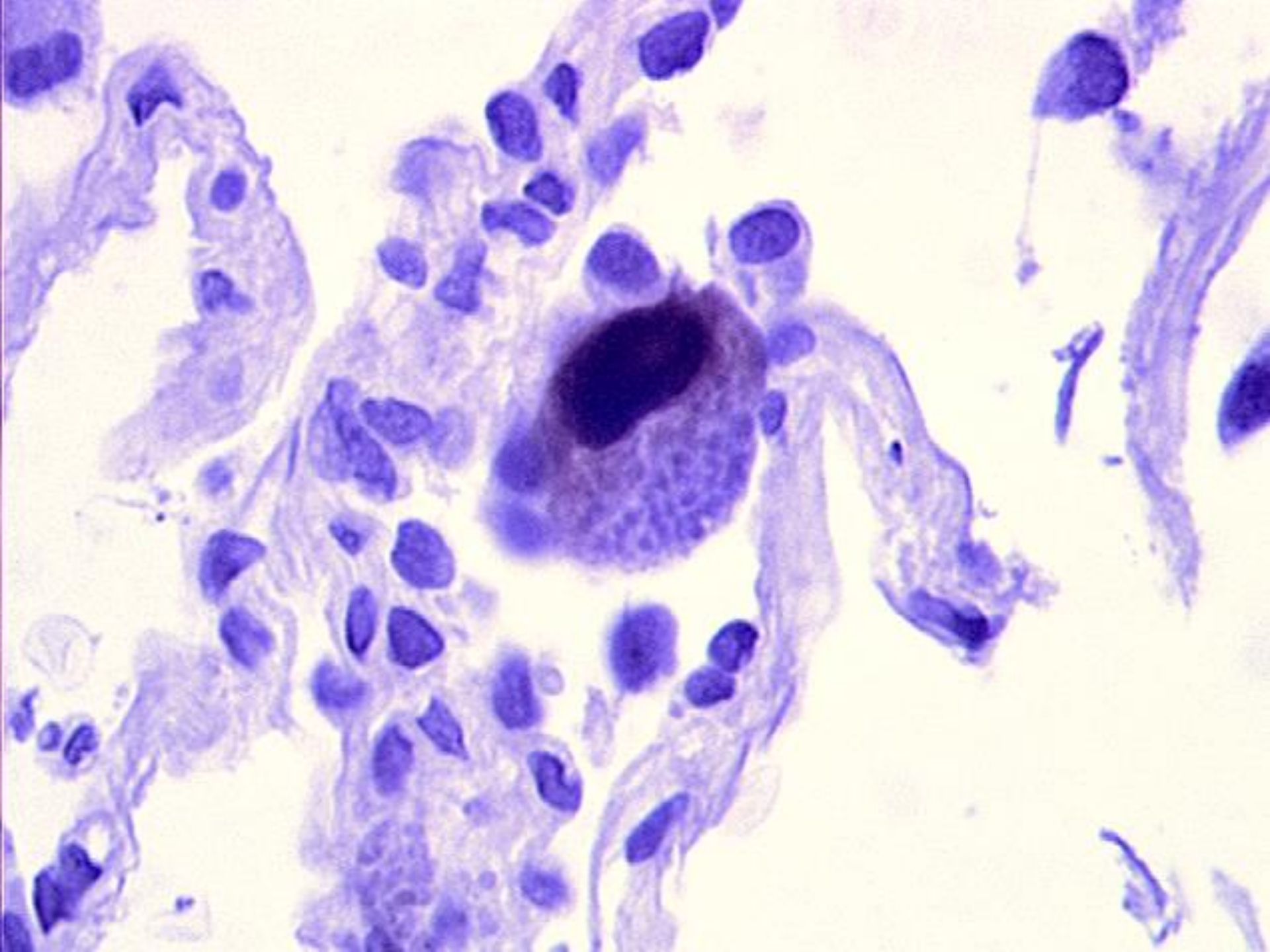
Current and Future Treatment of Cytomegalovirus Infection

Robin K. Avery MD, FIDSA, FAST
Professor of Medicine,
Division of Infectious Disease
Johns Hopkins

