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Bordeaux et la région Aquitaine
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au vendredi 17 juin 2022

CHU BDX CENTRE HOSPITALIER UNIVERSITAIRE BORDEAUX

université de BORDEAUX

Transplantation et CMV aujourd'hui et demain
En hématologie

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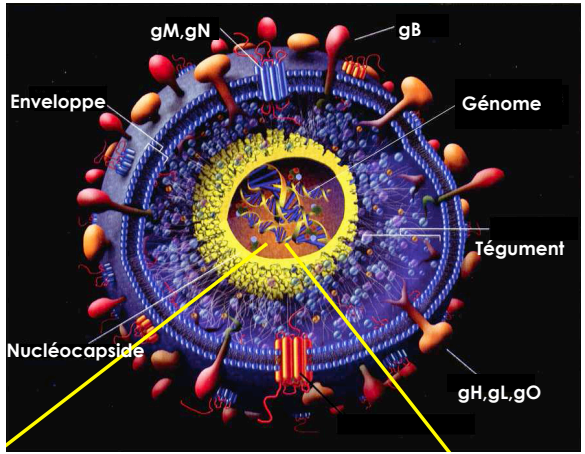
CHU Bordeaux

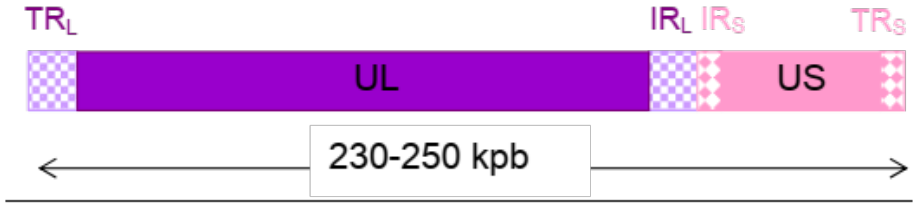
Déclaration d'intérêts de 2014 à 2021

- **Interventions ponctuelles :** Novartis, Gilead, GSK, Alexion
- **Financement congrès :** Neovii, Jazz, Novartis, Sanofi, Gilead, Alexion, MSD

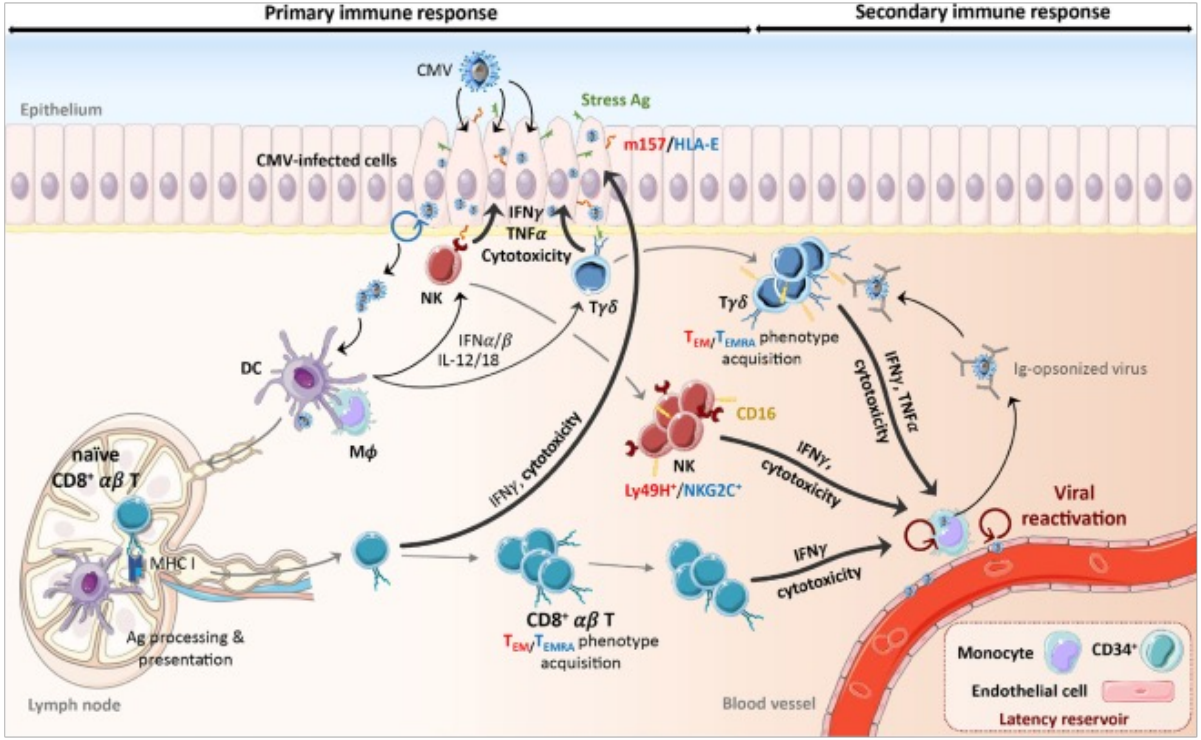
human CMV

- ***Herpesviridae* family**
- **Structure of the virus**
- **Latency and persistence**
- **Benefit of CMV PCR / pp65Ag**



