor of multiple CYPP450 pathways)**

Letermovir mechanism of action

Implications for PCR monitoring

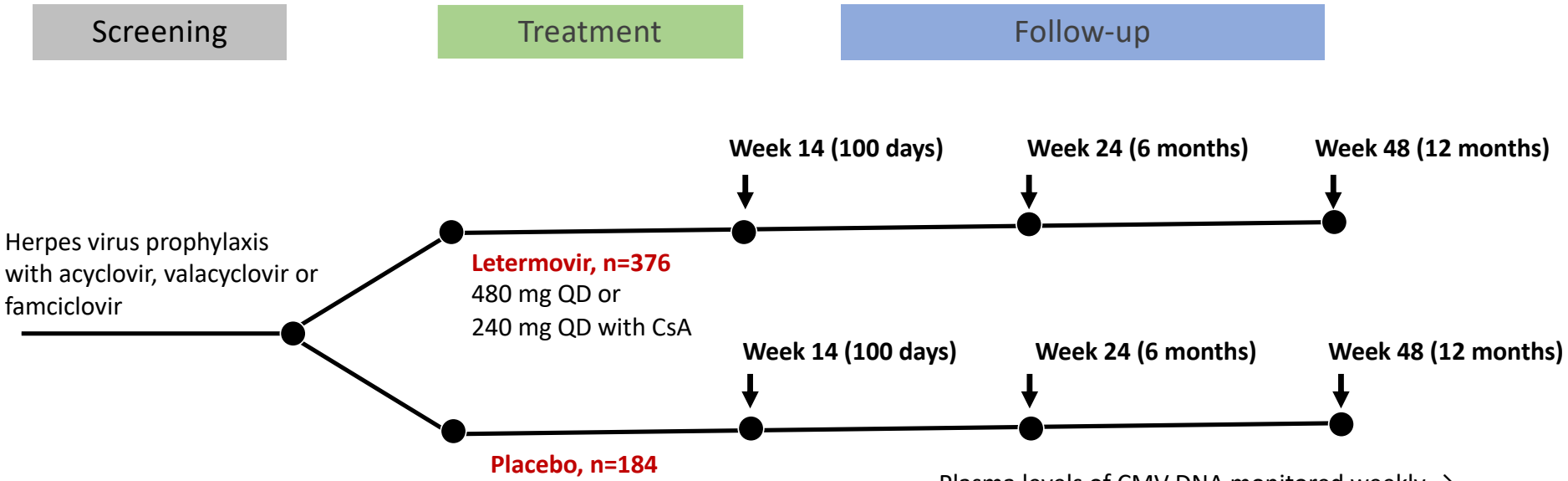
- **Standard qPCR used for preemptive management will not necessarily distinguish viable vs. non-viable virus in letermovir-treated patients**
- **Low-level DNAemia "blips" common (30%) during letermovir treatment- not infectious virus[1]**
- **Possible solutions:[1-3]**
  - DNAse 1-pretreatment of plasma digest concatemeric (non-replicative) DNA[1,2]
  - Confirmation of DNAemia with early shell-vial culture[3]
  - Use higher thresholds for initiating preemptive therapy rarely reached with abortive virus (e.g., 10,000 HCMV DNA copies/ml) [2-4]
  - Monitoring pp67 mRNA (late hCMV-gene transcript)



[1] Cassaniti I et al. Am J Transplant 2021; 21:1622–1628.
[2] Weinberger S, Steininger C. Antiviral Res. 2022 201:105299.
[3] Girmenia C et al. Clin Transplant 2019; 33:e13666.
[4] Einsele H et al. Blood. 2020 135:1619-1629.

Letermovir prophylaxis for CMV in allo-HCT

Phase III trial design



Plasma levels of CMV DNA monitored weekly → Every 2 weeks → every other month

Primary endpoint: defined CMV disease or CMV viremia Leading to preemptive treatment (> 150 copies/mL) for high risk* and > 300 copies/mL for low-risk

*High risk: having a related donor with at least one mismatch at one of the specified three HLA gene loci (HLA-A, B, or DR); having an unrelated donor with at least one mismatch at one of the specified four HLA gene loci (HLA-A, B, C, and DRB1); having a haploidentical donor; the use of umbilical cord blood as the stem-cell source; the use of ex vivo T-cell– depleted grafts; and having graft-versus-host disease of grade 2 or greater that led to the use of 1 mg or more of prednisone (or its equivalent) per kilogram of body weight per day.

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

Letermovir prophylaxis for CMV in allo-HCT

Underrepresentation of high-risk populations?

Table 1. Characteristics at Baseline of All the Patients Who Underwent Randomization and Received the Trial Regimen (Safety Population).*

Characteristic	Letermovir Group (N=373)	Placebo Group (N=192)
Age — yr		
Median	53	54
Range	18–75	19–78
Male sex — no. (%)	211 (56.6)	116 (60.4)
Race — no. (%)†		
White	301 (80.7)	162 (84.4)
Asian	40 (10.7)	18 (9.4)
Other	32 (8.6)	12 (6.2)
CMV-seropositive donor — no. (%)	230 (61.7)	114 (59.4)
Primary reason for hematopoietic-cell transplantation — no. (%)		
Acute myeloid leukemia	142 (38.1)	72 (37.5)
Myelodysplastic syndrome	63 (16.9)	22 (11.5)
Non-Hodgkin's lymphoma	47 (12.6)	28 (14.6)
Acute lymphocytic leukemia	35 (9.4)	17 (8.9)
Other disease	86 (23.1)	53 (27.6)
HLA matching and donor type — no. (%)		
Matched unrelated	138 (37.0)	78 (40.6)
Matched related	121 (32.4)	63 (32.8)
Mismatched related	63 (16.9)	24 (12.5)
Mismatched unrelated	51 (13.7)	27 (14.1)
Haploidentical related donor — no. (%)	60 (16.1)	21 (10.9)
Stem-cell source — no. (%)		
Peripheral blood	279 (74.8)	134 (69.8)
Bone marrow	82 (22.0)	47 (24.5)
Cord blood	12 (3.2)	11 (5.7)
Myeloablative conditioning regimen — no. (%)	186 (49.9)	97 (50.5)
Antithymocyte globulin use — no. (%)	140 (37.5)	58 (30.2)
Alemtuzumab use — no. (%)	12 (3.2)	11 (5.7)
Ex vivo T-cell depletion — no. (%)‡	9 (2.4)	5 (2.6)
Immunosuppressant use — no. (%)		
Cyclosporine	193 (51.7)	100 (52.1)
Tacrolimus	160 (42.9)	79 (41.1)
Mycophenolate§	120 (32.2)	51 (26.6)
Sirolimus or everolimus	30 (8.0)	20 (10.4)
Acute GVHD of grade ≥2 at randomization — no. (%)	2 (0.5)	1 (0.5)
Risk of CMV disease — no. (%)¶		
High risk	121 (32.4)	54 (28.1)
Low risk	252 (67.6)	138 (71.9)