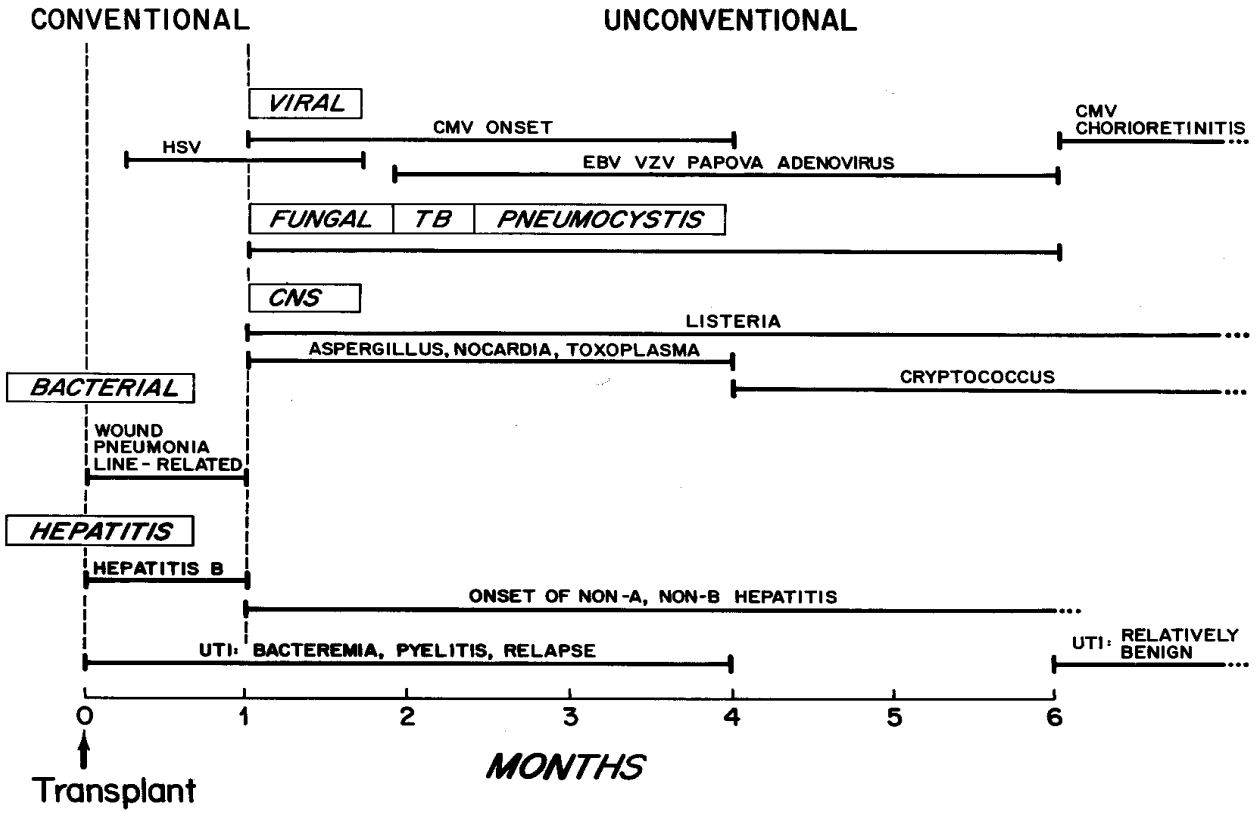
Disclosures

- Robin Avery MD has been a co-investigator on multicenter CMV-related studies funded by Shire, Viropharma, Merck, Astellas, Chimerix, and Oxford Immunotec.
- No personal financial remuneration from any pharmaceutical company.
- Off-label use of valganciclovir, leflunomide, IVIg, CMVIg; and investigational maribavir, brincidofovir, and letermovir will be discussed in this presentation.



Timetable of Infection Following Organ Transplantation

(Fishman and Rubin, NEJM 1998; 338:1741-51)



CMV – Still a major issue in transplantation

- Despite advances in prevention strategies, CMV has not been eliminated
- A variety of complex CMV syndromes still occur, including antiviral-resistant CMV, and refractory CMV without genotypic resistance
- These are some of the sickest patients and some of the most challenging situations that transplant clinicians see

Abbreviations

- CMV – cytomegalovirus
- SOT – solid organ transplant
- HSCT – hematopoietic stem cell transplant
- D+ (seropositive donor); D- (seronegative donor)
- R+ (seropositive recipient); R- (seronegative recipient)
- GCV – ganciclovir; VGCV - valganciclovir
- FOS – foscarnet; CDV – cidofovir
- IVIg – intravenous immune globulin

Background

- Historically, CMV has been one of the most important transplant-related infections in both SOT and HSCT recipients
- Donors and recipients are screened for CMV serology (CMV IgG) prior to transplant; serostatus is an important risk factor
- CMV reactivation can occur from the recipient's own strain, or a new strain can be acquired from the donor

Background

- D+/R- serostatus is the highest risk group in SOT and the most likely to develop high viral loads, tissue-invasive CMV disease, recurrences, and resistance
- HSCT is a different situation because the recipient reconstitutes their immune system from the donor. HSCT R+ with CMV negative donors have more difficulty controlling CMV

CMV Clinical Presentations

- Asymptomatic viremia
- “CMV Syndrome” (defined only for SOT): flulike syndrome with leukopenia, thrombocytopenia, slight LFT elevations
- Tissue-invasive CMV disease (end-organ disease): CMV pneumonitis, gastritis, colitis, esophagitis, hepatitis, meningoencephalitis, retinitis (Razonable and Humar, Am J Transplant 2013; 13:93-106; Ljungman P et al, Clin Infect Dis 2017; 64:87-91).

CMV Clinical Presentations

- Magnitude of CMV viral load often correlates with severity of illness (though not always)
- High viral load: risk for tissue-invasive disease, recurrences, resistance
- High viral load and highly symptomatic disease associated with long and complex courses, multiorgan dysfunction, debilitation

Prevention Strategies

- Prophylaxis: Administration of an antiviral (usually valganciclovir) to all transplant recipients at risk for CMV
- Pre-Emptive Therapy: Administration of an antiviral (usually valganciclovir) only to those who develop CMV viremia on serial monitoring of a sensitive test (CMV qPCR)

Prevention Strategies

- Prophylaxis generally used in SOT (3 mos for R+, 6 mos for D+/R-)
- Pre-emptive therapy generally used in HSCT (e.g. weekly CMV PCR to Day 100)
- In HSCT, prophylaxis has been avoided due to neutropenia risk from ganciclovir and valganciclovir

