Managing CMV risk in Hematopoietic Stem Cell Transplant during COVID-19 pandemic

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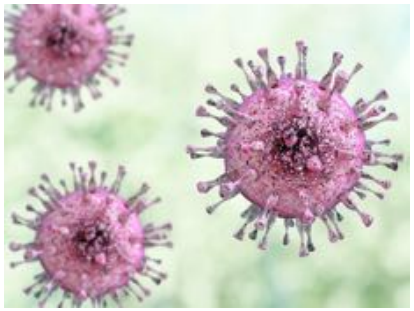
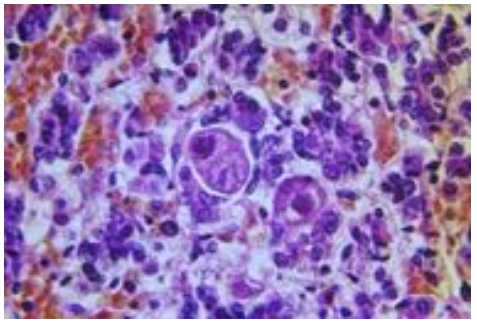
UNIVERSITÀ DEGLI STUDI DI BRESCIA

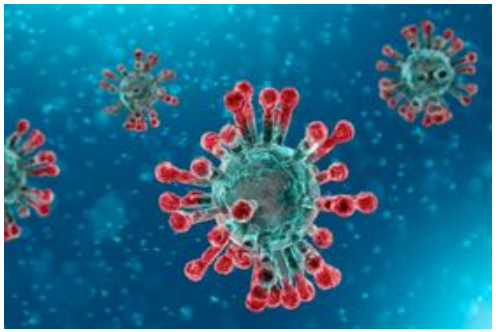
Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