14.3%

4%

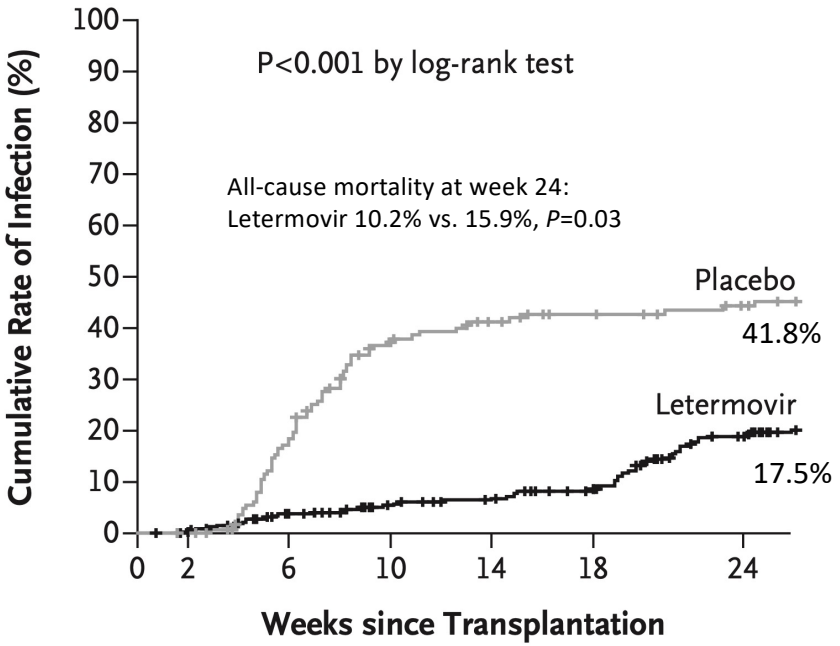
2.5%

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

Letermovir prophylaxis for CMV post HCT

Primary and secondary endpoints

Clinically Significant CMV Infection

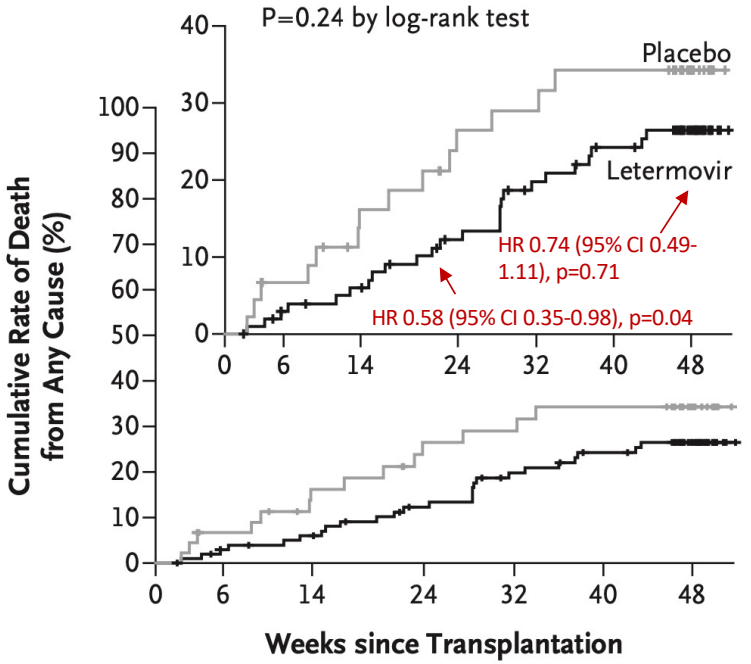


No. at Risk

Placebo	170	169	135	96	85	77	70
Letermovir	325	320	299	279	270	254	212

CMV disease was uncommon (occurring in 1.5% of the patients in the letermovir group and 1.8% of those in the placebo group) and involved the gastrointestinal tract in all cases.

Death from Any Cause through Wk 48, High-Risk Subgroup



No. at Risk

Placebo	45	40	34	28	27	25	12
Letermovir	102	96	92	82	73	67	44

Marty FM et al. N Engl J Med. 2017 377:2433-2444.
Ljungman P et al. Clin Infect Dis. 2020;70:1525-33

Letermovir prophylaxis for CMV post HCT

Safety

- **Treatment discontinuation:**
  - Letermovir 29% (vomiting, edema, dyspnea, afib/flutter)
  - Placebo 58.8% (CMV infection leading cause)
- **Preemptive therapy was administered in 24 (7.7%) letermovir-treated patients because of breakthrough DNAemia (3.7%)**
- **Acute kidney injury rates in letermovir group were similar to placebo**
- **No difference in time-to engraftment vs. placebo**

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

Guideline recommendations

ASTCT and ECIL-7

"We recommend letermovir prophylaxis for adult CMV seropositive allogeneic HCT recipients, to begin no later than 28 days after HCT and continuing through day 100 (A-I)."

- Based on clinical evidence to date and weighing other issues such as cost, some centers may choose to target higher-risk HCT recipients
- CMV DNA qPCR should be assessed before initiating letermovir prophylaxis (A-II) . If quantifiable CMV DNAemia is detected, PET should be considered

"We recommend monitoring through 6 months (Day 180) after HCT with initiation of PET according to institution-specific guidelines (A-II)."

