Viral Kinetic Correlates of Cytomegalovirus Disease and Death after Hematopoietic Cell Transplant

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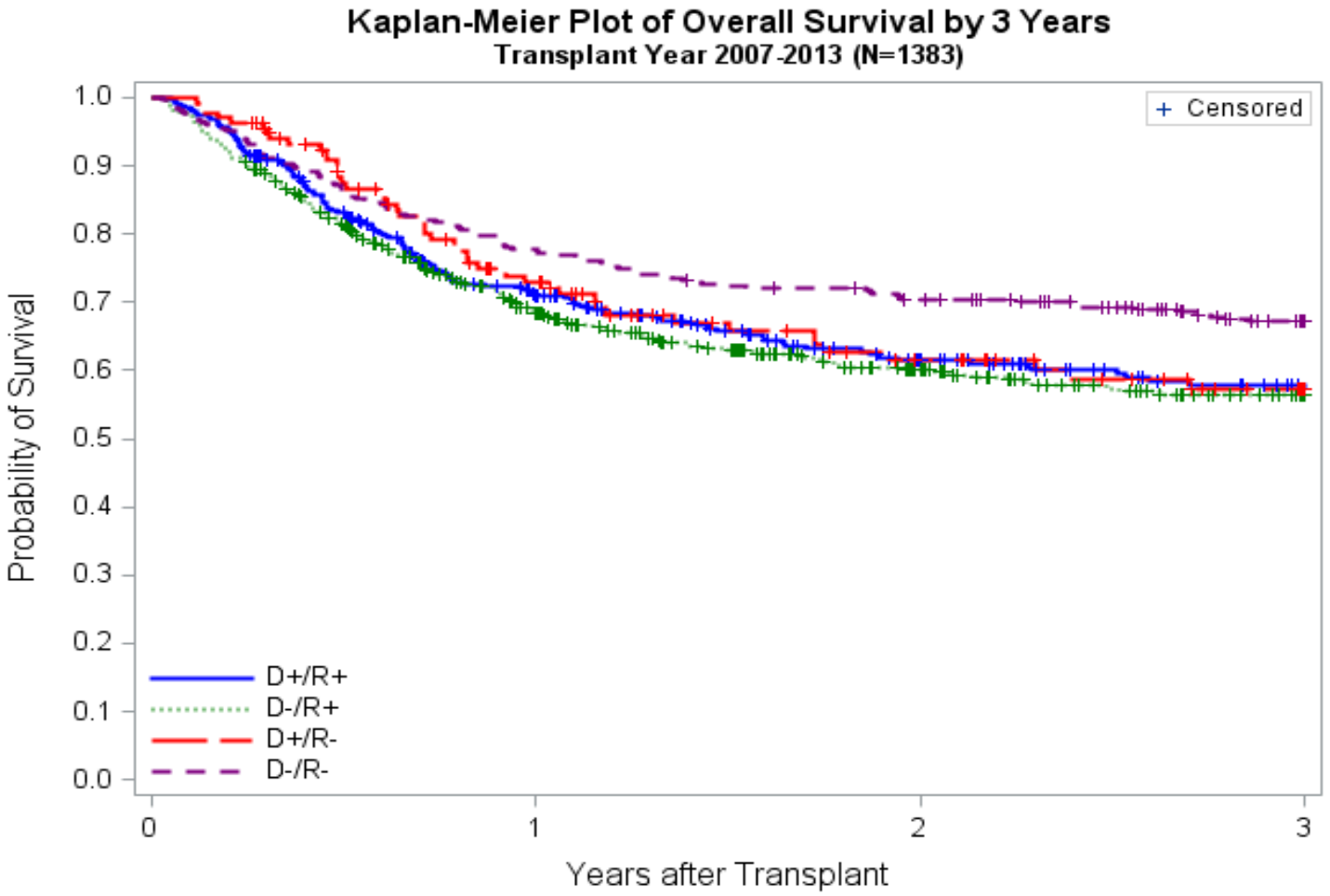
Impact of CMV Seropositivity

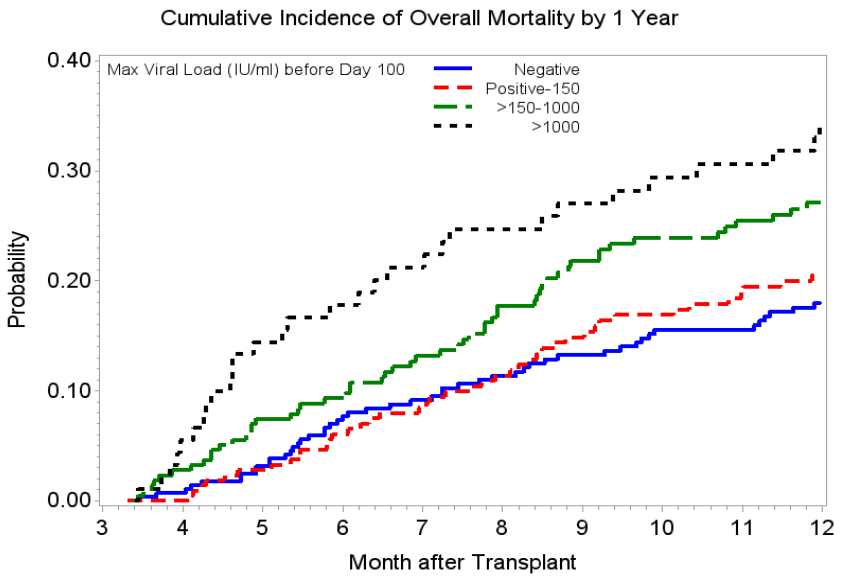


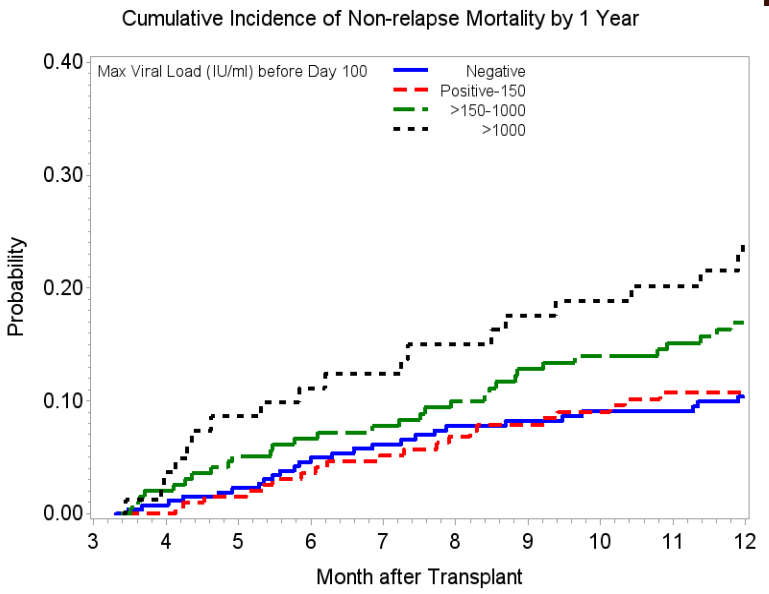
CMV Viral Load as Surrogate

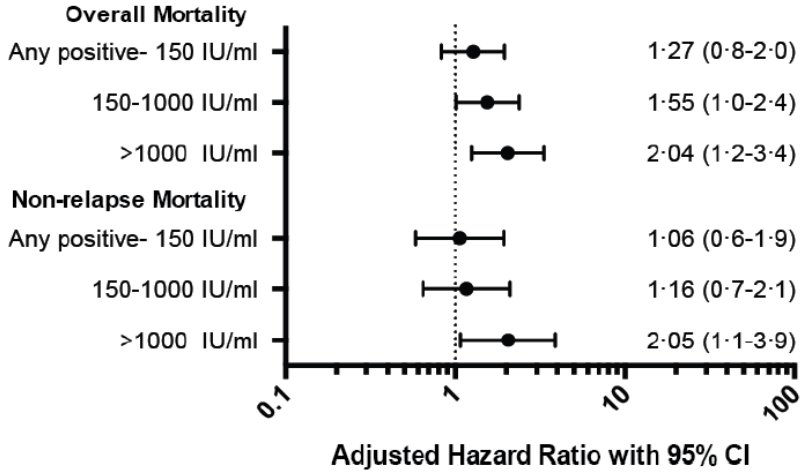
- **The surrogate endpoint has to be in the direct pathway of the disease pathogenesis (Fleming et al. 1996).**
  - **Does CMV viremia predict CMV disease?**
  - **Does the absence of CMV viremia predict absence of disease?**
  - **Does viral load, or viral kinetics, predict disease?**
  - **Does CMV viremia predict mortality or other important clinical endpoints?**