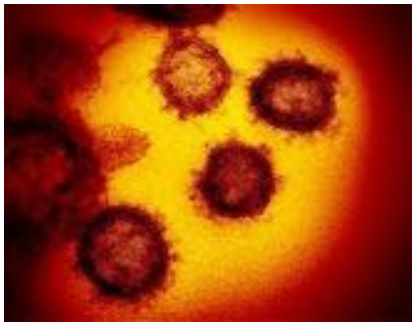
CMV





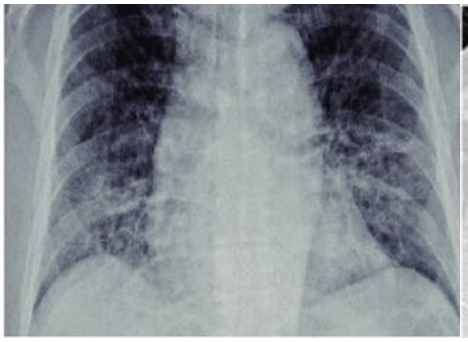
SARS CoV-2

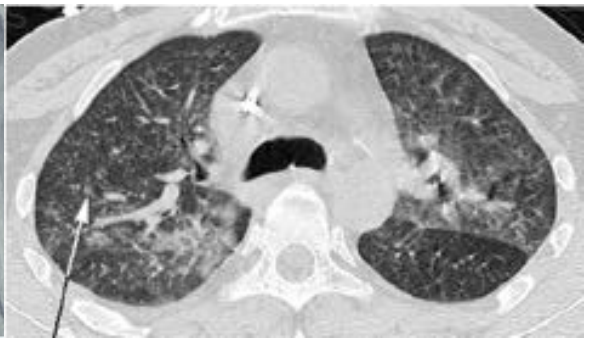


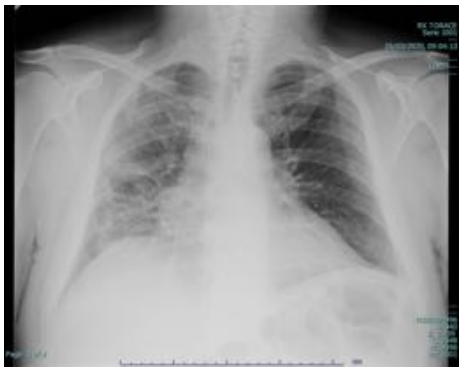


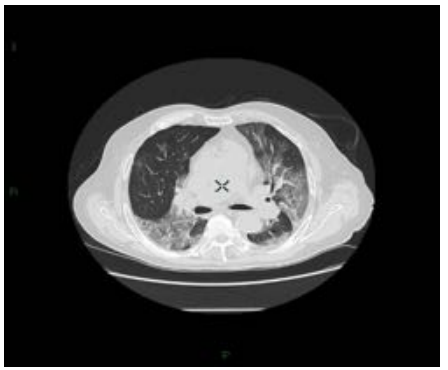
CMV Interstitial Pneumoniae

SARS CoV-2 Interstitial Pneumoniae

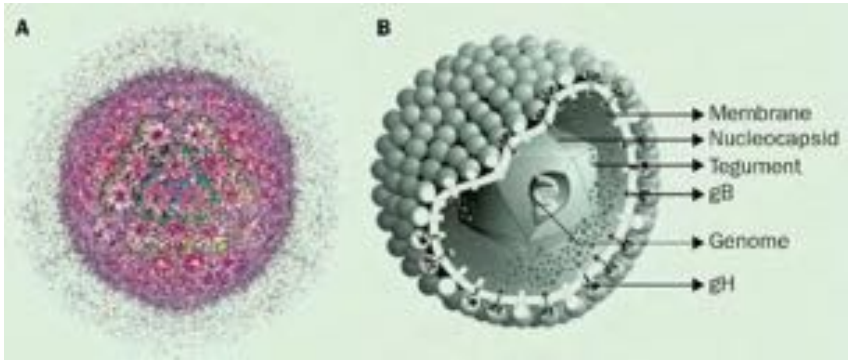








CMV



♦ Human Herpesvirus 5

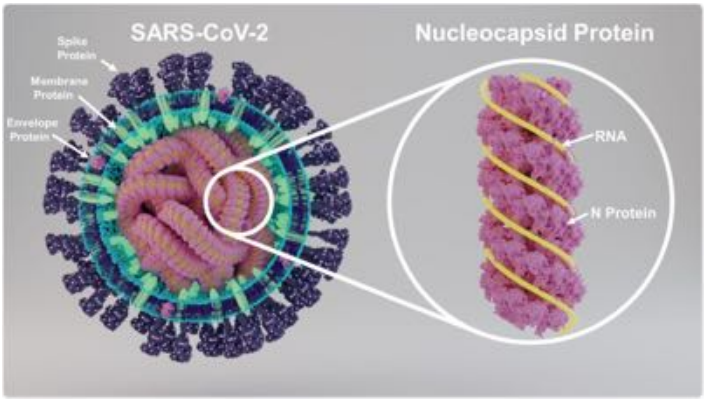
♦ Beta-HSV

♦ DNA Genome → 235 Kb

♦ Nucleocapsid with DNA encapsulated into a glico-proteine membrane

♦ **Cell invasion via ICAM-1 and surface integrins (CD11/18)**

SARS CoV-2



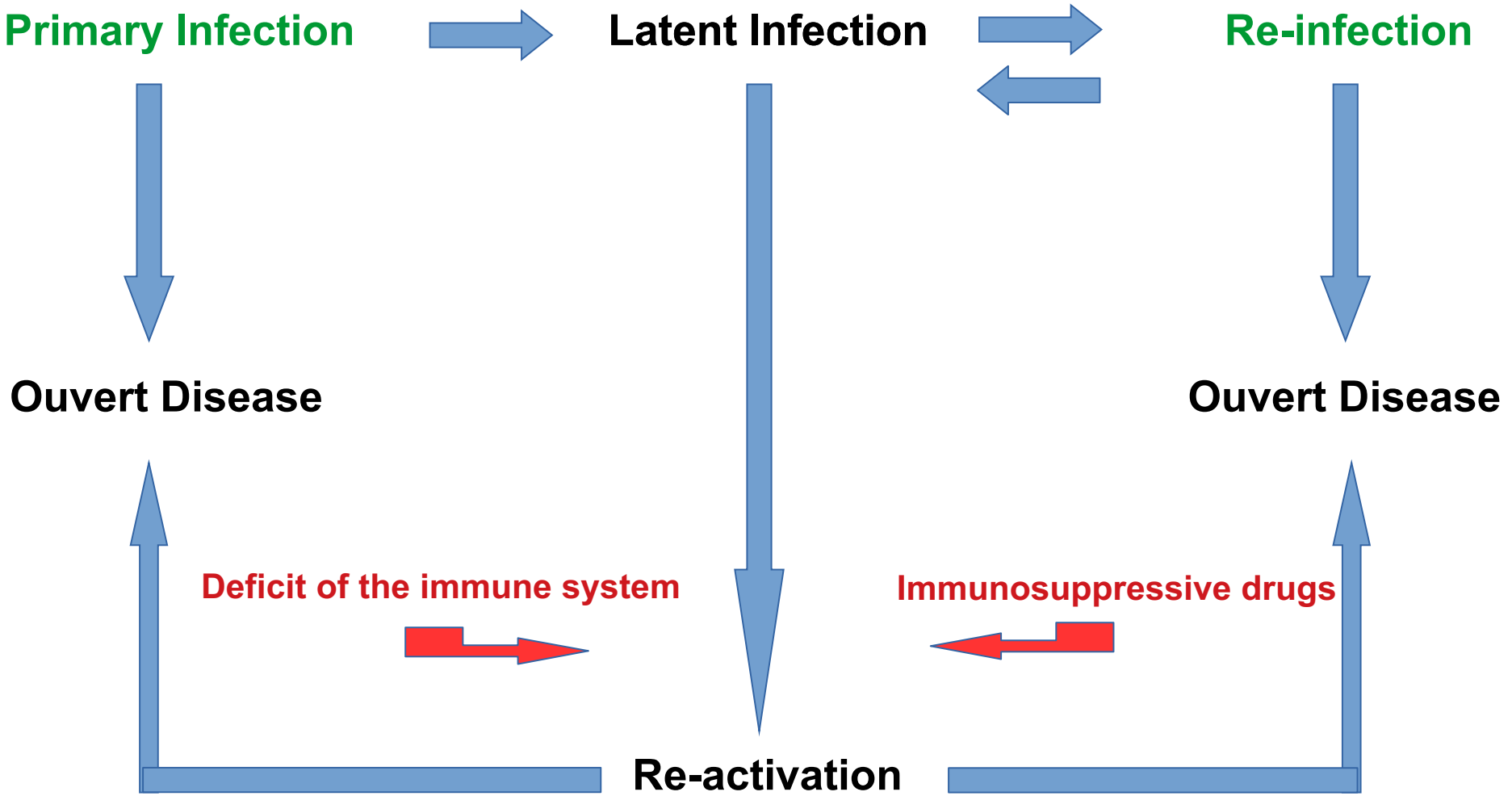
♦ Betacoronavirus

♦ Single strand RNA genome → 29,9 Kb

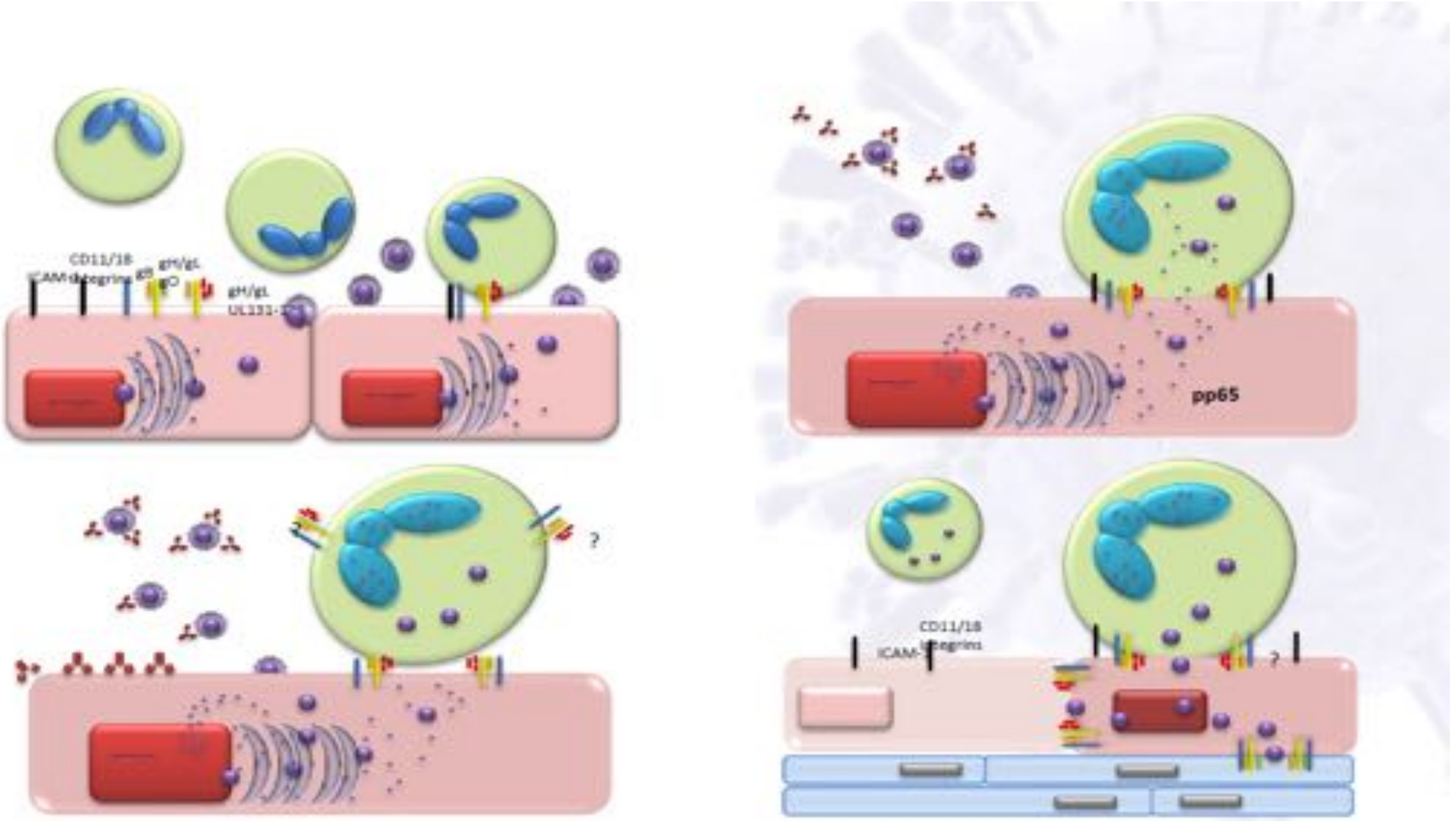
♦ 4 structural proteins
- S
- E → viral capsid
- M
- N → contains the genome