- Clinically significant CMV infection was observed by week 24 after stopping letermovir prophylaxis at week 14 in ~10% of all patients and in ~20% among those at higher risk for CMV infection
- Letermovir prophylaxis may delay CMV-specific cellular immune reconstitution compared to monitoring and PET, perhaps as a result of suppression of reactivation and consequent decreased CMV antigen exposure

PET-Preemptive therapy

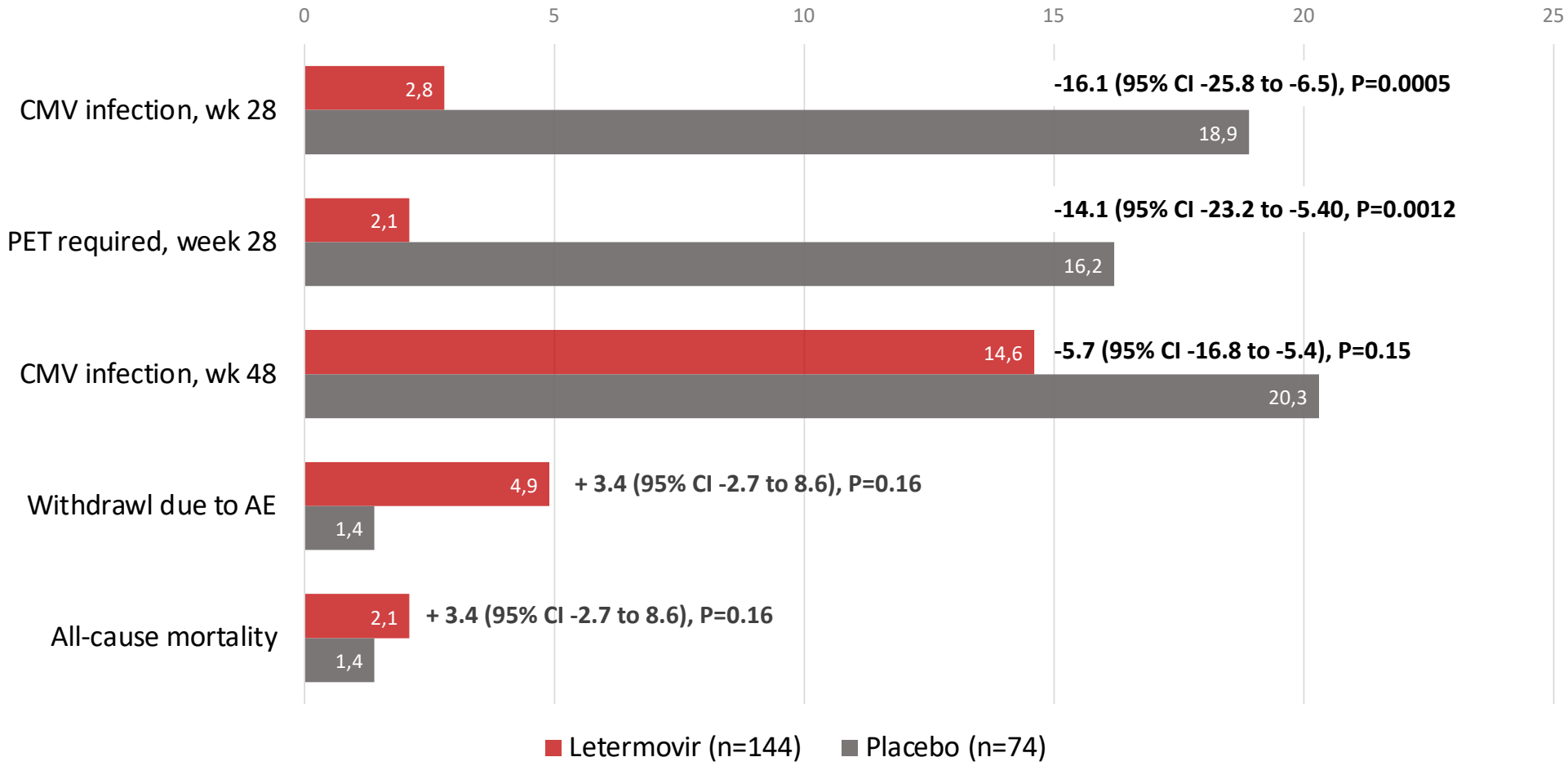
ASTCT Guidelines. Hakki M et al. Transplantation and Cellular Therapy 2021;27:707-719.
ECIL-7 Guidelines. Ljungman P et al. Lancet Infect Dis 2019;19:e260

When should prolonged letermovir (or continued intensive PET) be considered?

- **The following conditions persist after day 100:**
  - Lymphopenia (< 100 lymphocytes/mm^3)
  - CMV infection before day 100
  - GVHD requiring high-dose prednisone (≥ 0.5 mg/kg/d) or equivalent
  - Absence of CMV T-cell specific immunity (if measured)

ASTCT Guidelines. Hakki M et al. Transplantation and Cellular Therapy 2021;27:707-719.
ECIL-7 Guidelines. Ljungman P et al. Lancet Infect Dis 2019;19:e260

Extension of letermovir from day 100 to day 200 day for post-transplant prevention of CMV infection in HSCT



PET-Preemptive therapy

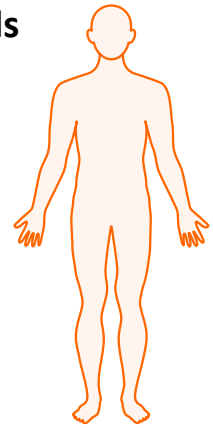
Clinicaltrials.gov Nov 1, 2022: NCT03930615

Letermovir resistance

Low barrier for resistance development

Patient risk factors: CMV DNAemia at time of randomization,* GI GVHD (impaired absorption), treatment interruptions, low letermovir concentrations in blood

N=55 patients with "virologic" failure in phase II/IIII clinical trials



Amino acid substitutions were observed in pUL56 more frequently in letermovir-treated subjects compared to placebo:

L134V, E157G, S227I, Q228H, V236M,* E237G, S255L, I313V, C325W;A366P, R410G, D414N, A425V/A, G430V, E495Q, Y575C, L658S, S705F, R816W, and P846L**

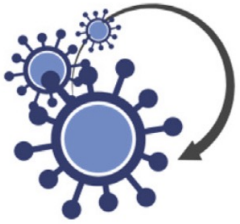
Phase III studies (n=30)

