A Phase II Randomized Double-Blind Placebo-Controlled Trial of Ganciclovir to Prevent Cytomegalovirus (CMV) Reactivation in Acute Critical Illness ["GRAIL" Study]

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DISCLOSURES relevant to this work

Boeckh: Genentech/Roche, Chimerix, Merck, Astellas, Shire, Helocyte (Consulting), Roche Molecular Systems, Chimerix, Merck, Astellas, Shire (research support)

Limaye: Merck (Consulting), Astellas (Clinical trial site), Helocyte (Consulting), Gilead (consulting)

Background & Rationale

- CMV reactivation is common in ICU patients
  - Associated with adverse outcomes (mortality, secondary infections, hospital & ICU length of stay, duration of mechanical ventilation)
  - Is CMV a marker or cause of adverse outcomes?
  - Phase 3 efficacy studies of CMV prevention required to clarify role of CMV in ICU patients
- Objectives:
  - Assess feasibility, safety, and antiviral efficacy of GCV for CMV prevention in ICU patients
  - Define the appropriate study population(s)
  - Explore the impact of GCV on clinical outcomes to identify potential clinical endpoints for phase 3 efficacy studies

Methods

- Randomized (1:1), double-blind, placebo-controlled, multicenter [N=14]
- Stratified by: trauma vs sepsis, clinical site
- IV GCV/matching placebo given within 5d of ICU admission & continued to hospital discharge or day 28, whichever occurred earlier

Key Inclusions

- CMV seropositive
- Age >18 yrs
- Sepsis or Severe Trauma (ISS>15)
- Positive pressure mechanical ventilation