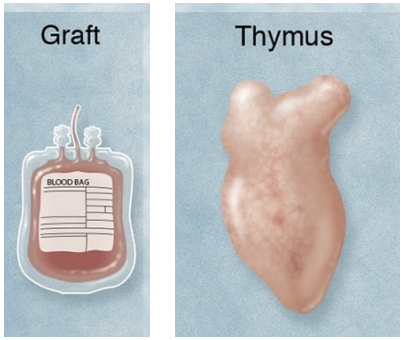


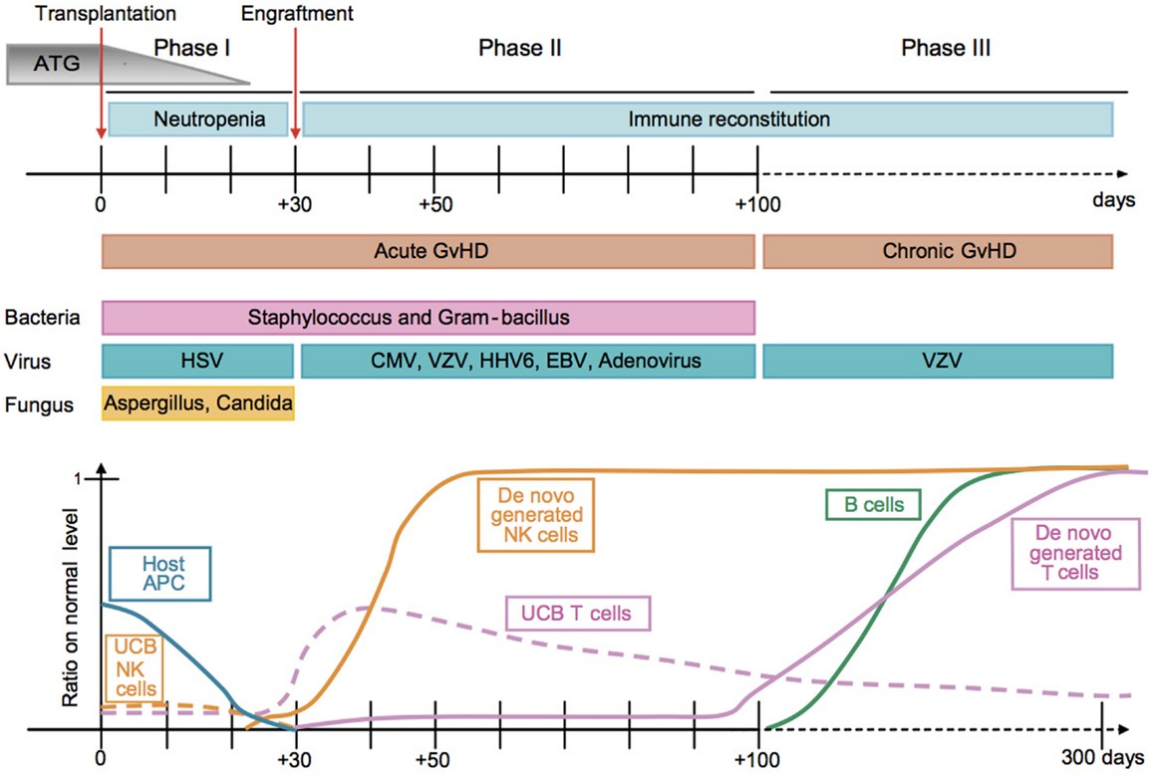
human CMV and immune response



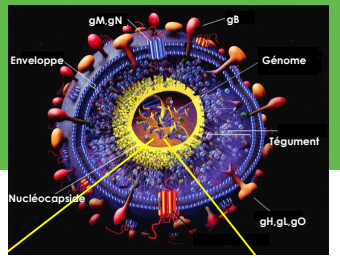
Khairallah *et al*, Front Immunol 2017

Immune Reconstitution after alloSCT





Risk factors for CMV infection in HSCT



- ***R/D CMV serostatus***

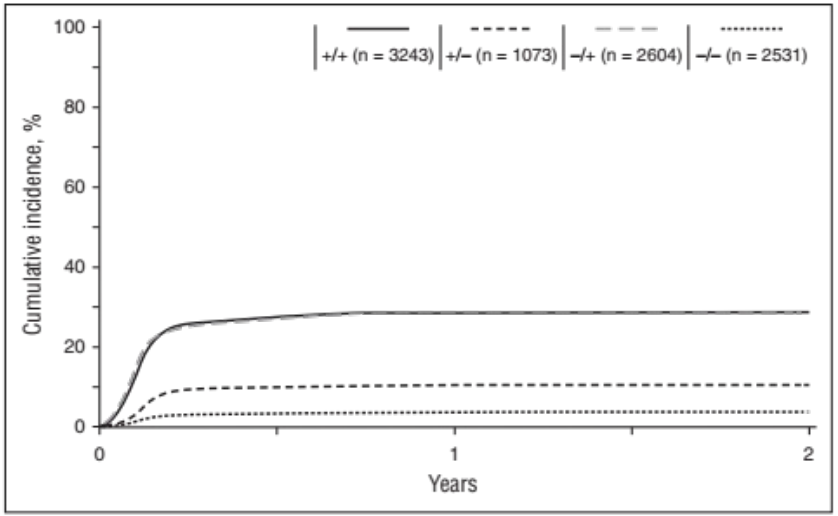


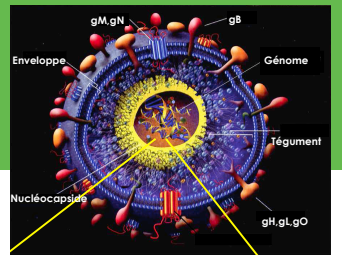
Figure 1. Cumulative incidence curves for CMV reactivation according to D/R serology.

34% in R+D+ or R+D-

11% in R-D+
4% in R-D-

Teira *et al,* Blood 2016

Risk factors for CMV infection in HSCT



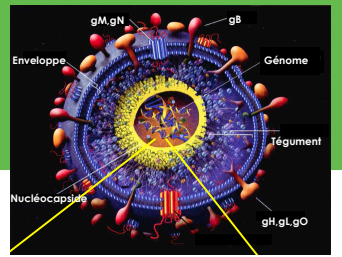
- *R/D CMV serostatus*
- *HLA matching*

Table 2. Impact of donor HLA status on overall mortality in a cohort of T-cell-replete transplant recipients

Donor/recipient CMV serostatus	Mortality for matched related donors (hazard ratio, 95% CI)	Mortality for mismatched related or unrelated donors (hazard ratio, 95% CI)
D−/R−	1.0 (reference)	1.0 (reference)
D+/R−	0.98 (0.70-1.38)	1.36 (1.06-1.74)
D−/R+	0.90 (0.65-1.24)	1.29 (1.04-1.60)
D+/R+	1.07 (0.81-1.42)	1.26 (1.01-1.58)

Nichols *et al,* J Infect Dis 2002

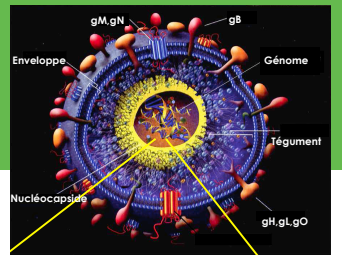
Risk factors for CMV infection in HSCT



- *R/D CMV serostatus*
- *HLA matching*
- *T cell depletion*
- *Acute and chronic GVHD (Cs)*