	Previously identified mutations
On treatment virologic failure	**3/8 (38%)**
Off-treatment virologic failures	**0/22 (0%)**

***31% of patients with detectable DNAemia** at the time of randomization to letermovir in the phase III prophylaxis required discontinuation and initiation of standard PET

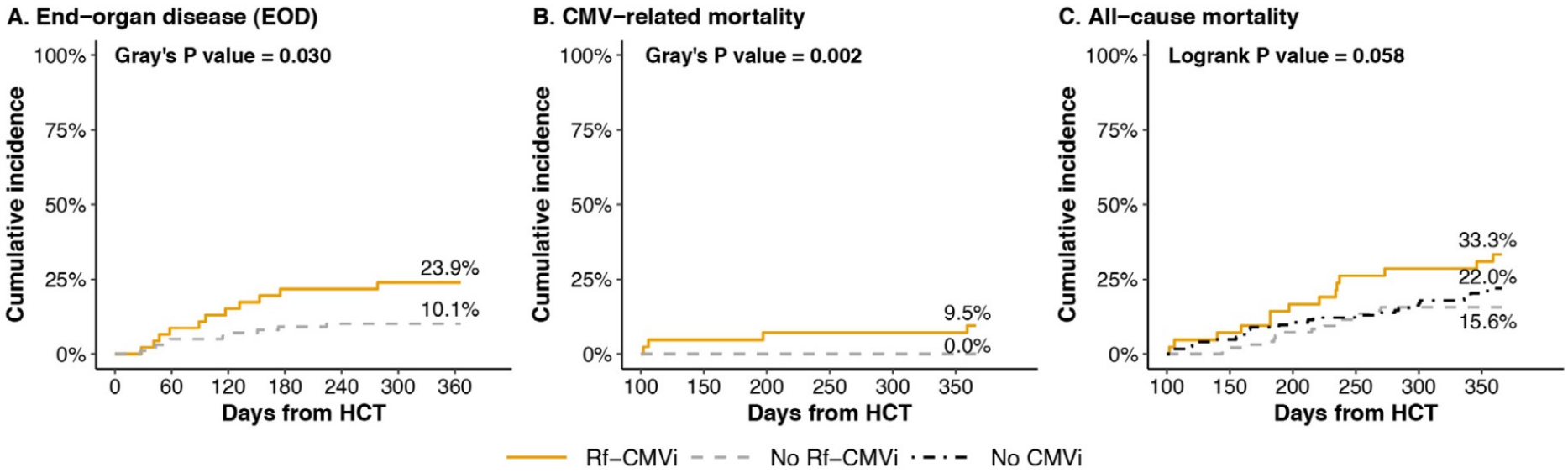
US FDA Clinical virology review NDA: 209939
Alain S et al. J Antimicrob Chemother 2020; 75:2253–2257.

Refractory CMV infection

R/R CMV Definitions	R/R CMV Risk Factors
Probable refractory CMV Infection Persistent virus[α] after ≥2 weeks of appropriately dosed antiviral therapy	 Prolonged antiviral treatment
Refractory CMV Infection CMV viremia that increases ≥1 log10 in blood or serum after 2 weeks of appropriate antiviral therapy	 Previous antiviral exposure
Antiviral Drug Resistance Viral genetic alterations of genes UL97, UL54, UL27, UL51, UL56, and UL89 that decreases the susceptibility to one or more anti-CMV drugs	 Recurrent Infection
	 Poor drug absorption or drug conversion
	 Type of transplant
	 Immunosuppressive therapy

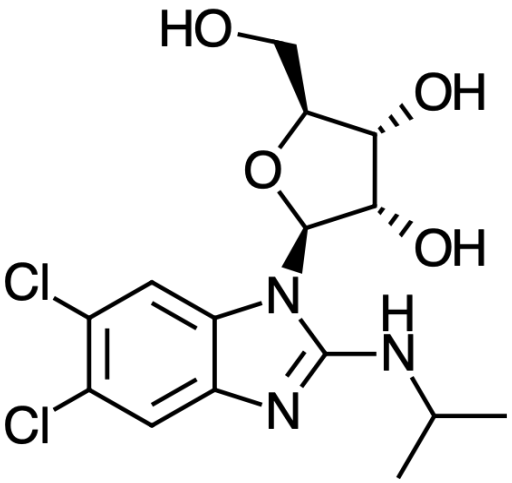
Khawaja F et al. Clin Microbiol Infect. 2022

Poor outcome in HCT patients with refractory CMV

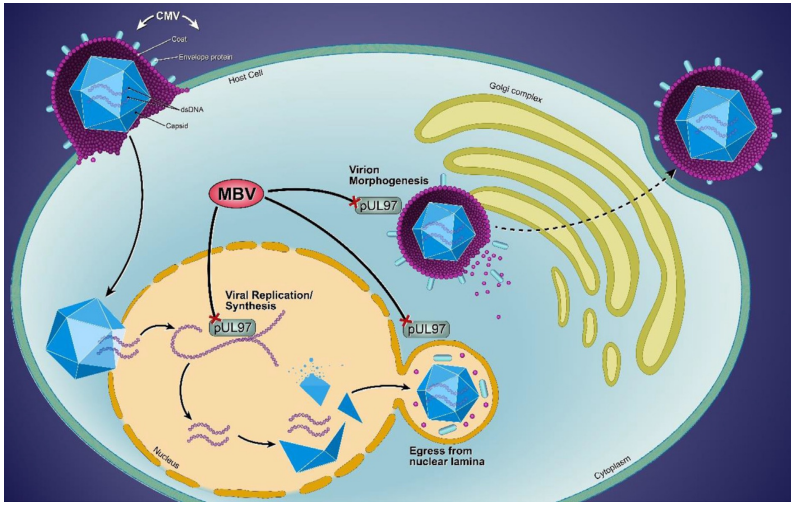


Karantoni E et al. Transplant Cell Ther. 2022 28:403.e1-403.e7.