♦ **S protein → high affinity for ACE2-R → cell invasion**

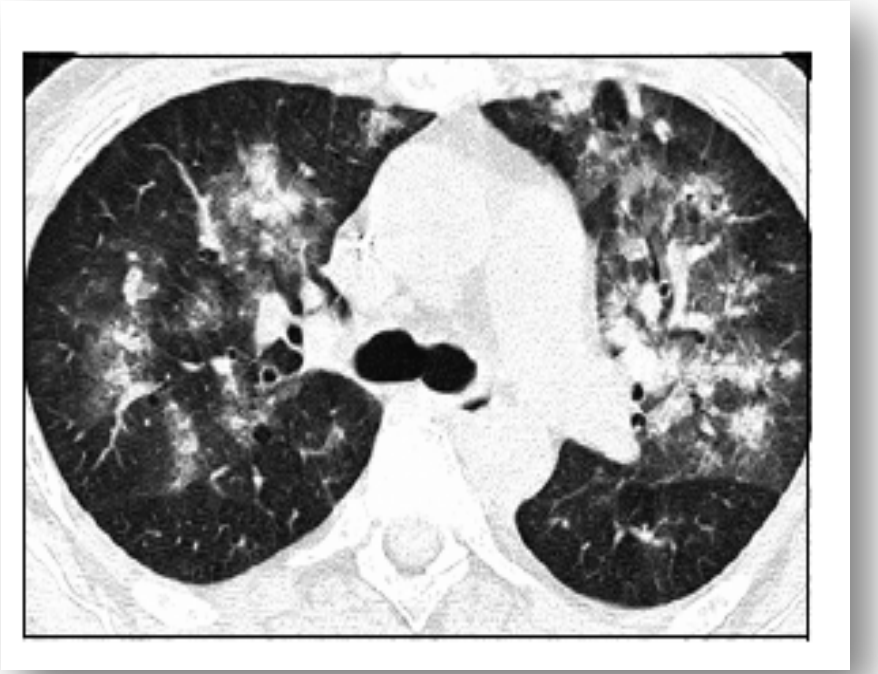
NATURAL HISTORY OF CMV INFECTION

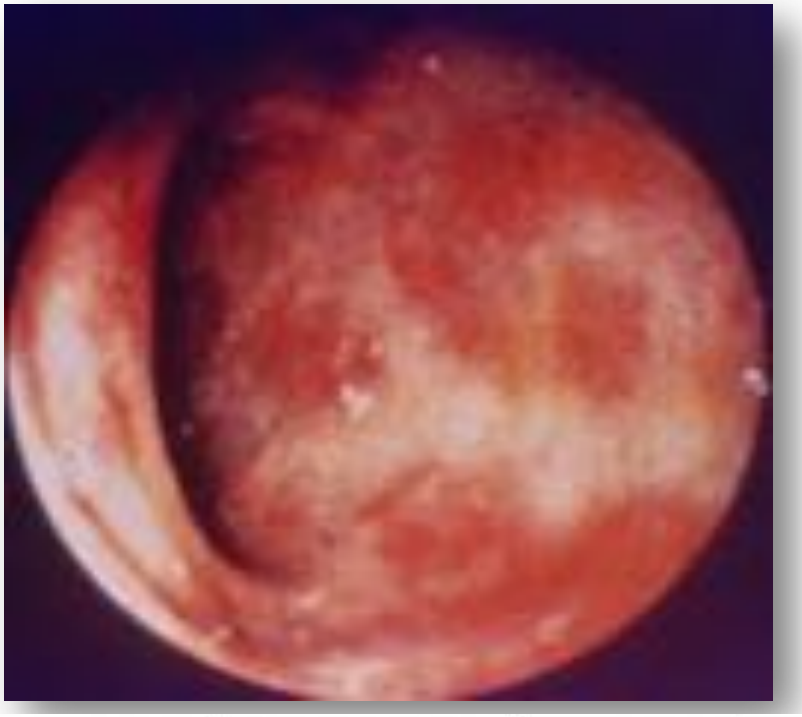


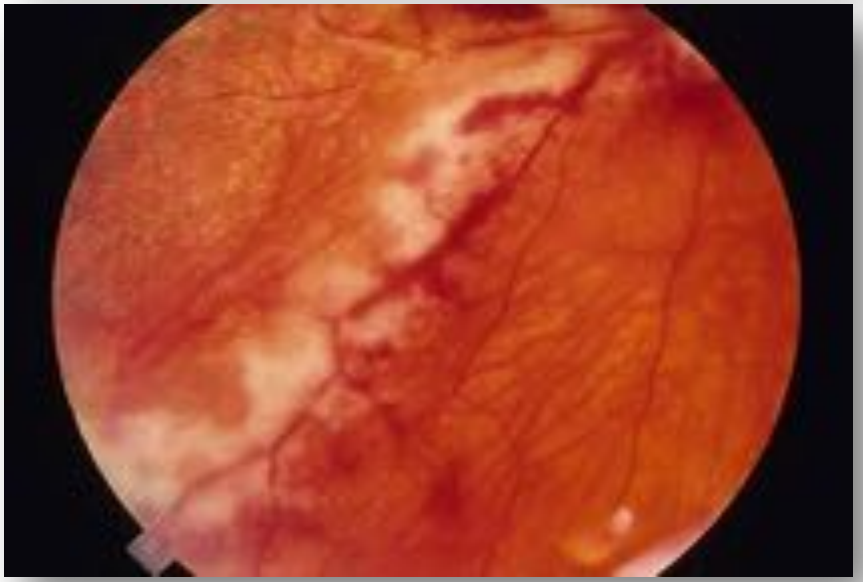
CMV RESERVOIR AND INFECTION DISSEMINATION (2)

