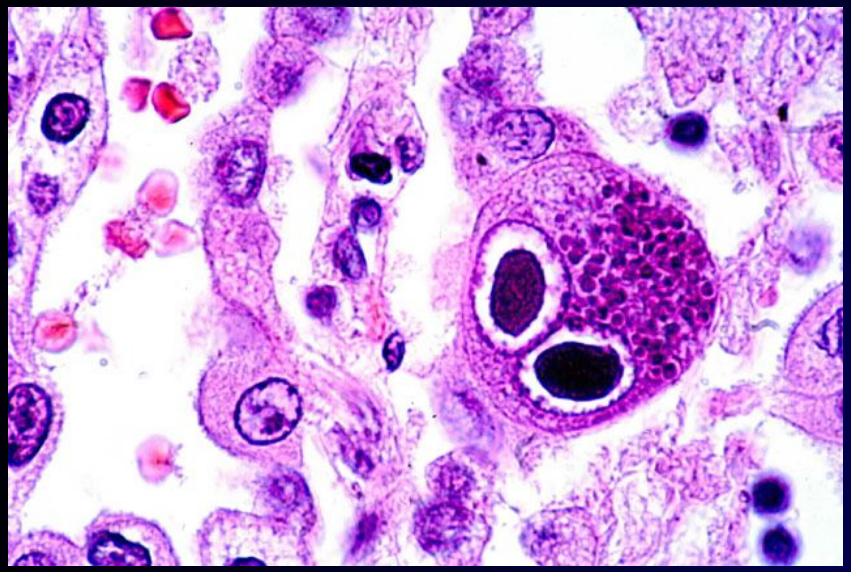
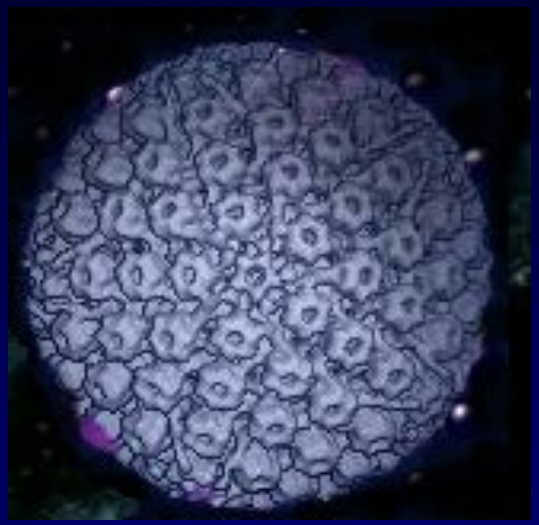
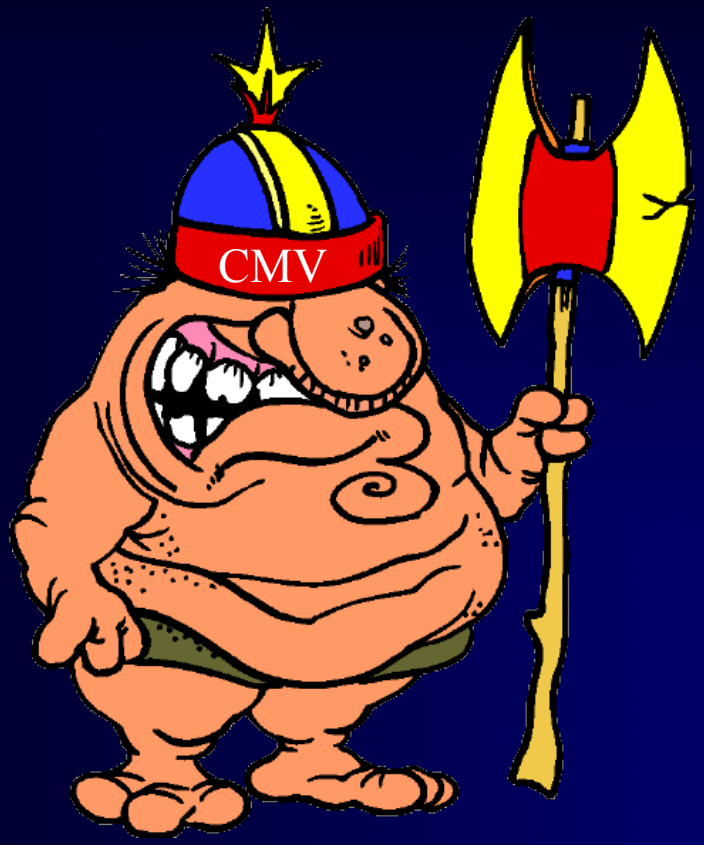
CMV infection in hematopoietic stem cell transplantation: current trends and perspectives





Prof. Per Ljungman
Center for Allogeneic Stem Cell Transplantation
Karolinska University Hospital and Karolinska Institutet
Stockholm, Sweden

What is the influence of CMV on outcome of a HSCT?



What is the influence of CMV on outcome of a HSCT?

- Being CMV seropositive is associated with decreased survival
- Having a CMV seropositive donor for a CMV seronegative patient is associated with decreased survival
- Having a CMV seronegative unrelated donor for a CMV seropositive patient is associated with decreased survival
- CMV replication is bad for the patient!!

TRANSPLANTATION

CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT

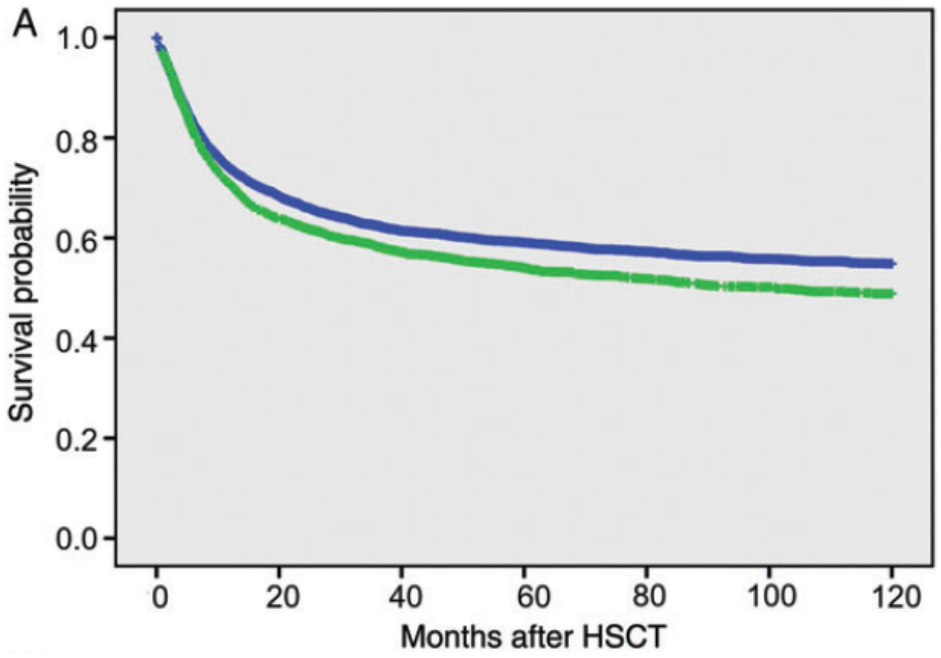
Martin Schmidt-Hieber,[1,2] Myriam Labopin,[3-6] Dietrich Beelen,[7,8] Liisa Volin,[9] Gerhard Ehninger,[10] Jürgen Finke,[11] Gerard Socié,[12] Rainer Schwerdtfeger,[13] Nicolaus Kröger,[14] Arnold Ganser,[15] Dietger Niederwieser,[16] Emmanuelle Polge,[4] Igor W. Blau,[2] and Mohamad Mohty[3-6,17]

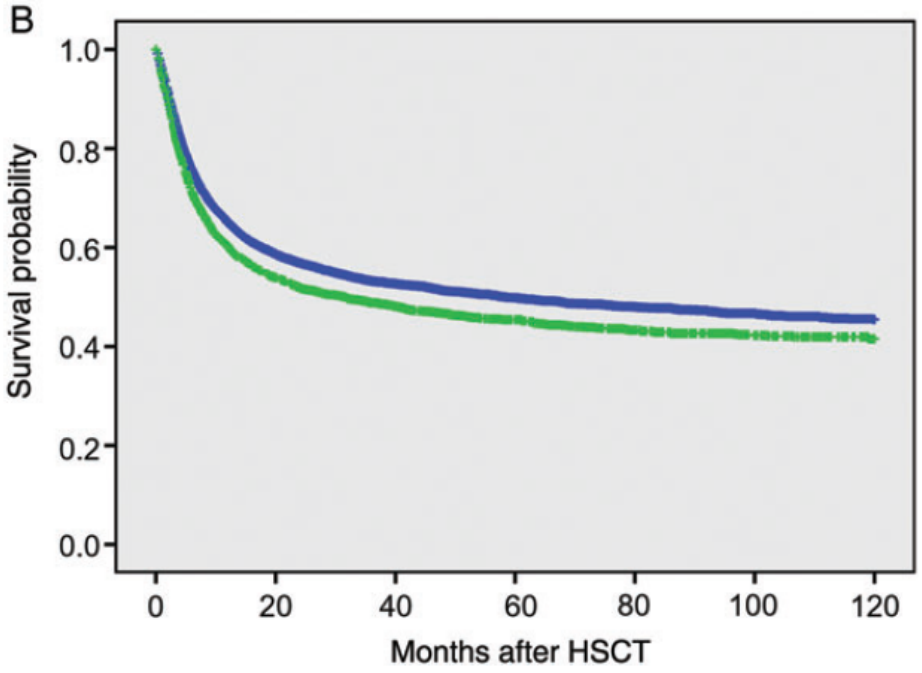
Table 2. Impact of CMV serostatus on LFS, RI, NRM, OS, chronic GVHD, and neutrophil engraftment

CMV serostatus	LFS	RI	NRM	OS	cGVHD	NEG
Total (n = 16628)	45	32	22	51	45	97
D-CMV$^-$/R-CMV$^-$	49	31	20	56	45	97
D-CMV$^+$/R-CMV$^-$	44	34	22	49	47	96
D-CMV$^-$/R-CMV$^+$	43	31	25	49	44	96
D-CMV$^+$/R-CMV$^+$	45	33	23	51	44	96
P	< .001	.11	< .001	< .001	.63	< .001
D-CMV$^-$/R-CMV$^-$	49	31	20	56	45	97
Other combination	44	32	23	50	45	96
P	< .001	.08	< .001	< .001	.6	.08