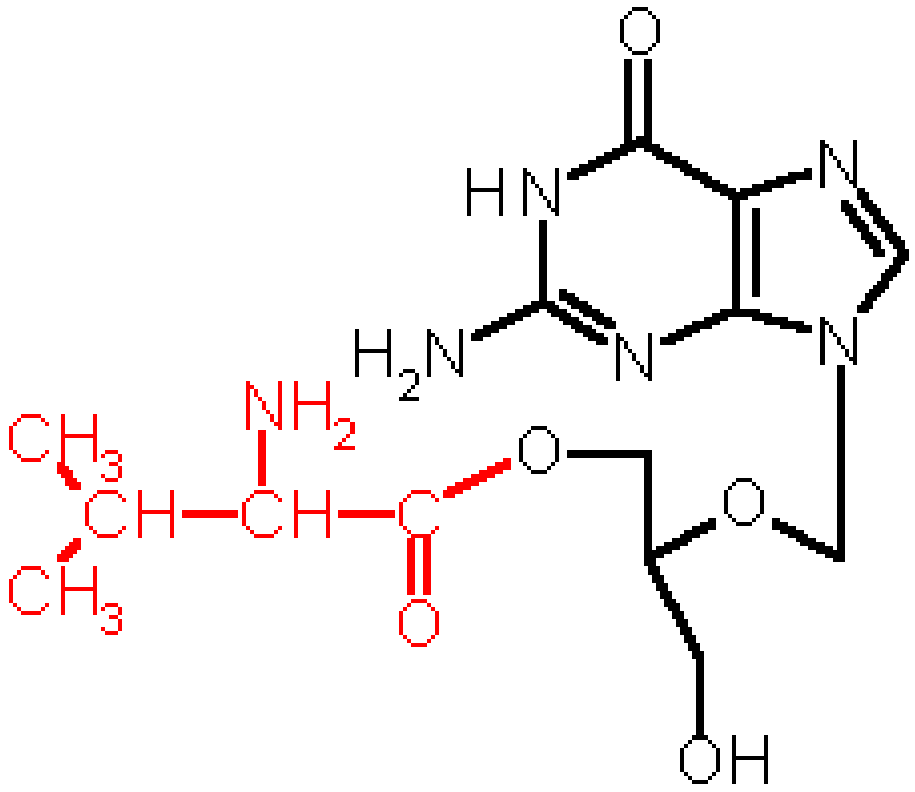
Treatment of CMV

- Historically was IV ganciclovir
- Oral ganciclovir was poorly bioavailable
- Valganciclovir is now used for treatment of viremia with low-to-moderate viral load and/or mild to moderate symptoms
- IV ganciclovir used for severe disease, high viral load, valganciclovir failure, or GI absorption issues

Treatment of CMV: Currently Available Drugs

- Ganciclovir and valganciclovir
- Foscarnet
- Cidofovir
- Occasionally, adjunctive therapy with IVIg or CMV hyperimmune globulin (CMVIg), especially in HSCT with CMV pneumonitis

Valganciclovir



Valganciclovir

- Oral agent with higher bioavailability than oral GCV; levels closer to those of IV GCV
- Ease of administration allows for possibility of lengthy courses and long-term viral suppression
- Secondary prophylaxis after a 1st CMV episode
- Disadvantages include cost, toxicity (neutropenia, thrombocytopenia), need for close monitoring, teratogenicity
- Neutropenia - a huge problem in real-world clinical practice

VICTOR Study

- The VICTOR study was a multinational, randomized, noinnferiority trial of 321 SOT pts with CMV
- Included tissue-invasive disease (40%)
- About ¾ were kidney recipients; few lung recipients
- Randomized to IV GCV vs. oral valganciclovir therapy (21d), followed by oral valganciclovir "tail" 28d
- Detailed sequential viral load monitoring

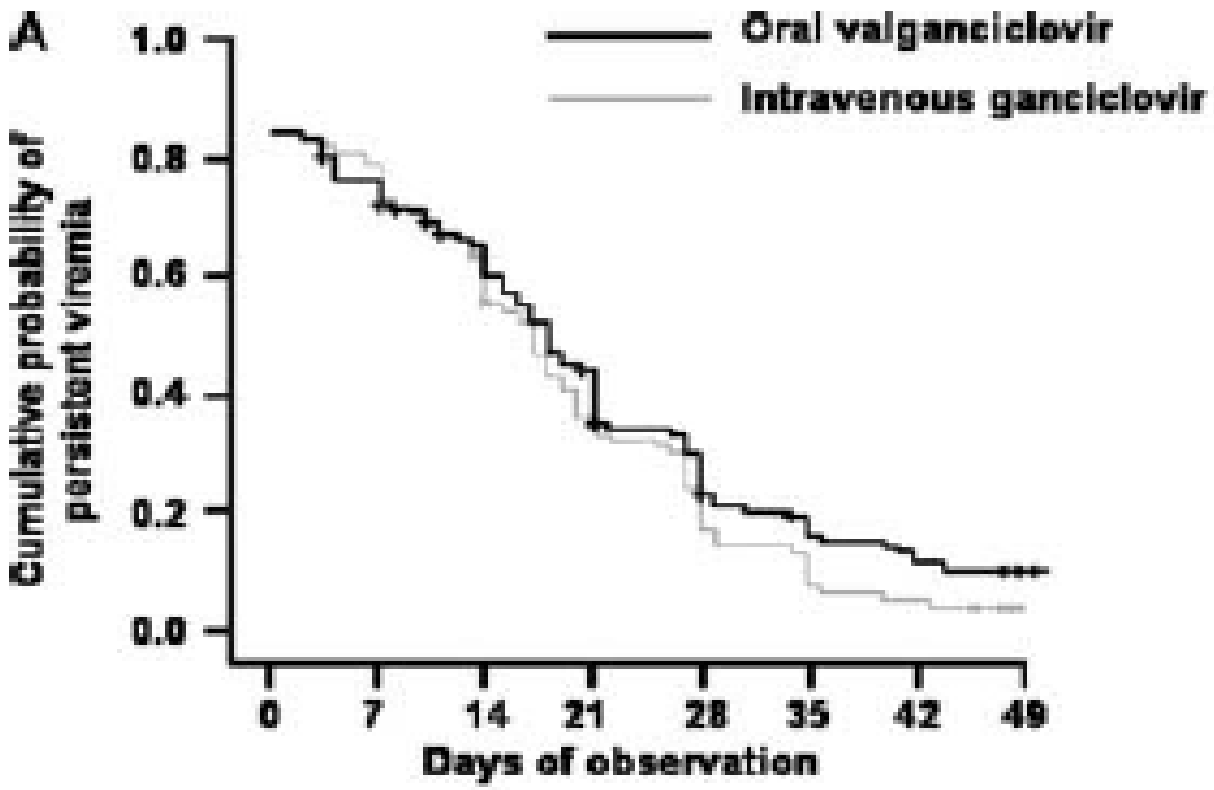
(Asberg et al, Am J Transplant 2007; 7:2106-2113)