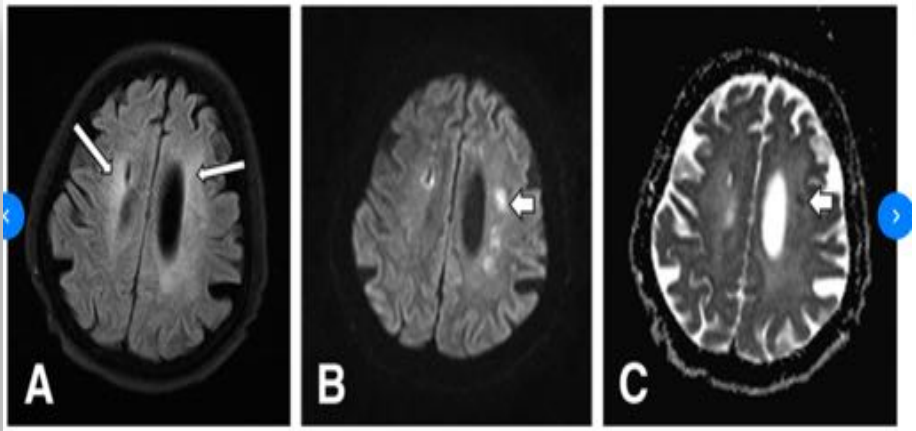


CMV Disease



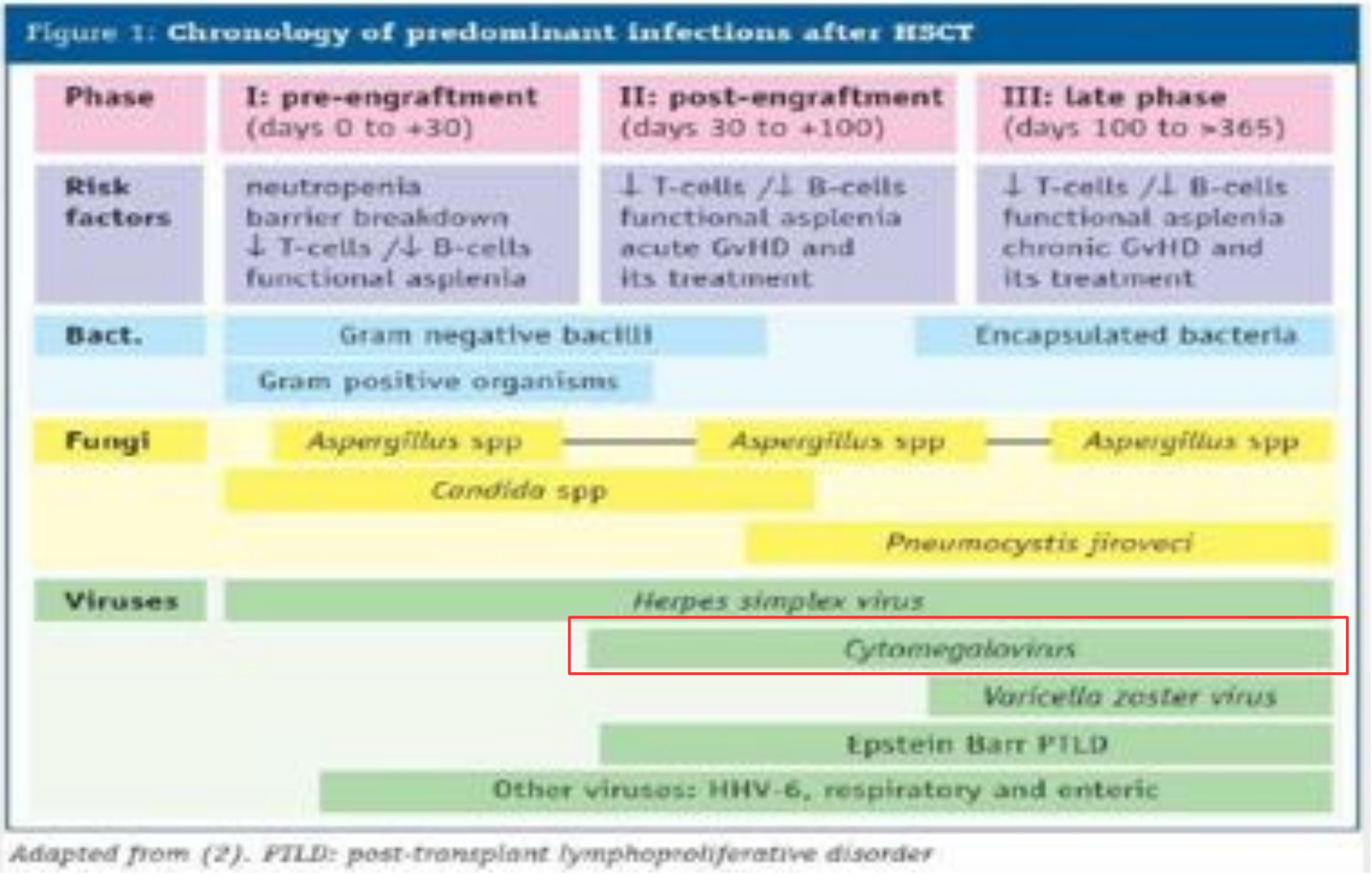






Cytomegalovirus encephalitis: a 32-year-old man diagnosed with ALL presented with dizziness and headache. Axial FLAIR image (A) demonstrates abnormal ill defined lesions in the periventricular areas and corona radiata (long arrows, A), some of which were restricted on diffusion (short arrows, B, C). Lower images (not shown) demonstrate similar lesions in the basal ganglia and thalami. The polymerase chain reaction was high in the CSF (152 000 copies/mL).

INFECTIONS AFTER allo-SCT



Adapted from Kedia S et al, 2013

CMV & allo-SCT

Clinical Infectious Diseases

INVITED ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association

IMMUNOCOMPROMISED HOSTS: David R. Snydman, Section Editor

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

CMV Infection & disease

- ***Latent CMV infection*** represents lifelong persistence of virus without replication in healthy seropositive host.
- ***CMV active infection*** : actively replicating virus, can be diagnosed by nucleic acid-based assays or antigenemia.
- ***CMV disease*** is defined by evidence of CMV infection with attributable symptoms, it can be :-
  - ***CMV syndrome*** (fever, fatigue, leukopenia and/or thrombocytopenia, and an increased CMV titer from a specific diagnostic assay)
  - ***Invasive CMV disease*** (e.g., pneumonitis, hepatitis, or gastrointestinal involvement such as colitis or enteritis, or involvement of the allograft itself).