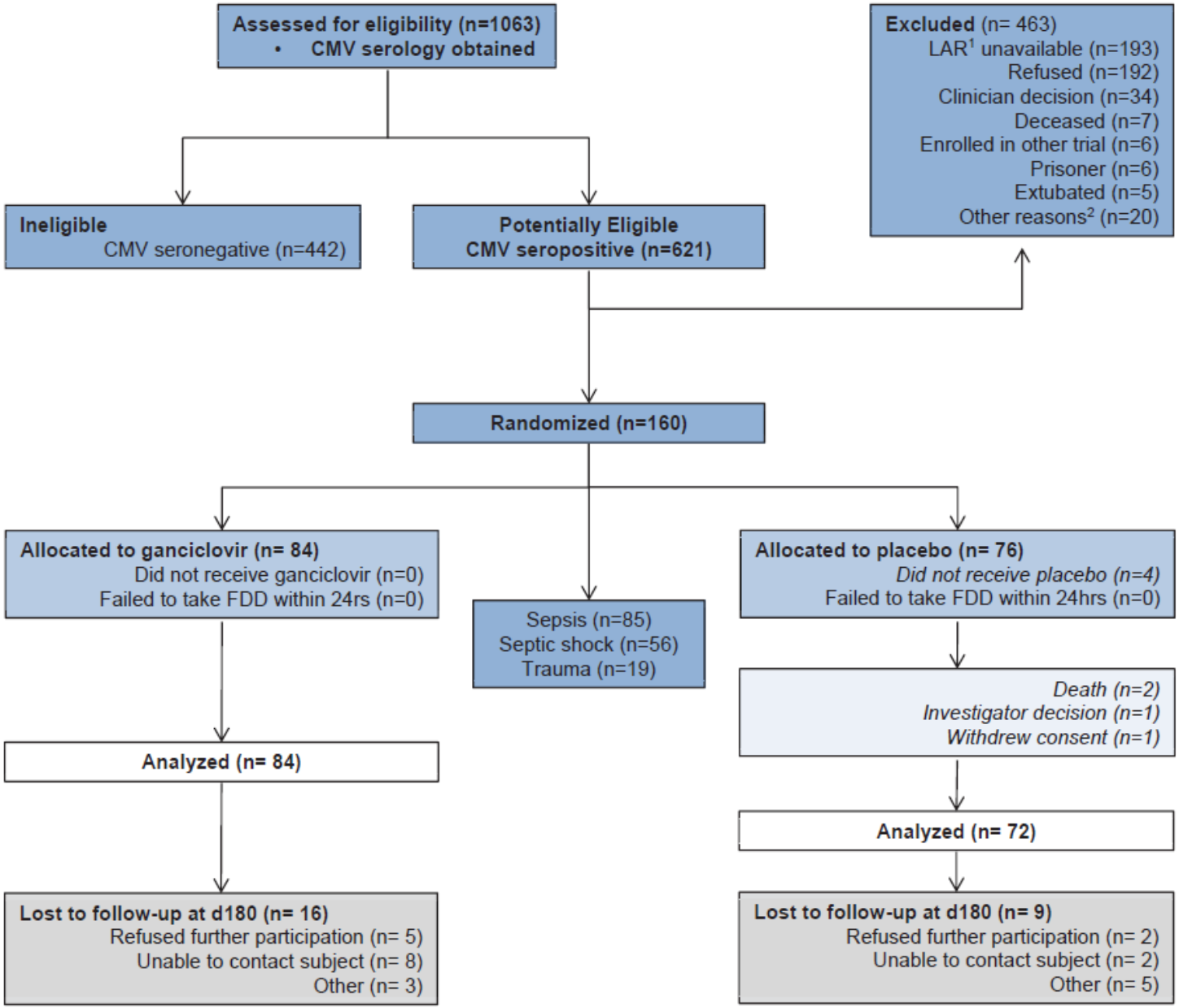
Key Exclusions

- Immunosuppressed
- Specific underlying medical conditions:
  - Cirrhosis Child's C,
  - interstitial lung disease,
  - BMI >60

Study Outcomes

- Primary: change in serum IL-6 between day 1 and 14.
  - Associated with mortality in prior ICU studies
  - Linked to CMV reactivation *in vitro* & *in vivo*
  - Feasibility considerations for phase II trial
- Secondary (day 28):
  - Safety (hematologic)
  - Incidence of CMV reactivation (blood, lung)
  - Mechanical ventilation days (MVD)
  - Ventilator-free days (VFD)
  - ICU & hospital length of stay (LOS)
  - Mortality (through day 180)

Consort Diagram



[1] Legally authorized representative
[2] Other reasons: out of window, DNR/DNI, no longer septic, non-English speaking, transfer to other hospital, home ventilation, unable to perform study procedures