Ljungman *et al,* Hematol Oncol Clin North Am 2011

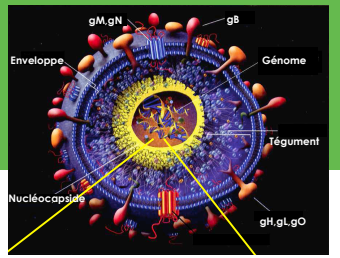
Guidelines - ECIL



- Donor and recipient CMV serology must be performed before HSCT
- CMV qPCR monitoring should be performed in alloSCT recipients
- CMV qPCR is more sensitive than pp65 Ag
- Monitoring should be performed weekly after alloSCT until day100
- Longer monitoring should be done in patients with GVHD, previous history of CMV, high risk alloSCT (mmUD, CBT)
- Immunological monitoring (ELISpot assay) useful to anticipate CMV recurrence

Ljungman *et al,* Lancet Infect Dis 2019

CMV and HSCT outcome



R/D CMV serostatus

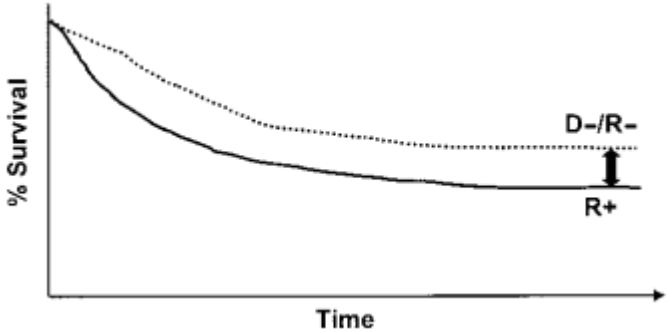
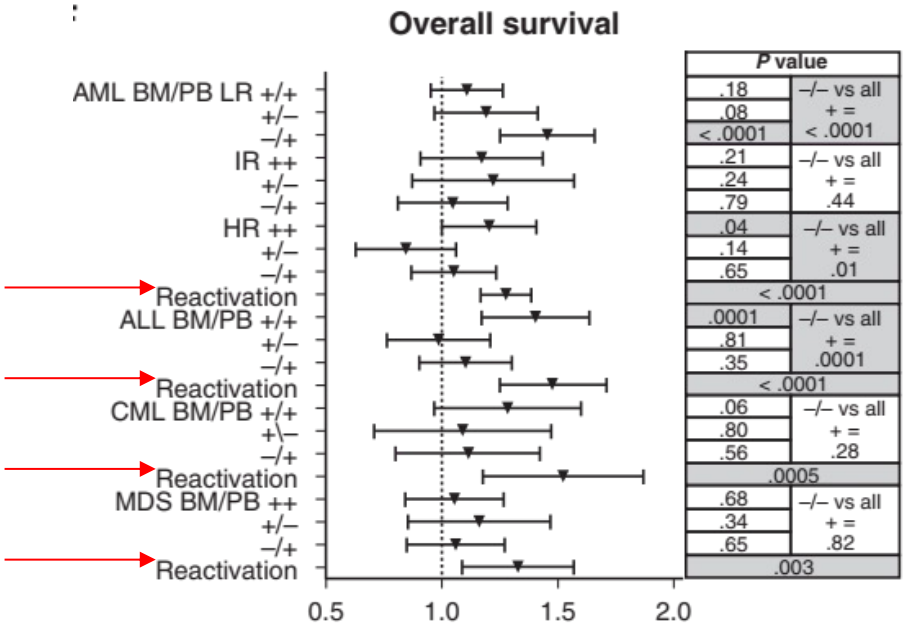


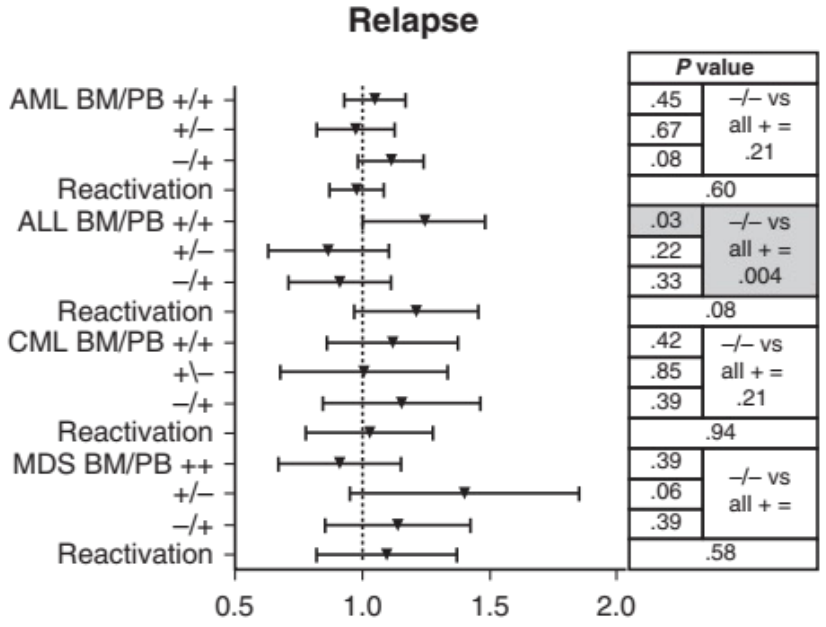
Table 1. Impact of recipient CMV serostatus on outcome after HSCT: recent studies

Reference, by first author	No. patients	Underlying disease	T-cell-depleted donors, %	Unrelated donors, %	Results among CMV-seropositive recipients compared with CMV-seronegative recipients with a seronegative donor
Broers[7]*	115	Mixed	95	0	24% absolute decline in OS ($P = .01$)
McGlave[8]	1423	CML	23	100	20% relative decline in DFS ($P = .002$)
Cornelissen[9]*	127	ALL	26	100	38% relative decline in DFS ($P = .05$)
Craddock[6]†	106	CML	100	100	22% absolute decline in OS ($P = .006$)
Kroger[10]	125	Mixed	100	100	41% absolute decline in OS ($P < .001$)
Castro-Malaspina[11]	510	MDS	24	100	46% relative decline in DFS ($P = .001$)
Nichols[4]	1750	Mixed	0	57	26% relative decline in OS ($P = .03$)
Kollman[3]	6978	Mixed	25	100	7% absolute decline in OS ($P < .001$)
Meijer[12]	48	Mixed	100	100	41% absolute rise in TRM ($P < .001$)
Doney[13]	182	ALL	0	52	99% relative rise in TRM ($P = .01$)

