XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

Evoluzione della diagnosi e del trattamento del citomegalovirus

Corrado Girmenia

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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TAKEDA					X	X	
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JANSSEN					X	X	
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The Changing Impact of Human Cytomegalovirus Serology and Infection on Patient Outcome After Allogeneic Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey in the Era of Letermovir Prophylaxis

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GITMO

GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

AMCLI associazione microbiologi clinici italiani

Risk of CMV infection in allo-HSCT according to recipient and donor CMV serostatus

Risk of CMV infection	Recipient CMV serostatus	Donor CMV serostatus
+	Negative	Negative
++	Negative	Positive
+++	Positive	Positive
++++	Positive	Negative

R+/D- > R+/D+ > R-/D+ > R-/D-

Styczynski J. Infect Dis Ther. 2018;7:1–16

The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy

BLOOD, 15 MARCH 2004 • VOLUME 103, NUMBER 6

Michael Boeckh and W. Garrett Nichols

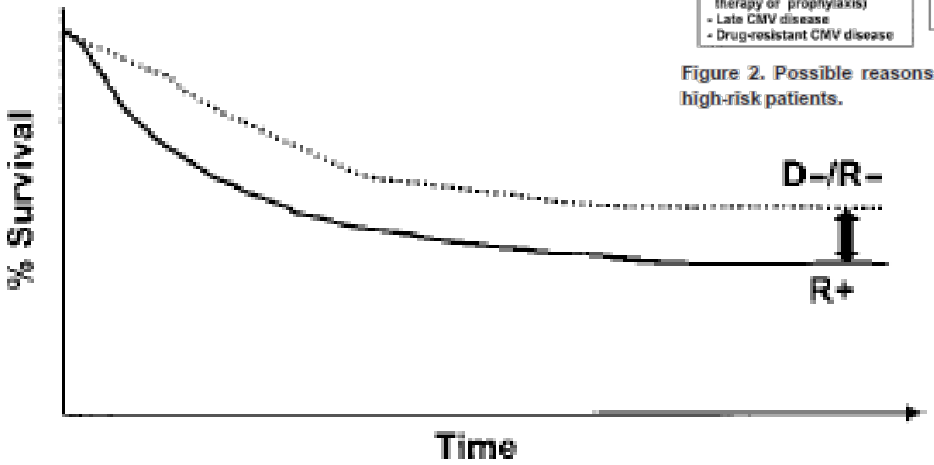


Figure 1. Schema demonstrating the impact of pretransplant CMV infection on overall survival after allogeneic HSCT. Despite the near-complete elimination of early CMV disease with current strategies, a survival disadvantage persists for high-risk, CMV-seropositive patients (R+) compared with D−/R− patients.

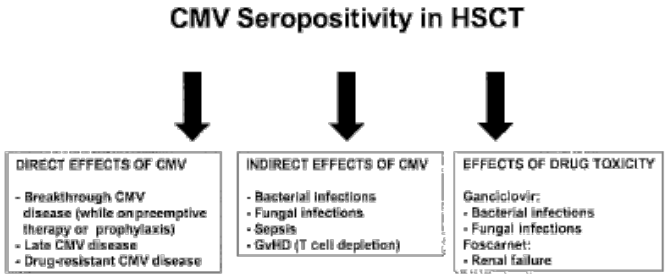


Figure 2. Possible reasons for association of CMV with poor outcome in high-risk patients.

Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis

BLOOD, 19 MAY 2016 • VOLUME 127, NUMBER 20

Pierre Teira,[1,*] Minoo Battiwalla,[2,*] Muthalagu Ramanathan,[3,*] A. John Barrett,[2,*] Kwang Woo Ahn,[4,5] Min Chen,[4] Jaime S. Green,[6] Ayman Saad,[7] Joseph H. Antin,[8] Bipin N. Savani,[9] Hillard M. Lazarus,[10] Matthew Seftel,[11] Wael Saber,[4] David Marks,[12] Mahmoud Aljurf,[13] Maxim Norkin,[14] John R. Wingard,[14] Caroline A. Lindemans,[15] Michael Boeckh,[16] Marcie L. Riches,[17] and Jeffery J. Auletta[18]