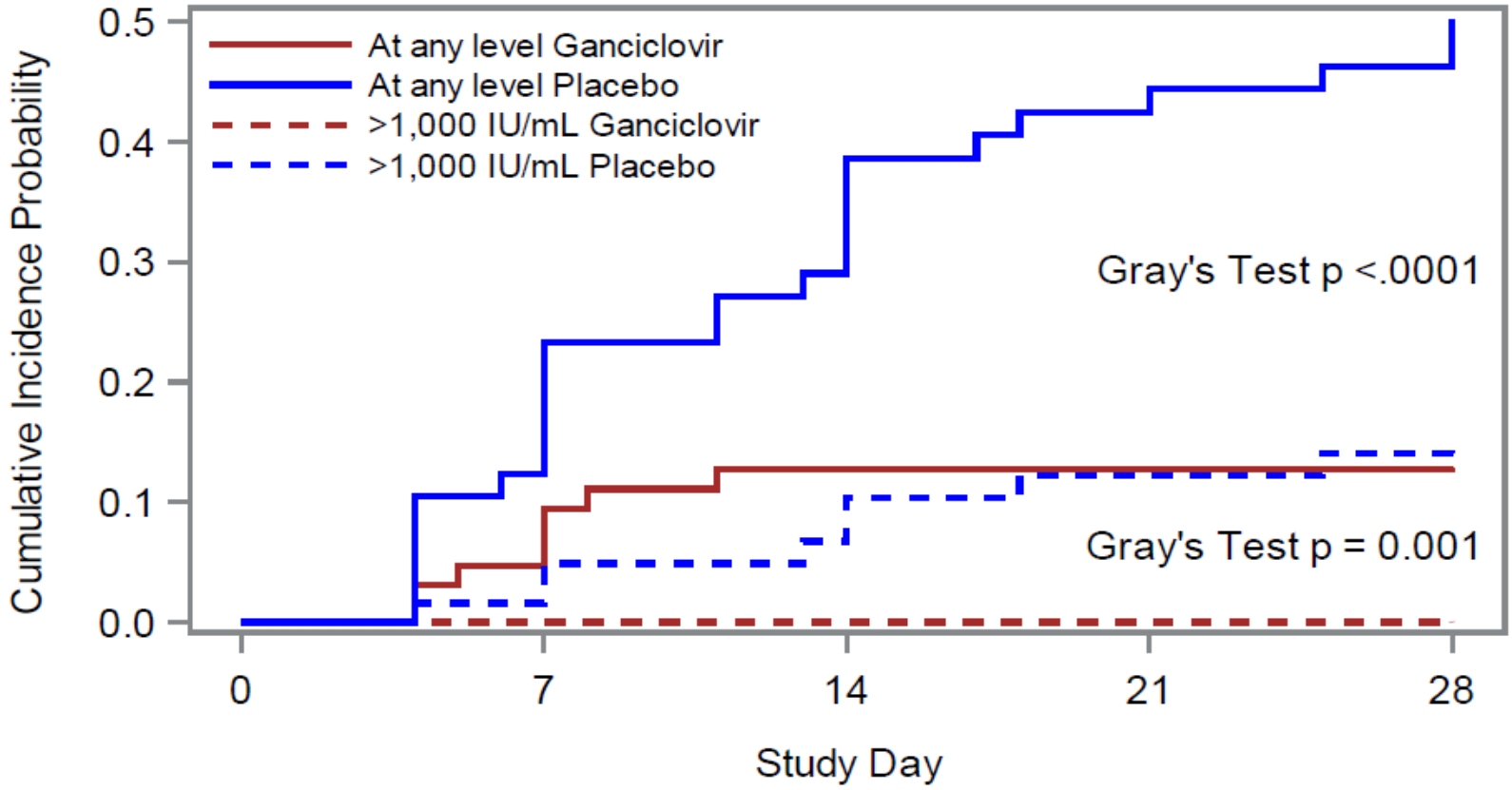
STUDY POPULATION

Characteristic	Total (n=156)	Intent-to-Treat (n=156)		Sepsis Subset (n=137)	
		Placebo (n=72)	GCV (n=84)	Placebo (n=66)	GCV (n=71)
Age, mean	56.5	58	57	57	61
Male, No. (%)	89 (57)	40 (56)	49 (58)	37 (56)	37 (52)
Sepsis, No. (%)	137 (88)	66 (92)	71 (85)		
Trauma, No. (%)	19 (12)	6 (8)	13 (15)		
Apache III score, median	71	71	71	71.5	73
MODS score day 1, mean		12.63	12.77	12.57	12.91
Baseline PaO2/FiO2 ratio, mmHg, median	201	200	186	189	200
Baseline CMV viremia, No. (%)	10 (6)	3 (4)	7 (8)	3 (5)	7 (10)