- **Evidence**
  - **Observational studies**
  - **Metaanalyses**
  - **Randomized placebo controlled trials**

Association of Maximum CMV Viral Load before Day 100 with Overall and Non-relapse mortality after Day 100





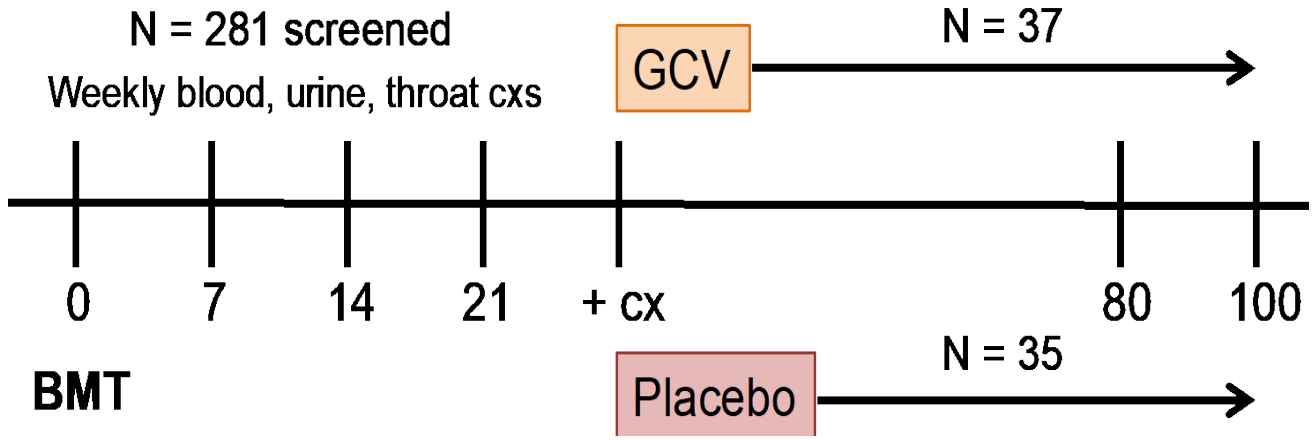


Green ML et al., Lancet Haematology, 2016

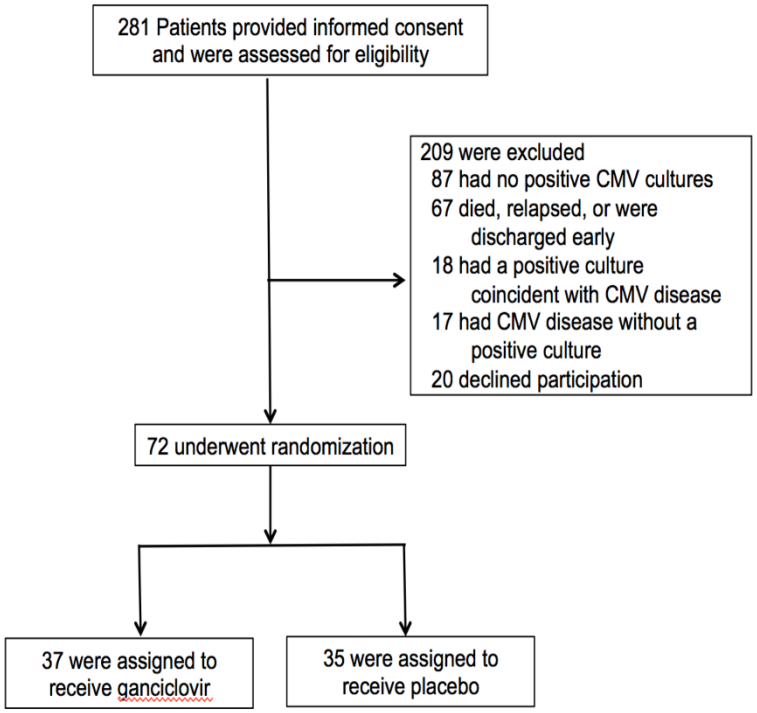
EARLY TREATMENT WITH GANCICLOVIR TO PREVENT CYTOMEGALOVIRUS DISEASE AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

JAMES M. GOODRICH, PH.D., M.D., MOTOMI MORI, PH.D., CURT A. GLEAVES, M.S., CHARLES DU MOND, PH.D., MONICA CAYS, R.N., DARLENE F. EBELING, M.S., WILLIAM C. BUHLES, PH.D., BERNADETTE DEARMOND, M.D., M.P.H., AND JOEL D. MEYERS, M.D.*