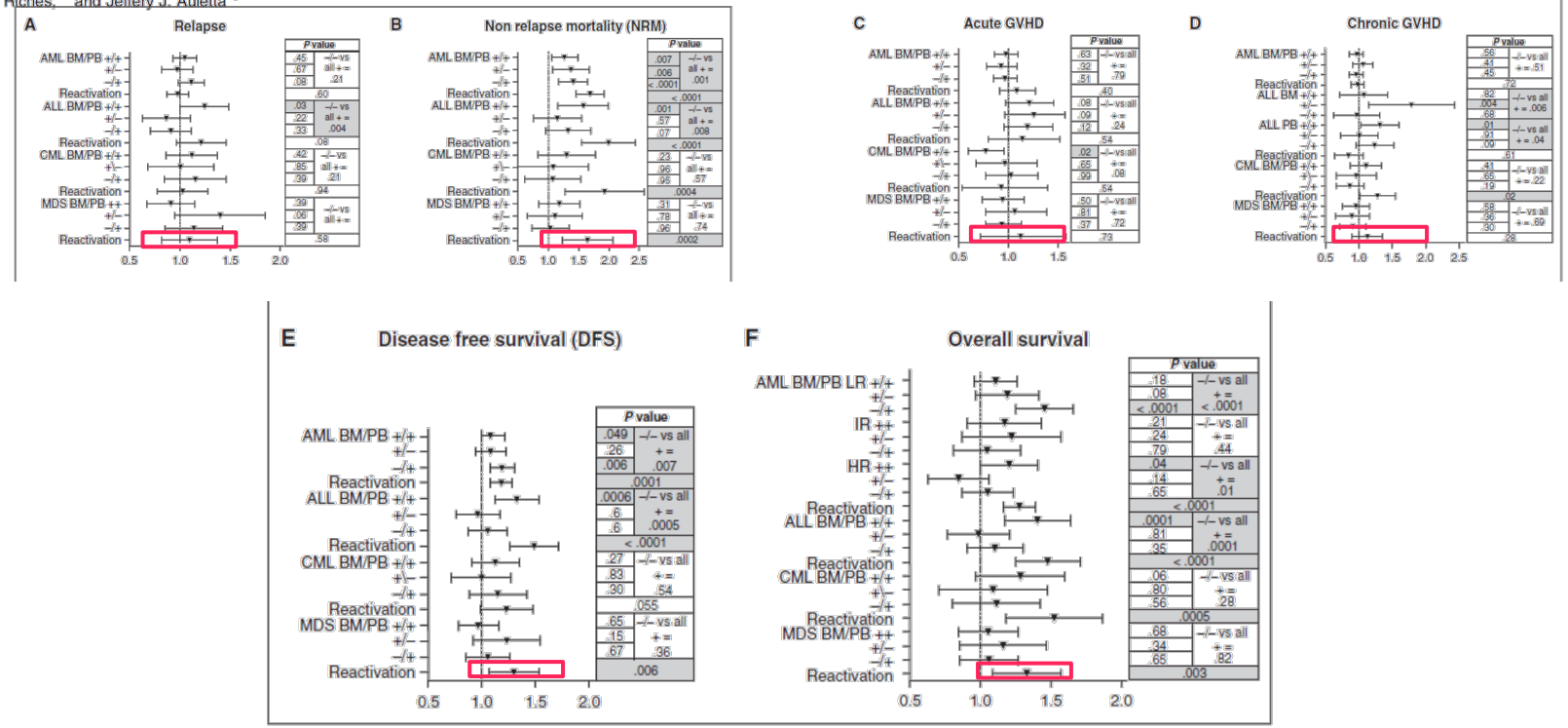
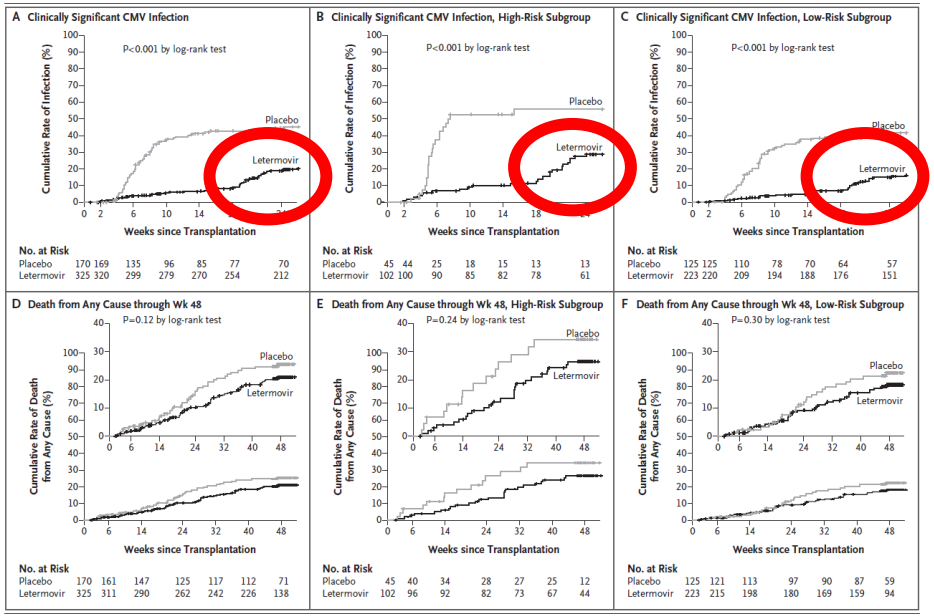


Figure 3. Multivariable analysis of risk factors for outcomes depending on CMV donor/recipient serology or CMV reactivation. (A) Relapse, (B) NRM, (C) aGVHD D) cGVHD, (E) DFS, and (F) OS. For multivariate analysis, D−/R− = 1, and no CMV reactivation = 1.

Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

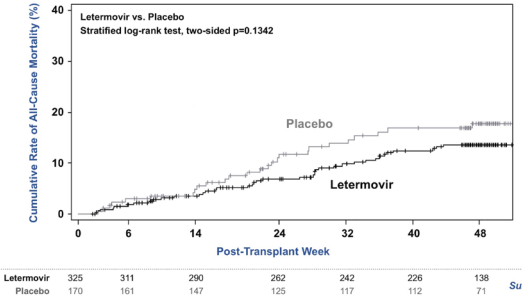
F.M. Marty, P. Ljungman, R.F. Chemaly, J. Maertens, S.S. Dadwal, R.F. Duarte, S. Haider, A.J. Ullmann, Y. Katayama, J. Brown, K.M. Mullane, M. Boeckh, E.A. Blumberg, H. Einsele, D.R. Snydman, Y. Kanda, M.J. DiNubile, V.L. Teal, H. Wan, Y. Murata, N.A. Kartsonis, R.Y. Leavitt, and C. Badshah

N Engl J Med 2017;377:2433-44.



Non-Relapse Mortality through Week 48

Primary Efficacy Population



Time to Engraftment through Week 24 post-HCT

Patients who started study drug before engraftment, Safety Population

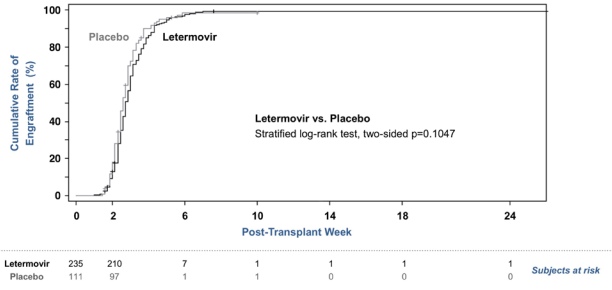


Table 3. Adverse Events (Safety Population).*

Event	Letermovir Group (N=373)	Placebo Group (N=192)	Difference (95% CI)	P Value
	number of patients with event (percent)		*percentage points*	
Any adverse event	365 (97.9)	192 (100)	−2.1 (−4.2 to −0.2)	0.07

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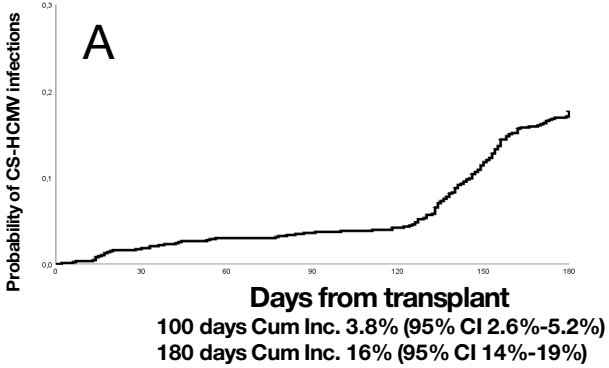
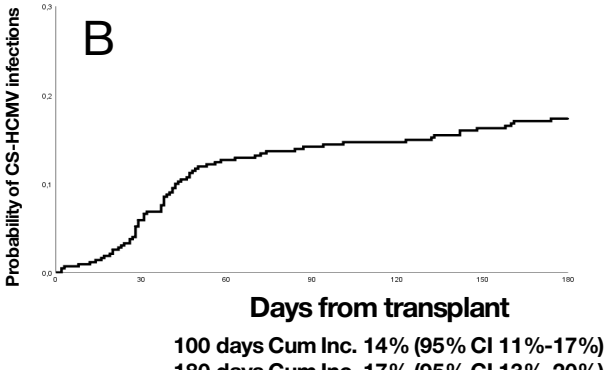