- Multicentric (CIBMTR)
- Patients: 9469 allo-SCTs (1º) (2003-2010). PB / BM

CMV reactivation (0-100 days): Higher mortality	**AML (Nº 5310)**	**ALL (Nº 1883)**	**CML (Nº 1079)**	**MDS (Nº 1197)**
TRM (at 3 years) RR	**1.65**	**1.95**	**1.90**	**1.61**
OS (at 3 years) RR	**1.27**	**1.46**	**1.49**	**1.31**
Relapse (at 3 years)	**N.S**	**N.S**	**N.S**	**N.S**

CMV reactivation:

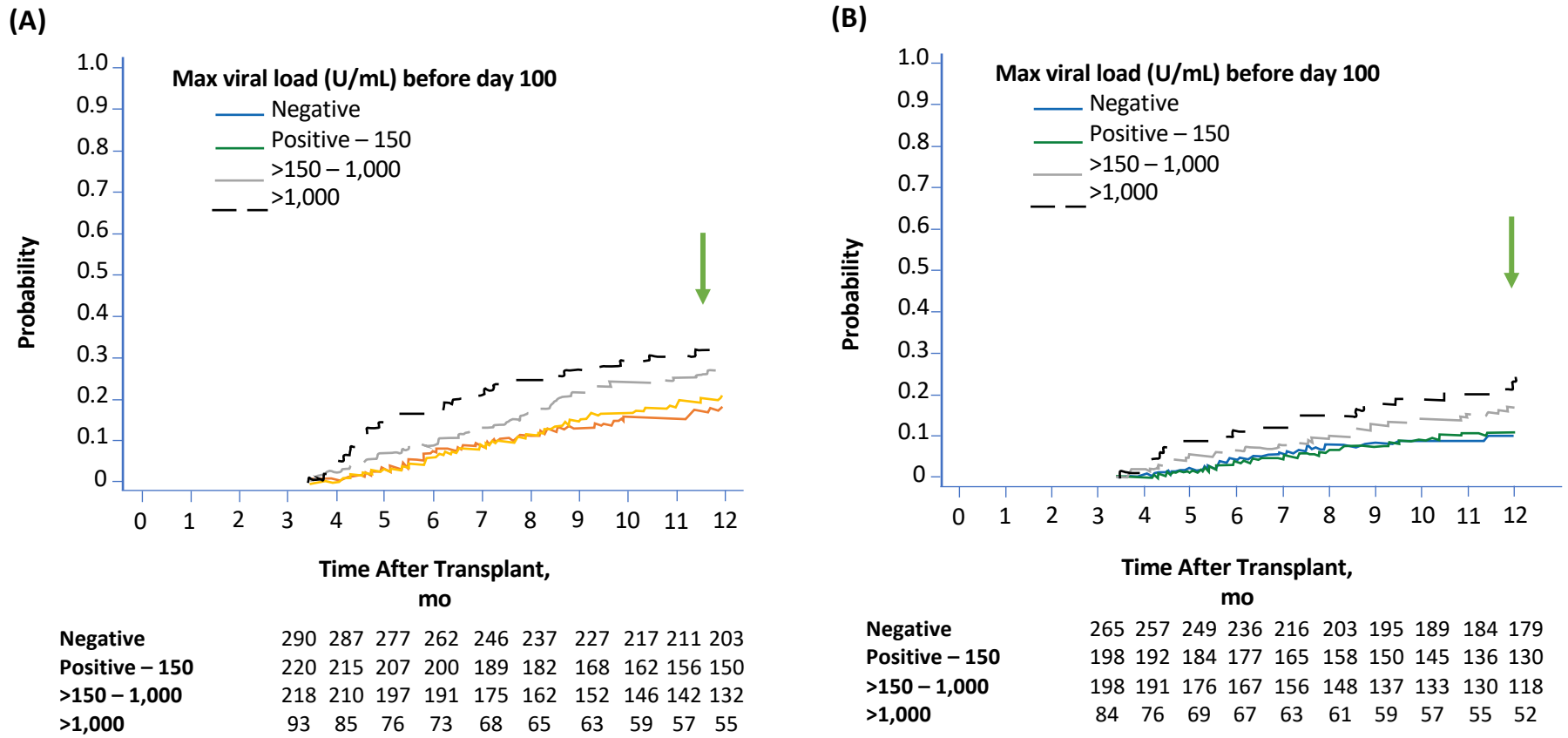
- Does not protect against relapse
- Continues to be a risk factor for poor post-HCT outcome (more TRM, less OS)

Teira P. Blood 2016; 127: 2427

Cemaly-1

CMV Viral Load and Mortality After HCT in the Era of Preemptive Therapy

Cumulative Incidence of Overall Mortality (A) and Nonrelapse Mortality (B) at 1 Year After HCT in Survivors at Day 100 (n = 832) Stratified by Max CMV VL Before Day 100



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

Direct and Indirect Effects of CMV Infection/Disease

CMV Viral Syndrome

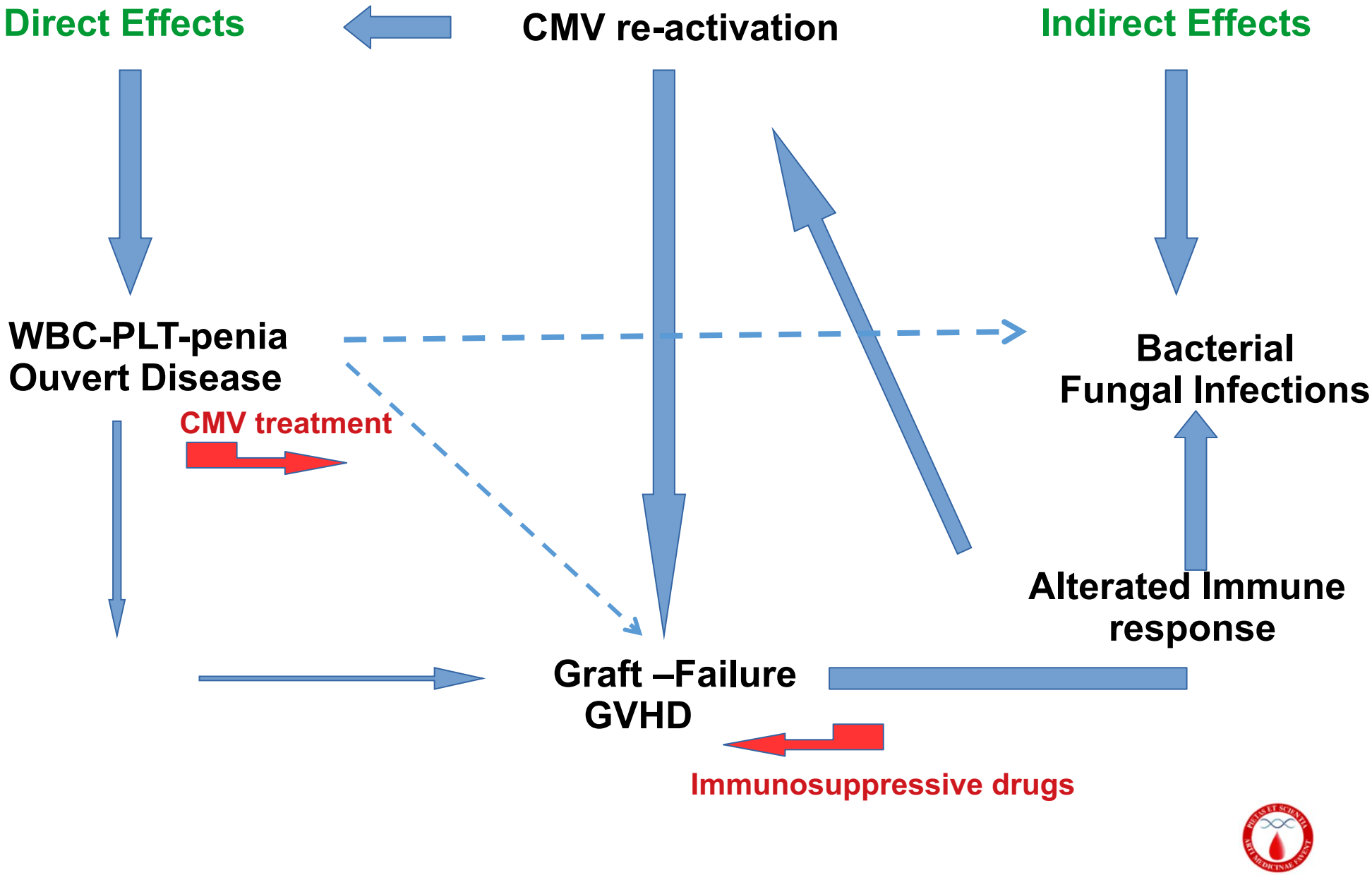
- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia
- Tissue Invasive Disease