Vol. 325 No. 23 Dec. 5, 1991

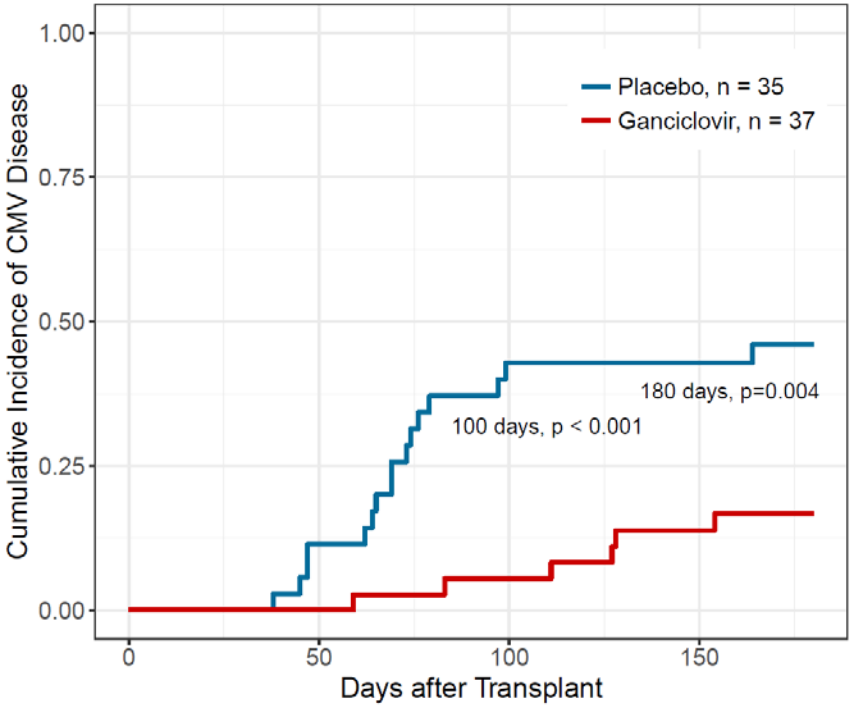


Study Population

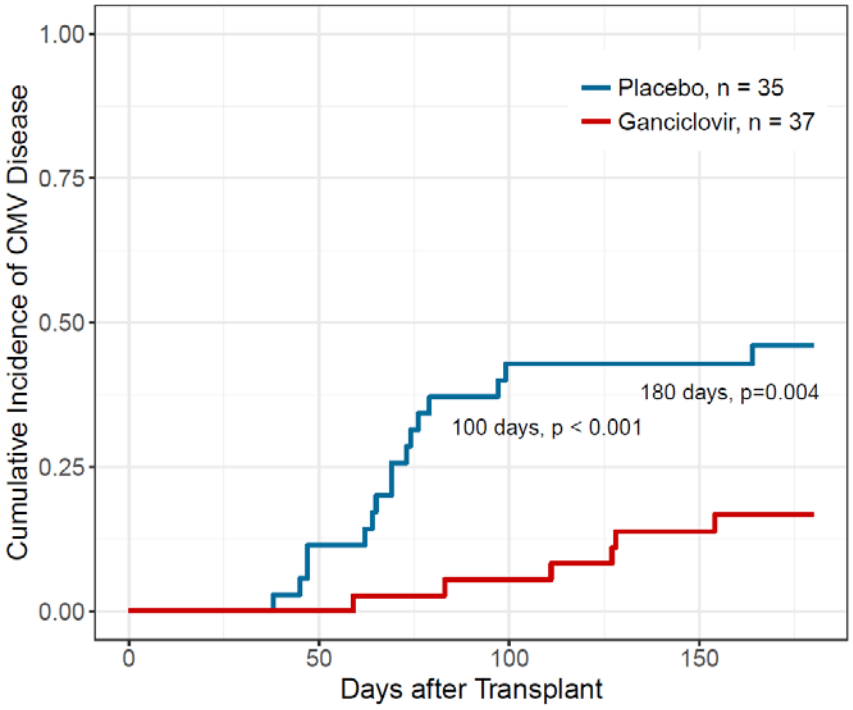


CHARACTERISTIC	GANCICLOVIR	PLACEBO
No. of patients	37	35
Age – mean yr (range)	33 (2-56)	31 (3-51)
Sex – F/M*	20/17	15/20
Underlying disease – no. (%)		
Acute lymphocytic leukemia	4 (11)†	7 (20)
Acute nonlymphocytic leukemia	16 (43)	11 (31)
Chronic myelogenous leukemia	11 (30)	11 (31)
Hodgkin's disease	1 (3)	0 (0)
Non-Hodgkins lymphoma	2 (5)	4 (11)
Other	3 (8)	2 (6)
HLA matching – no. (%)		
Patient matched with related donor	21 (57)	28 (80)**
Patient matched with unrelated donor	5 (14)	4 (11)
Patient mismatched with donor	11 (30)	3 (9)
Acute GVHD – no. (%)‡		
Present	24 (65)§	24 (69)
Not present	13 (35)	11 (31)
CMV status before transplantation – no. (%)		
Patient negative, donor positive	3 (8)¶	3 (9)¥
Patient positive, donor negative	15 (41)	13 (37)
Patient and donor positive	19 (51)	19 (54)
Days from transplantation to study entry – mean (range)	54 (18-79)	48 (16-77)

CMV Disease


1.00
0.75
0.50
0.25
0.00
Cumulative Incidence of CMV Disease
Placebo, n = 35
Ganciclovir, n = 37
180 days, p=0.004
100 days, p < 0.001
0
50
100
150
Days after Transplant

CMV Disease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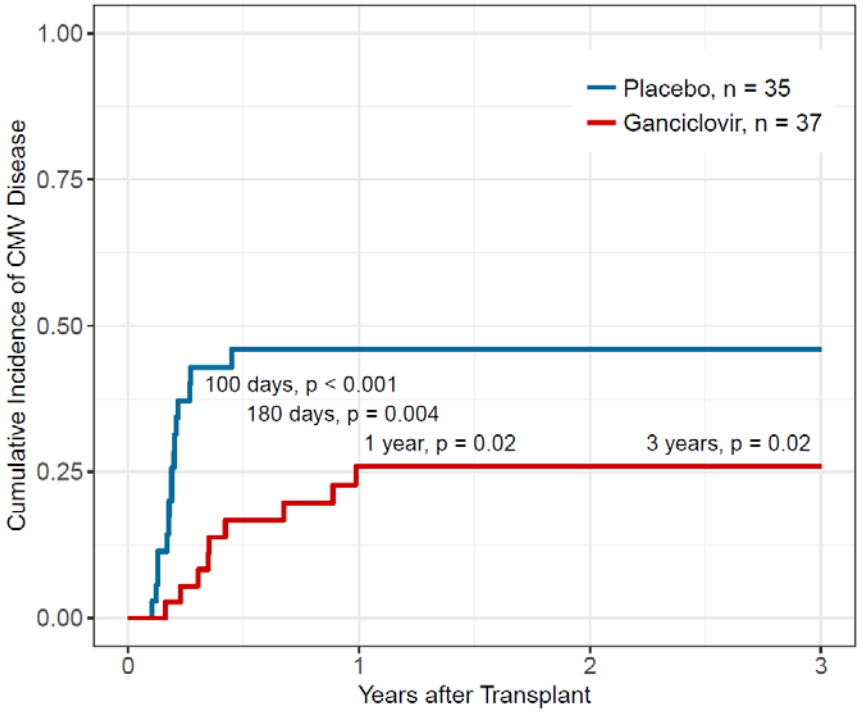
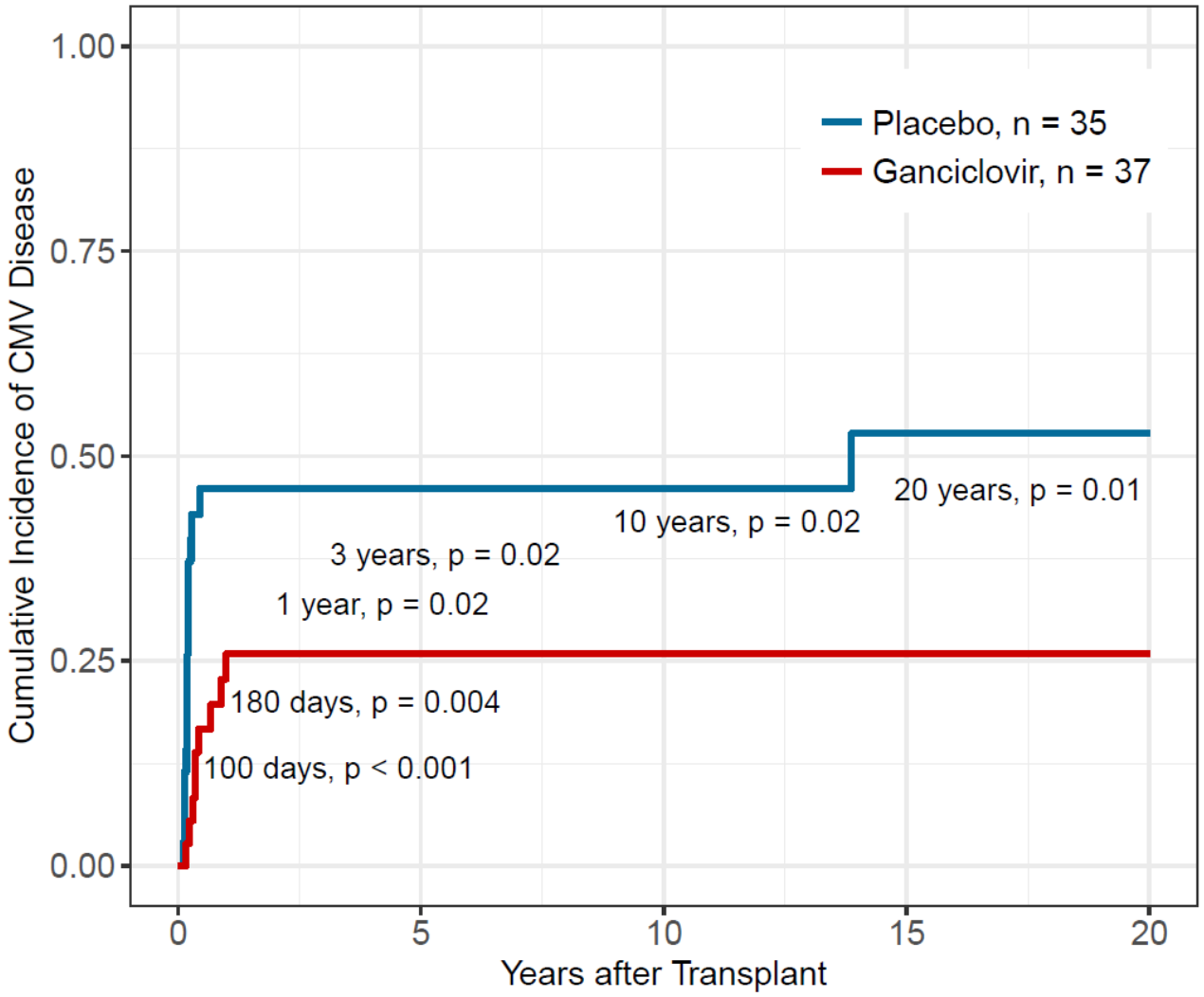
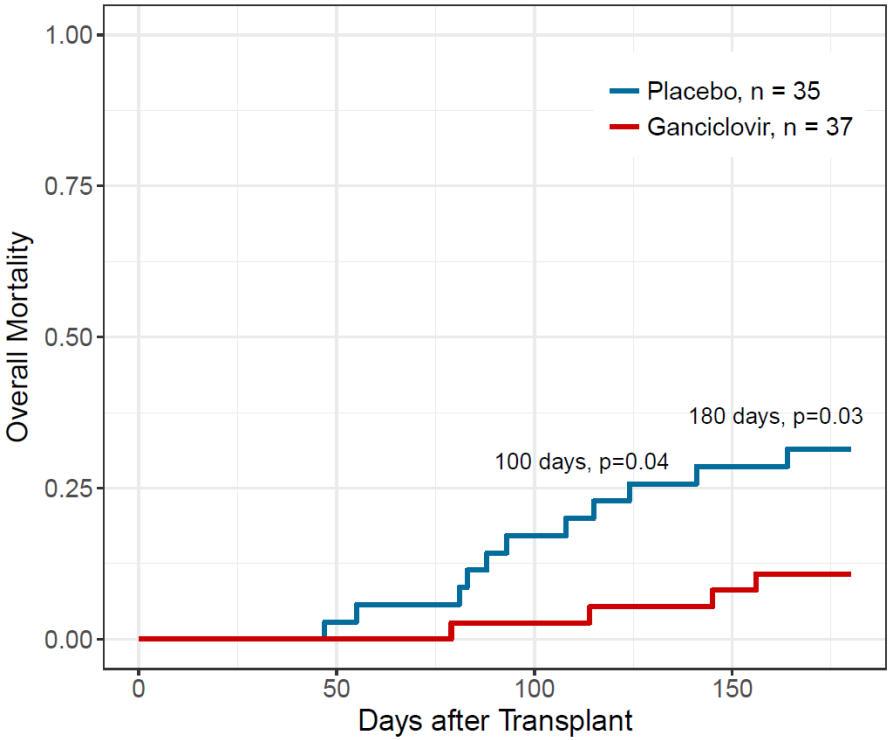