Schmidt-Hieber M et al. Blood 2013;122:3359-3364

Survival of CMV seronegative patients; influence of donor serostatus





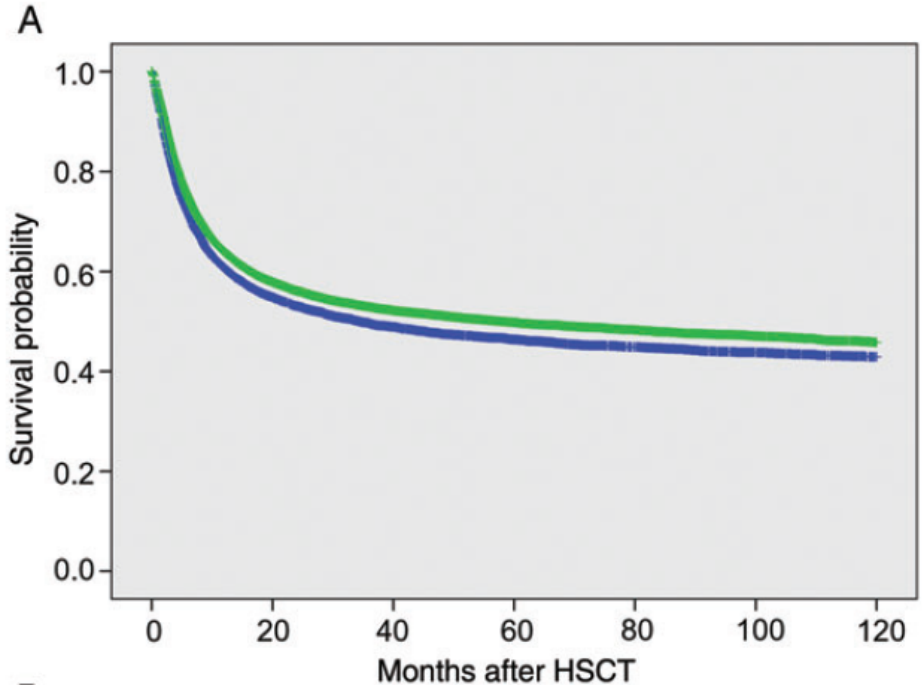
HLA id siblings

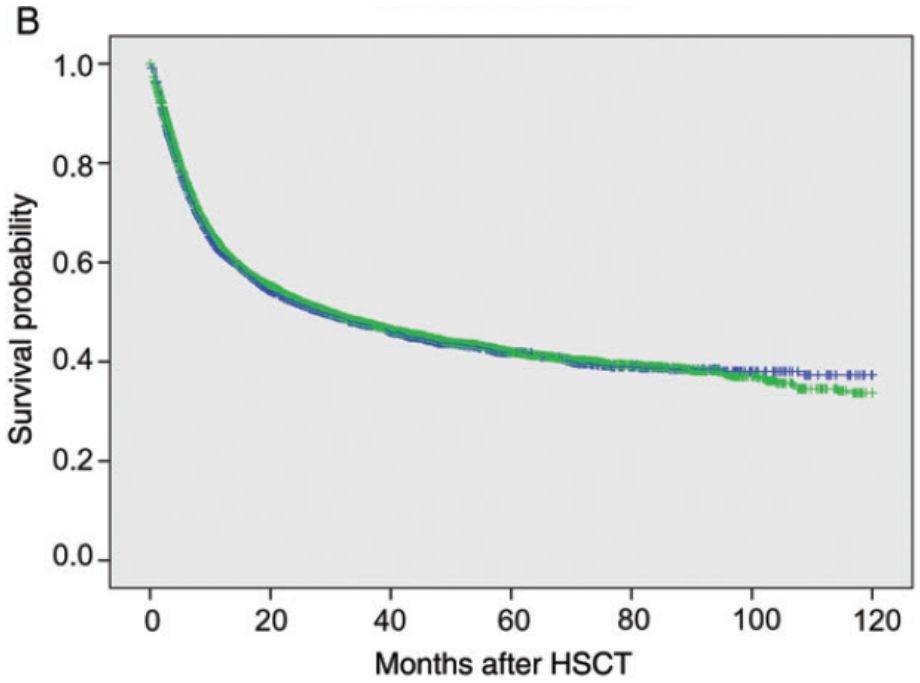
Unrelated donors

CMV pos donor

CMV neg donor

Survival of CMV seropositive patients; influence of donor serostatus





Myeloablative conditioning

Reduced intensity conditioning

CMV pos donor

CMV neg donor

Is CMV disease a problem in 2017?

CMV Disease: Preemptive Era—Placebo Group in Randomized Trials

Author	Journal	Year	N	Period	Incidence
Marty et al.[1]	*Lancet Infect Dis*	2011	227	Early	2.4%
Marty et al.[2]	*N Engl J Med*	2013	59	Early	3.0%
Chemaly et al.[3]	*N Engl J Med*	2014	33	Early	0%
Boeckh et al.[4]	*Ann Int Med*	2015	89	Late	2.0%

1. Marty FM et al. *Lancet Infect Dis*. 2011;11:284-292. 2. Marty FM et al. *N Engl J Med*. 2013;369:1227-1236.
3. Chemaly RF et al. *N Engl J Med*. 2014;370:1781-1789. 4. Boeckh M et al. *Ann Intern Med*. 2015;162:1-10.

New definitions

Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials

Per Ljungman,[1,2] Michael Boeckh,[4,5] Hans H. Hirsch,[6] Filip Josephson,[3] Jens Lundgren,[7] Garrett Nichols,[8] Andreas Pikis,[9] Raymund R. Razonable,[10] Veronica Miller,[11] and Paul D. Griffiths[12]; for the Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum[a]

[1]Departments of Allogeneic Stem Cell Transplantations and Hematology, Karolinska University Hospital, Solna, [2]Division of Hematology, Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, and [3]Swedish Medical Products Agency, Uppsala, Sweden; [4]Vaccine and Infectious Disease and Clinical Research Division, Fred Hutchinson Cancer Research Center, and [5]Department of Medicine, University of Washington, Seattle; [6]Department of Biomedicine, University of Basel, Switzerland; [7]Centre for Health and Infectious Disease Research (CHIP), Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark; [8]Chimerix, Inc, Durham, North Carolina; [9]Division of Antiviral Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland; [10]Division of Infectious Diseases, Department of Medicine, William J. von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, Minnesota; [11]Forum for Collaborative HIV Research, University of California, Berkeley; and [12]Institute for Immunity and Transplantation, University College London Medical School, United Kingdom

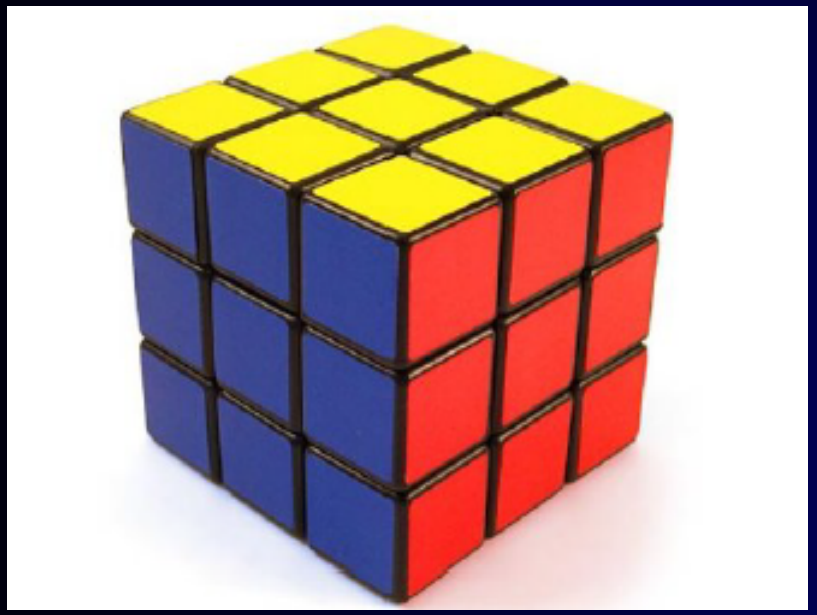
Ljungman et al CID 2017

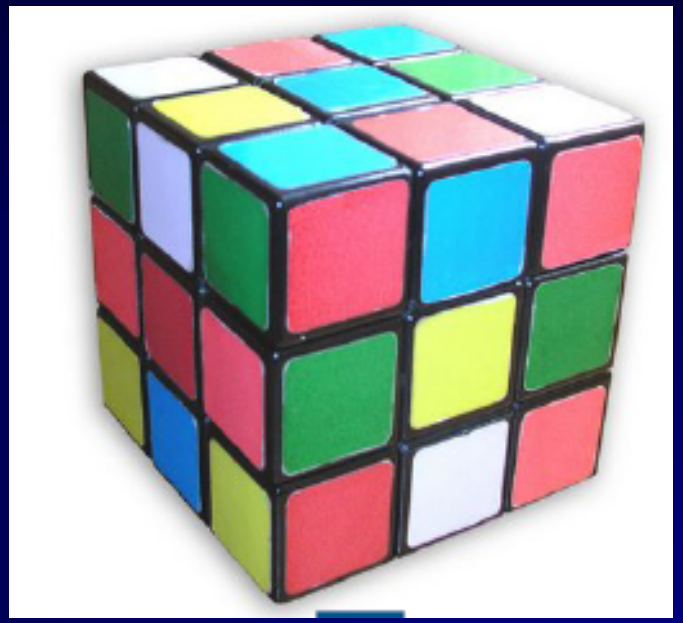
CMV disease categories and required quality of evidence

Disease	Proven	Probable	Possible
Pneumonia	Yes	Yes	(Yes)
Gastrointestinal disease	Yes	Yes	(Yes)
Hepatitis	Yes	No	No
Retinitis	Yes	No	No
Encephalitis/ventriculitis	Yes	Yes	No
Nephritis	Yes	No	No
Cystitis	Yes	No	No
Myocarditis	Yes	No	No
Pancreatitis	Yes	No	No
Other end-organ diseases	Yes	No	No
Syndrome	No	Yes	No

All 3 categories require appropriate clinical symptoms and/or signs.

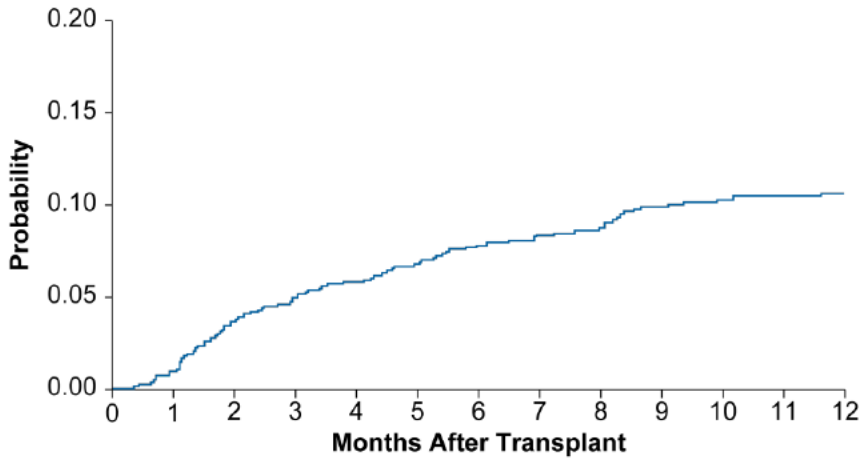
Patients in and outside of clinical trials





Real life probability of CMV disease

CMV Disease[1]



- 95 patients with disease
  - 33 pneumonia
  - 62 gastrointestinal
  - 3 retinitis
- 3 patients with concurrent pneumonia and GI disease