VICTOR Study

- Results: Valganciclovir was noninferior; similar rates of virologic clearance at 21 and 49 days
- Followup study did not show excess of GCV resistance nor recurrences, nor allograft dysfunction in either group
- Keep in mind that the most severely ill patients were not included and this was predominantly kidney recipients

VICTOR Study

(Asberg A et al, Am J Transplant 2007; 7: 2106-2113)



So what's the problem?

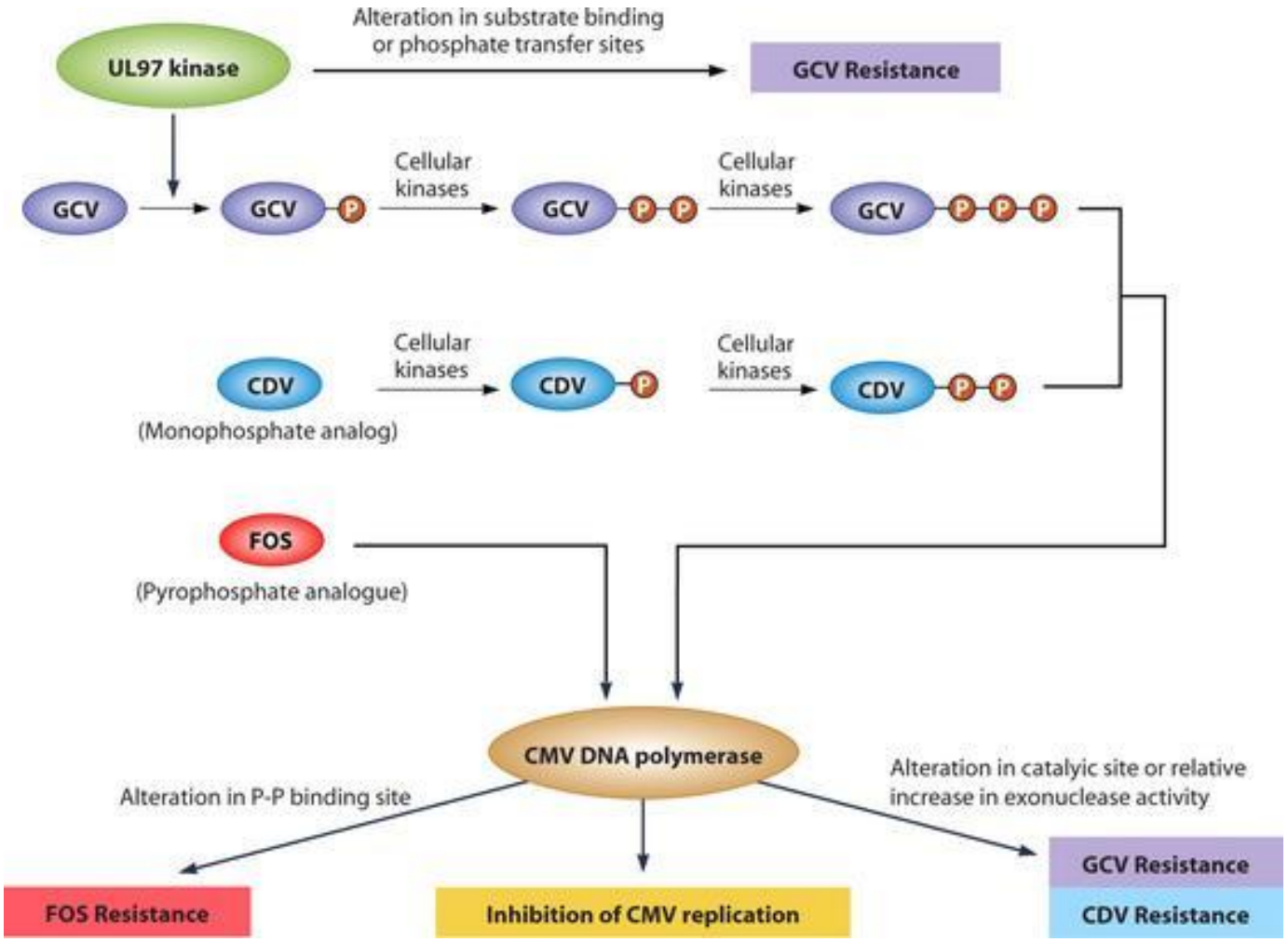
- Valganciclovir did not eradicate viremia in all patients in the VICTOR study (45-48% at 21 days, 67-70% at 49 days)
- Baseline viral load predictive of eradication
- Leukopenia occurred in 11- 12% in the VICTOR study, but it is higher in actual usage
- Recurrences occur, and resistance becomes more likely over time