1.00
0.75
0.50
0.25
0.00
Cumulative Incidence of CMV Disease
Placebo, n = 35
Ganciclovir, n = 37
100 days, p < 0.001
180 days, p = 0.004
1 year, p = 0.02
3 years, p = 0.02
0
1
2
3
Years after Transplant

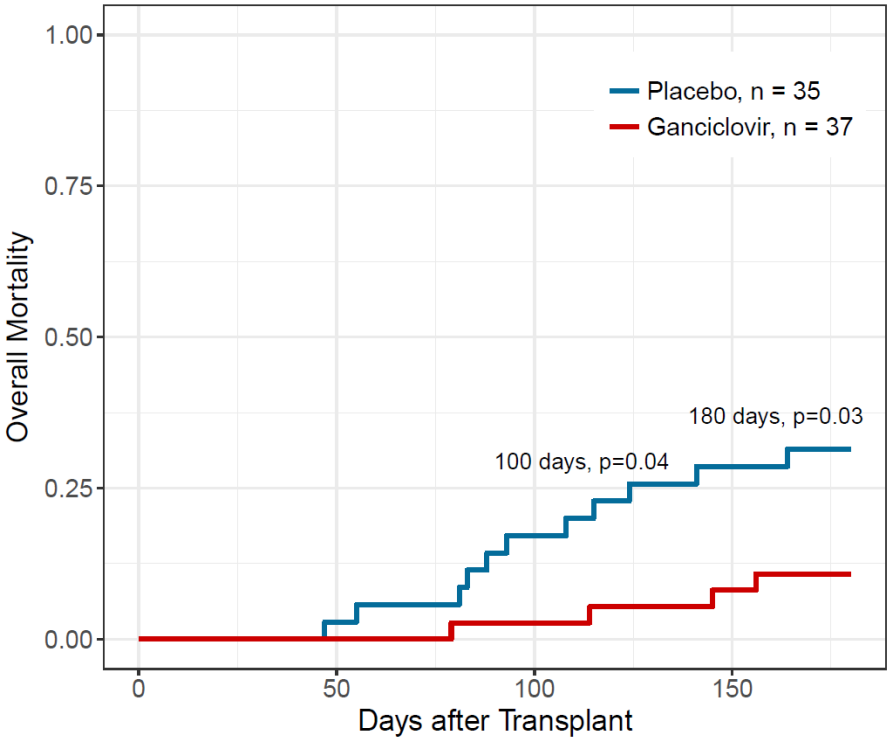
CMV Disease

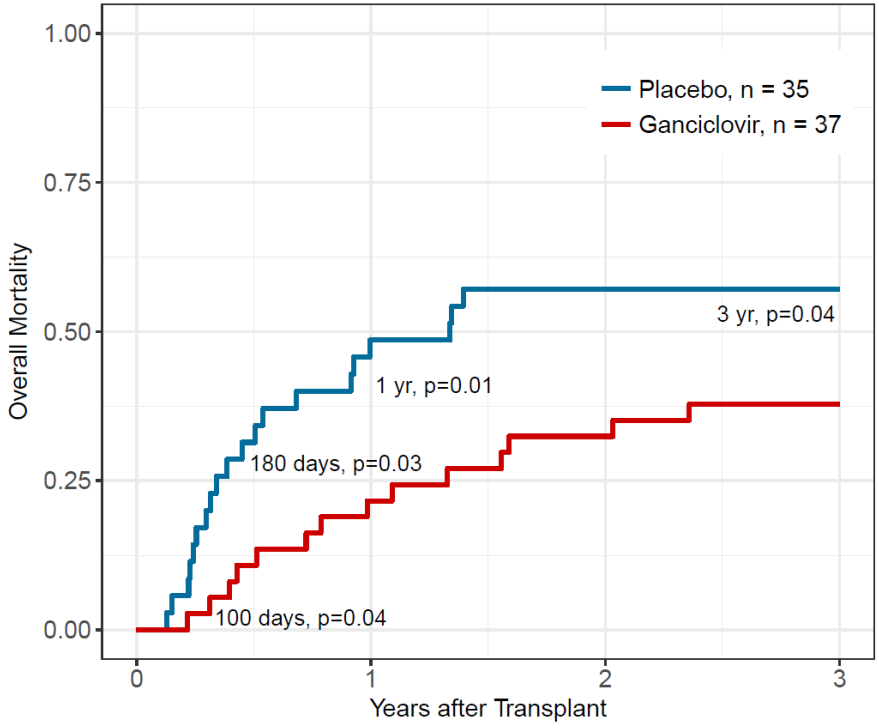

Placebo, n = 35
Ganciclovir, n = 37
Cumulative Incidence of CMV Disease
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Years after Transplant
20 years, p = 0.01
10 years, p = 0.02
3 years, p = 0.02
1 year, p = 0.02
180 days, p = 0.004
100 days, p < 0.001