N = 926

R+, D+/R-

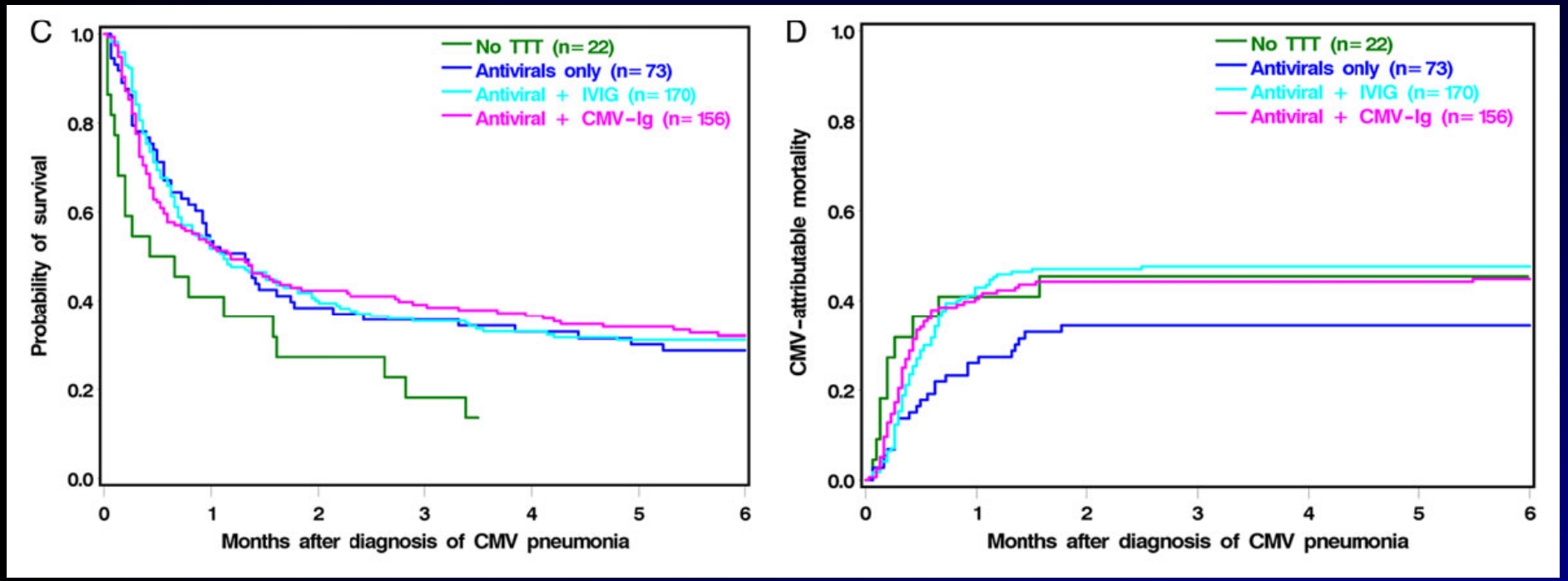
First allogeneic transplant

1. Green ML et al. *Lancet Haematol*. 2016;3:e119-127.

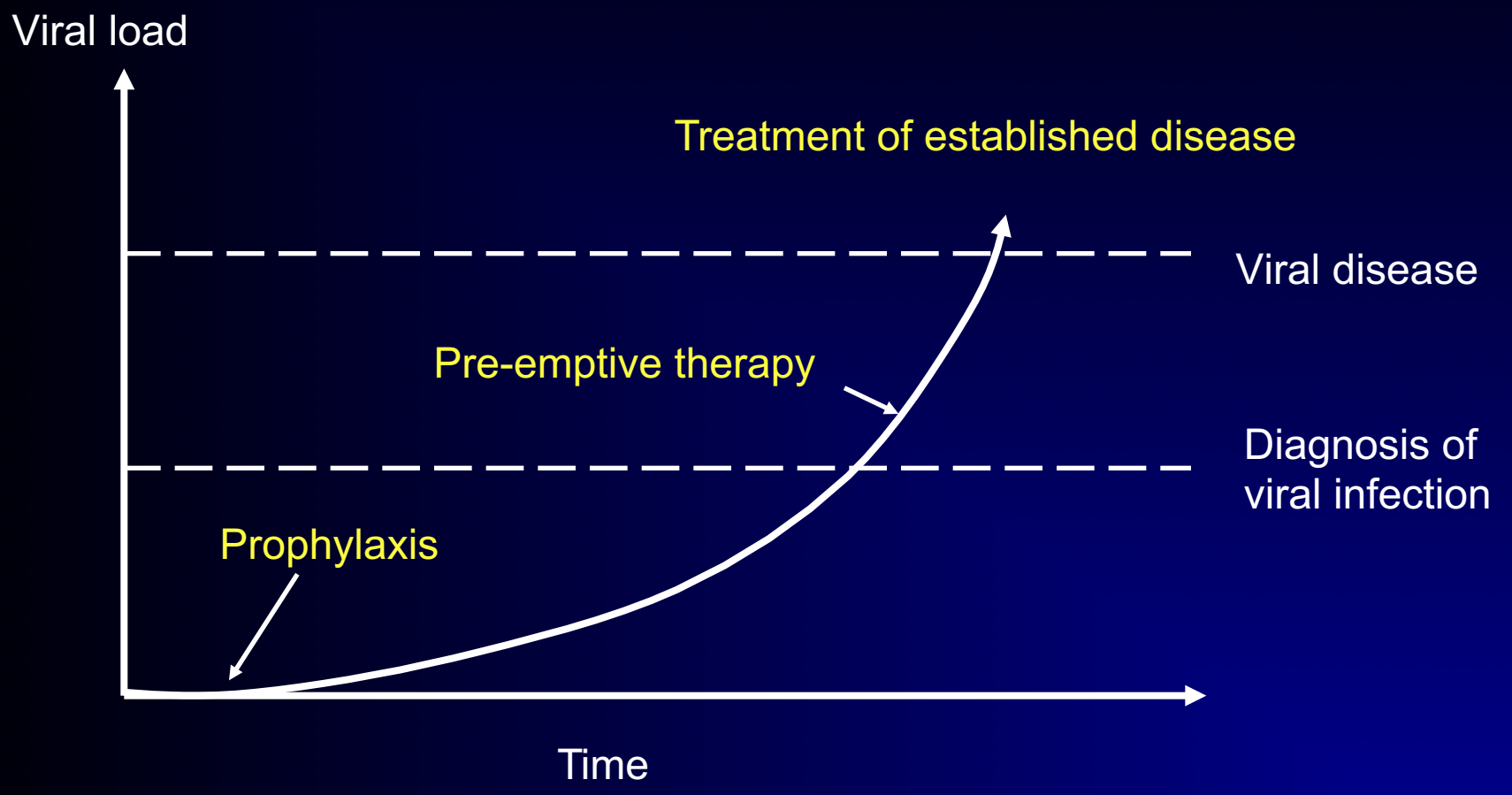
Antiviral therapy + iv Ig
(CMV Ig or standard)

- Iv Ig has never been shown effective in a controlled trial for treatment of any CMV associated complication
- Some supporting data in CMV pneumonia
- Indirect data that it does not improve outcome
- Expensive

Does Ig make a difference in treatment of CMV pneumonia?

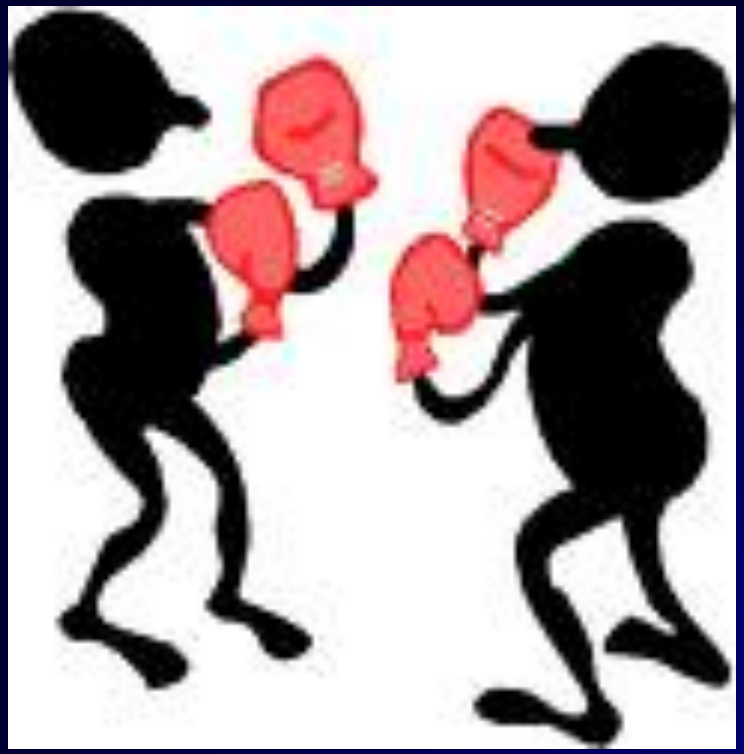


Timing of management options



The fight!

Prophylaxis



Preemptive therapy

What is the rationale for monitoring and preemptive treatment

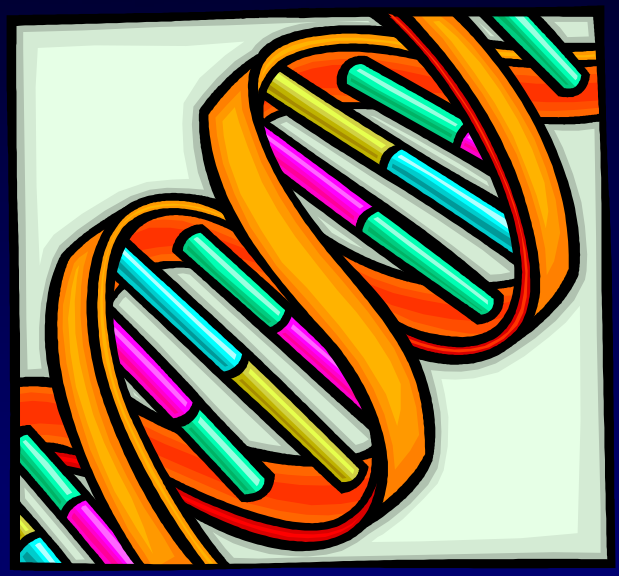
- A sensitive diagnostic test is available
- A positive result is predictive for development of disease
- Early intervention can prevent disease
- An effective (and safe) antiviral drug is available

What is the rationale for monitoring and preemptive treatment

- A sensitive diagnostic test is available
- CORRECT – Many studies
- A positive result is predictive for development of disease
- CORRECT – Emery et al, Lancet 2000
- Early intervention can prevent disease
- CORRECT – Einsele et al, Blood 1995
- An effective (and safe) antiviral drug is available
- YES AND NO

Testing issues

- All PCRs are not created equal!!
  - Starting materials
  - DNA extraction methods
  - Primer/probe selection
  - Variability
  - International standard!!



- Cut-offs for start therapy – undefined and variable

1:st line therapies

- I.v ganciclovir
- Valganciclovir
- (Foscarnet)

Repeated CMV reactivations

- Common in high risk patients
- Frequently poor activity/tolerability of existing antiviral drugs
- Associated with poor T-cell control of CMV
- Increased risk for resistant strains

CMV resistance; mutations in the viral genome

- Ganciclovir/valganciclovir: UL 97 (kinase) mutations, UL54 (polymerase) mutations
- Foscarnet: UL54 (polymerase) mutations
- Cidofovir: UL54 mutations
- New drugs (maribavir, letermovir, brincidofovir) – unclear importance of mutations but likely

How common is it?

Varies between patient populations

Ganciclovir resistance

0% in a prospective randomized study (Boeckh et al Ann Intern Med 2015)