Maribavir

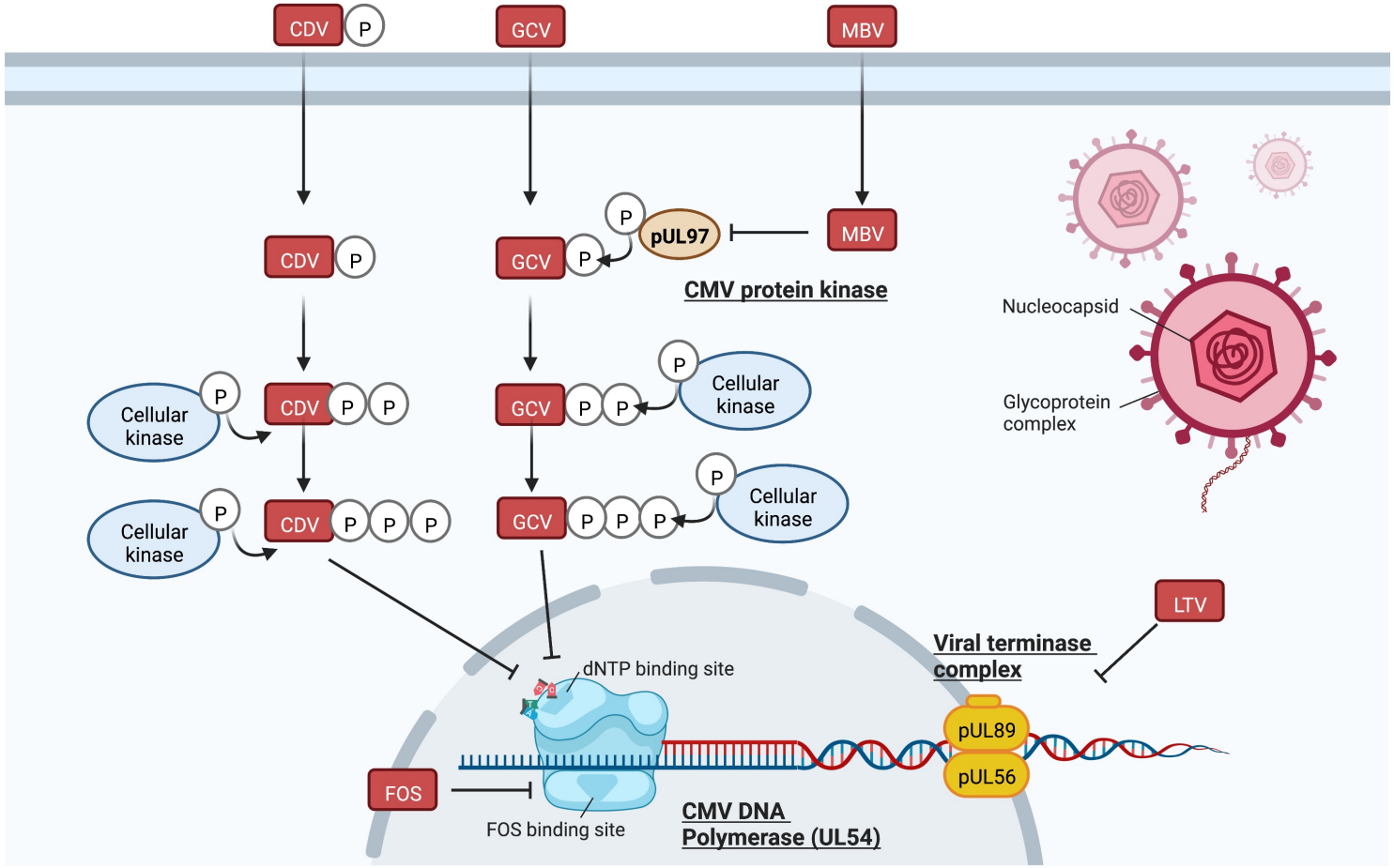


- Oral benzimidazole nucleoside recently approved in US/EMA for treatment of R/R CMV
- Mechanism of action: Inhibits UL97 polymerase, which impacts viral replication, DNA encapsulation and egress
- Some risk of cross-resistance with current nucleoside analogues
  - UL97 mutations confer resistance to maribavir
  - Some UL97 mutations associated with cross-resistance to both ganciclovir and maribavir
- Spectrum of action: hCMV only (Epstein Barr *in vitro*)

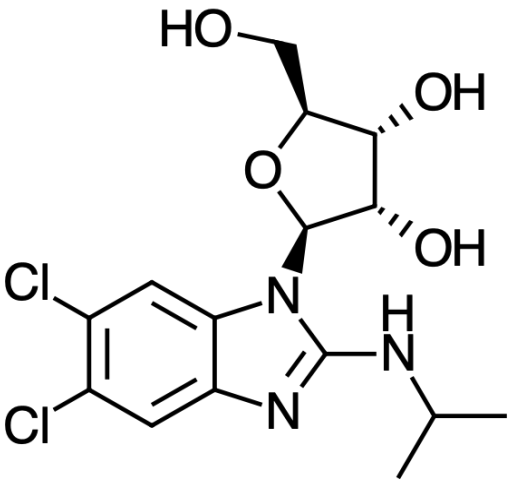


Khawaja F et al. Clin Microbiol Infect. 2022

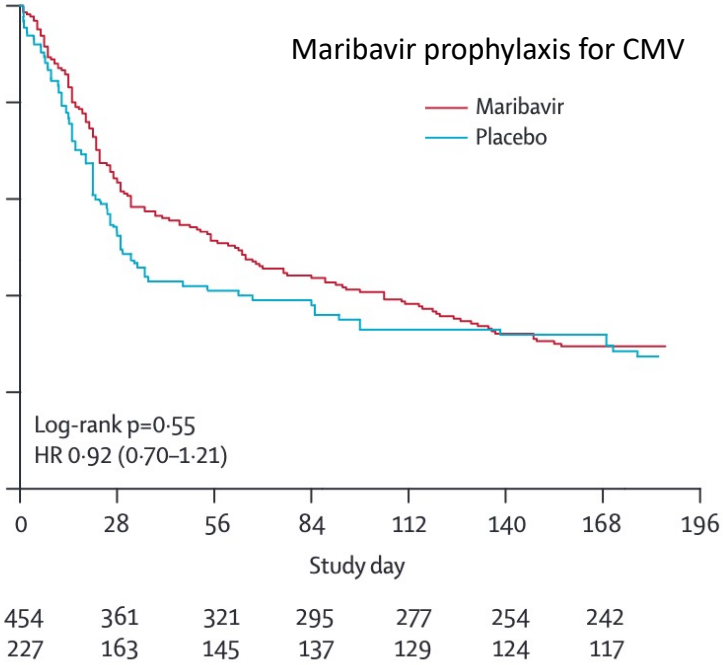
Maribavir will antagonize ganciclovir



Maribavir



- Initially studied as prophylactic agent for CMV in transplant patients, but in a pivotal Phase III trial the incidence of CMV disease was similar to placebo[1]
  - Study design problems: CMV disease as endpoint in the era of effective preemptive therapy, use of too-low doses (100 mg BID)