100 days Cum Inc. 3.8% (95% CI 2.6%-5.2%)
180 days Cum Inc. 16% (95% CI 14%-19%)



100 days Cum Inc. 14% (95% CI 11%-17%)
180 days Cum Inc. 17% (95% CI 13%-20%)

Cumulative incidence of CS-HCMV infections in 879 allo-HSCT recipients who received letermovir prophylaxis.

Overall, a HCMV end-organ diseases was documented in 7 patients who received LET-PP at 20, 126, 127, 135,138, 152 and 162 days from transplant, respectively. They were HCMV pneumonia in 5 cases and gastrointestinal disease in 2 cases. In only one case the end-organ HCMV disease was a breakthrough infection documented during LET-PP while in the remaining 6 cases the disease occurred after LET-PP discontinuation.

Cumulative incidence of CS-HCMV infections in 431 allo-HSCT recipients who did not receive letermovir prophylaxis.

Overall, a HCMV end-organ diseases was documented in 3 patients who did not receive LET-PP at 29, 47 and 123 days from transplant, respectively. They were HCMV pneumonia in 2 cases and gastrointestinal disease in 1 case.

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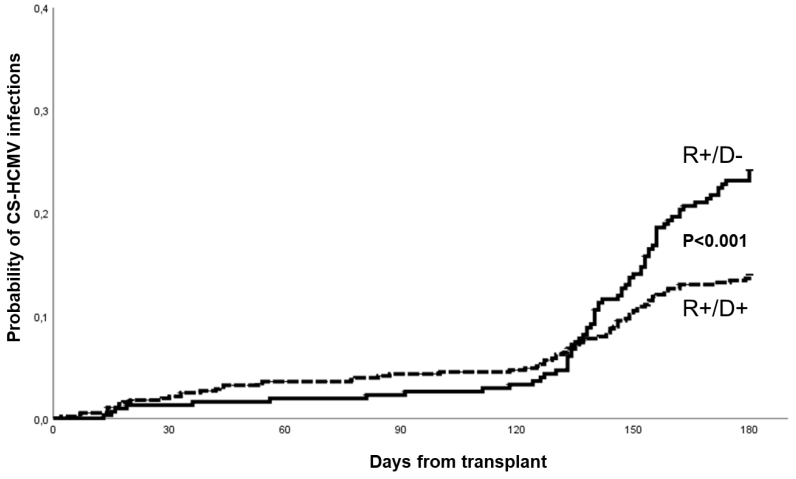
By multivariate analysis variables associated with increased risk of late CS-HCMV-i in patients receiving LET-PP were:

- a transplant from a **HCMV seronegative donor** (HR 2.30; 95% CI 1.55-3.40; p<0.001),
- a transplant from a **haploidentical donor** (HR 3.51; 95% CI 1.70-7.25; p<0.001),
- **T cell depletion** (HR 1.86; 95% CI 1.19-2.91; p=0.006),
- > 20 days duration to obtain **engraftment** (HR 1.51; 95% CI 1.02-2.22; p=0.038),
- grade II-IV **acute GVHD** (HR 1.65; 95% CI 1.08-2.51; p=0.021),
- a clinically significant **EBV DNAemia** (HR 1.59; 95% CI 1.02-2.47; p=0.047)
- an invasive **fungal disease** (HR 2.02; 95% CI 1.05-3.89; p=0.036).



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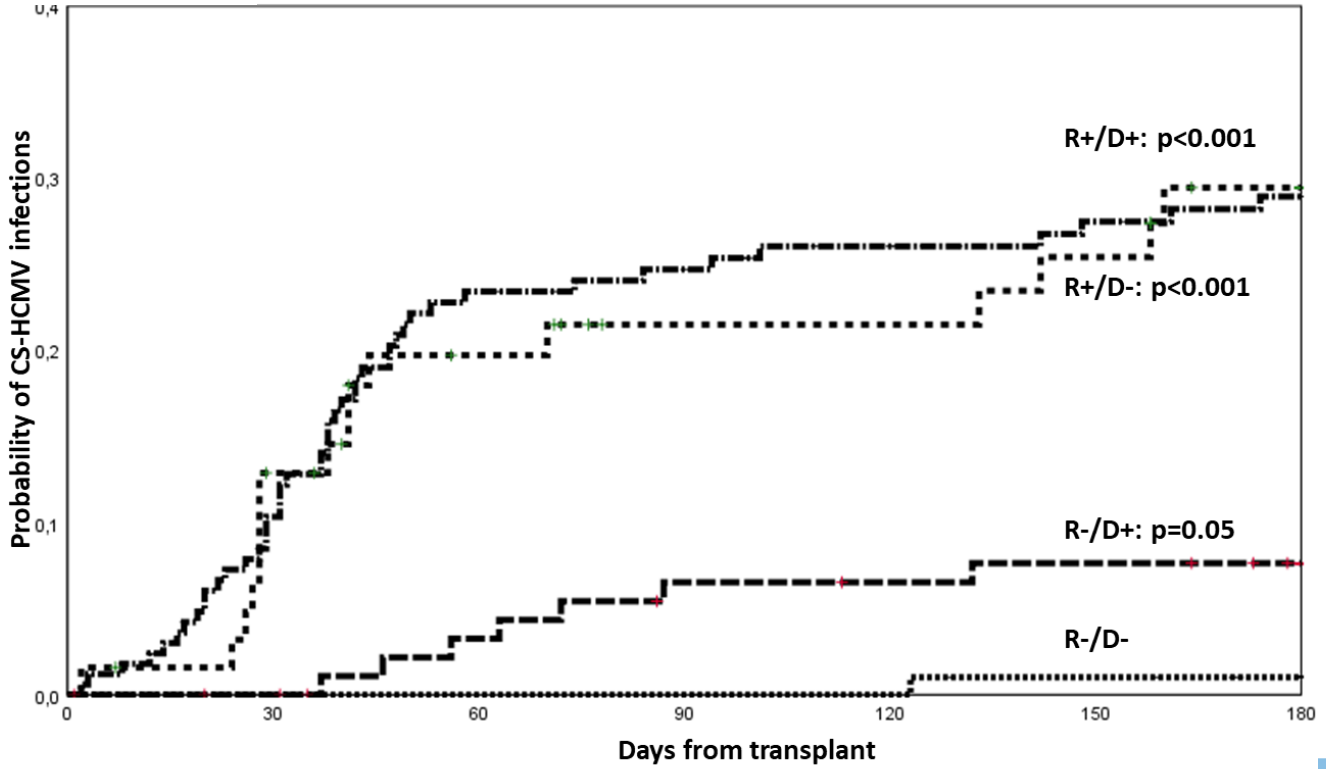