STUDY OUTCOMES

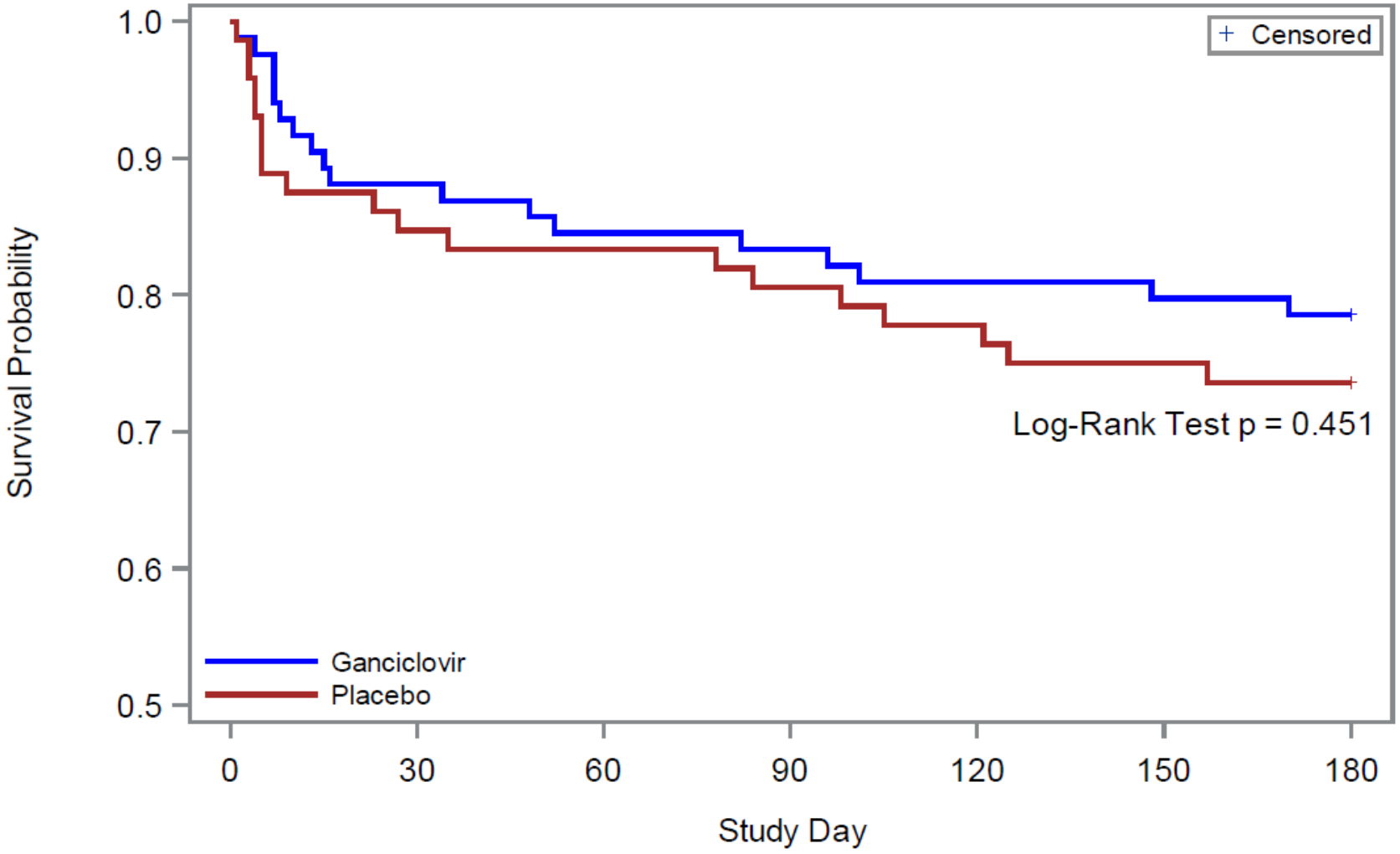
	Intent-to-Treat (n=156)			Sepsis Subset (n=137)		
	Placebo (n=72)	GCV (n=84)	P-value	Placebo (n=66)	GCV (n=71)	P-value
Primary Outcome						
Difference in plasma IL-6 between day 1 and 14, log10, mean	-0.79	-0.79	1.0	-0.88	-0.81	0.83
Secondary Outcomes						
Incidence of CMV viremia, No. (%)	28 (39)	10 (12)	<0.0001	26 (39)	10 (14)	0.0009
Mechanical ventilation days, median	6	5	0.16	6	5	0.06
Ventilator-free days, median	19.5	23	0.05	20	23	0.03
ICU length of stay, days, median	8.5	8.5	0.76	8	7	0.36
Hospital length of stay, days, median	13	14	0.92	13	13	0.76
2^0 bacteremia or fungemia, No. (%)	11 (15)	13 (15)	0.97	9 (14)	10 (14)	0.96
Mortality, No. (%)	11 (15)	10 (12)	0.54	10 (15)	9 (13)	0.68