Boeckh and Nichols, Blood 2004

CMV and HSCT outcome





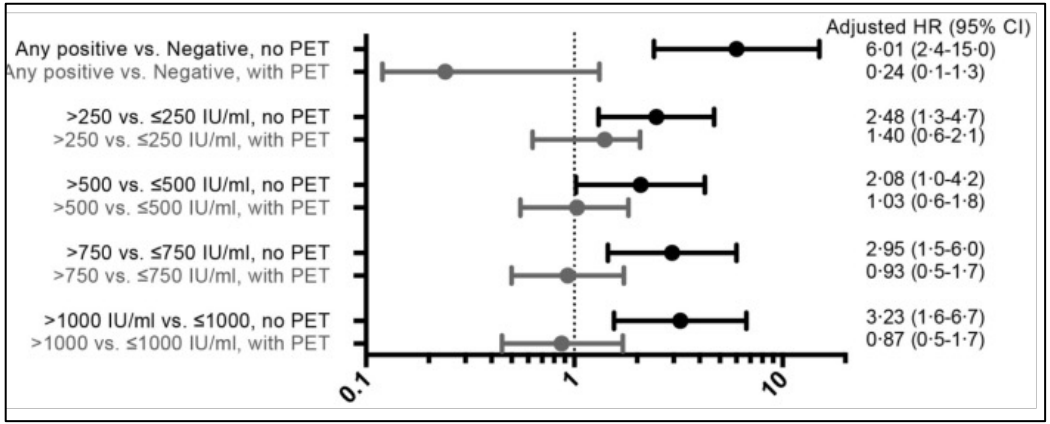
According to D/R pair

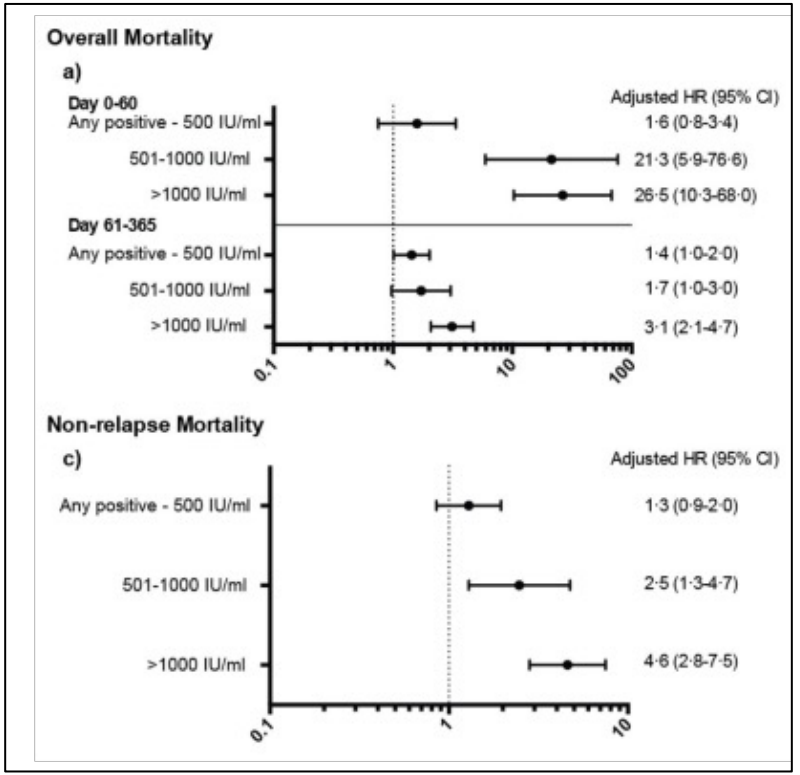
Teira *et al,* Blood 2016

CMV and HSCT outcome

Does the viral load matter?