Mortality

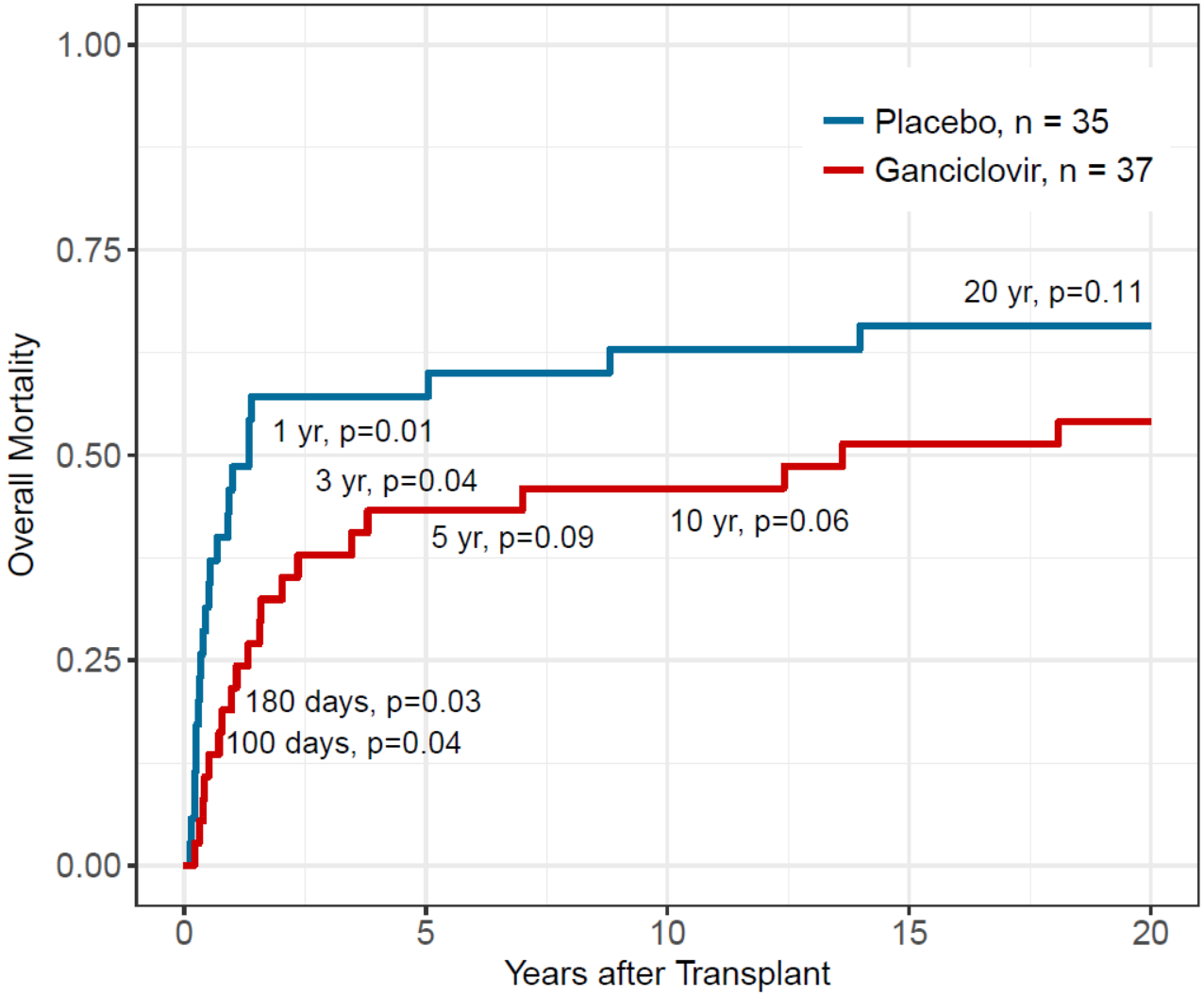

1.00
0.75
0.50
0.25
0.00
Overall Mortality
0
50
100
150
Days after Transplant
Placebo, n = 35
Ganciclovir, n = 37
180 days, p=0.03
100 days, p=0.04

Mortality

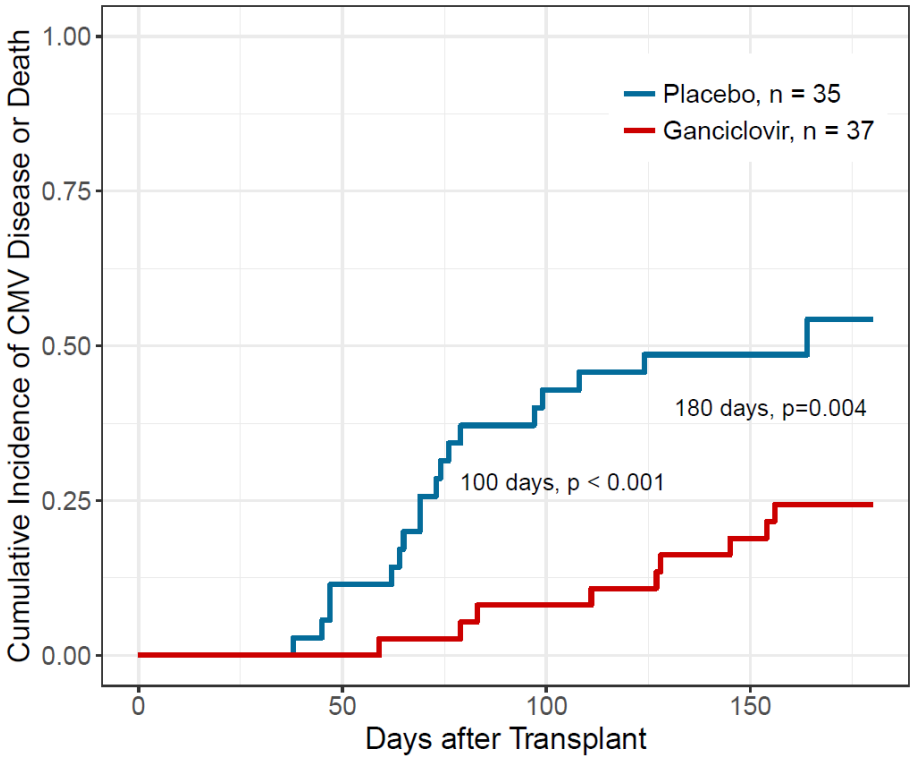

1.00
0.75
0.50
0.25
0.00
Overall Mortality
0
50
100
150
Days after Transplant
Placebo, n = 35
Ganciclovir, n = 37
180 days, p=0.03
100 days, p=0.04


1.00
0.75
0.50
0.25
0.00
Overall Mortality
0
1
2
3
Years after Transplant
Placebo, n = 35
Ganciclovir, n = 37
3 yr, p=0.04
1 yr, p=0.01
180 days, p=0.03
100 days, p=0.04