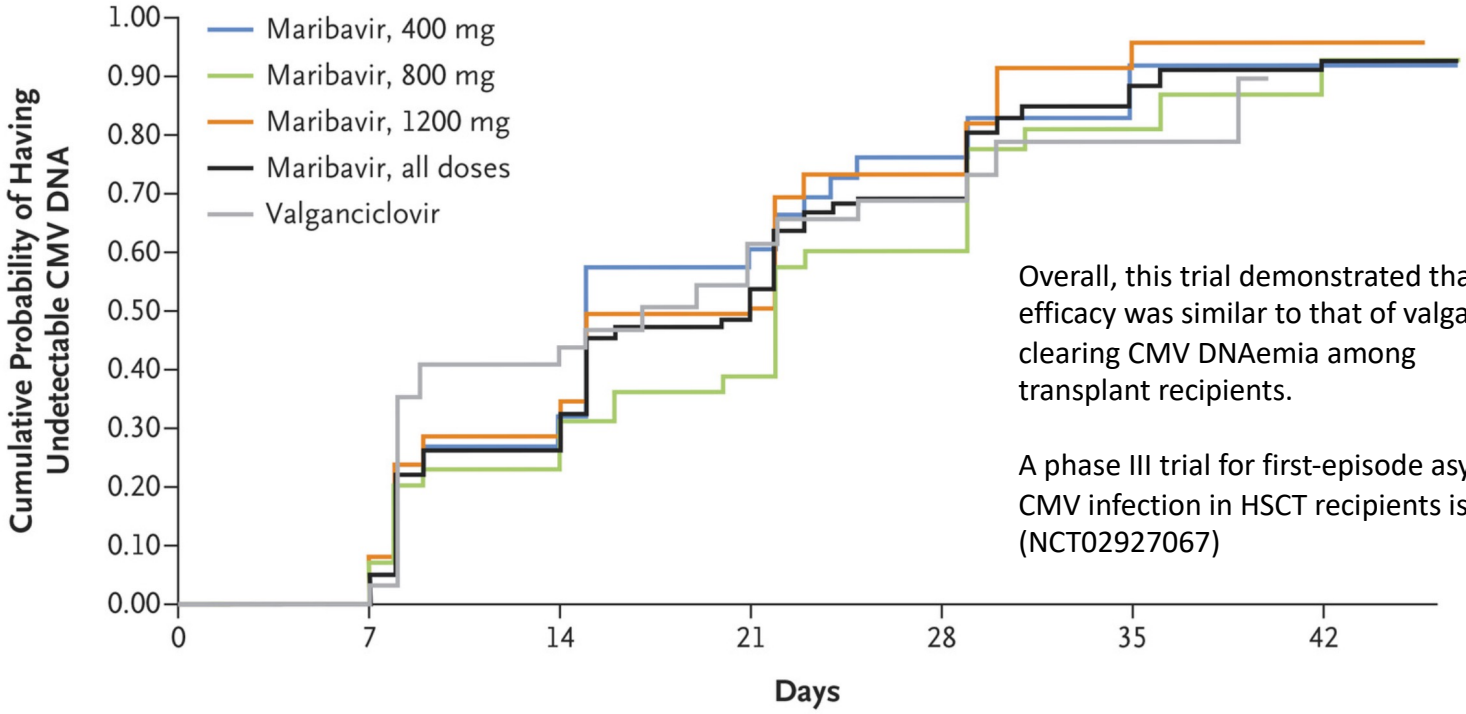
Marty FM et al. Lancet Infect Dis 2011;11:284-92.

Maribavir: Key pharmacology issues

- **Oral tablet, bioavailability (30-40%)**
- Maribavir does not cross blood-brain barrier →breakthrough CMV encephalitis
- **Greater drug interaction potential at higher doses**
  - Weak inhibitor of CYP3A4, P-gP, BRCP
    - ↑ cyclosporine, tacrolimus, sirolimus
  - **Strong CYP3A4 inducers decrease maribavir plasma concentrations**

Gandhi RG, Kotton CN. Evaluating the Safety of Maribavir for the Treatment of Cytomegalovirus. TCRM 2022; 18:223–232.