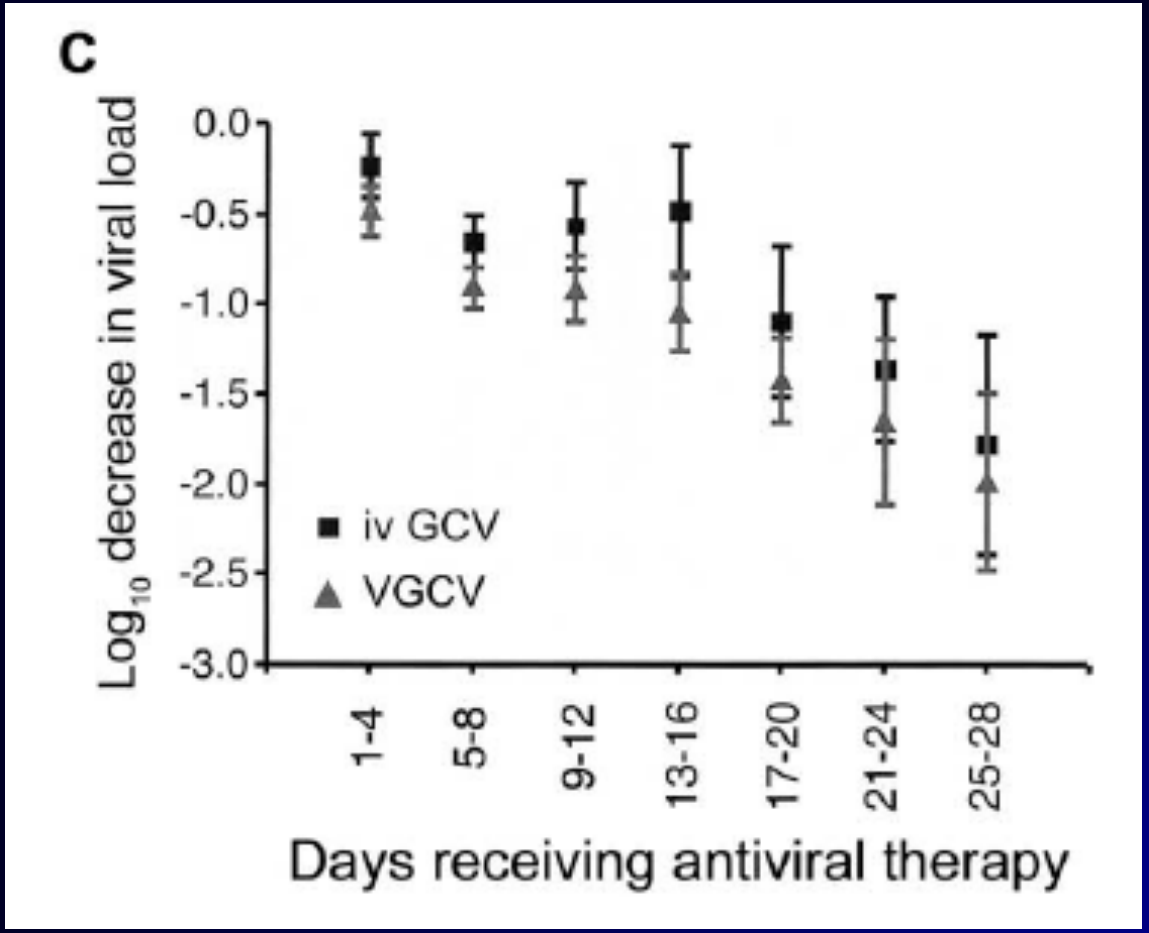
0% in auto and allo SCT non-haplo recipients in a large prospective cohort study

9.6% in haploidentical allo SCT recipients (Shmueli et al JID 2013

Causes for “clinical” resistance

- If you give oral therapy, does the patient take the drug? Vomiting?
- Does the patient absorb the oral drug?
- What are the drug levels? TDM for ganciclovir
- Viral replication kinetics
- Poor T-cell function

Response to antiviral therapy takes some time!



Mattes et al JID 2005

Treatment of resistant/refractory patients

- Foscarnet
- Cidofovir
- T-cells
- Maribavir/letermovir/brincidofovir
- Leflunomide
- Artesunate

Maribavir

- Sucessful phase II study for prophylaxis
- Failed phase III study for prophylaxis
- Case series on refractory patients Phase II study of refractory patients finalized.
- Phase III studies ongoing
- Drug not available for use

Phase II results

- 120 patients
- Resistant or refractory to GCV or foscarnet
- Three dose levels (400, 800, 1200 mg BID)
- Primary endpoint: CMV DNA neg within 6 weeks

- 67% (80 patients) reached the primary endpoint
- No difference between dose levels
- 30 (37.5%) recurred

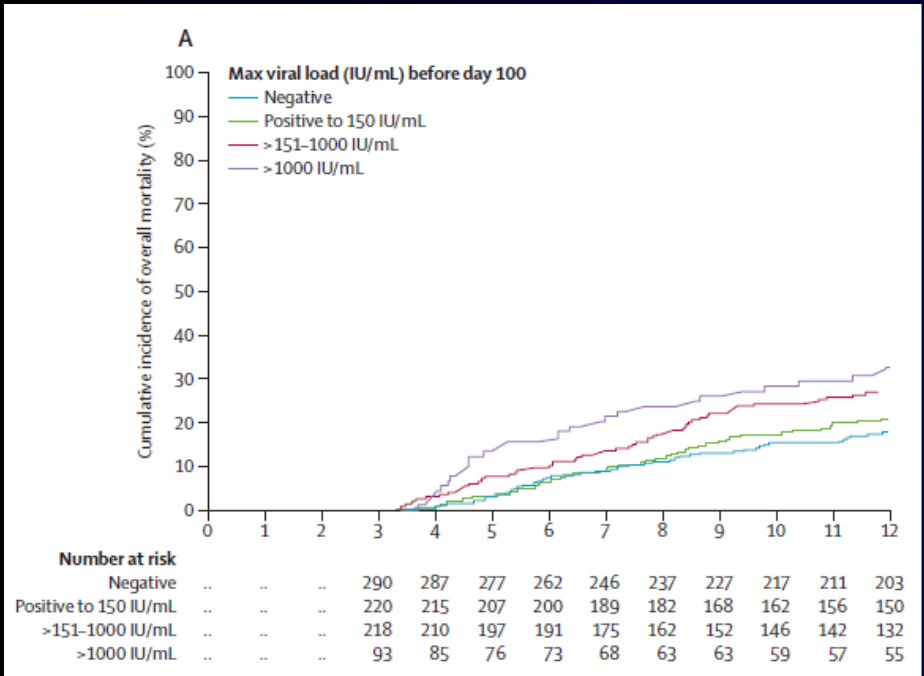
ID week, 2016

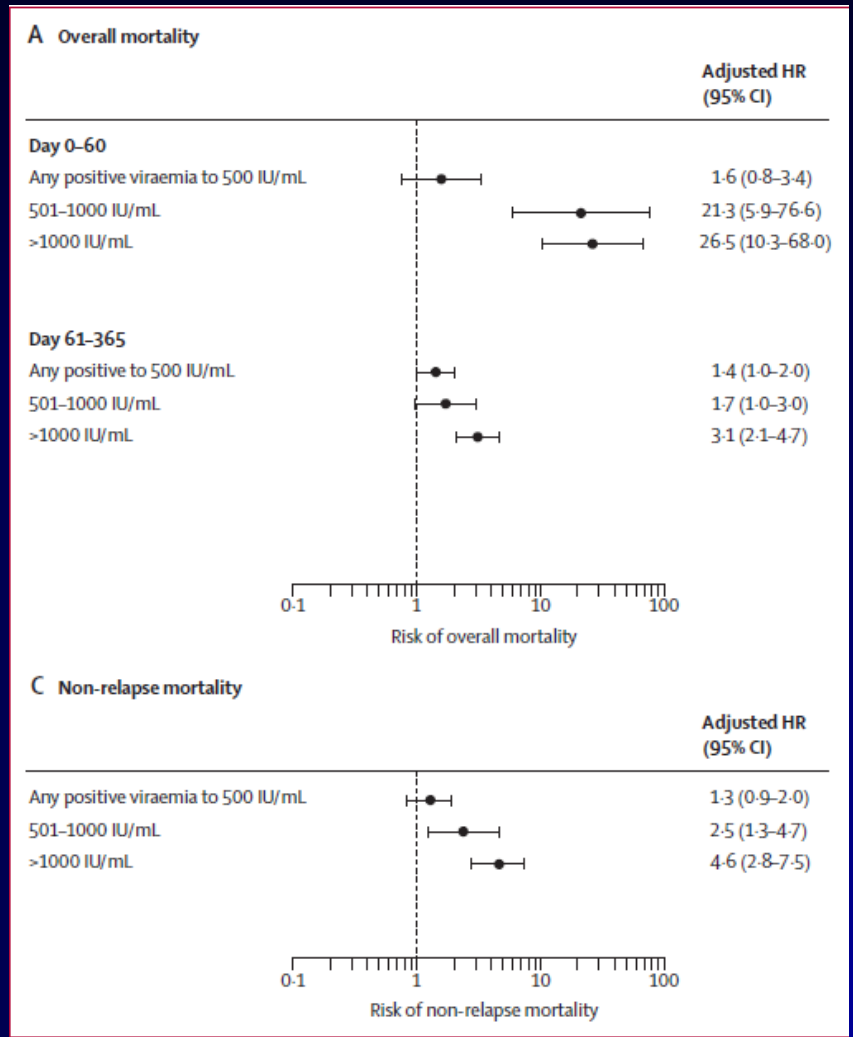
This strategy reduces the risk from CMV disease

What about the effects of CMV replication?

Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study

Margaret L Green, Wendy Leisenring, Hu Xie, T Christopher Mast, Yadong Cui, Brenda M Sandmaier, Mohamed L Sorror, Sonia Goyal, Sezen Özkök, Jessica Yi, Farah Sahoo, Louise E Kimball, Keith R Jerome, Morgan A Marks, Michael Boeckh





Lancet Haematol 2016;
3: e119–27

Karolinska Institutet

Can an effective antiviral prophylaxis influence outcome?

What is the rationale for prophylaxis?

- To prevent CMV disease we should prevent CMV replication
- CMV seropositivity in the patient decreases survival
- CMV replication negatively influences NRM despite preempitve therapy.
- CMV is associated with indirect effects most likely based on the replication itself

Prophylaxis – previous studies

- Ganciclovir and foscarnet are effective but toxic
- Aciclovir/valaciclovir are not effective enough
- Maribavir failed in phase III
- Immune globulin is not effective

Prophylaxis – recent/ongoing studies

- Brincidofovir (CMX-001)
- Letermovir (AIC-246)
- Transvax (CMV vaccine)
- Monoclonal antibodies (Novartis)

Brincidofovir phase III study

- 450 patients
- Randomization 2:1
- Start between d 1 and 28 post SCT
- Prophylaxis given to day 100 post SCT
- Primary endpoint ”clinical significant” CMV infection at 24 weeks post HSCT

Marty et al; Tandem meetings 2016

Primary endpoint

BCV prevented CMV during the prophylactic period
(BCV 24%; placebo 38%)

but

the effect was lost at 24 weeks
(46% vs. 49%; p =.06)

Stronger effect in high risk than in low risk patients

Safety problems in the BCV arm

	BCV	placebo
More diarrhea	61%	vs. 36%
More abdominal pain	34%	vs. 17%
More ALT elevation	11%	vs. 6%
More GVHD	57%	vs. 32%
Especially gut GVHD	57%	vs. 27%
Increased risk for death	15%	vs. 10%

Letermovir for Prevention of Cytomegalovirus Infection

Results from a Phase III Randomized, Double-Blind, Placebo-Controlled Trial in Adult Allogeneic Hematopoietic Cell Transplant Recipients

P Ljungman, FM Marty, R Chemaly, J Maertens, RF Duarte, V Teal, H Wan, NA Kartsonis, RY Leavitt, C Badshah

Marseille, March 28, 2017

Letermovir

Inhibits CMV through a novel mechanism involving the viral terminase complex

Enzyme required for DNA cleavage into unit-length genome & packaging into procapsids