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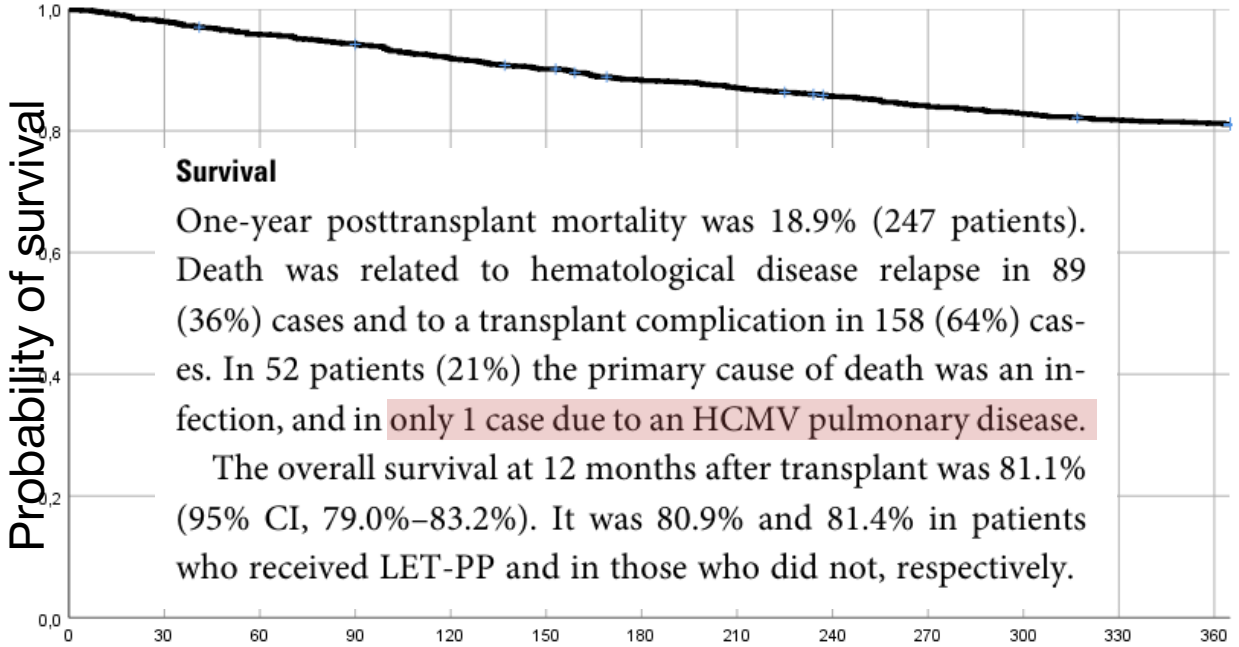
Probability of survival at 12 months from transplant



Survival

One-year posttransplant mortality was 18.9% (247 patients). Death was related to hematological disease relapse in 89 (36%) cases and to a transplant complication in 158 (64%) cases. In 52 patients (21%) the primary cause of death was an infection, and in only 1 case due to an HCMV pulmonary disease.

The overall survival at 12 months after transplant was 81.1% (95% CI, 79.0%–83.2%). It was 80.9% and 81.4% in patients who received LET-PP and in those who did not, respectively.

81.1%

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In **patients who received LET-PP** factors independently associated with increased mortality rate were:

- a diagnosis of **acute leukemia**,
- a disease **not in complete remission** at the time of HSCT,
- an **ECOG** performance status >1,
- prolonged (> 20 days) **pre-engraftment neutropenia**,
- acute grade II-IV **GVHD**,
- clinically significant **EBV DNAemia**,
- **Gram negative** bacteremia,
- invasive **fungal disease**

In **patients who did not receive LET-PP** factors associated with increased mortality rate were:

- **recipient HCMV seropositivity**,
- high **HCT comorbidity index** at transplant,
- **cord blood** transplant
- **Gram negative** bacteremia

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Take home messages from the CYTOALLO GITMO-AMCLI study

- Recipient/donor serology **no more impact** on HCMV infection risk and survival in patients who receive LET-PP
- Recipient serology **still represent a risk** of HCMV infection and poorer outcome in patients who do not receive LET-PP
- HCMV **end organ disease** is an uncommon complication particularly during LET-PP
- HCMV DNAemia **BLIPS** during LET-PP is a phenomenon that requies careful evaluation
- LET-PP should be extended to HCMV seropositive **children**
- Management of late HCMV infections is a key issue in the LET-PP era
  - ✓ Extended **duration LET-PP**
  - ✓ HCMV **T-cell reconstitution** monitoring
  - ✓ Use of **CMV specific IVIG** in association with antivirals
  - ✓ **Effective and safe** antiviral therapy to administer in an **outpatient setting** (oral drugs)
  - ✓ Management of **resistant-refractory infections**