Maribavir for the treatment of CMV reactivation
Results from Phase II trials



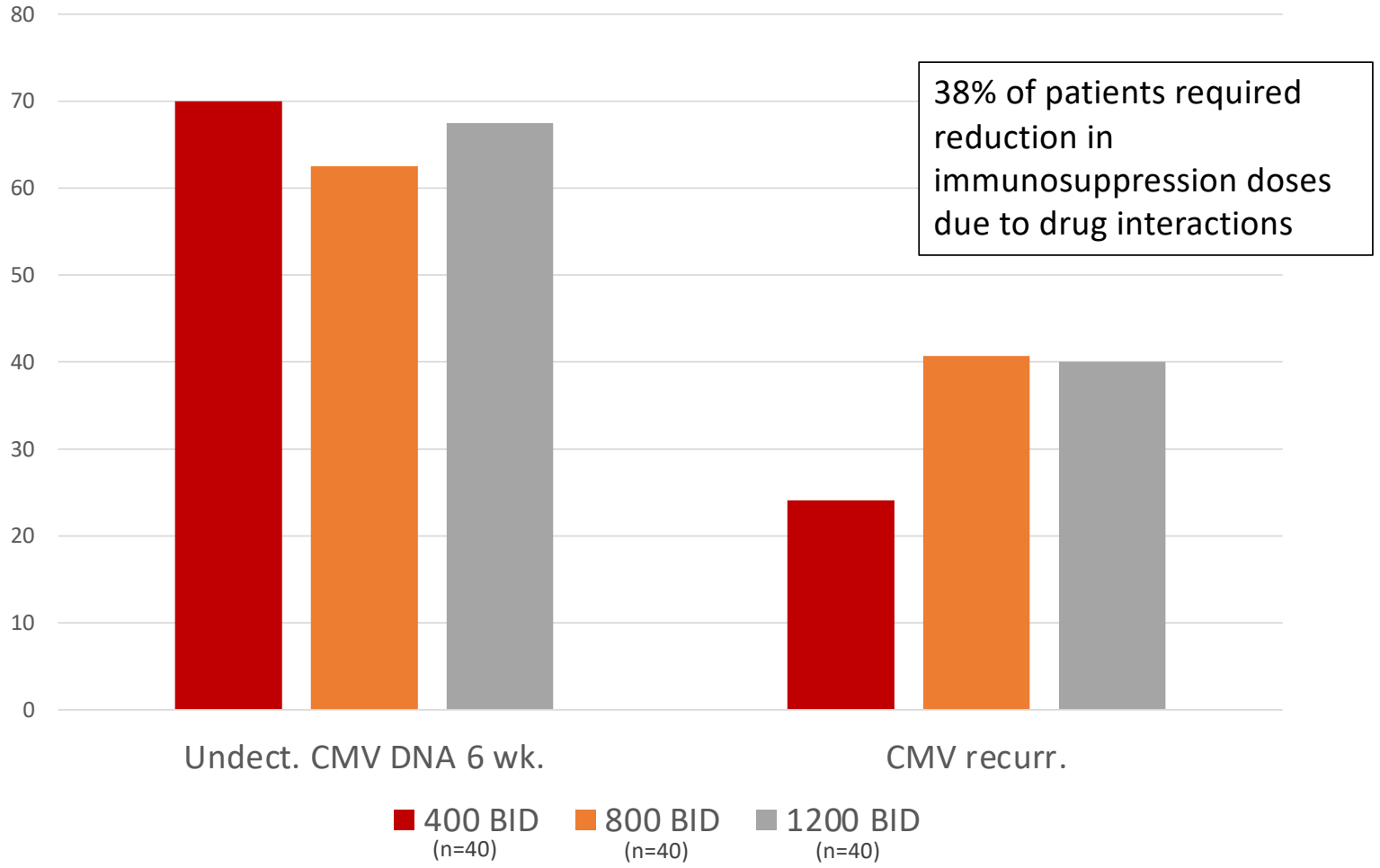
No. at Risk							
Maribavir, 400 mg	39	38	26	15	7	4	2
Maribavir, 800 mg	40	39	30	23	14	6	3
Maribavir, 1200 mg	38	35	24	13	6	2	1
Maribavir, all doses	117	112	80	51	27	12	6
Valganciclovir	39	37	20	13	8	2	0

Overall, this trial demonstrated that maribavir's efficacy was similar to that of valganciclovir for clearing CMV DNAemia among transplant recipients.

A phase III trial for first-episode asymptomatic CMV infection in HSCT recipients is ongoing (NCT02927067)

Maertens J, et al. N Engl J Med. 2019 381:1136-1147.

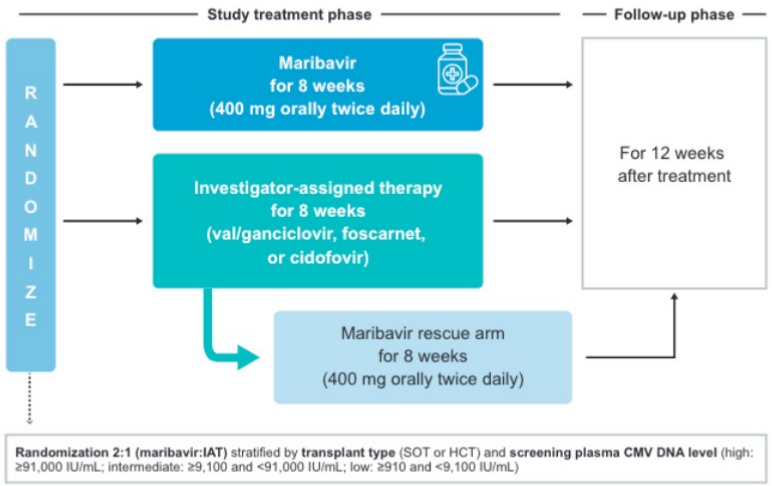
Maribavir for the treatment of resistant/refractory CMV infection Phase II trial



Papanicolaou GA et al. Clin Infect Dis 2019; 68:1255–1264.

Maribavir for the treatment of resistant/refractory CMV infection in HSCT and SOT recipient- A Phase III trial