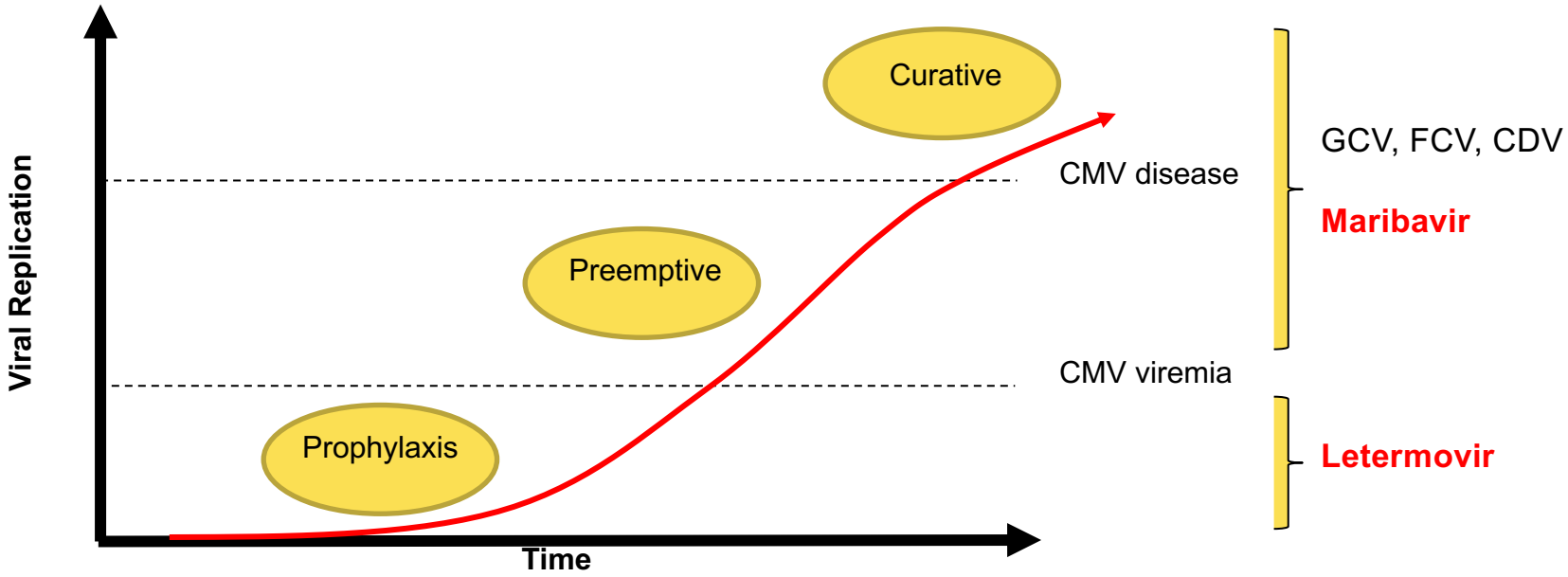
Risk of CMV disease by 1 year



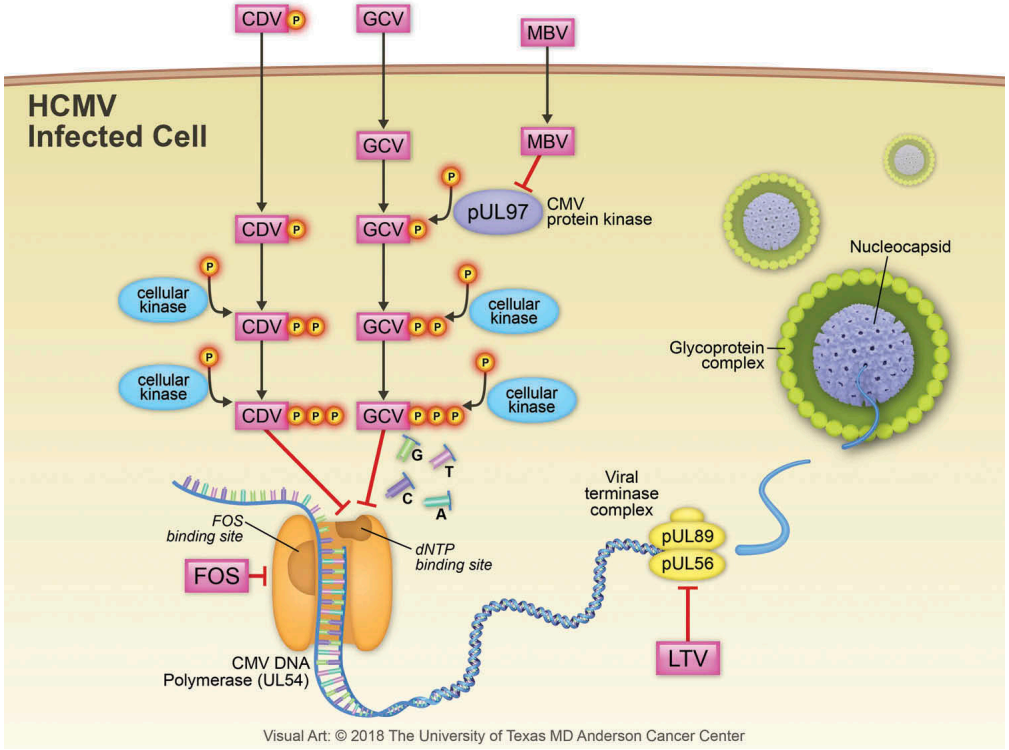


Green *et al,* Lancet Hematol 2017

Management of CMV: different strategies



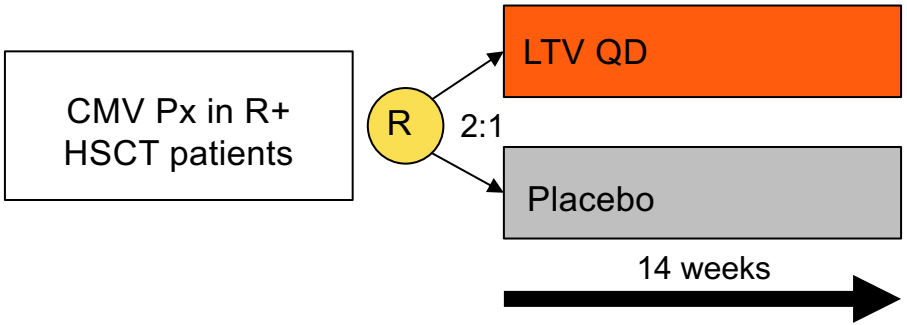
An ideal prophylaxis ?



1. **Safety**
   - Haematology
   - Renal
2. **Efficacy and resistance risk**
   - 10-20% clinical non responders
   - 1-3% virological resistance

Foolad *et al*, Expert review of clincal Pharmacology 2018

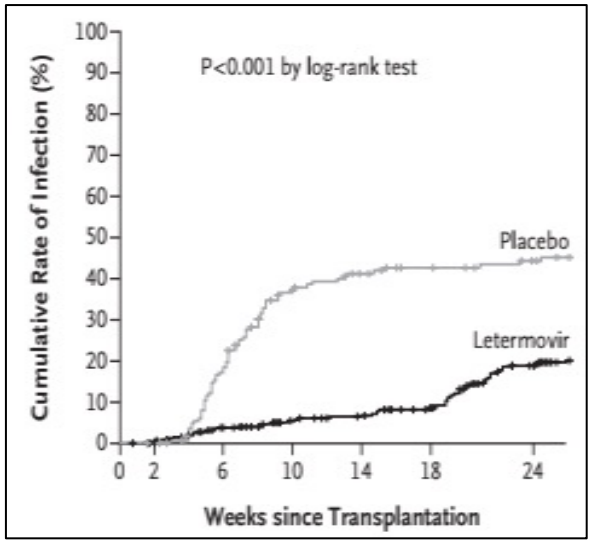
CMV prophylaxis with Letermovir



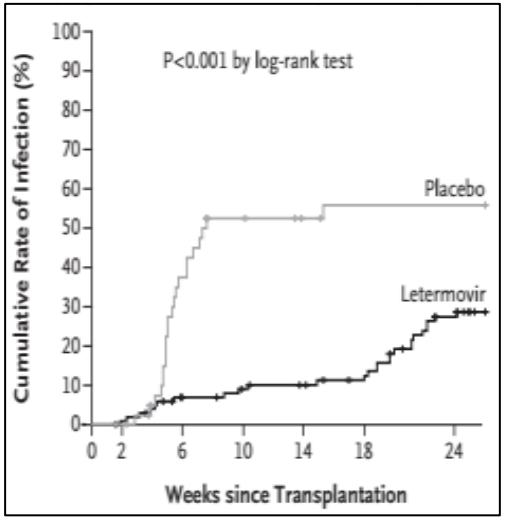
Marty *et al*, NEJM 2017

CMV prophylaxis with Letermovir

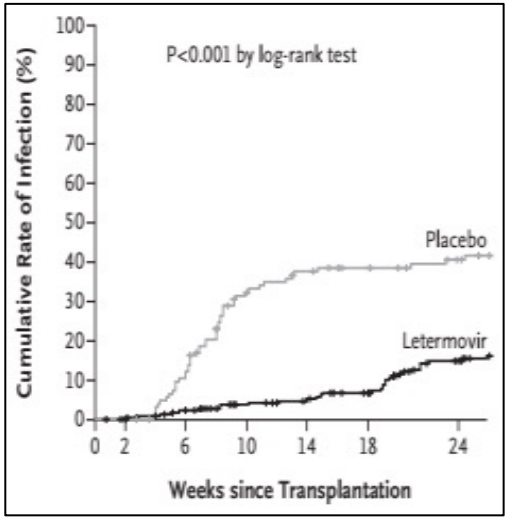
Incidence of clinically significant CMV infection