Antiviral-Resistant CMV

- UL97 mutations most common: GCV resistance (triphosphorylation by viral thymidine kinase)
- UL54 mutations (DNA polymerase) less common and may confer GCV, FOS, or CDV resistance
- Risk factors: D+/R-, recurrences, intensified immunosuppression
- Very important: Subtherapeutic concentrations of GCV/VGCV when the viral load is rapidly rising

Antiviral Resistance Sites

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



Traditional Therapy for GCV-Resistant/Refractory CMV

- Foscarnet – nephrotoxicity, electrolytes, GU ulcers
- Cidofovir – nephrotoxicity, ocular toxicity (uveitis, loss of intraocular pressure)
- Combination GCV/FOS (Mylonakis, Clin Infect Dis 2002)
- High-dose IV ganciclovir
- CMVIg as adjunct to therapy
- Reduction of immunosuppression and/or switch to mTOR-based immunosuppression

GCV-R CMV in Lung Transplant, Foscarnet Outcomes (UPMC Series)

- CMV infection in 170/607 (28%). UL97 mutations 9.4% (16/170); also 4/16 UL54
- 12% cleared successfully; 31% failed; 51% cleared but relapsed with viremia
- 87% (14/16) foscarnet; 78% developed toxicity
- 11/16 had CMV pneumonitis; 4/16 (25%) died; high viral load assoc with mortality.

(Minces L et al, Antimicrob Agents Chemother 2014; 58:128-135)

Foscarnet Outcomes

(Johns Hopkins series)

- Retrospective study of transplant recipients treated with foscarnet for CMV, 2005-15
- 39 pts (22 SOT, 17 HSCT); 38.5% had GCV resistance; 28% tissue-invasive CMV
- Median duration of FOS was 32 days. Virologic failure in 13/39 (33%).
- Mortality 31% (higher in HSCT)

(Avery R et al, Transplantation 2016; 100:e74-e80)

Foscarnet Outcomes

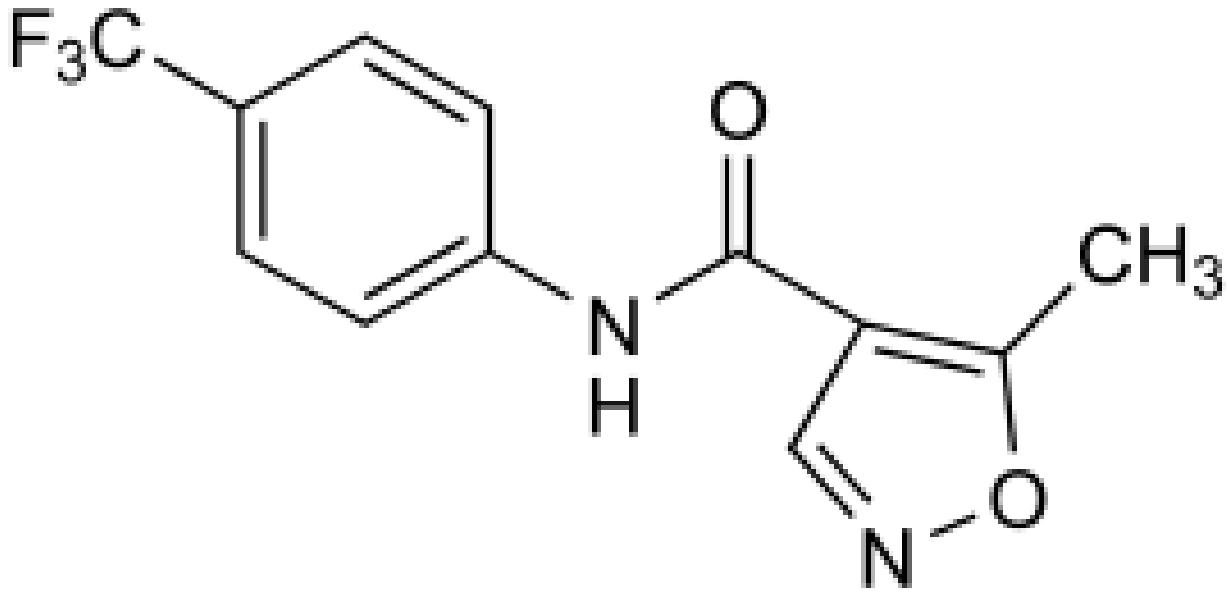
(Johns Hopkins series)

- GCV resistance more common in SOT than HCT, although mortality higher in HCT
- Renal dysfunction in 51% by end of treatment, and persisted in 28%, 6 mos later
- Conclusion: Outcomes of existing treatment for resistant/refractory CMV are suboptimal in terms of virologic clearance, renal dysfunction, and mortality.