Potent CMV activity *in vitro* & *in vivo*

No effect on other herpesviruses

No cross-resistance with drugs currently used in treatment of CMV

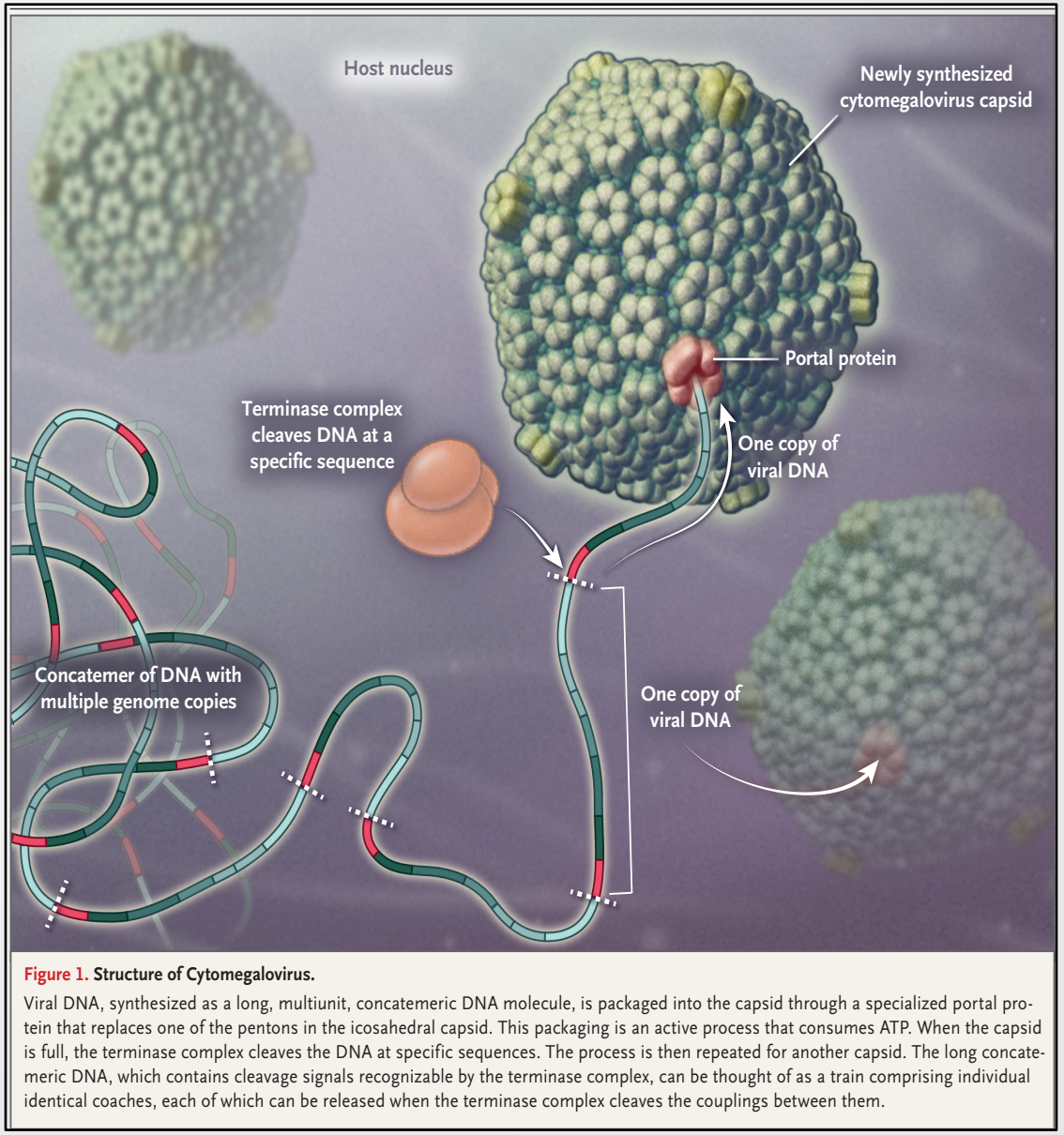


Figure 1. Structure of Cytomegalovirus.

Viral DNA, synthesized as a long, multiunit, concatemeric DNA molecule, is packaged into the capsid through a specialized portal protein that replaces one of the pentons in the icosahedral capsid. This packaging is an active process that consumes ATP. When the capsid is full, the terminase complex cleaves the DNA at specific sequences. The process is then repeated for another capsid. The long concatemeric DNA, which contains cleavage signals recognizable by the terminase complex, can be thought of as a train comprising individual identical coaches, each of which can be released when the terminase complex cleaves the couplings between them.

Figure courtesy of Griffiths & Emery, N Engl J Med 2014;370:1844-6

Key Inclusion Criteria

- ≥ 18 years of age
- Allogeneic HCT recipient
- CMV seropositive (CMV R+)
- No CMV DNAemia at screening (≤5 days from start)
- No acute liver injury (ALT > 5xULN, Bilirubin > 2.5xULN)
- GFR ≥ 10 mL/min
- Able to begin study drug before Day +28 post-transplant
  - Patients could start study drug pre- or post-engraftmen

Key Design Features

- Prophylaxis could be started between day +1 and 28 post HCT and was to be given until 14 weeks post-HCT
- Follow up for 10 weeks
- Letermovir dose
  - 480 mg/day, or
  - 240 mg/day if concomitant cyclosporine use
  - Letermovir available PO and IV
- 2:1 randomization (360 letermovir; 180 placebo)

Primary Efficacy Endpoint

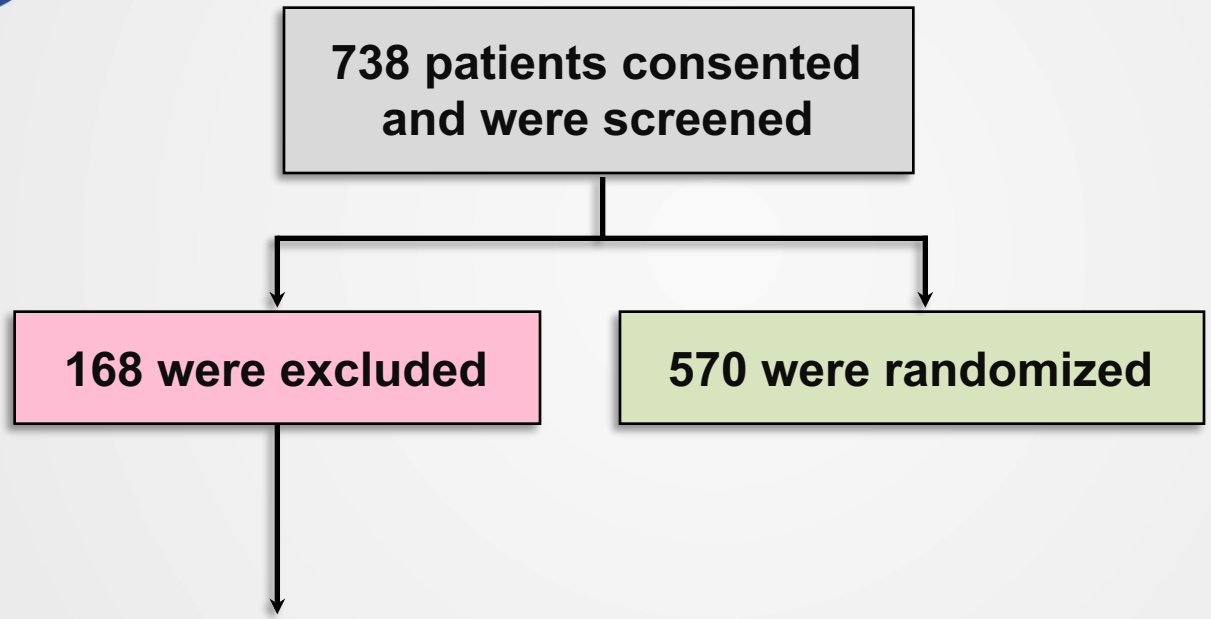
Incidence of clinically significant CMV infection through Week 24 post-HCT among patients without detectable CMV DNA at start of study treatment (stratum adjusted).

Clinically significant CMV infection was defined as:

- Onset of CMV disease –or–
- Initiation of anti-CMV Preemptive Therapy (PET), based on central laboratory confirmation of CMV viremia and the clinical condition of the patient.

Subjects who discontinued the study before W24 for any reason or had missing outcomes at W24 were considered failures for the primary endpoint when using NC=F for imputing missing data.

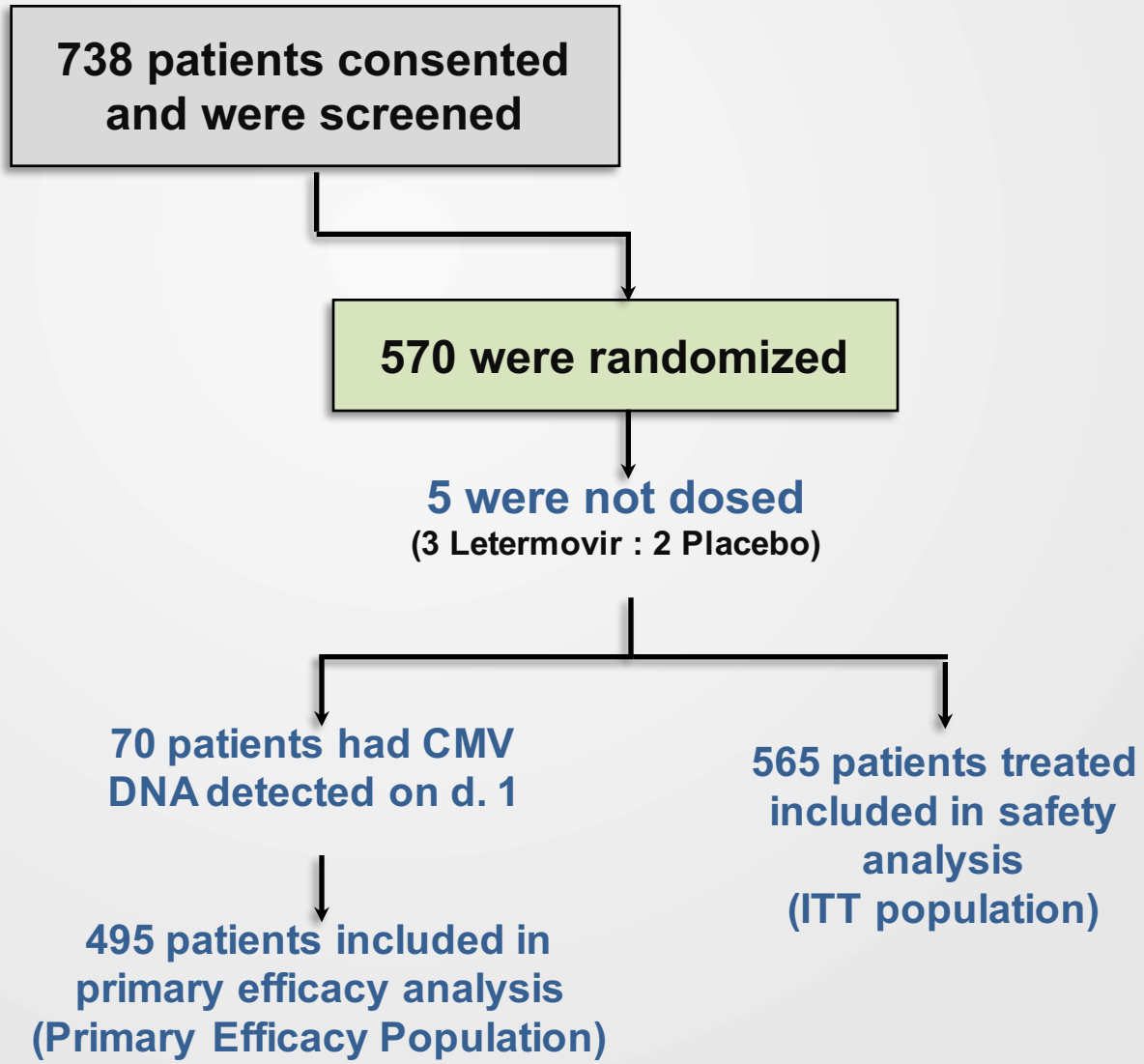
Study Subject Distribution



Reasons

117	(70%)	CMV viremia detected prior to randomization
16	(10%)	Use of CMV active antivirals
5	(3%)	Exclusionary renal or liver function
5	(3%)	Withdrew consent
4	(2%)	Recipient CMV seronegative
21	(12%)	Other reasons

Study Subject Distribution



Characteristics – ITT Population

CMV Infection Risk	Letermovir	Placebo
N (%)	373	192
Low risk	252 (67.6)	138 (71.9)
High risk	121 (32.4)	54 (28.1)
Donor		
Haploidentical	62 (16.6)	23 (12.0)
Mismatched unrelated	46 (12.3)	20 (10.4)
Mismatched related	20 (5.4)	6 (3.1)
Cord blood	13 (3.5)	10 (5.2)
Ex vivo T-cell depletion	9 (2.4)	5 (2.6)
Grade ≥2 GVHD	2 (0.5)	1 (0.5)