High Risk



Low Risk



HR = Haplo; mmUD; UCBT; Ex-vivo TCD; aGVHD -> Cs

Marty *et al*, NEJM 2017

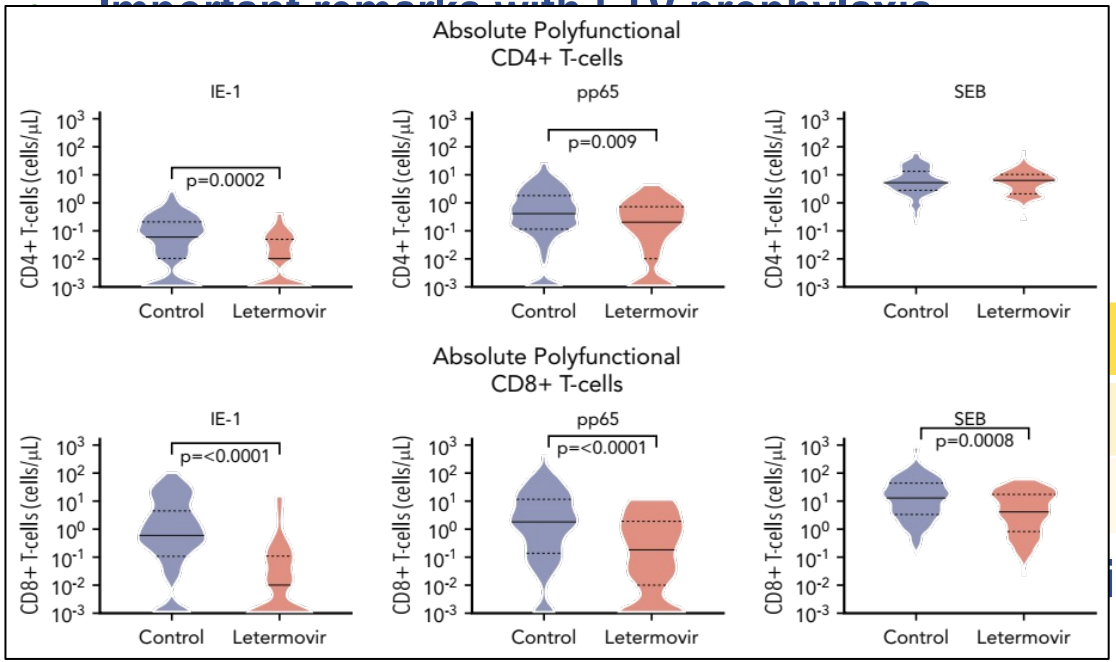
CMV prophylaxis with Letermovir

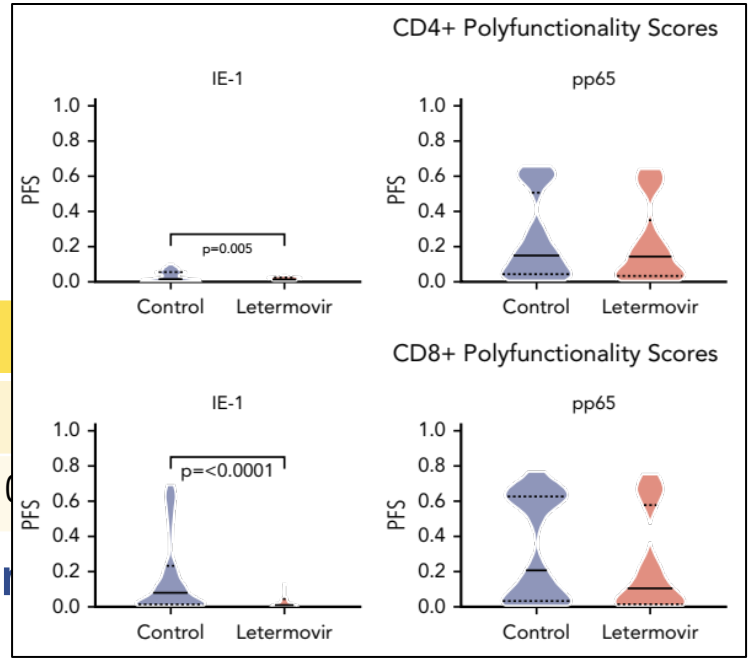
Safety profile

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
GVHD	146 (39.1)	74 (38.5)	0.6 (−8.0 to 8.9)	0.96
Diarrhea	97 (26.0)	47 (24.5)	1.5 (−6.3 to 8.8)	0.77
Nausea	99 (26.5)	45 (23.4)	3.1 (−4.6 to 10.3)	0.49
Fever	77 (20.6)	43 (22.4)	−1.8 (−9.2 to 5.2)	0.70
Rash	76 (20.4)	41 (21.4)	−1.0 (−8.4 to 5.9)	0.87
Vomiting	69 (18.5)	26 (13.5)	5.0 (−1.7 to 11.0)	0.17
Cough	53 (14.2)	20 (10.4)	3.8 (−2.2 to 9.2)	0.25
Peripheral edema	54 (14.5)	18 (9.4)	5.1 (−0.8 to 10.4)	0.11
Fatigue	50 (13.4)	21 (10.9)	2.5 (−3.6 to 7.8)	0.49
Mucosal inflammation	46 (12.3)	24 (12.5)	−0.2 (−6.4 to 5.3)	0.99
Headache	52 (13.9)	18 (9.4)	4.6 (−1.3 to 9.8)	0.15
Abdominal pain	44 (11.8)	18 (9.4)	2.4 (−3.3 to 7.5)	0.47
Acute kidney injury	36 (9.7)	25 (13.0)	−3.4 (−9.5 to 1.9)	0.28
Decreased appetite	38 (10.2)	22 (11.5)	−1.3 (−7.2 to 3.9)	0.74
Hypertension	31 (8.3)	21 (10.9)	−2.6 (−8.4 to 2.3)	0.38
Constipation	27 (7.2)	20 (10.4)	−3.2 (−8.8 to 1.5)	0.26