STUDY DESIGN



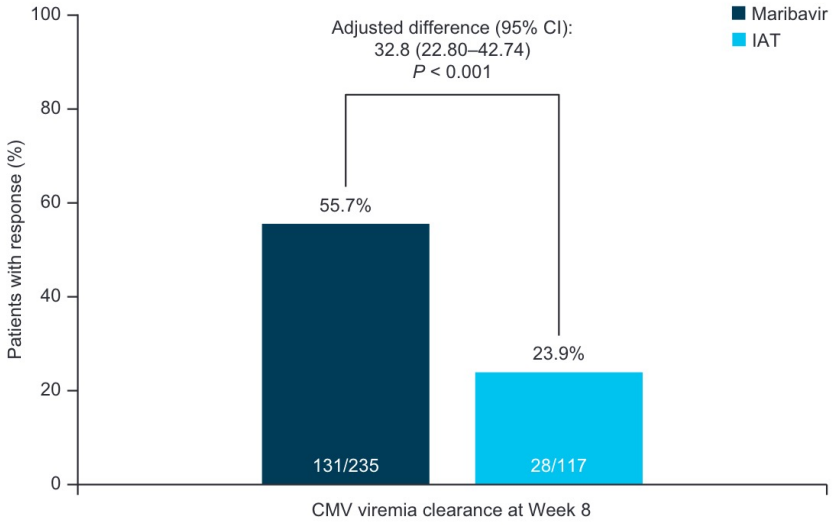
STUDY ENDPOINTS

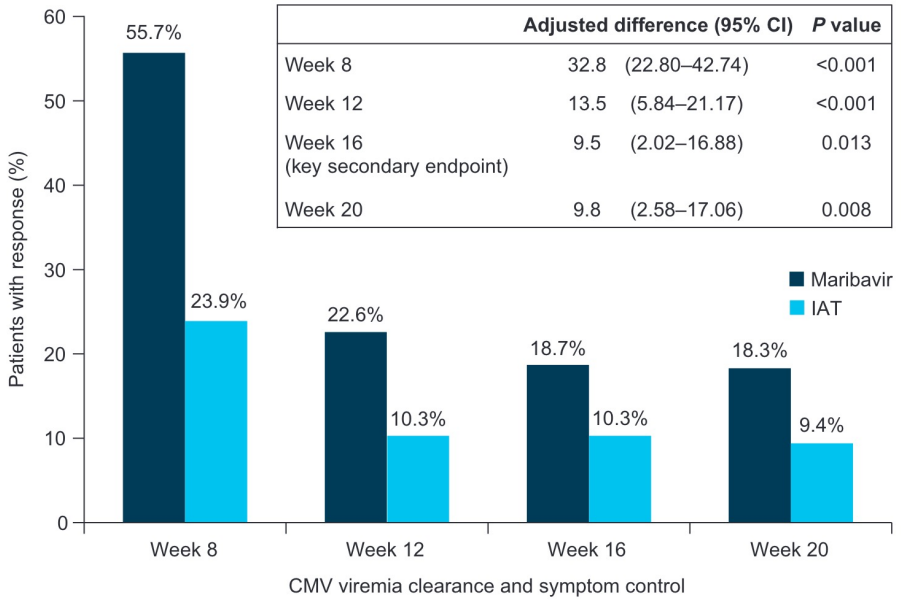
The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

Avery RK, et al. Clinical Infectious Diseases 2022; 75:690–701.

Maribavir for the treatment of resistant/refractory CMV infection in HSCT and SOT recipient- A Phase III trial

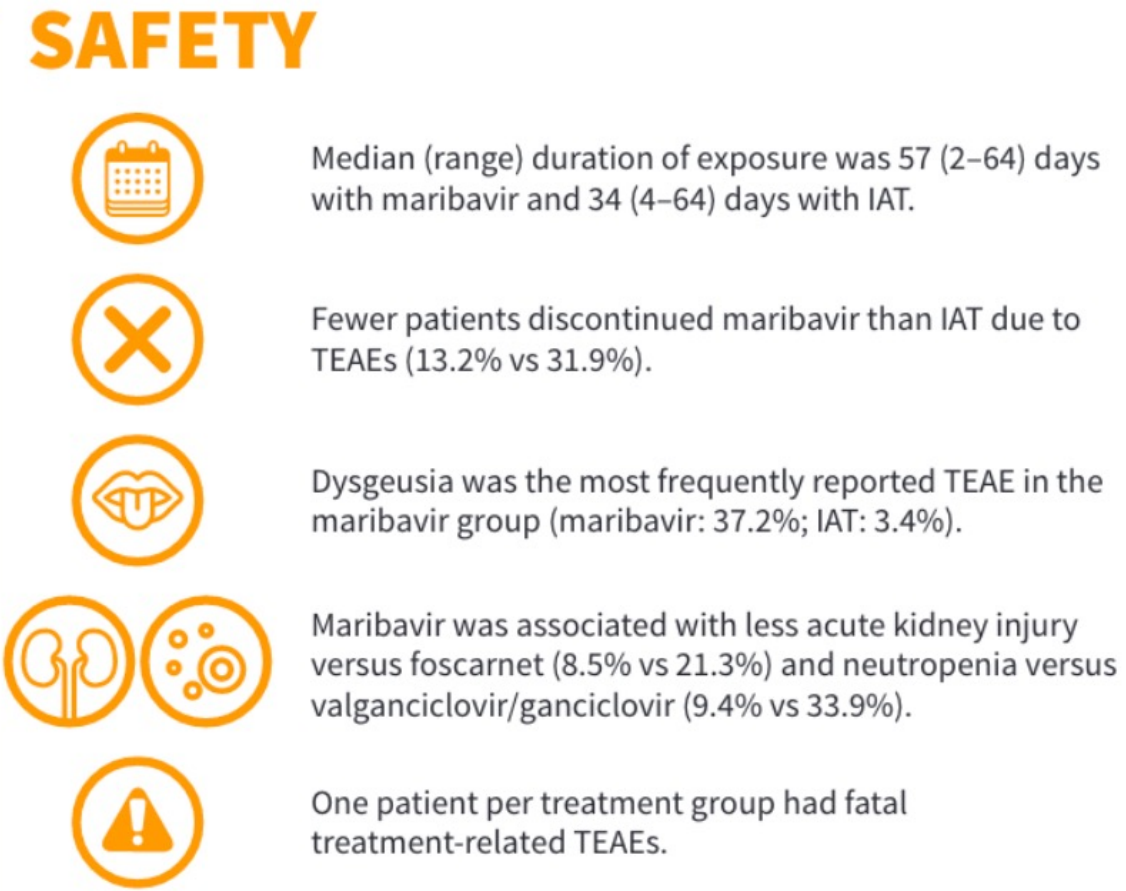




"The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits."

Avery RK, et al. Clinical Infectious Diseases **2022**; 75:690–701.

Maribavir for the treatment of resistant/refractory CMV infection in HSCT and SOT recipient- A Phase III trial



Avery RK, et al. Clinical Infectious Diseases 2022; 75:690–701.

Summary

- **Letermovir prophylaxis is now the preferred strategy for reducing CMV-specific morbidity and mortality**
- **However, entire spectrum of CMV management will likely change:**
  - Letermovir (prophylaxis) → maribavir vs. ganciclovir/foscarnet (PET?) → combination therapy/adoptive immunotherapy (resistant/refractory?)
- **Key future questions:**
  - How long to continue prophylaxis/PET (CMI monitoring?)
  - Optimal treatment approach to resistant/refractory CMV?
  - Can immune augmentation strategies (vaccines, moAbs, T-cell therapy) demonstrate benefit?

CMV management post HSCT

Effective and less toxic antivirals: A cause for optimism