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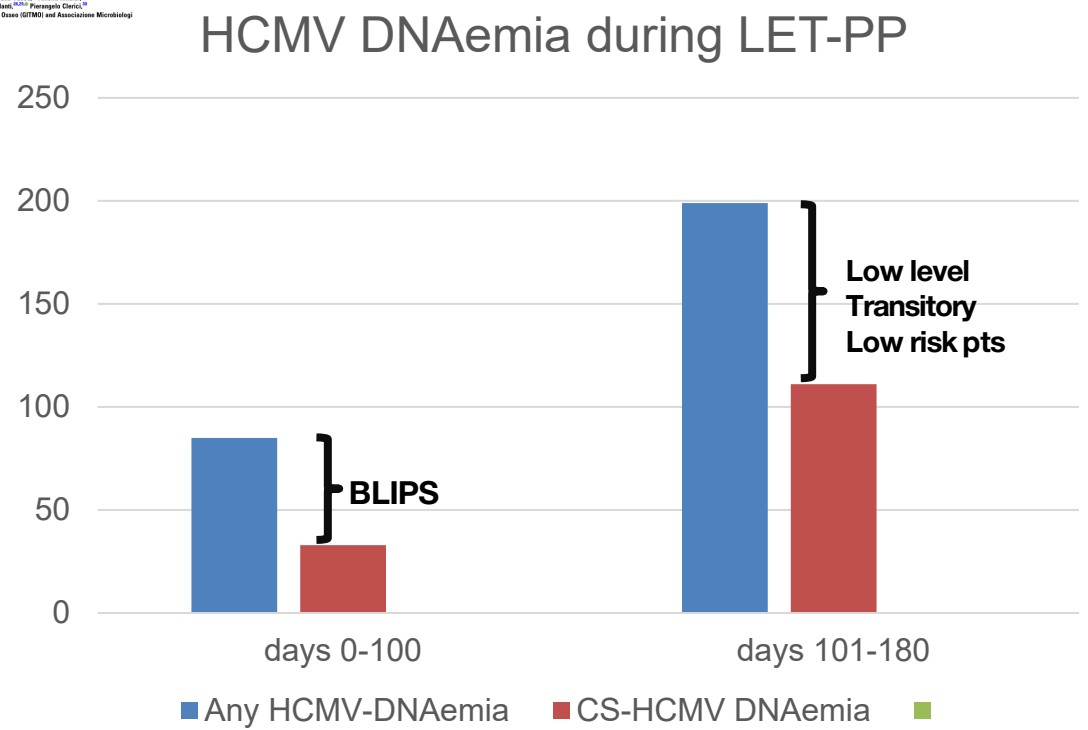

Journal of Clinical Microbiology May 2024 Volume 62 Issue 5

Virology | New-Data Letter

CMV-RNAemia as new marker of active viral replication in transplant recipients

Giulia Piccirilli,[1] Federica Lanna,[2] Liliana Gabrielli,[1] Vincenzo Motta,[2] Martina Franceschiello,[1] Alessia Cantiani,[2] Matteo Pavoni,[2] Marta Leone,[2] Eva Caterina Borgatti,[2] Dino Gibertoni,[2] Renato Pascale,[4] Maddalena Giannella,[4] Francesca Bonifazi,[4] Tiziana Lazzarotto[1,3]

A total of 254 blood samples from 47 CMV-DNAemia-positive episodes that occurred in 44 transplant recipients were retrospectively tested for the detection and quantification of CMV-RNAemia, using the CMV RNA ELITe MGB kit on ELITe InGenius instrument (ELITechGroup).

test targeting the virion-associated UL21.5 mRNA, a late transcript highly expressed during lytic infection

TABLE 1 Characteristics of study population, infective episodes, and samples analyzed

	LMV-prophylaxis	LMV off-label treatment[b]	Pre-emptive therapy[c]
No. of transplant recipients	23	7	14
No. of CMV-DNAemia-positive episodes[d]	25	7	15
CMV-DNAemia-positive/total samples	97/106	35/37	95/111
Median CMV DNAemia levels in whole blood (copies/mL[e], range)	3.9×10^2 (3×10^2–1.9×10^5)	1.4×10^3 (3×10^2–7.3×10^4)	2.8×10^3 (3×10^2–2.4×10^6)
No. of CMV-RNAemia-positive episodes[f]	6	6	15

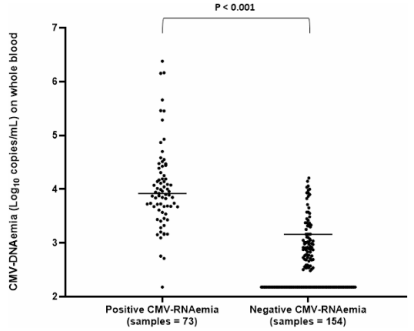

FIG 1 Comparison of CMV-DNAemia levels in samples positive and negative for CMV-RNAemia. Positive values under the lower limit of quantification (300 copies/mL) were reported as equal to 150 copies/mL. Higher median CMV-DNAemia values were observed in specimens positive for CMV-RNAemia than in the negatives: 8,289 copies/mL [interquartile range (IQR): 4,664–21,286.2] vs 373 copies/mL (IQR: 300–1,106.7), respectively; $P < 0.001$ (Mann–Whitney test).

In the 12 episodes in which CMV-RNAemia was detected during LMV administration, the active viral replication was documented by CMV-viremia and/or DNase tests.

In the 20 episodes in which CMV-RNAemia was not detected during LMV administration, the active viral replication was excluded by CMV-viremia and/or DNAse tests suggesting aborting infections

CMV-RNAe mia was positive in all 15 episodes from 14 patients receiving pre-emptive therapy

Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Domenico Russo, Michael Schmitt, Sylvain Pilorge, Matthias Stelljes, Toshiro Kawakita, Valerie L Teal, Barbara Haber, Charlene Bopp, Sanjeet S Dadwal*, Cyrus Badshah*

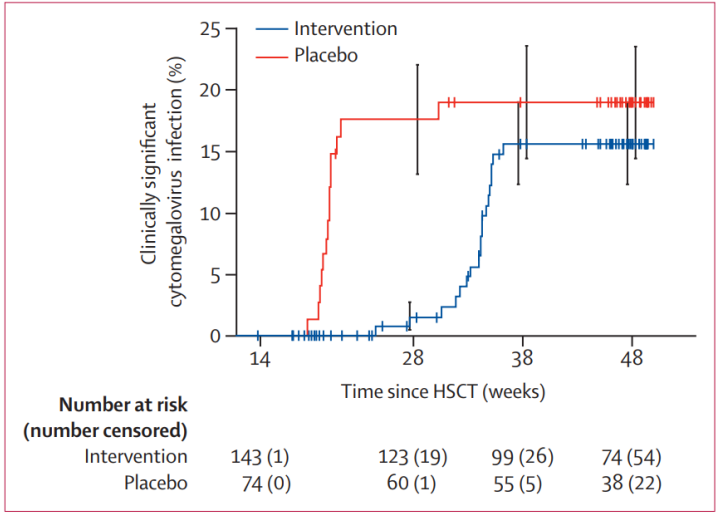

***Figure 2*: Cumulative rate of clinically significant cytomegalovirus infection in the primary efficacy population**
Kaplan-Meier plot for the time to onset of clinically significant cytomegalovirus infection from randomisation at week 14 to week 48 following HSCT.