Newer Options for GCV-R CMV

- (Off-label: Leflunomide)
- Investigational: Brincidofovir (CMX001)
- Investigational: Maribavir
- Investigational: Letermovir (AIC246)
- Adoptive immunotherapy (including 3rd party donor CMV-specific T cells)

Leflunomide

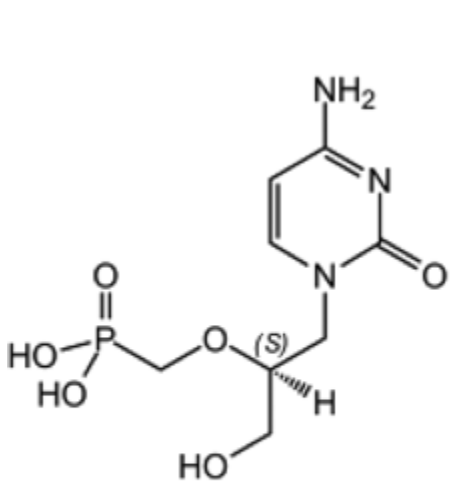


Leflunomide for CMV

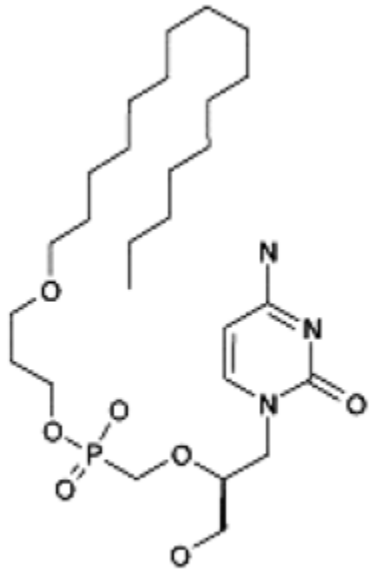
(Cleveland Clinic Series)

- 17 patients with complex CMV syndromes
- 14 had viral load responses to leflunomide
- 9 achieved long-term viral suppression (Avery et al, Transplantation 2010; 90:419-426)
- Toxicities include anemia, thrombocytopenia, LFT's, diarrhea, nausea, neuropathy
- Since that time, less successful

Structures of Cidofovir and Brincidofovir (CMX001)



Cidofovir
(CDV)



Hexadecyloxypropyl-Cidofovir
(CMX001)

Brincidofovir Activity Against dsDNA Viruses

Viral Family	Virus	Brincidofovir EC_{50} (µM)	Cidofovir EC_{50} (µM)	Ganciclovir* EC_{50} (µM)	Foscarnet EC_{50} (µM)	Acyclovir EC_{50} (µM)	Maribavir EC_{50} (µM)	Letermovir EC_{50} (µM)
Herpes	Cytomegalovirus (CMV)	0.001	0.4	3.8	50-800	>200	0.31	0.005
	Epstein-Barr Virus (EBV)	0.03	65.6	0.9	<500	6.2	0.63	>10
	Human Herpesvirus 6A (HHV-6A)	0.003	2.7	5.8	16	10	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	>100	Inactive	No data
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92-95	3.8	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91-96	4.4	Inactive	>10
	Varicella Zoster Virus (VZV)	0.0004	0.5	1.3	39.8	3.6	Inactive	>10
Adenovirus	Adenovirus 7 (AdV7)	0.02	1.3	4.5-33	Inactive (AdV2)	>100	No data	>10 (AdV2)
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	>200	No data	No data
	JC Virus (JCV)	0.045	>0.1	No data	Inactive	No data	No data	No data
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	No data	Inactive	No data	No data
Pox	Variola	0.1	27	No data	No data	No data	No data	No data
	Vaccinia	0.8	46	>392	Inactive	>144	No data	No data

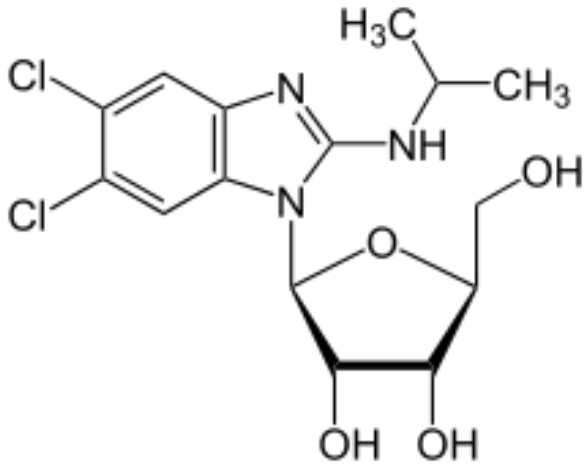
EC_{50} = concentration in µM required to reduce viral replication by 50% *in vitro*.
Data are compiled from multiple sources and include multiple materials and methodologies.
*Valganciclovir is rapidly converted to ganciclovir *in vivo*. Therefore, ganciclovir is the relevant compound for cell activity studies.

Brincidofovir Phase 3 HSCT Prophylaxis Study

- Oral cidofovir analogue, dosed 2x/wk, lacks nephrotoxicity of IV cidofovir
- SUPPRESS: Phase 3 randomized trial of 14 wks brincidofovir prophylaxis vs placebo in HSCT
- Failed to meet primary endpoint of prevention of CMV infection through Week 24; more GI GVHD and steroid use in the brincidofovir arm

(Marty F et al, BMT Tandem Meeting, Feb 2016)

Maribavir (SHP620)



Benzimidazole with novel mechanism: inhibits UL97 protein kinase; inhibits viral encapsidation, nuclear egress of viral particles

Maribavir

- Inhibits CMV and EBV (not HSV/VZV)
- No renal, hepatic, or hematologic toxicity
- Major side effect is dysgeusia
- Phase 3 prophylaxis trials in HSCT and liver transplant failed (using dose 100 mg BID)
- E-IND cases: 6 recipients with refractory CMV: some responses at doses of 400 – 800 mg BID
  (Avery RK et al, Transpl Infect Dis 2010; 12:489-496)

Maribavir E-IND Patient #2

(Avery et al, Transpl Infect Dis 2010; 12:489-496)