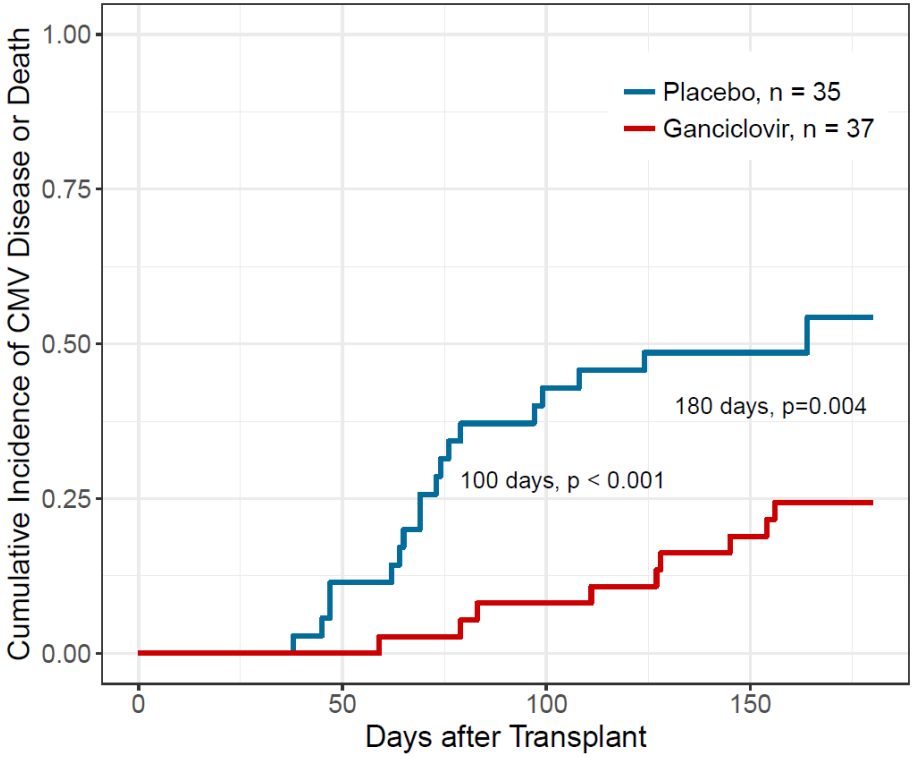
Mortality

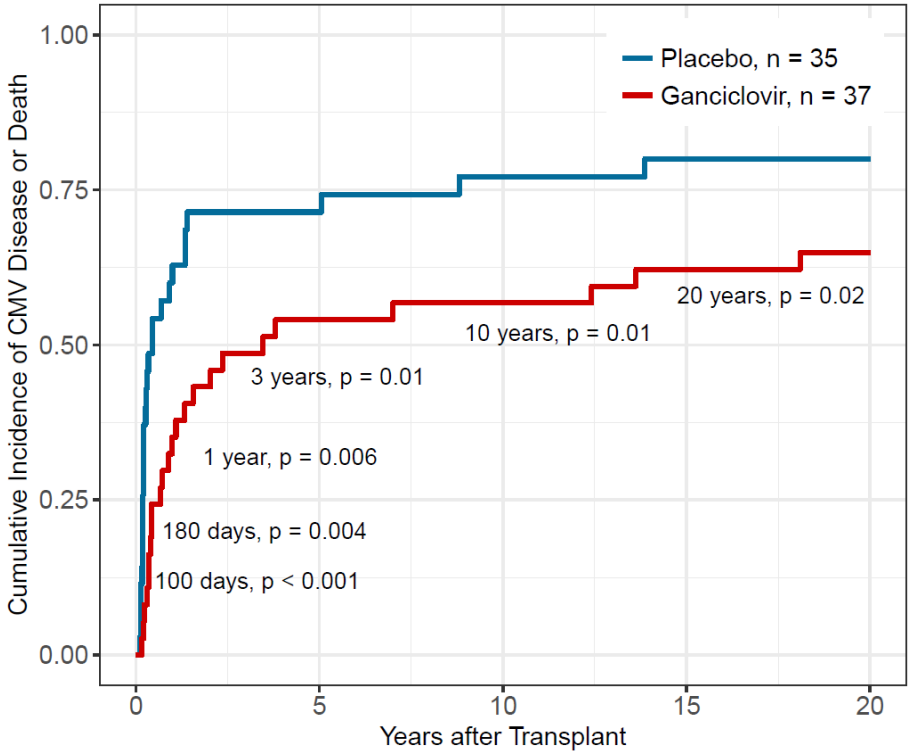

1.00
0.75
0.50
0.25
0.00
Overall Mortality
0
5
10
15
20
Years after Transplant
Placebo, n = 35
Ganciclovir, n = 37
20 yr, p=0.11
1 yr, p=0.01
3 yr, p=0.04
5 yr, p=0.09
10 yr, p=0.06
180 days, p=0.03
100 days, p=0.04

CMV Disease or Death

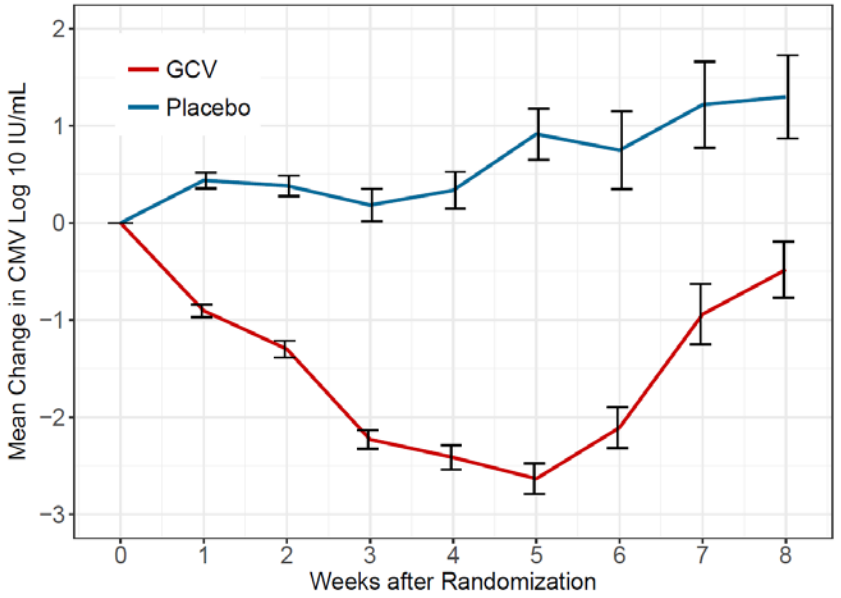


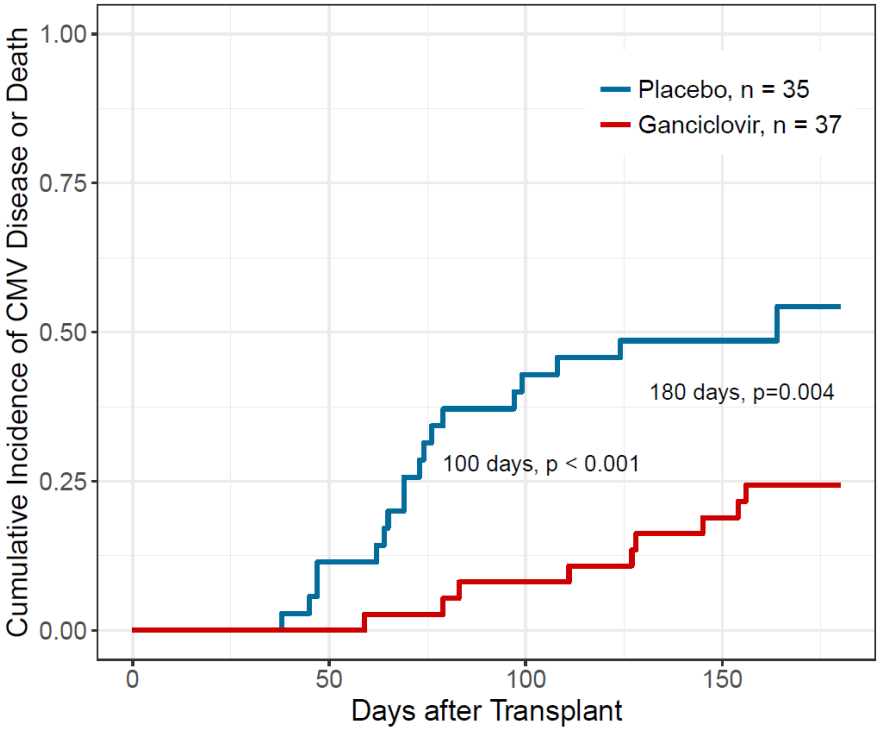
CMV Disease or Death





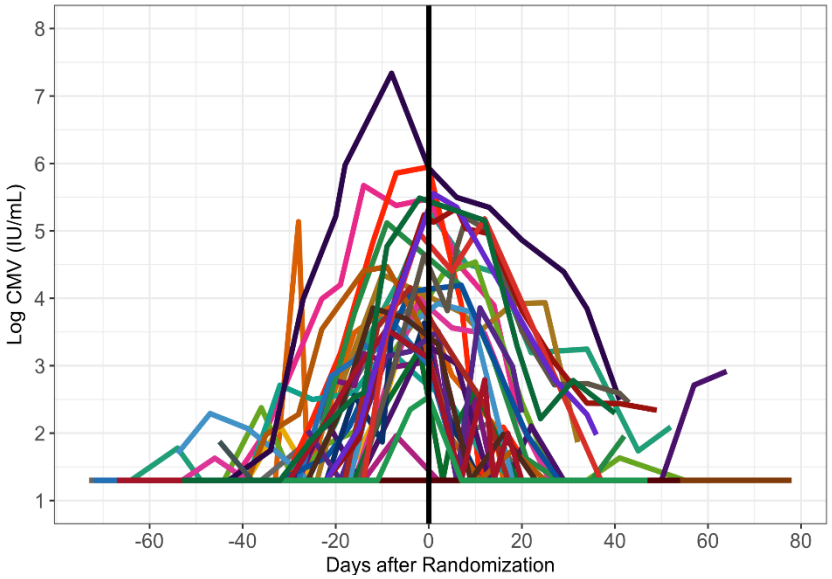
Viral Load


GCV
Placebo
Mean Change in CMV Log 10 IU/mL
2
1
0
−1
−2
−3
0
1
2
3
4
5
6
7
8
Weeks after Randomization