Open Forum Infectious Diseases
MAJOR ARTICLE
Infectious Diseases Society of America
HIV Medicine Association
OXFORD

The Changing Impact of Human Cytomegalovirus Serology and Infection on Patient Outcome After Allogeneic Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey in the Era of Letermovir Prophylaxis

Lancet Haematol 2023
Published Online
December 21, 2023

By multivariate analysis variables associated with increased risk of late CS-HCMV-i in patients receiving LET-PP were:

- a transplant from a **HCMV seronegative donor** (HR 2.30; 95% CI 1.55-3.40; p<0.001),
- a transplant from a **haploidentical donor** (HR 3.51; 95% CI 1.70-7.25; p<0.001),
- **T cell depletion** (HR 1.86; 95% CI 1.19-2.91; p=0.006),
- > 20 days duration to obtain **engraftment** (HR 1.51; 95% CI 1.02-2.22; p=0.038),
- grade II-IV **acute GVHD** (HR 1.65; 95% CI 1.08-2.51; p=0.021),
- a clinically significant **EBV DNAemia** (HR 1.59; 95% CI 1.02-2.47; p=0.047)
- an invasive **fungal disease** (HR 2.02; 95% CI 1.05-3.89; p=0.036).

Clinical Infectious Diseases
MAJOR ARTICLE

Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

Robin K. Avery,[1] Sophie Alain,[2] Barbara D. Alexander,[3] Emily A. Blumberg,[4] Roy F. Chemaly,[5] Catherine Cordonnier,[6] Rafael F. Duarte,[7] Diana F. Florescu,[8] Nassim Kamar,[9] Deepali Kumar,[10] Johan Maertens,[11] Francisco M. Marty,[12] Genovefa A. Papanicolaou,[13,14] Fernanda P. Silveira,[15] Oliver Witzke,[16] Jingyang Wu,[17] Aimee K. Sundberg,[18] and Martha Fournier[18]; for the SOLSTICE Trial Investigators[a]

Clinical Infectious Diseases® 2022;75(4):690–701

Clinical Infectious Diseases
MAJOR ARTICLE

Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients Including Resistant and Refractory CMV for Use in Clinical Trials: 2024 Update From the Transplant Associated Virus Infections Forum

Per Ljungman,[1,2,a] Roy F. Chemaly,[3] Fareed Khawaya,[3] Sophie Alain,[4] Robin Avery,[5] Cyrus Badshah,[6] Michael Boeckh,[7,8] Martha Fournier,[9] Aimee Hodowanec,[10] Takashi Komatsu,[10] Ajit P. Limaye,[11] Oriol Manuel,[12] Yoichiro Natori,[13] David Navarro,[14,15] Andreas Pikis,[16] Raymund R. Razonable,[16,17,b] Gabriel Westman,[18,19] Veronica Miller,[20] Paul D. Griffiths,[21] and Camille N. Kotton[22]; for the CMV Definitions Working Group of the Transplant Associated Virus Infections Forum

Clinical Infectious Diseases® 2024;79(3):787–94

Refractory CMV infection was defined as a documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level after ≥2 weeks of ganciclovir, valganciclovir, or foscarnet treatment. Resistant CMV infection was defined as a refractory CMV infection with documentation of at least 1 genetic mutation associated with resistance to ganciclovir or foscarnet by local testing results.

Clinical Infectious Diseases
MAJOR ARTICLE

Clinical Infectious Diseases® 2022;75(4):690–701

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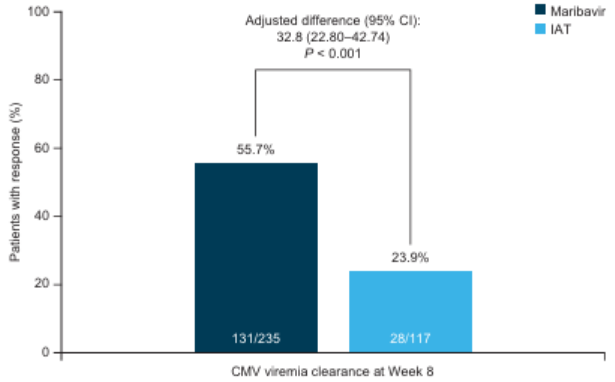
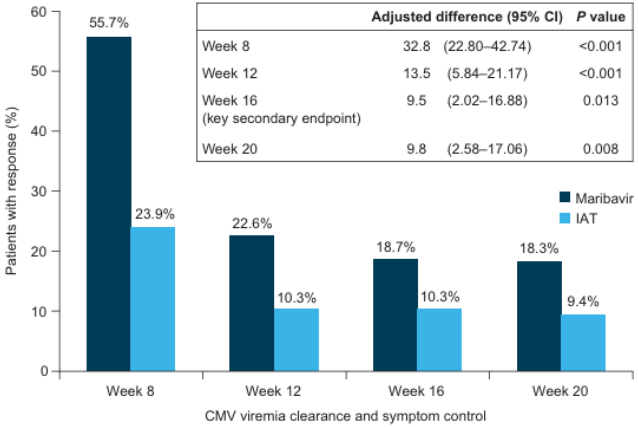
Characteristic	Maribavir	IAT	Adjusted difference in proportion of responders (95% CI)
Age group			
18–44 years	28/55 (50.9)	8/32 (25.0)	26.4 (6.06–46.74)
45–64 years	71/126 (56.3)	19/69 (27.5)	29.9 (16.18–43.64)
≥65 years	32/54 (59.3)	1/16 (6.3)	53.9 (36.81–71.08)
Sex			
Male	87/148 (58.8)	15/65 (23.1)	35.7 (22.76–48.58)
Female	44/87 (50.6)	13/52 (25.0)	27.4 (11.35–43.46)
Region			
North America	72/134 (53.7)	19/71 (26.8)	26.9 (13.75–40.11)
Europe	56/97 (57.7)	8/39 (20.5)	42.0 (26.90–57.05)
Asia	3/4 (75.0)	1/7 (14.3)	56.1 (−25.30 to 100.00)
Transplant type			
SOT	79/142 (55.6)	18/69 (26.1)	30.5 (17.31–43.61)
HCT	52/93 (55.9)	10/48 (20.8)	36.1 (20.92–51.37)
IAT			
Valganciclovir/ganciclovir	NA	15/56 (26.8)	31.7 (18.63–44.78)
Foscarnet	NA	9/47 (19.1)	36.4 (23.37–49.40)
>1 IAT	NA	4/7 (57.1)	−3.2 (−40.31 to 33.96)
Baseline CMV viral load			
Low	95/153 (62.1)	21/85 (24.7)	37.4 (25.41–49.37)
Intermediate/high	36/82 (43.9)	7/32 (21.9)	21.8 (3.93–39.67)
Presence of IAT resistance mutation			
Yes	76/121 (62.8)	14/69 (20.3)	44.1 (31.33–56.94)
No	42/96 (43.8)	11/34 (32.4)	12.6 (−6.24 to 31.43)
Anti-lymphocyte globulin use			
Yes	53/100 (53.0)	12/49 (24.5)	29.9 (14.30–45.46)
No	78/135 (57.8)	16/68 (23.5)	35.0 (21.94–48.01)
Symptomatic CMV infection by EAC			
Yes	10/21 (47.6)	1/8 (12.5)	30.6 (−7.46 to 68.57)
No	121/214 (56.5)	27/109 (24.8)	32.5 (22.05–43.01)