Altered host immune response

- Acute/chronic graft rejection
- Bacterial or fungal superinfection
- Decreased graft and/or patient survival
- Development of EBV related PTLD

*some are controversial

DIRECT AND INDIRECT EFFECTS OF CMV INFECTION



Cytomegalovirus Reactivation after Allogeneic Hematopoietic Stem Cell Transplantation is Associated with a Reduced Risk of Relapse in Patients with Acute Myeloid Leukemia Who Survived to Day 100 after Transplantation: The Japan Society for Hematopoietic Cell Transplantation Transplantation-related Complication Working Group

BBMT 2015

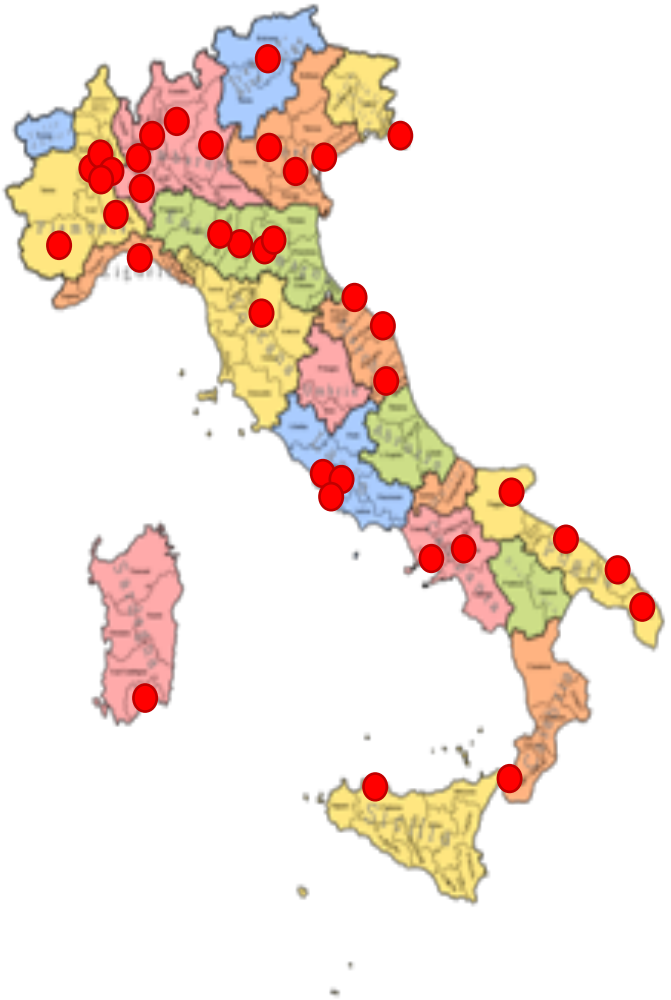
Katsuto Takenaka [1,*], Tetsuya Nishida [2], Yuki Asano-Mori [3], Kumi Oshima [4], Kazuteru Ohashi [5], Takehiko Mori [6], Heiwa Kanamori [7], Koichi Miyamura [8], Chiaki Kato [9], Naoki Kobayashi [10], Naoyuki Uchida [3], Hirohisa Nakamae [11], Tatsuo Ichinohe [4], Yasuo Morishima [12], Ritsuro Suzuki [13], Takuhiro Yamaguchi [14], Takahiro Fukuda [15]

RISK FACTOR	CMV REACTIVATION	CMV DISEASE
D-/R+		
GVHD		
UD/MMD		
AGE (↑)		

Table 2
Patient Characteristics according to Post-transplantation CMV Reactivation

Characteristic	All Patients	Patients without CMV Reactivation	Patients with CMV Reactivation	P Value
No. of patients	3539	2021 (57%)	1518 (43%)	
Patient age				
Median (range)	43 (16-74)	40 (16-72)	47 (16-74)	
<50	1883 (53%)	1197 (60%)	686 (44%)	<.01
≥50	1656 (47%)	794 (40%)	862 (56%)	
Patient sex				
Male	2082 (59%)	1165 (59%)	917 (59%)	NS
Female	1457 (41%)	826 (41%)	631 (41%)	
Donor type				
Related	1930 (55%)	1215 (61%)	715 (46%)	<.01
Unrelated	1609 (46%)	776 (39%)	833 (54%)	
Donor/recipient sex				
Female/male	812 (23%)	466 (23%)	346 (23%)	NS
Other combinations	2706 (77%)	1518 (77%)	1188 (77%)	
Stem cell source				
BM	2533 (72%)	1352 (68%)	1181 (76%)	<.01
PB	1006 (28%)	639 (32%)	367 (24%)	
Recipient/donor CMV serology				
Negative/negative	243 (8%)	175 (11%)	68 (5%)	<.01
Negative/positive	313 (11%)	230 (14%)	83 (6%)	
Positive/negative	481 (16%)	228 (14%)	253 (19%)	
Positive/positive	1909 (65%)	993 (61%)	916 (69%)	
Negative/negative	243 (8%)	175 (11%)	68 (5%)	<.01
Other combinations	2703 (92%)	1451 (89%)	1252 (95%)	
Disease type				
AML	1836 (52%)	1041 (52%)	795 (51%)	NS
ALL	911 (26%)	533 (27%)	378 (24%)	
CML	223 (6%)	134 (7%)	89 (6%)	
MDS	569 (16%)	283 (14%)	286 (19%)	
Disease status				
Standard	2442 (69%)	1432 (72%)	1010 (66%)	<.01
Advanced	1082 (31%)	554 (28%)	528 (34%)	
Performance status				
0-1	3355 (95%)	1901 (96%)	1454 (95%)	NS
2-4	162 (5%)	80 (4%)	82 (5%)	
Preparative regimens				
MA	2726 (78%)	1561 (79%)	1165 (76%)	.01
Nonmyeloablative	791 (23%)	413 (21%)	378 (25%)	
GVHD prophylaxis				
CSP-based	2122 (61%)	1279 (65%)	843 (55%)	<.01
FK506-based	1363 (39%)	682 (35%)	681 (45%)	
Acute GVHD				
Grade 0-1	2272 (65%)	1525 (77%)	745 (49%)	<.01
Grade 2-4	1242 (35%)	455 (23%)	787 (51%)	