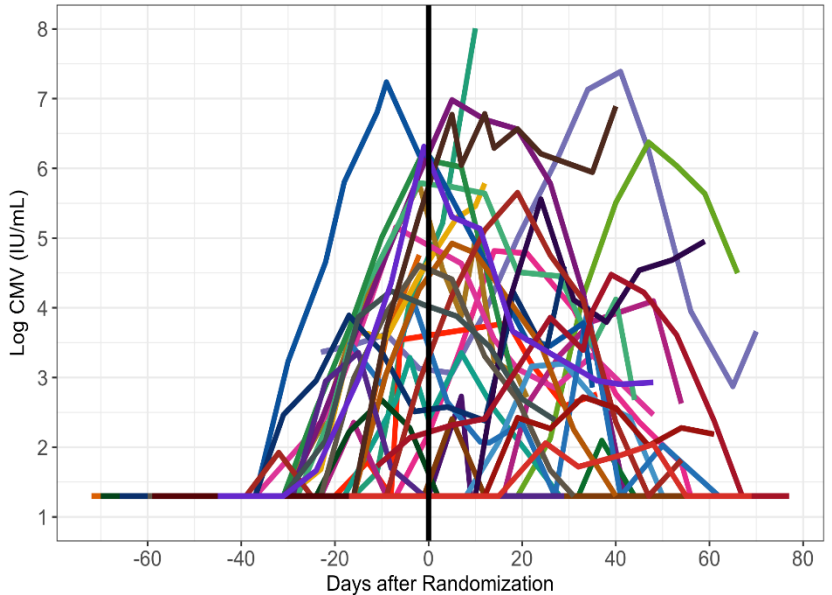

Placebo, n = 35
Ganciclovir, n = 37
Cumulative Incidence of CMV Disease or Death
1.00
0.75
0.50
0.25
0.00
180 days, p=0.004
100 days, p < 0.001
0
50
100
150
Days after Transplant