Cumulative incidence of CMV Viremia



At any level Ganciclovir	66	60	50	50	50
At any level Placebo	59	48	37	30	28
>1,000 IU/mL Ganciclovir	77	74	67	65	64
>1,000 IU/mL Placebo	67	59	51	48	45

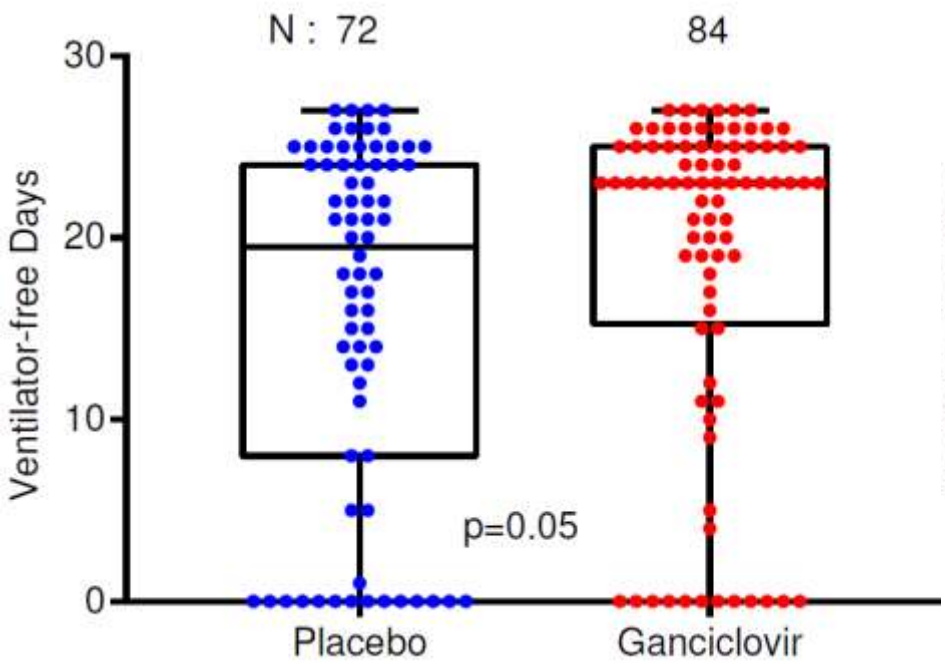
Kaplan-Meier Survival Plot through Day 180



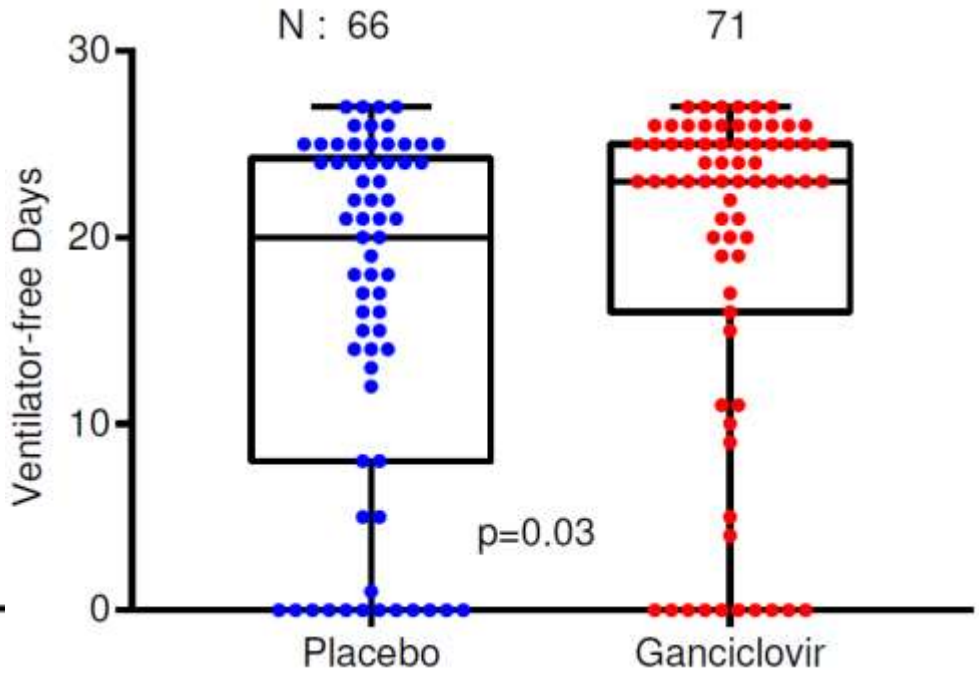
Ganciclovir	84	74	71	70	68	67	66
Placebo	72	61	60	58	56	54	53