Primary Endpoint: Clinically Significant CMV Infection through Week 24

Primary Efficacy Population

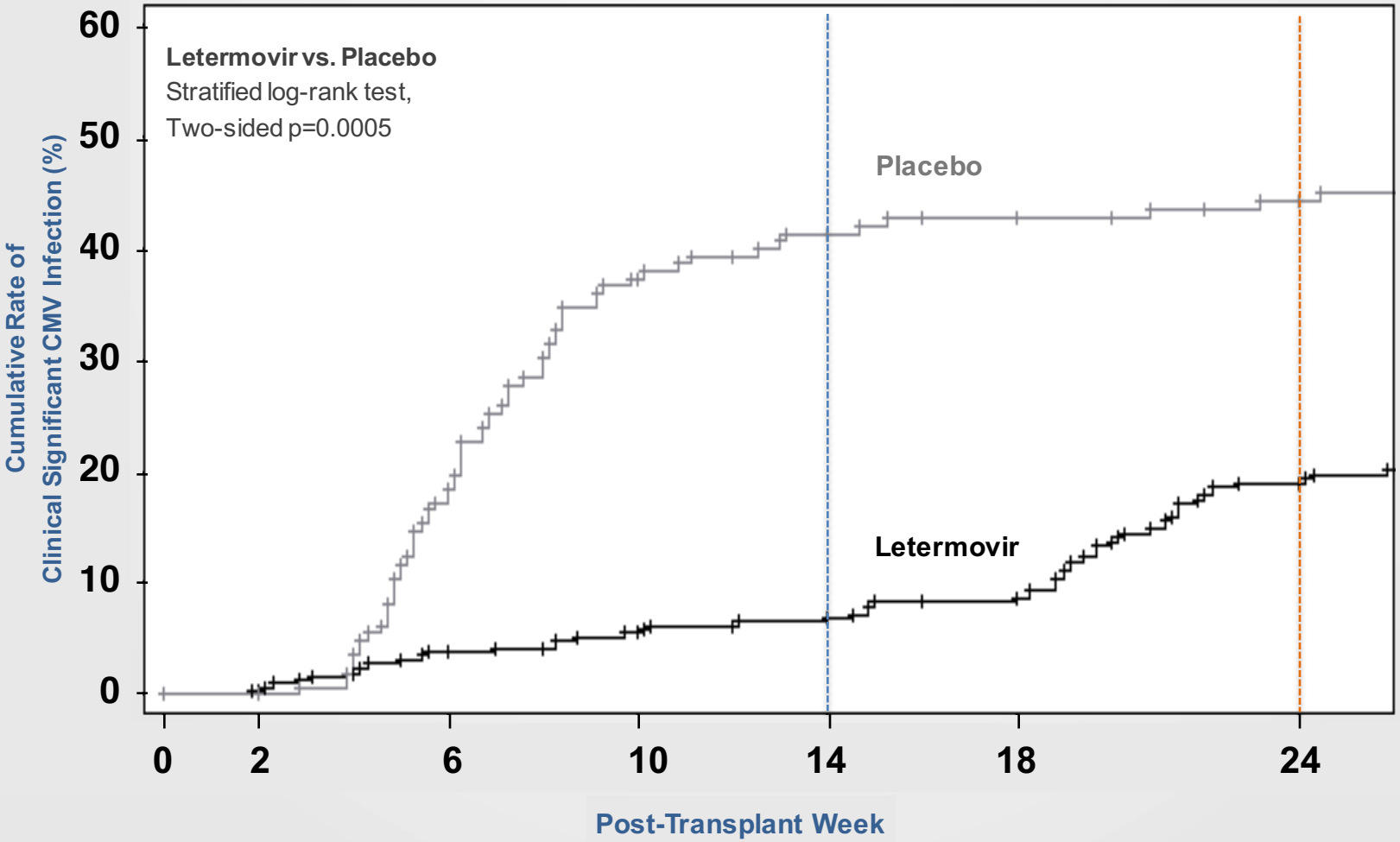
	Letermovir	Placebo
N (%)	325	170
Failures	122 (37.5)	103 (60.6)
Clinically significant CMV	57 (17.5)	71 (41.8)
PET for CMV	52 (16.0)	68 (37.6)
CMV disease	5 (1.5)	3 (1.8)
Early discontinuation	56 (17.2)	27 (15.9)
Adverse event	6 (1.8)	1 (0.6)
Death without CMV	28 (8.6)	12 (7.1)
Other reasons	22 (6.8)	14 (8.2)
Missing outcome	9 (2.8)	5 (2.9)

Stratum-adjusted treatment difference: -23.5 (95% CI, -32.5 to -14.6), p<0.0001*

*one-sided test α=0.0249

Time to Clinically Significant CMV Infection

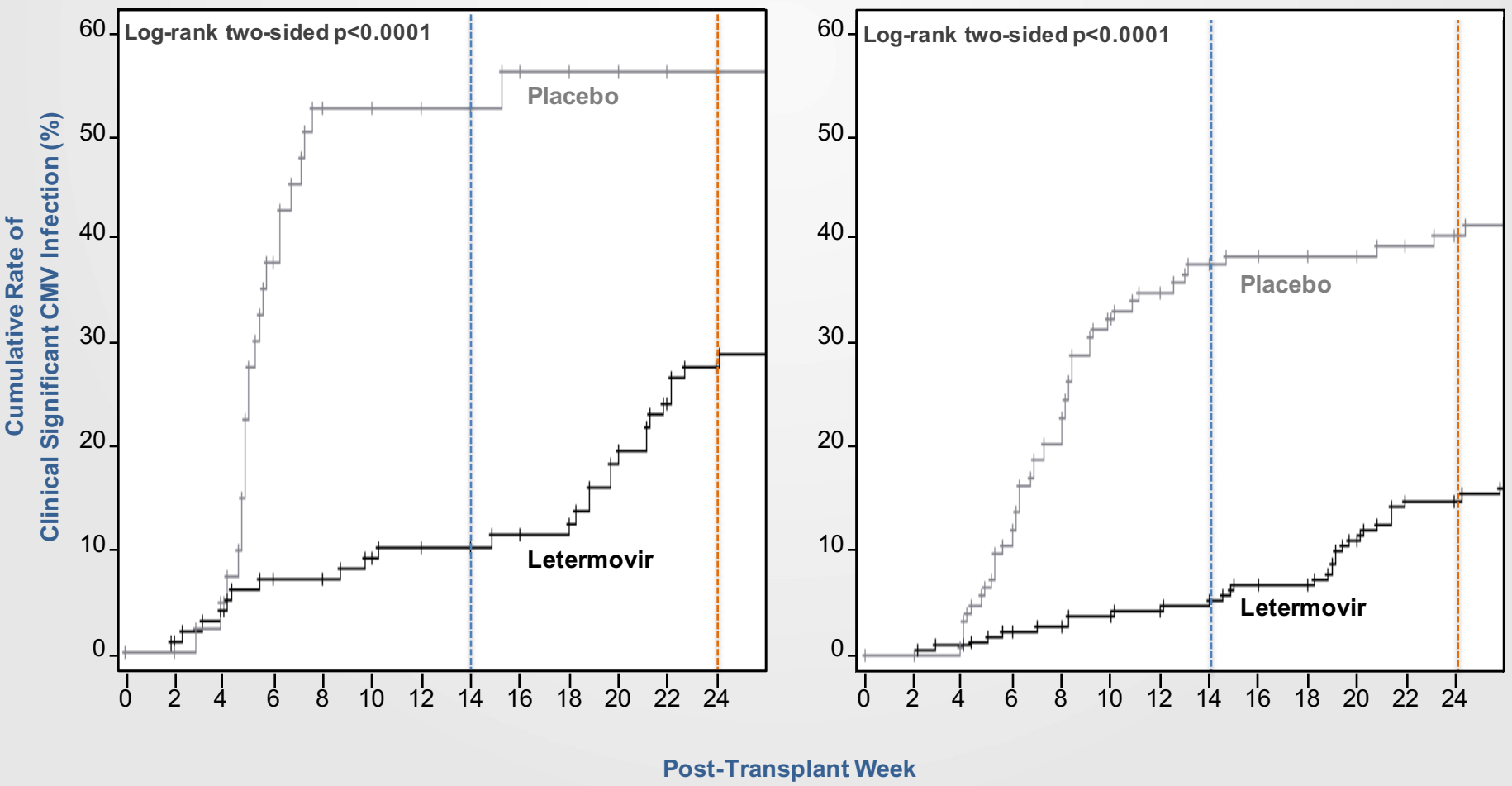
Primary Efficacy Population; Patients without Detectable CMV DNA at Randomization



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

Time to Clinically Significant CMV Infection

Primary Efficacy Population; Patients without Detectable CMV DNA at Randomization



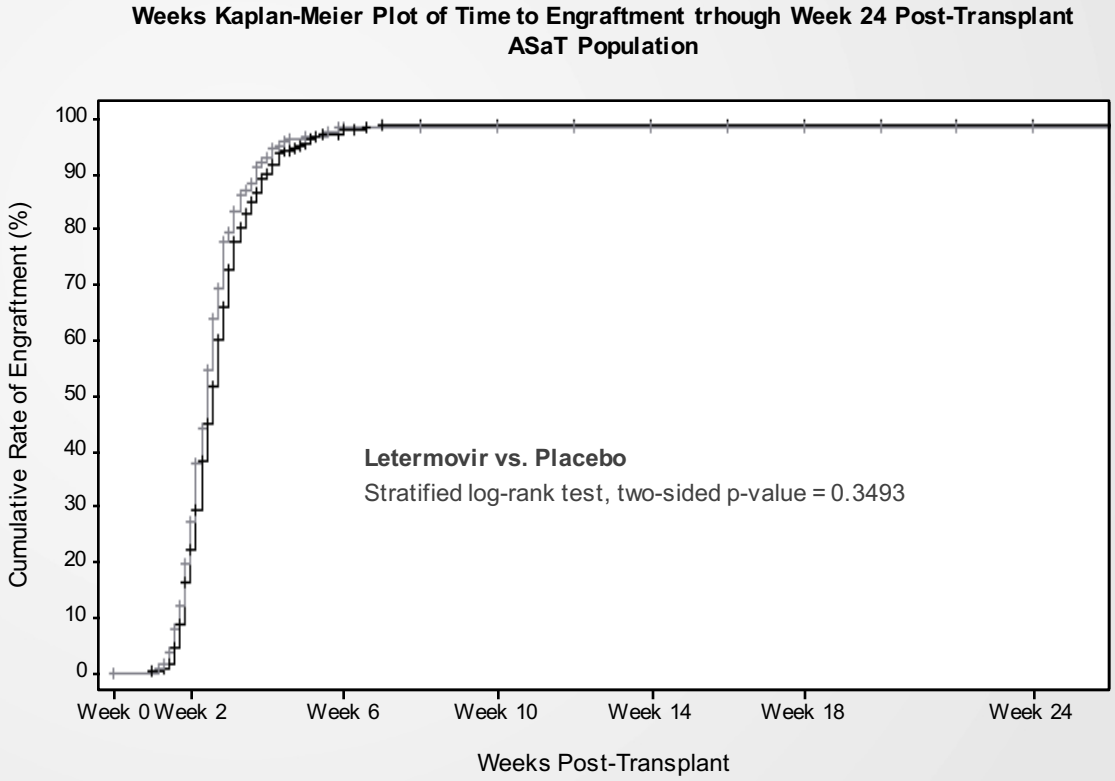
Overall Summary of Adverse Events, Treatment Phase; ITT Population

	Letermovir	Placebo
N (%)	373	192
AE, any grade	365 (97.9)	192 (100)
Drug-related AE	63 (16.9)	23 (12.0)
Serious AE	165 (44.2)	90 (46.9)
Discontinued due to AE	72 (19.3)	98 (51.0)
• *CMV treatment*	23 (6.2)	75 (39.1)
• *Other AE*	49 (13.1)	23 (12.0)
Median treatment duration, days [range]	82 [1, 113]	56 [4,115]

No Evidence of Myelotoxicity

More than 60% of subjects had not engrafted at baseline:

- Incidence of engraftment similar between letermovir (95%) & placebo (91%)
- Median time to engraftment similar between letermovir (19 days) & placebo (18 days)



Number of subjects at risk

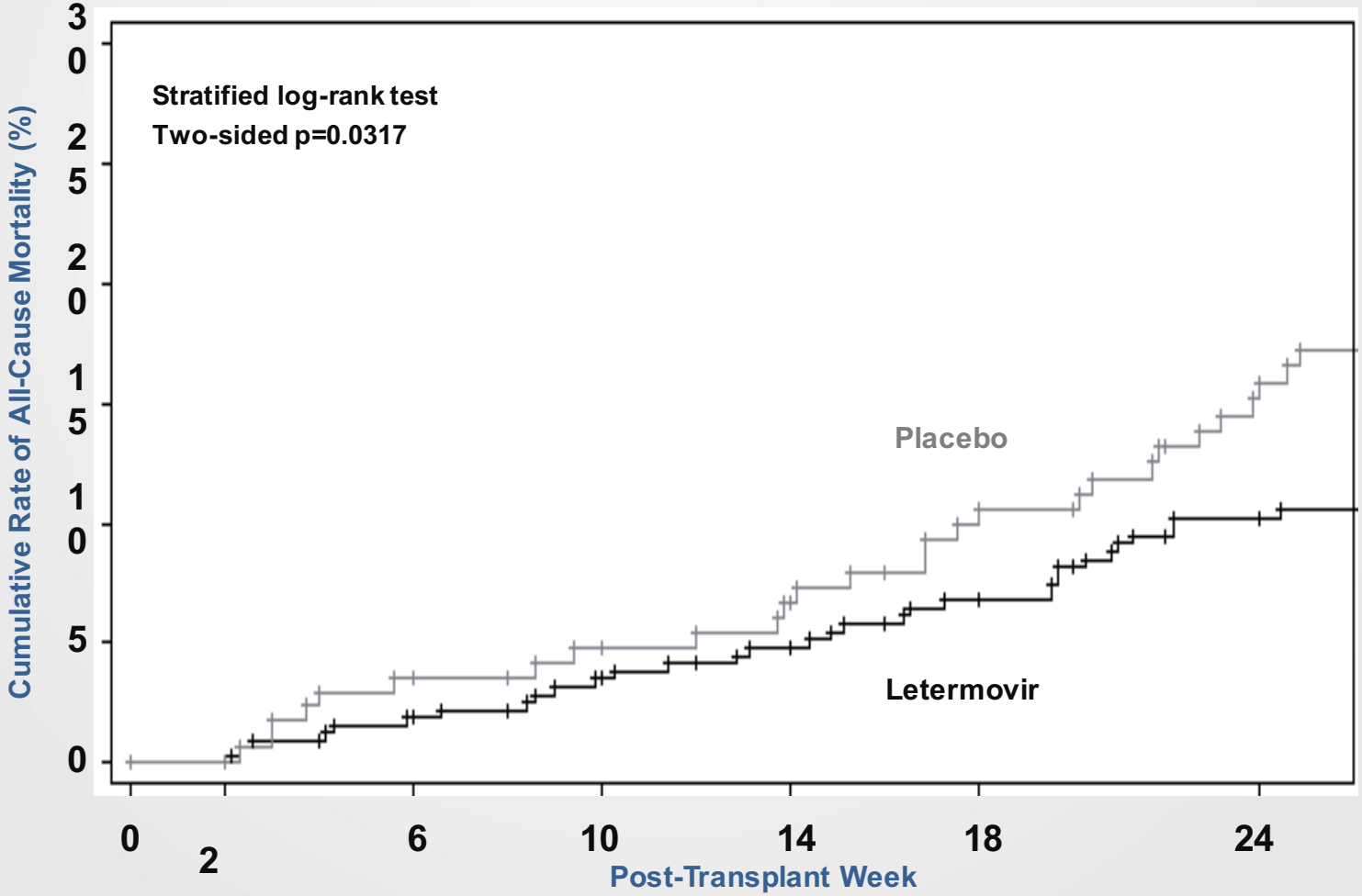
Letermovir	371	307	11	5	5	5	5
Placebo	188	150	3	3	2	2	2

Source: [P001V01: analysis-adtte]

Most Common Adverse Events, Any Severity Treatment Phase; ITT Population

N (%)	Letermovir (n=373)	Placebo (n=192)
GVHD	146 (39.1)	74 (38.5)
Diarrhea	97 (26.0)	47 (24.5)
Nausea	99 (26.5)	45 (23.4)
Fever	77 (20.6)	43 (22.4)
Rash	76 (20.4)	41 (21.4)
Vomiting	69 (18.5)	26 (13.5)
Cough	53 (14.2)	20 (10.4)
Peripheral edema	54 (14.5)	18 (9.4)
Fatigue	50 (13.4)	21 (10.9)
Headache	52 (13.9)	18 (9.4)

All-Cause Mortality through Week 24 Primary Efficacy Population



Letermovir	325	323	311	297	290	278	262	*Subjects at risk*
Placebo	170	170	161	153	147	139	125	

Karolinska Institutet

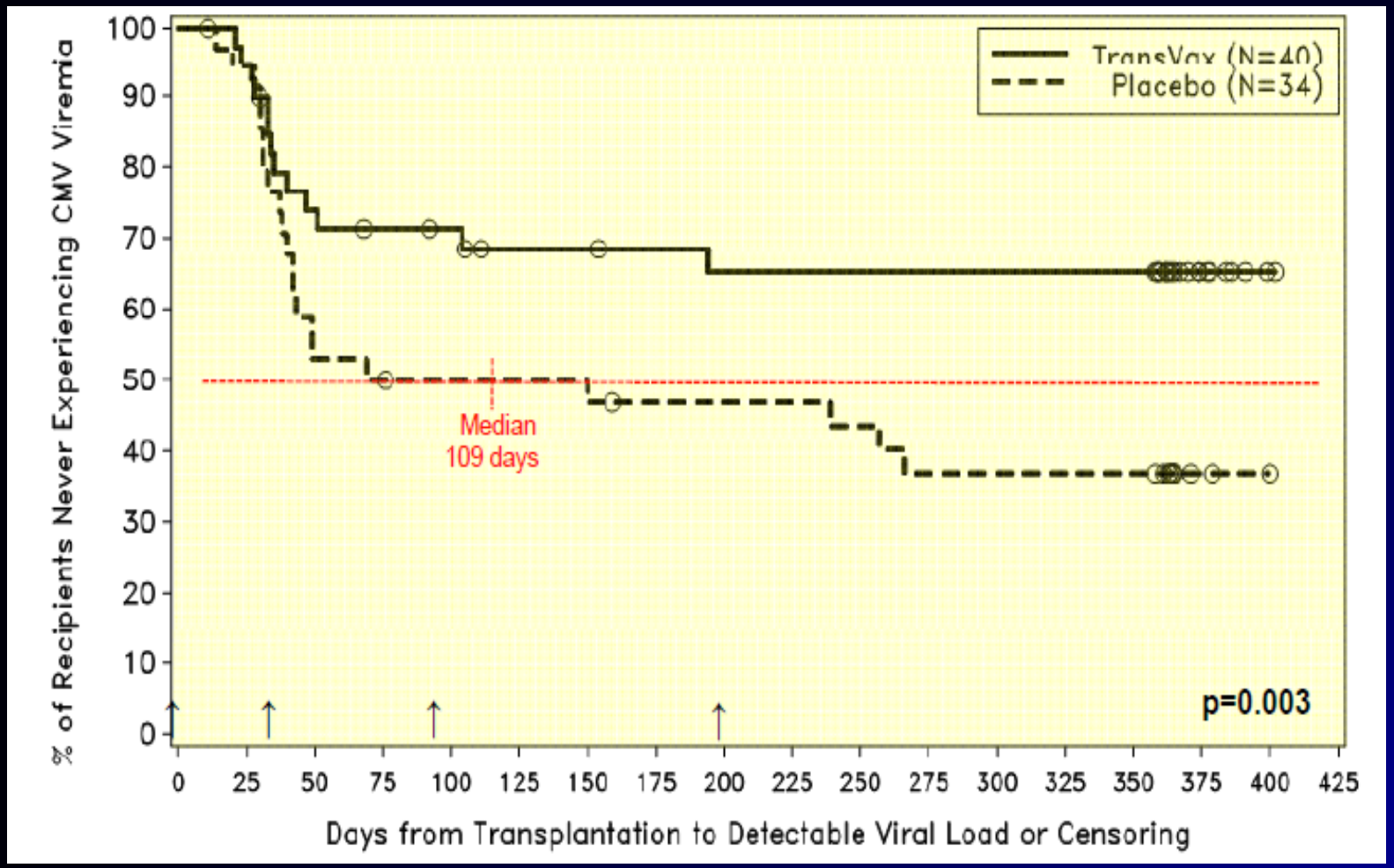
Articles

A novel therapeutic cytomegalovirus DNA vaccine in allogeneic haemopoietic stem-cell transplantation: a randomised, double-blind, placebo-controlled, phase 2 trial

Mohamed A Kharfan-Dabaja, Michael Boeckh, Marissa B Wilck, Amelia A Langston, Alice H Chu, Mary K Wloch, Don F Guterwill, Larry R Smith, Alain P Rolland, Richard T Kenney