Marty *et al*, NEJM 2017

CMV prophylaxis with Letermovir

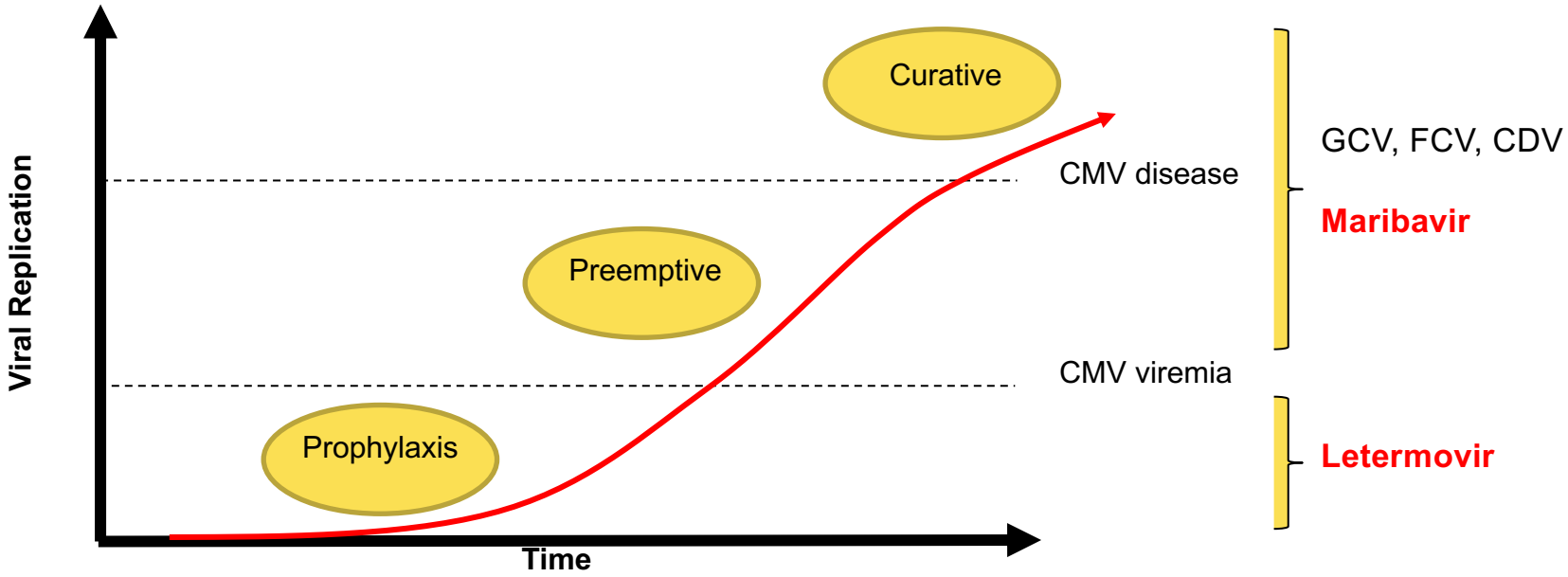




Polyfunctionality assessed by flow : IFNg + (CD107a, IL2, TNFa)

Marty *et al*, NEJM 2017; Ljungman *et al*, CID 2019; Zammora *et al*, Blood 2021; Robin C *et al*, BBMT 2020

Management of CMV: different strategies



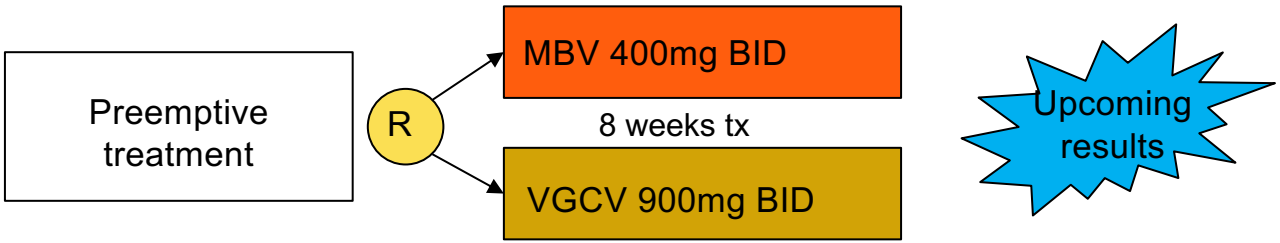
Maribavir for preemptive treatment

ORIGINAL ARTICLE

Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation

MBV (400, 800, 1200 BID) is equivalent to VGCV with a different safety profile

CMV in HSCT NCT02927067



Maertens *et al*, NEJM 2019

Management of CMV: different strategies

When should I look for resistance?

- **Refractoriness: 1 log10 increase after 2 weeks of well conducted therapy**
- **Probable refractoriness: stable viral load after 2 weeks of appropriate antiviral therapy**
- **Resistance: if symptoms of CMV disease worsen after 2 weeks of appropriate antiviral therapy**

What to do in case of resistant CMV ?

- **Look for genotypic resistance and drug level**
- **Consider 2nd line therapy**
  - Alternate drug
  - CDV
  - Artesunate, anti-CMV Ig
  - Taper IS treatment
  - Cellular therapy
- **If documented genotypic resistance, consider MBV, LTV…**

Maribavir for R/R CMV

Solstice trial

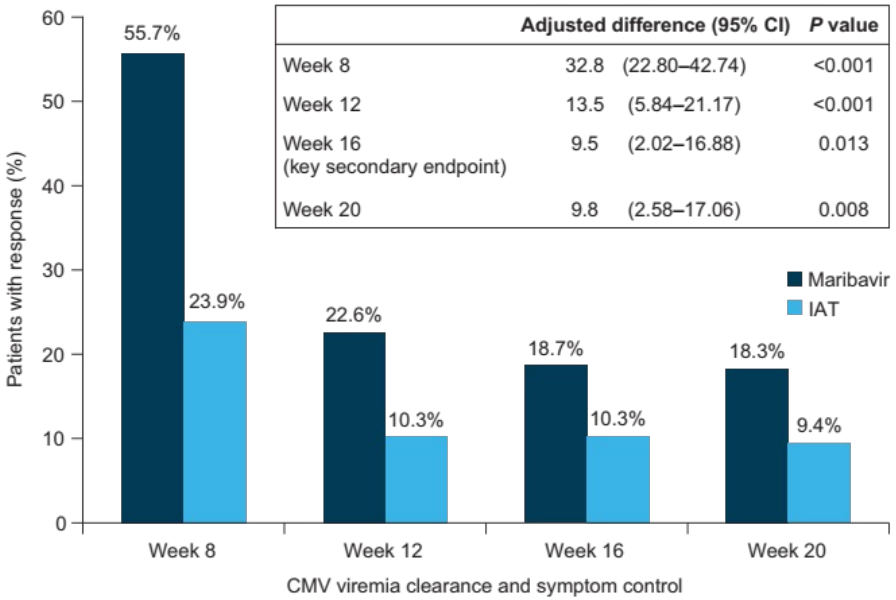
R/R CMV (HSCT or SOT)