Ventilator-free days by day 28

All participants (ITT)



Sepsis subset



	All participants (ITT)		Sepsis subset	
Median VFDs	**19.5**	**23**	**20**	**23**

SAFETY ASSESSMENTS

	Placebo (n=72)	Ganciclovir (n=84)	Total (n=156)	P-value
≥1 transfusion, No. (%)	26 (34)	31(37)	57(35.6)	0.92
RBCs, No. (%)	26 (100)	31 (100)	57 (100)	0.92
Platelets, No. (%)	7 (27)	1 (3)	8 (14)	0.02
Transfusions per patient, median, No. [IQR]	1 [1-4]	2 [1-2]	2 [1-4]	0.63
RBCs per patient, median, No. [IQR]	1 [1-4]	2 [1-2]	2 [1-3]	0.72
Platelets per patient, median, No. [IQR]	1 [1-2]	1 [1-1]	1 [1-2]	0.49
New tumors by day 180, No. (%)	0	0	0	
Neutropenia by day 35, No. (%)	0 (0)	0 (0)	0 (0)	
GCSF use, No. (%)	0 (0)	0 (0)	0 (0)	
Renal insufficiency, No. (%)	41 (57)	36 (43)	77 (49)	0.08
Pregnancies, No. (%)	0 (0)	1 (1)	1 (0.6)	
Adverse Events				
≥ one protocol-defined AE, No. (%)	13 (17)	17 (20)	30 (19)	0.73
≥ one protocol-defined SAE, No. (%)	12 (17)	15 (18)	27 (17)	0.84

Summary & Conclusions

- Among CMV seropositive adults with critical illness, ganciclovir:
  - Was safe and well-tolerated
  - Effectively prevented CMV reactivation
  - Was associated with increased ventilator-free days
  - Did not impact: overall mortality, IL-6 levels, secondary infections, hospital or ICU length of stay

- A phase 3 efficacy study of CMV prophylaxis in CMV seropositive adults with sepsis is warranted, feasible, and should be prioritized

Additional Slides

Days of Mechanical Ventilation to Day 28

	Placebo	Ganciclovir	P-value
Died before day 28			
Intent to treat			
No./Total No. (%)	11/72 (15)	10/84 (11)	
Days on MV, median [IQR]	5 [3-6]	8.5 [4.25-13.25]	0.08
Sepsis			
No./Total No. (%)	10/66 (15)	9/71 (13)	
Days on MV, median [IQR]	5.5 [3-6]	8 [4-11]	0.18
Survived to 28 days			
Intent to treat			
No./Total No. (%)	61/72 (85)	74/84 (88)	
Days on MV, median [IQR]	7 [3-13]	5 [3-8]	0.01
Sepsis			
No./Total No. (%)	56/66 (85)	62/71 (83)	
Days on MV, median [IQR]	6.5 [3-12.25]	4 [2.25-7]	0.005