−50 −40 −30 −20 −10 0 10 20 30 40 50 60 70 80 90 100

Favors IAT — Favors maribavir





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

Clinical Infectious Diseases
MAJOR ARTICLE

Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

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Clinical Infectious Diseases® 2022;75(4):690–701

Table 2. Treatment-Emergent Adverse Events Occurring in ≥10% of Patients in Either Treatment Group or for Individual Investigator-Assigned Therapy (Safety Population)

			IAT Type[a]		
System Organ Class Preferred Term	Maribavir (n = 234)	IAT (n = 116)	Ganciclovir/Valganciclovir (n = 56)	Foscarnet (n = 47)	Cidofovir (n = 6)
Any TEAE	228 (97.4)	106 (91.4)	51 (91.1)	43 (91.5)	5 (83.3)
Blood and lymphatic system disorders					
Anemia	29 (12.4)	14 (12.1)	4 (7.1)	9 (19.1)	0
Leukopenia	7 (3.0)	8 (6.9)	7 (12.5)	1 (2.1)	0
Neutropenia	22 (9.4)	26 (22.4)	19 (33.9)	7 (14.9)	0
Gastrointestinal disorders					
Diarrhea	44 (18.8)	24 (20.7)	13 (23.2)	9 (19.1)	1 (16.7)
Nausea	50 (21.4)	25 (21.6)	8 (14.3)	14 (29.8)	1 (16.7)
Vomiting	33 (14.1)	19 (16.4)	7 (12.5)	8 (17.0)	2 (33.3)
General disorders and administration site conditions					
Fatigue	28 (12.0)	10 (8.6)	7 (12.5)	3 (6.4)	0
Edema peripheral	17 (7.3)	9 (7.8)	3 (5.4)	5 (10.6)	0
Pyrexia	24 (10.3)	17 (14.7)	6 (10.7)	9 (19.1)	2 (33.3)
Infections and infestations					
CMV viremia[b]	24 (10.3)	6 (5.2)	4 (7.1)	1 (2.1)	0
Metabolism and nutrition disorders					
Hypokalemia	8 (3.4)	11 (9.5)	1 (1.8)	9 (19.1)	1 (16.7)
Hypomagnesemia	9 (3.8)	10 (8.6)	2 (3.6)	7 (14.9)	1 (16.7)
Hypophosphatemia	4 (1.7)	5 (4.3)	0	5 (10.6)	0
Nervous system disorders					
Dysgeusia	87 (37.2)	4 (3.4)	2 (3.6)	0	1 (16.7)
Headache	19 (8.1)	15 (12.9)	6 (10.7)	8 (17.0)	0
Paresthesia	4 (1.7)	5 (4.3)	0	5 (10.6)	0
Renal and urinary disorders					
Acute kidney injury	20 (8.5)	11 (9.5)	1 (1.8)	10 (21.3)	0
Vascular disorders					
Hypertension	9 (3.8)	8 (6.9)	1 (1.8)	6 (12.8)	0

Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies

Lancet Infect Dis 2025

Per Ljungman, Sophie Alain, Roy F Chemaly, Hermann Einsele, Federica Galaverna, Hans H Hirsch, Alicja Sadowska-Klasa, David Navarro, Jan Styczynski, Rafael de la Camara

	ESCMID grade	
	Adults	Children
Maribavir is effective for treatment of resistant or refractory CMV infection and disease and is associated with lower risk for side-effects than the other alternatives	AI	BIIt*
Maribavir is not indicated for CMV disease involving the CNS and the eyes	DIIt	DIIt
If resistance is suspected, it should be documented by genotyping	AII	AII
Change of therapy is recommended before having results of resistance testing available	BII	BII
Foscarnet is an alternative therapy for resistant or refractory CMV infections, in particular in the CNS and eyes, but is associated with clinically significant toxicity	BII	AII
Cidofovir is an option for the treatment of CMV retinitis	BII	BII
CMV-specific T cells are an option for treatment of resistant or refractory CMV infection or disease, if available	BII	CIIu
Combination therapy for resistant or refractory CMV infections could be considered	BII	CII
The combination of maribavir with valganciclovir or ganciclovir should not be used	DIIt	CIII
Letermovir is not indicated for pre-emptive therapy of CMV infection or treatment of CMV end-organ disease including resistant or refractory infections	DIII	DIIt

CMV=cytomegalovirus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. *Can be considered when the patient is older than 12 years. However, it is not approved by the European Medical Association for individuals younger than 18 years.

Table 3: **Treatment of resistant or refractory CMV**

ECIL 10 recommends that maribavir be considered for patients with neutropenia who cannot be treated with valganciclovir (BI) or patients with renal function impairment who foscarnet (BII) is not appropriate for.