TransCOVID GITMO Survey

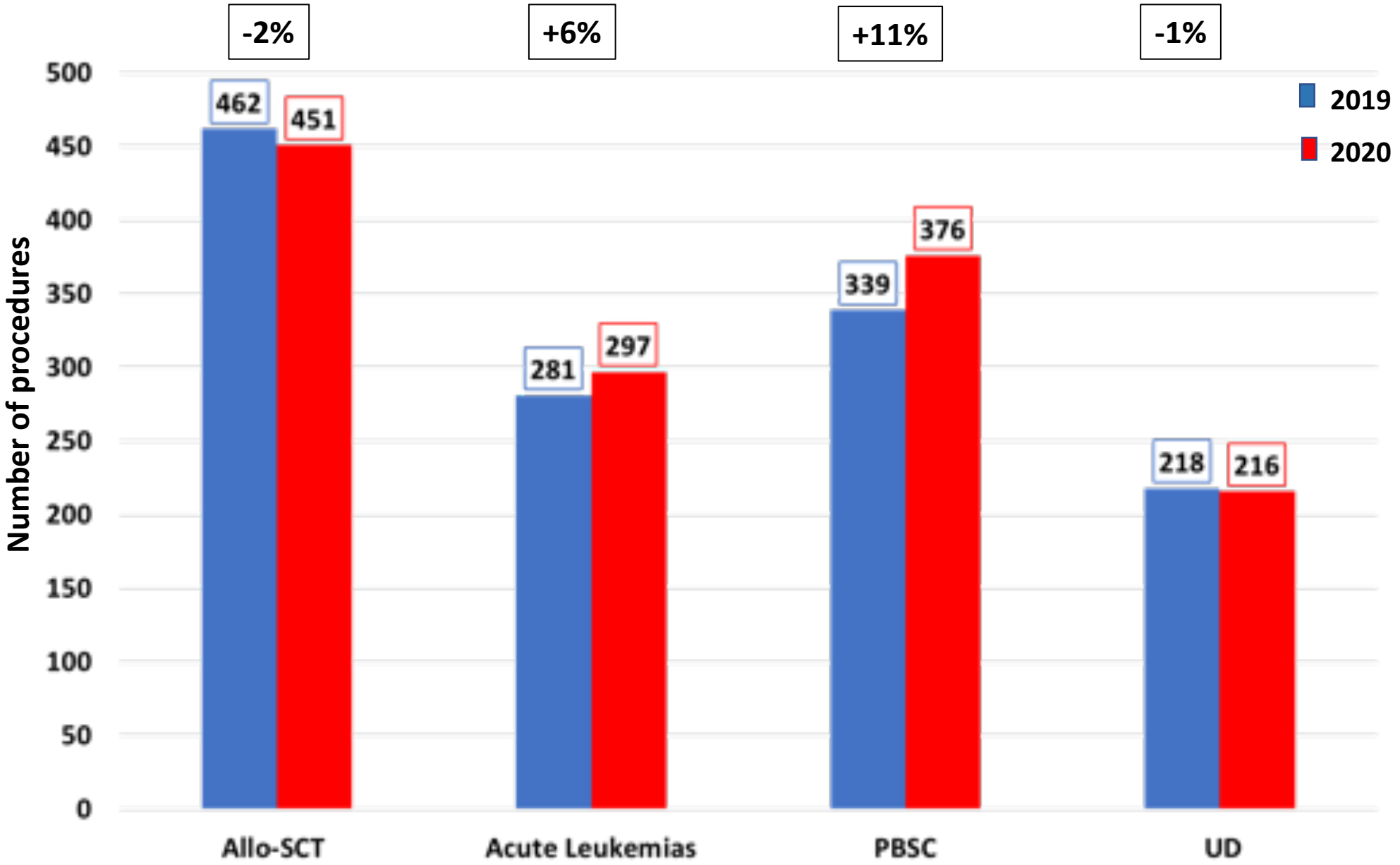


GITMO - Partecipating Centers (39)		
Alessandria	Candiolo (TO)	Palermo
Ancona	Cuneo	Pavia
Ascoli Piceno	Firenze	Pesaro
Avellino	Genova	Reggio Calabria
Bari	Lecce	Reggio Emilia
Bergamo	Mestre	Roma (Umberto I)
Bologna (Adulti)	Milano (Maggiore)	Roma (S. Camillo)
Bologna (Ped)	Milano (HSR)	Roma (Gemelli)
Bolzano	Modena	S. Giovanni Rotondo (FG)
Brescia (Adulti)	Monza	Torino (Molinette)
Brescia (Ped)	Napoli	Torino (Ped)
Brindisi	Orbassano (TO)	Trieste
Cagliari	Padova	Vicenza