- Lung transplant recipient, CMV D+/R-, had GCV-R CMV with UL97 mutation, treated with foscarnet c/by renal failure, cleared temporarily
- 5 mos later had steroid pulse for rejection, and GCV-R CMV recurred with pneumonitis and peak VL 250,000. This time refractory to FOS/GCV, CMVIg, LEF; Cr judged too high for cidofovir

Maribavir E-IND Patient #2

- Maribavir was obtained via emergency IND
- Starting dose was 400 mg po BID; starting CMV VL around 60,000 c/ml
- Cyclosporine also changed to sirolimus
- Within 7 days, CMV viral load was undetectable and remained so for >4 yrs; maribavir discontinued after 6 mos
- Maribavir Patient #5 (intestinal transplant) similar striking response

E-IND Patient #4: Maribavir Resistance

- Patient #4 (heart transplant recipient with very high viral load) developed viral UL97 mutations T409M and H411Y, which confer maribavir resistance (Strasfeld L et al, JID 2010; 202:104-8)
- Maribavir resistance can also occur at UL27; pUL27 has nucleolar localization but with resistance mutations, loses this localization and is found in cytoplasm (Hakki M, Antiviral Res 2011; 92:313-8)

Maribavir Phase 2 Trials

- Study 202: Randomized 1:1:1, blinded trial of 3 doses of maribavir (400 mg, 800 mg, 1200 mg BID) for resistant/refractory CMV
- Study 203 (Europe): Randomized controlled trial of maribavir vs valganciclovir for uncomplicated CMV
- (Abstract presentations at ID Week 2016, BMT Tandem Meetings 2017, Am Transplant Congress 2017)

Maribavir Study 202 (Resistant/Refractory CMV)

- Randomized trial of maribavir 400 mg, 800 mg, 1200 mg BID in SOT or HSCT patients who had failed previous therapies
- Primary endpoint: viremia clearance at 6 wks
- Treatment could continue up to 24 wks
- Secondary endpoints: time to first undetectable CMV PCR, time to recurrence

(Pereira M et al, Am Transplant Congress, May 2017, Chicago, IL)

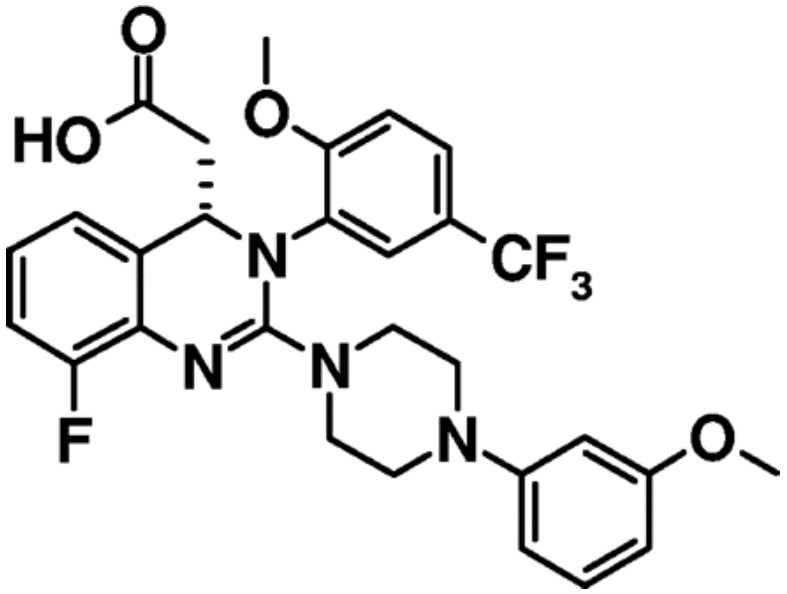
Maribavir Study 202 (Resistant/Refractory CMV)

- 70 SOT (60.8%), 47 HSCT (39.2%) randomized
- Viremia clearance similar between all doses (66.7% overall)
- No difference between SOT and HSCT
- Median time to first undetectable CMV PCR was 23 d (no difference between doses)
- 30/86 (34.9%) had a recurrence (Pereira M et al, Am Transplant Congress, May 2017, Chicago, IL)

Maribavir Study 202 (Resistant/Refractory CMV)

- Adverse effects: Dysgeusia in 65% overall, nausea 34%; overall favorable safety profile
- Although no placebo arm, no evidence of myelosuppression or nephrotoxicity
- Two Phase 3 multicenter studies now in progress: Study 303 (Resistant/Refractory) and Study 302 (Pre-Emptive Therapy in HSCT)

Letermovir (MK-8228, AIC246)



Oral or IV, potent, selective terminase inhibitor

First Report Of Letermovir For Treatment

- Lung recipient with tissue-invasive CMV involving lungs, GI treat, retina (U Mich)
- Refractory to all known drugs including leflunomide and brincidofovir
- Obtained letermovir from AiCuris via E-IND; resulted in rapid clinical, virological, and radiological resolution of disease. (Kaul D et al, Am J Transplant 2011; 11:1079-84)