R

MBV 400mg BID

8 weeks tx

IAT (VGCV/FCV/CDV)



	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

Avery *et al*, CID 2021

Letermovir for R/R CMV

N = 47 pts (27 SOT et 21 HSCT)

Clinical indications for letermovir[c]	
Resistance	15 (32)
Clinically refractory	6 (13)
Intolerance to other treatments	36 (77)
Oral agent preferred	9 (19)
Other (combination therapy desired)	1 (2)

Characteristic	Number (percent)
CMV end organ disease (including all proven/probable/possible)[a]	17/47 (36)
CMV syndrome (solid organ only)	16/27 (59)
Resistance (proven by genotyping)	17/47 (36)
UL97	15/17 (88)
UL54	4/17 (24)

	CMV Syndrome or DNAemia *n* = 30 (64%)		End organ disease *n* = 17 (36%)	
	<1000 IU/ml atLET start (*n* = 26)	>1000 IU/ml at LET start (*n* = 4)	<1000 IU/ml at LET start (*n* = 11)	>1000 IU/ml at LET start (*n* = 6)
Persistent or worsening symptoms while on LET	0	0	1 (9%)	3 (50%)
Death[a]	8 (31%)	0	2 (18%)	3 (50%)
Death direct result of CMV	0	0	0	1
Death indirect result of CMV	1[b] (3%)	0	0	2[b] (33%)

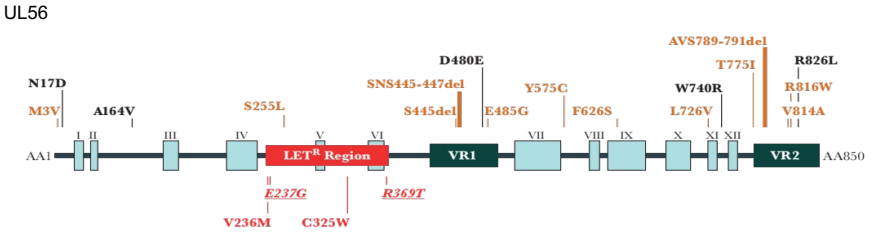
Linder *et al*, Transpl Infect Dis 2021

Breakthrough infections and resistance with Letermovir

Phase II LTV HSCT
15/98 breakthrough infections (lower dose of LTV +++)
NGS variants 6/15 (1 mutation, 5 polymorphism)

Phase III LTV HSCT *: 1/325 (1 mut)*

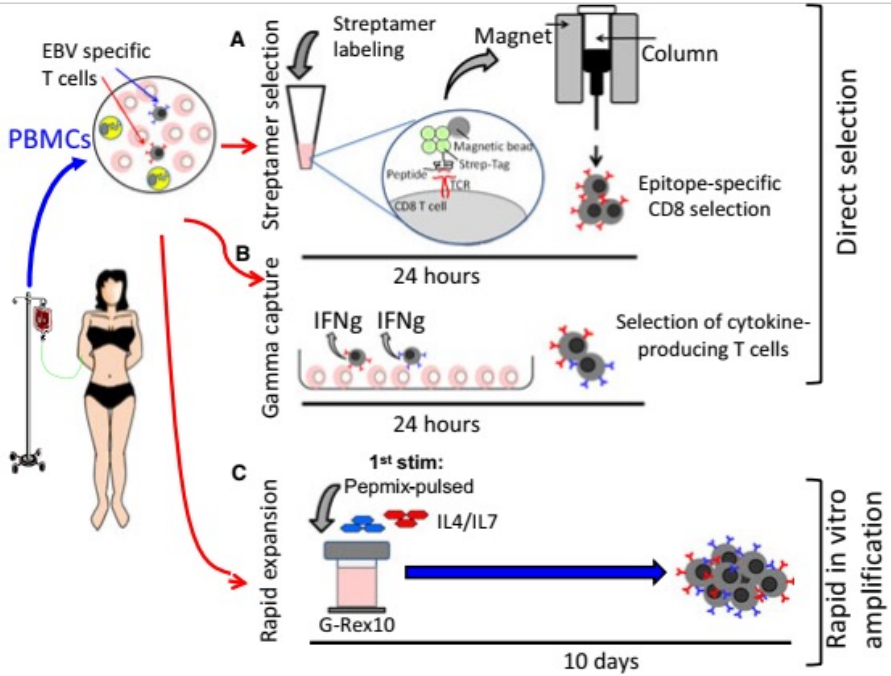
Risk Factors
- *DNAemia before LTV*
- *LTV low dose*
- *Gut GVHD*



LTV group : 50/79 productive NGS
2/50 showed UL56 variants associated with resistance

Chemaly *et al*, NEJM 2014; Marty *et al*, NEJM 2017 ; Douglas *et al*, JID 2020

Cellular therapy



Rooney *et al*, Immunological review 2014

Take home message

CMV infection risk regarding the proportion of R+ in HSCT

Letermovir is powerful drug with excellent safety profile for prophylaxis strategy

Recent and ongoing randomized trials for LTV and MBV with promising results

Importance to look for virological resistance in specific situations

NAVIRE cohort (PI: Pr Sophie ALAIN – CNR)

Acknowledgments

- Service d'Hématologie Clinique et Thérapie cellulaire (Pr Pigneux)
- Service des maladies infectieuses
- Service de pneumologie
- Service de Médecine Intensive Réanimation
- Laboratoire de Virologie
- Laboratoire de Myco-parasitology
- Laboratoire HLA

- Equipe J Déchanet-Merville
- Equipe P Blanco

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- CNR CMV (S Alain, Limoges)

SFGM-TC