Lancet ID 2012 Jan 10

Freedom from viremia

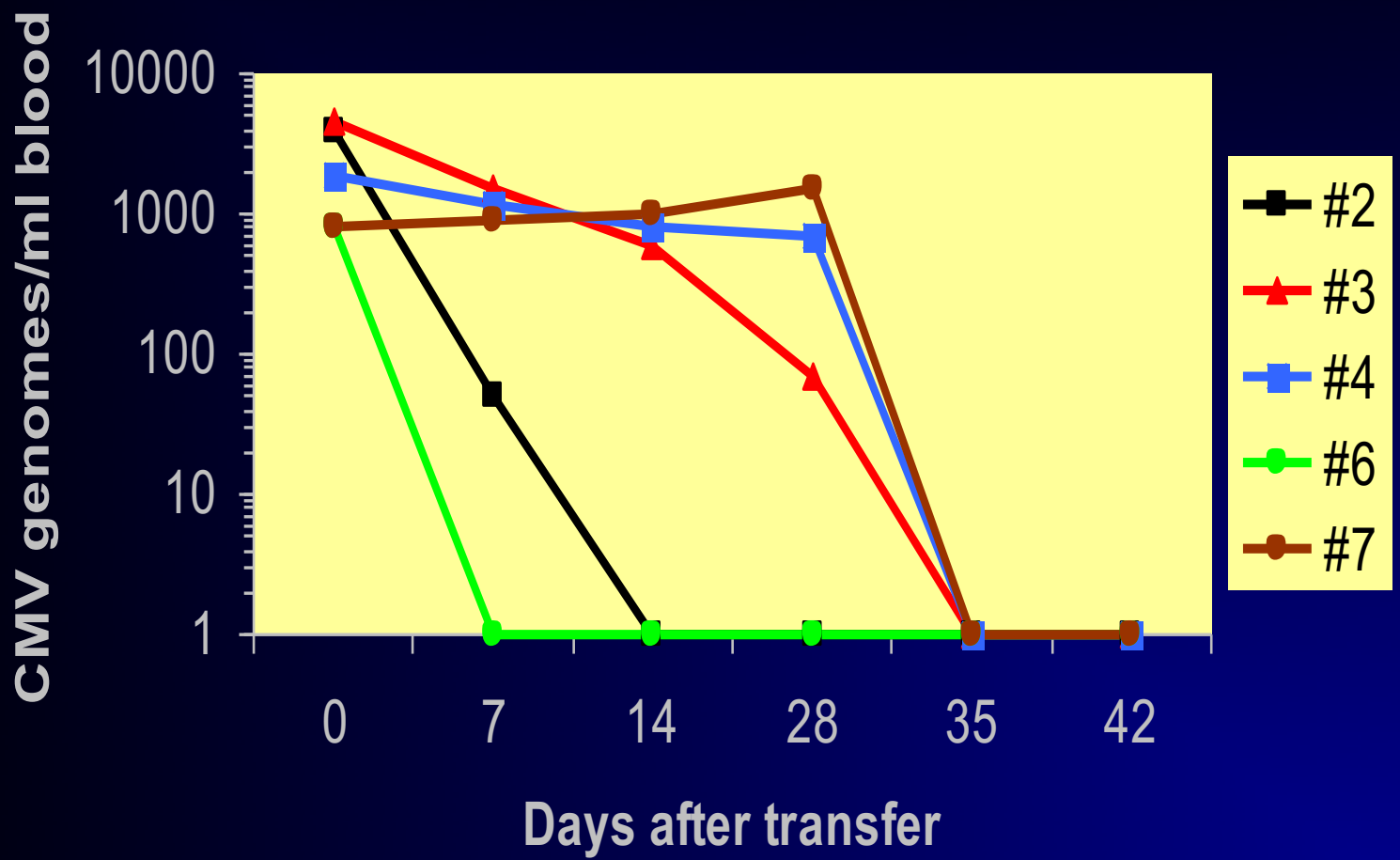


Lancet ID 2012 Jan 10

Adoptive T-cell therapy

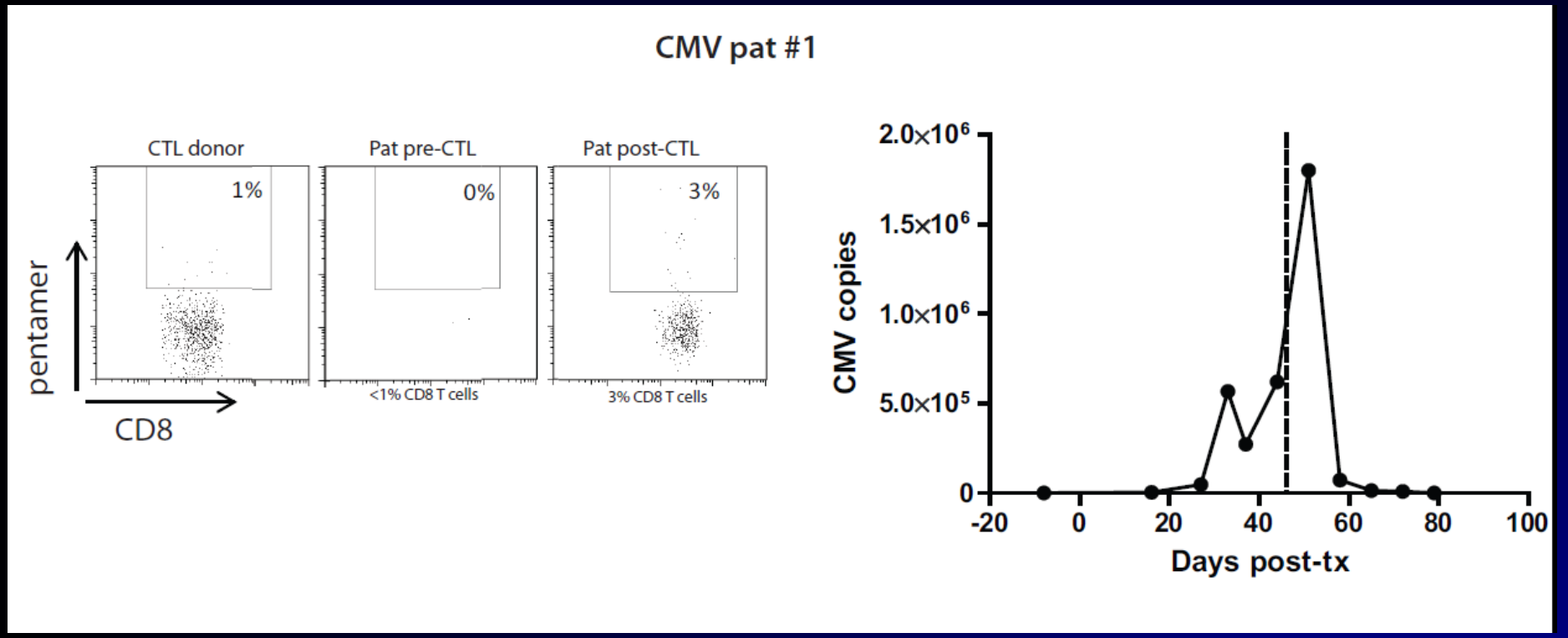
- In development for > 25 years
- Major advances in technology have been achieved over the last few years
- However, still far away from routine therapy available at most centers

Viral load upon adoptive transfer of CMV-specific T cell lines



Hebart et al, Blood 2002

Effect of CTL



Uhlin et al CID 2012

Randomized studies – adoptive cellular therapy (ACT)

- Two studies have been performed in the UK
  - One phase II studying the addition of CMV CTL to antiviral therapy in unrelated donor SCT (CMV-ACE/ASPECT)
  - One phase III studying the addition of CMV CTL to antiviral therapy in HLA identical sibling donor SCT (CMV-IMPACT)

- Preliminary data has been presented (ASH 2014).

Duration of antiviral therapy

	ACT (n=20)	Control (n=31)	p
Mean (stdv)	19.1 (27.8)	27.3 (31.3)	0.14
Median (min:max)	11 (0 : 114)	25 (0 : 133)	

Multi-specificity T-cells

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

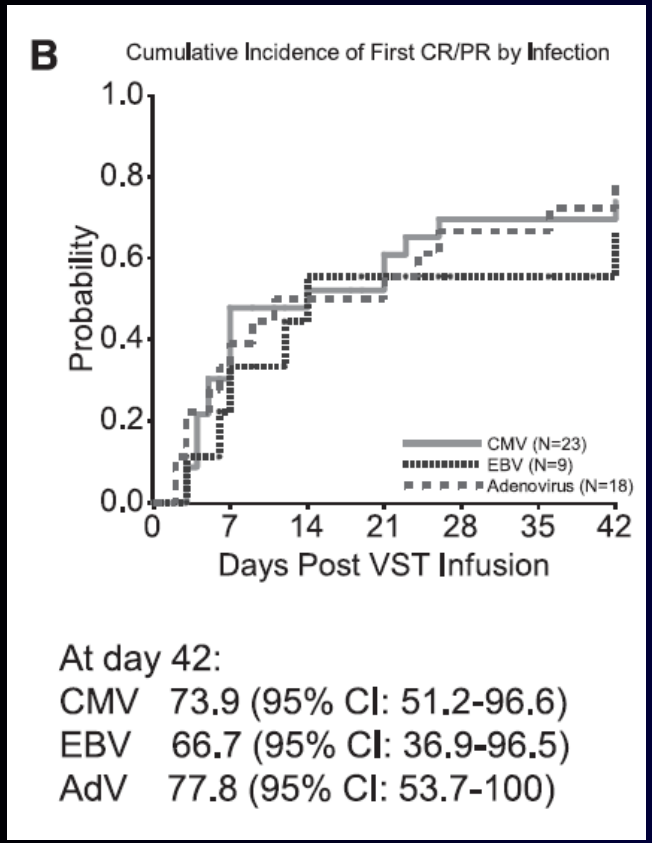
Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation

Ann M. Leen,[1] Catherine M. Bollard,[1] Adam M. Mendizabal,[2] Elizabeth J. Shpall,[3] Paul Szabolcs,[4] Joseph H. Antin,[5] Neena Kapoor,[6] Sung-Yun Pai,[5,7] Scott D. Rowley,[8] Partow Kebriaei,[2] Bimalangshu R. Dey,[9] Bambi J. Grilley,[1] Adrian P. Gee,[1,10] Malcolm K. Brenner,[1] Cliona M. Rooney,[1,10] and Helen E. Heslop[1]

[1]Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, The Methodist Hospital, Houston, TX; [2]The EMMES Corporation, Rockville, MD; [3]MD Anderson Cancer Center, Houston, TX; [4]Duke University Medical Center, Durham, NC; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Children's Hospital of Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA; [7]Boston Children's Hospital, Boston, MA; [8]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; [9]Massachusetts General Hospital, Boston, MA; and [10]Production Assistance for Cell Therapy Center at Baylor College of Medicine, Houston, TX

Leen AM. ***Blood 2013***

Multi-specificity T-cells

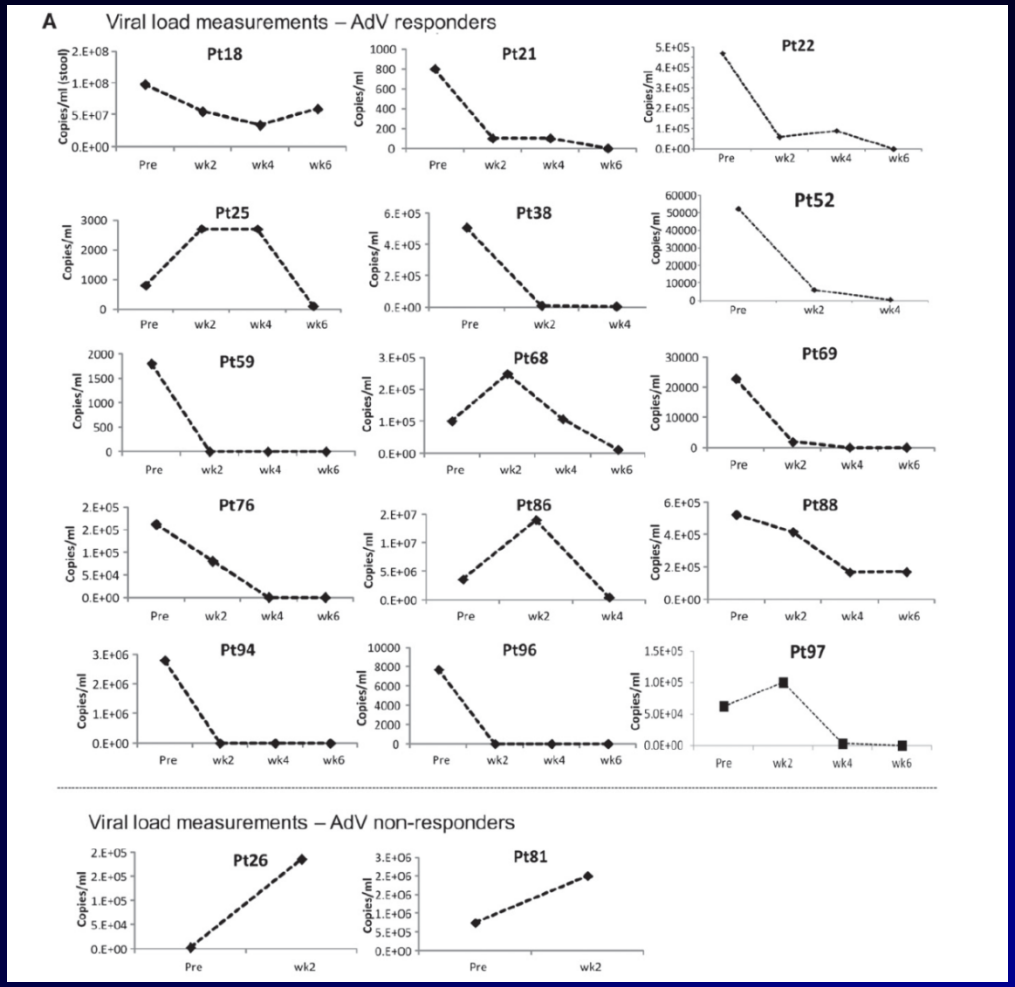


At day 42:

CMV 73.9 (95% CI: 51.2-96.6)

EBV 66.7 (95% CI: 36.9-96.5)

AdV 77.8 (95% CI: 53.7-100)



Leen AM. *Blood 2013*

Primum non nocere?

"The person who takes medicine must recover twice, once from the disease and once from the medicine."

- William Osler, M.D.