The Journal of Infectious Diseases
MAJOR ARTICLE
The Journal of Infectious Diseases® 2024;229:413–21

Drug Resistance Assessed in a Phase 3 Clinical Trial of Maribavir Therapy for Refractory or Resistant Cytomegalovirus Infection in Transplant Recipients

Sunwen Chou,[1,2] Sophie Alain,[3,9] Carlos Cervera,[4] Roy F. Chemaly,[5] Camille N. Kotton,[6] Jens Lundgren,[7,8] Genovefa A. Papanicolaou,[8,9] Marcus R. Pereira,[10] Jingyang J. Wu,[11] Rose Ann Murray,[11] Neil E. Buss,[12] and Martha Fournier[11]

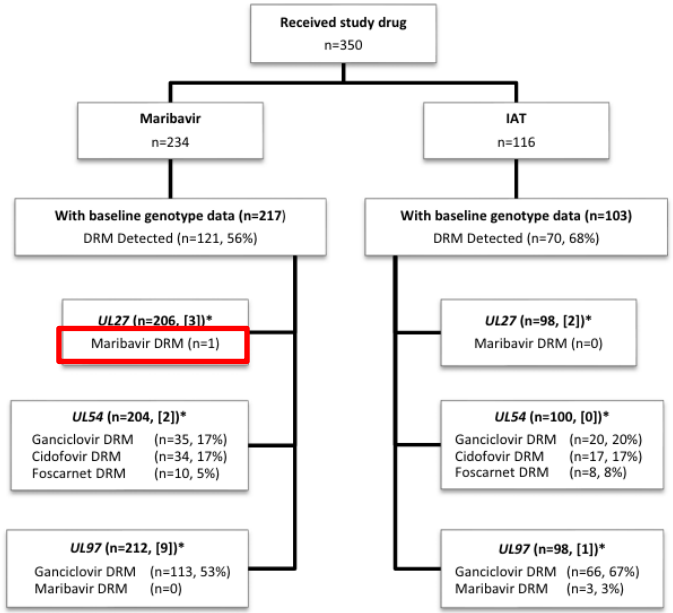

Figure 1. Baseline drug resistance mutations by assigned drug and viral gene. Asterisks indicate number of patients with genotyping in the indicated gene, and in square brackets the number of patients with incomplete data for the gene. Abbreviations: DRM, drug resistance mutation; IAT, investigator-assigned therapy.

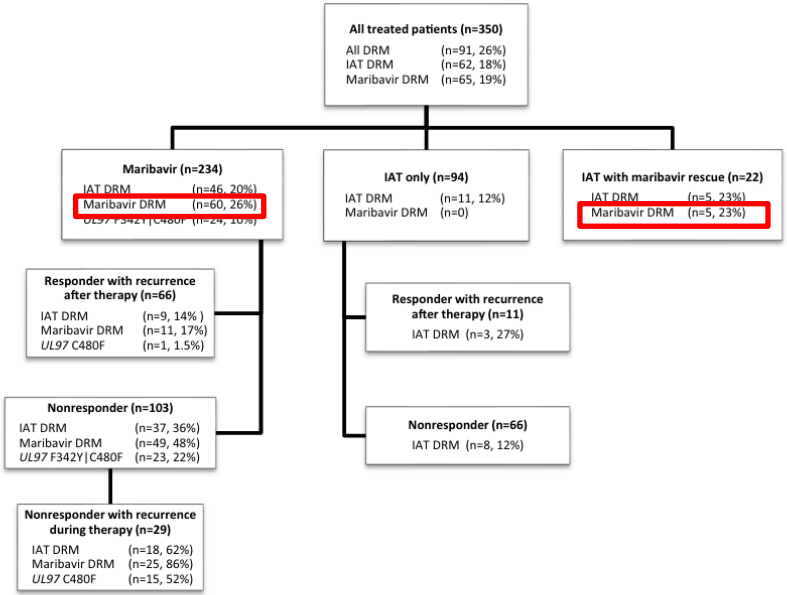

Figure 2. Treatment-emergent drug resistance mutations by patient category. Each treatment and outcome category is listed in bold with the number of patients (n). The number and percent of each group that developed maribavir-DRMs or IAT-DRMs is listed. *UL97* F342Y and C480F are counted under both maribavir-DRMs and IAT-DRMs, and also listed separately if present. Abbreviations: DRM, drug resistance mutation; IAT, investigator-assigned therapy.

The Journal of Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD
The Journal of Infectious Diseases® 2025;231:e470–

Comparative Emergence of Maribavir and Ganciclovir Resistance in a Randomized Phase 3 Clinical Trial for Treatment of Cytomegalovirus Infection

Sunwen Chou,[1,2] Drew J. Winston,[3] Robin K. Avery,[4,a] Catherine Cordonnier,[5] Rafael F. Duarte,[6] Shariq Haider,[7] Johan Maertens,[8] Karl S. Peggs,[9] Carlos Solano,[10] Jo-Anne H. Young,[11,a] Joan Gu,[12] Ginger Pocock,[12] and Genovefa A. Papanicolaou[13]

Table 1. Emergent Drug Resistance After ≥21 Days of Study Drug

Randomized Study Drug	Maribavir	Valganciclovir	*P* Value (Test)
Received ≥21 d, n	241	241	
Days of study drug treatment, median (range)	56 (21–62)	55 (21–63)	
Primary end point achieved, n (%)	187 (77.6)	210 (87.1)	.008[a]
Recurrence of CMV DNA while on therapy, n (%)	14 (5.8)	0	.0001[a]
Baseline plasma CMV DNA ≥9100 IU/mL, n	42	44	
Developed resistance mutation for study drug, n (%)	24 (10)	6 (2.5)	.001[a]
Days of study drug treatment, median (range)	56 (40–60)	55.5 (32–58)	
Days to detection of first DRM, median (range)	56 (35–125)	89.5 (66–110)	.007[b]
Recurrence of CMV DNA while on therapy, n (%)	12 (50)	0	
Baseline plasma CMV DNA ≥9100 IU/mL, n (%)	12 (50)	3 (50)	
Primary end point achieved, n (%)	4 (16.7)	4 (66.7)	.03[a]

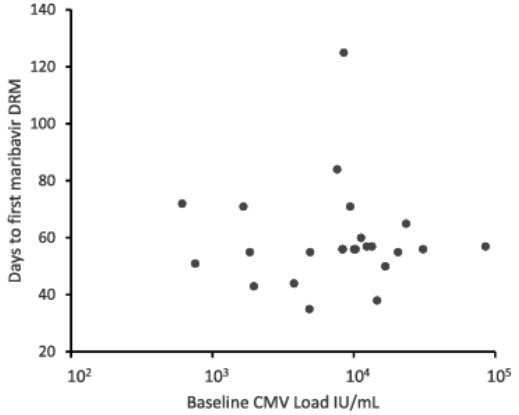

Figure 1. Baseline viral loads and interval to emergence of maribavir resistance. Each point represents the baseline CMV load and days to emergence of maribavir resistance for an individual patient. There is no correlation of the parameters (Pearson correlation coefficient −0.04). Abbreviations: CMV, cytomegalovirus; DRM, drug resistance mutation.

After 3–8 weeks of therapy, maribavir resistance emerged earlier and more frequently than ganciclovir resistance but was usually treatable using alternative therapy.