Viral Load Kinetics

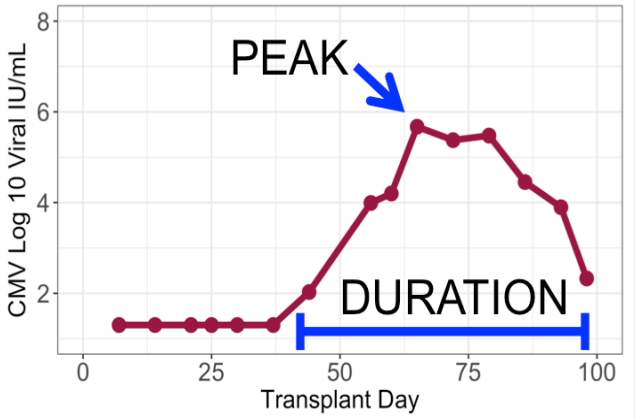
Ganciclovir

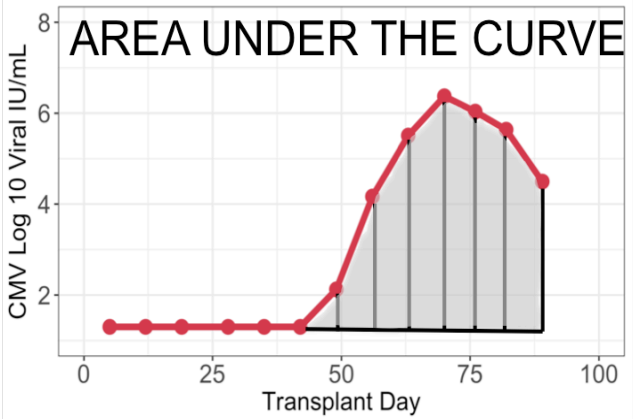


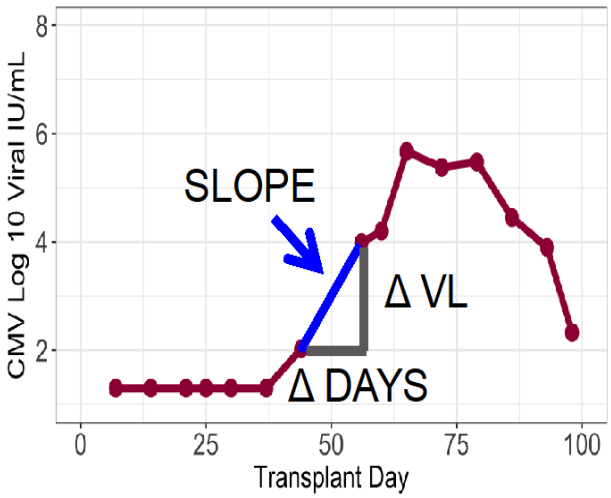
Placebo

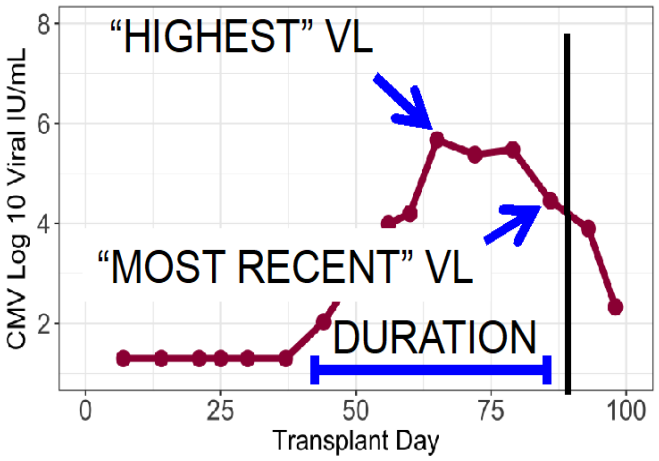


Kinetics Parameters

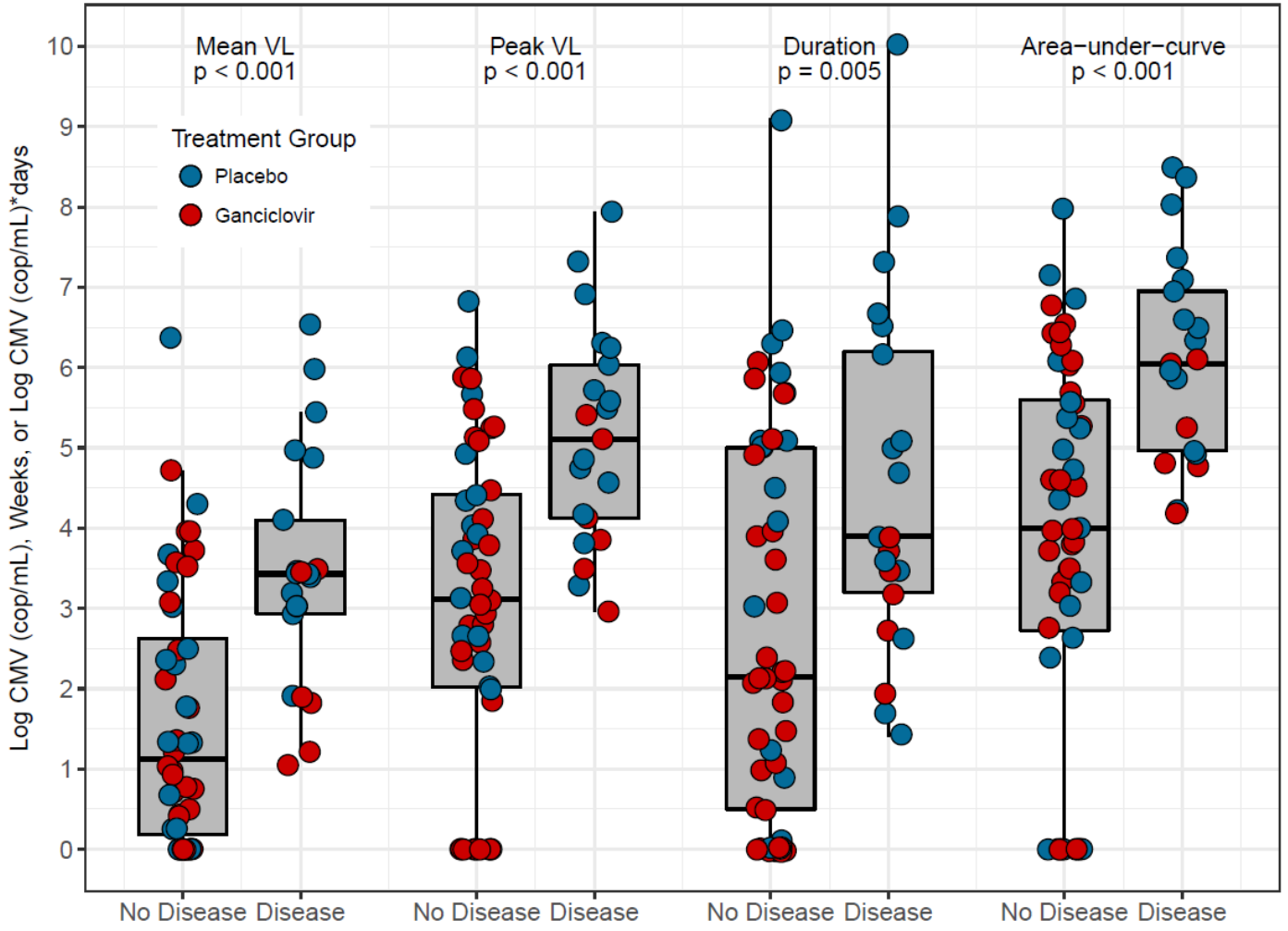




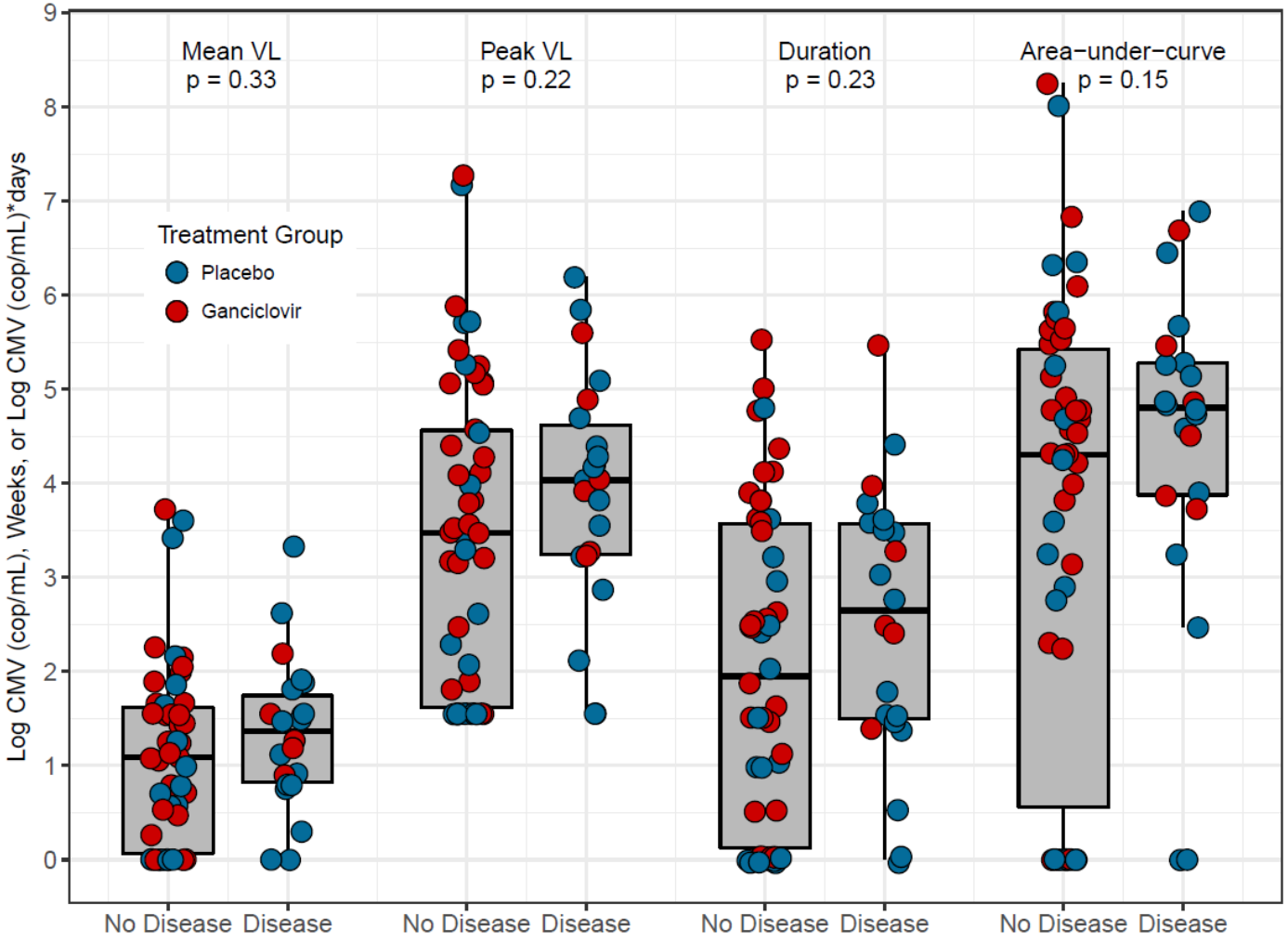




CMV Kinetics Post Randomization



CMV Kinetics Pre Randomization



Viral Load and CMV Disease

Associations between post-randomization CMV kinetics and CMV disease 180 days post-transplant (adjusted for aGVHD, donor CMV serostatus, treatment group).

Viral Kinetic Marker	HR (CI)	p-value
Most recent VL (for each log increase)	1.5 (1.1,2)	0.004
Highest VL (for each log increase)	1.7 (1.2,2.3)	0.002
Duration of viremia (for each week increase)	1.2 (0.9,1.5)	0.23
Duration of viremia (for each 25% increase)	1.7 (1.1,2.4)	0.008
Slope (for each log/d increase)	5.9 (1.3,26)	0.02
AUC (for each log AUC increase)	1.7 (1.2,2.3)	0.002

Prentice criterion 1: Associations between ganciclovir and clinical outcome

Variable	HR	95% CI	p
CMV disease day 100	0.1	0-0.5	0.003
CMV disease day 180	0.3	0.1-0.7	0.008
CMV disease or death day 100	0.2	0-0.5	0.004
CMV disease or death day 180	0.3	0.1-0.7	0.005

Prentice criterion 2: Associations between viral load post-randomization and outcome

Most recent viral load first event of CMV disease or death 100 days post-transplant

Model	Predictor variable	HR (CI)	p-value
Placebo group with VL predictor only	VL	1.7(1.2,2.5)	0.004
Both treatment groups with GCV predictor only	GCV	0.2(0,0.5)	0.004
Both treatment groups with VL and GCV predictors	VL	1.5(1.1,2)	0.007
	GCV	0.2(0.1,0.9)	0.03
Both treatment groups with VL/GCV interaction	Interaction	0.7(0.4,1.3)	0.22

Prentice criterion 3: Association between the Surrogate Endpoint and the Clinical Outcome be the same in the Treatment and Placebo Group

1. Model: association between each viral kinetic and the clinical outcome adjusted for treatment group.

2. Model: interaction between ganciclovir and the proposed viral load surrogates.

Association between each viral kinetic and the clinical outcome adjusted for treatment group

- All except duration in weeks were associated with both clinical outcomes at day 100 and day 180.
- However, treatment group was also significantly associated with clinical outcomes except most recent viral load and
  - CMV disease at day 180 (HR 0.4, 95% CI 0.1-1.0, p = 0.06) and
  - CMV disease or death at day 180 (HR 0.4, 95% CI 0.2-1.0, p = 0.05).
- This finding supports Prentice criterion 2 (proposed surrogates are correlated with clinical outcomes in both treatment groups)
- However, the fact that ganciclovir's association remained significant despite adjustment for viral load kinetics suggests that ganciclovir's effect on clinical outcomes may not be entirely mediated by viral load kinetics.

Interaction between Ganciclovir and the Proposed Viral Load Surrogates

- Would imply that the degree of association between viral load and clinical outcomes may be different depending on treatment group.
- We found evidence for significant interactions
  - between most recent viral load and CMV disease at 180 days
  - between slope and CMV disease at 180 days
  - between slope and first event of CMV disease or death at days 100 and 180
- However, we found no evidence for interactions
  - in highest viral load
  - percentage of days with viremia
  - area-under-the-curve

Summary

- Viral load suppression in this randomized placebo controlled trial correlates with improved clinical outcomes
- Our data provides strong support for viral load kinetics (aside from duration of viremia) as surrogate endpoints in terms of Prentice criteria 1 and 2.
- However, our findings provided only partial support for fulfillment of Prentice criterion 3.

Discussion

- Different cell source, treatment later than in modern cohorts (also a strength for the study)
- Small number of disease events in the treatment group
  - Data support but are not robust enough to support a formal surrogate endpoint analysis
- CMV viral load does not appear to be a full surrogate due to localized tissue disease kinetics not correlating completely with plasma viral load dynamics

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Heather Andrew
Darneshia Smith

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