Letermovir Phase 3 HSCT Prophylaxis Trial

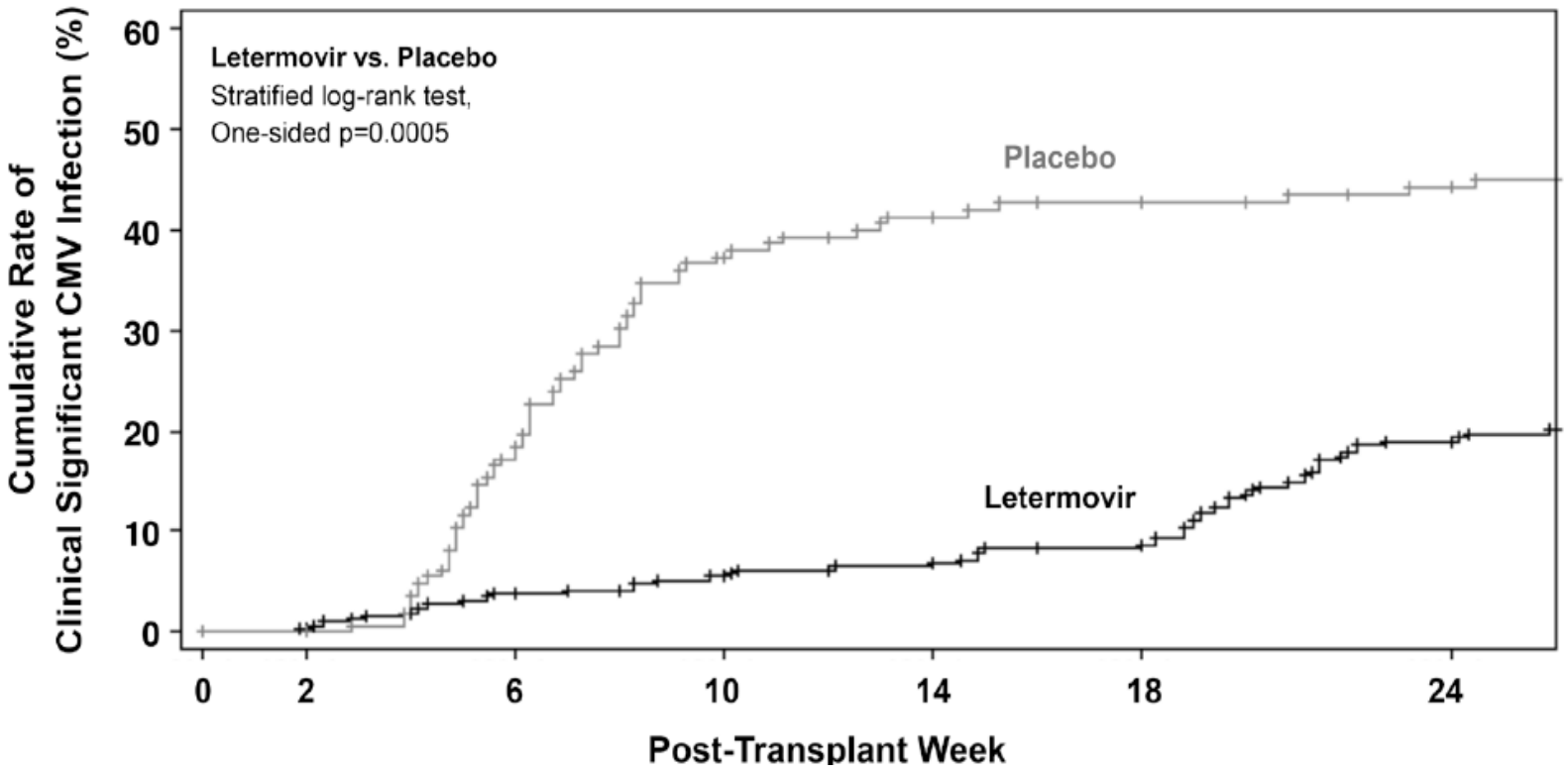
(Marty F et al, BMT Tandem Meeting Feb 2017)

- Phase 3, double-blind, placebo-controlled trial
- Randomized 2:1 letermovir 480 mg/d vs placebo through Week 14 after HSCT
- Primary endpoint was the proportion with clinically significant (CS) CMV through 24 wks
- Of 495 subjects, fewer in the LET group (122/325, 38%) had CS CMV or failure at 24 wks, c/w 103/170 (61%) placebo ($p<0.0001$)

Letermovir Phase 3 HSCT Prophylaxis Trial
(Marty F et al, BMT Tandem Meeting 2017)

Figure 1. Time to Onset of Clinically Significant CMV Infection

Subjects with undetectable CMV DNA at Randomization



Questions Which Remain

- Will this change strategy in HSCT programs (traditionally was pre-emptive therapy?)
- Letermovir for treatment? Only 1 case report
- Will different drugs have different roles?
- Combination therapy? (Maribavir and GCV are antagonistic, but other combinations?)
- Cost-effectiveness?

Other New Frontiers

- CMV-specific T cell therapy (including 3rd party) – promising, but labor and time-intensive
- Use of CMV-specific immune function tests (CMV T-spot, CMV IGRA) for monitoring, risk stratification, duration of prophylaxis
- CMV vaccines? (HSCT trial data being analyzed; Kidney transplant D+/R- study completed)

Conclusions

- Current treatment for CMV is largely valganciclovir- or ganciclovir-based therapy. Treatment is successful in the majority, but a significant fraction of patients experience toxicity (especially neutropenia) and some develop resistant or refractory CMV.
- Other licensed drugs (foscarnet, cidofovir) are characterized by high toxicity risk and suboptimal outcomes.

Conclusions

- Several investigational drugs have potential utility for prophylaxis and/or treatment of CMV.
- From the clinician's standpoint, we need to expand the armamentarium, ideally with all of these drugs; this represents an unmet need in transplant recipients.
- Robust enrollment in ongoing and future clinical trials is very important.

THANK YOU

- Thank you to the organizers of this meeting for inviting me
- Thank you to the audience for your attention!
- Questions?

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