Data unpublished

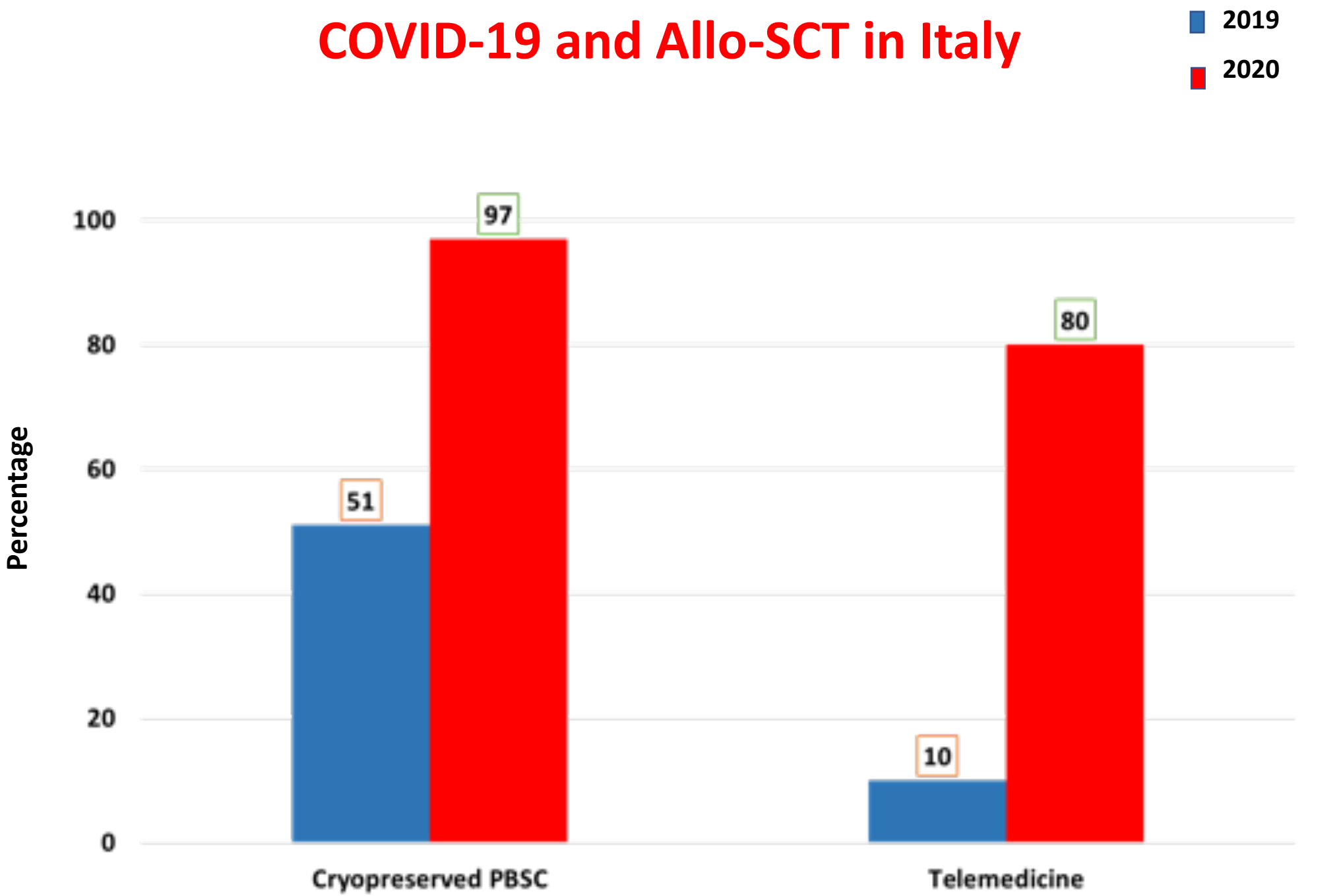
COVID-19 and Allo-SCT procedures in Italy

Comparison between Mar-July 2019 and Mar-July 2020



TransCOVID GITMO Survey *Data unpublished*

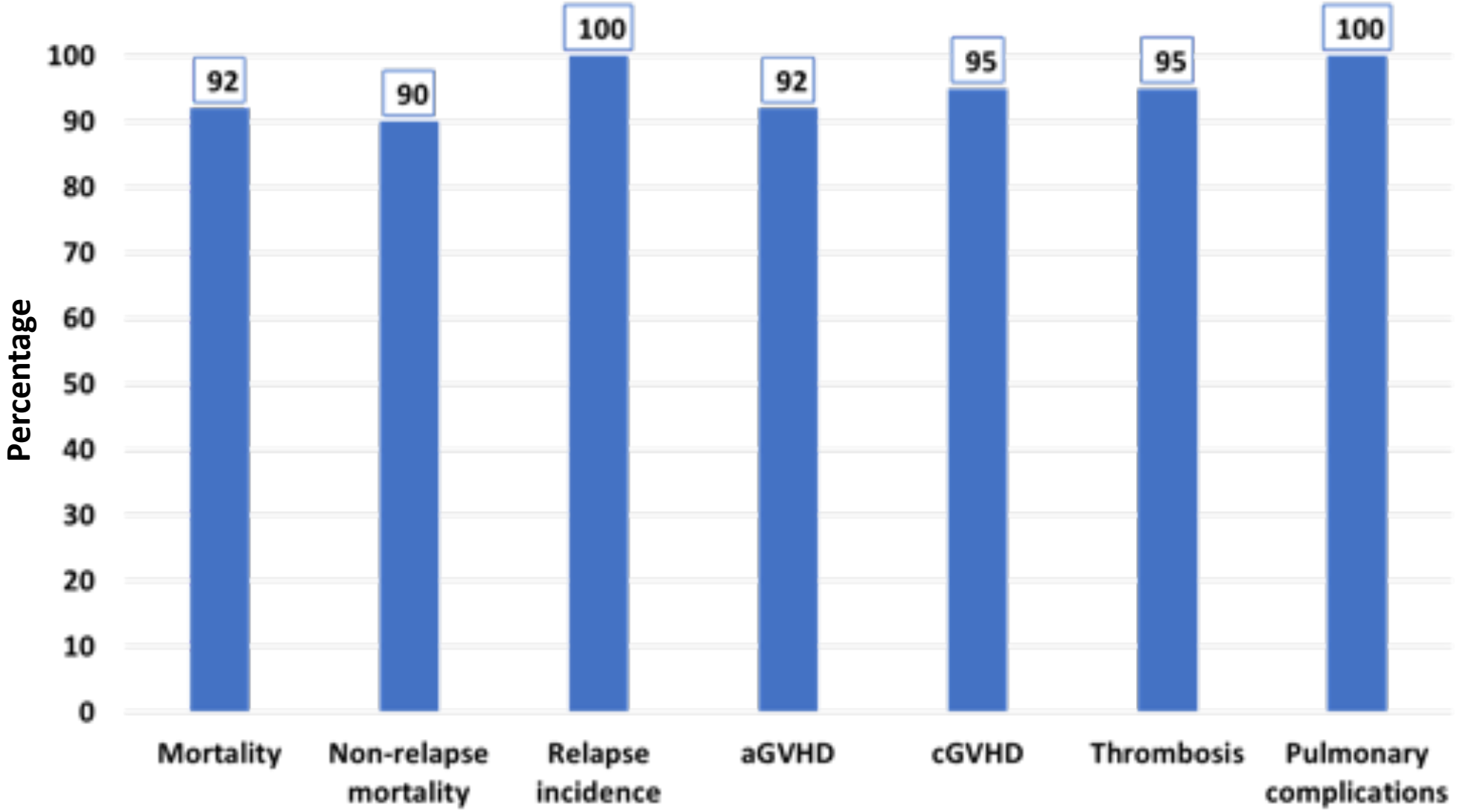
COVID-19 and Allo-SCT in Italy



TransCOVID GITMO Survey *Data unpublished*

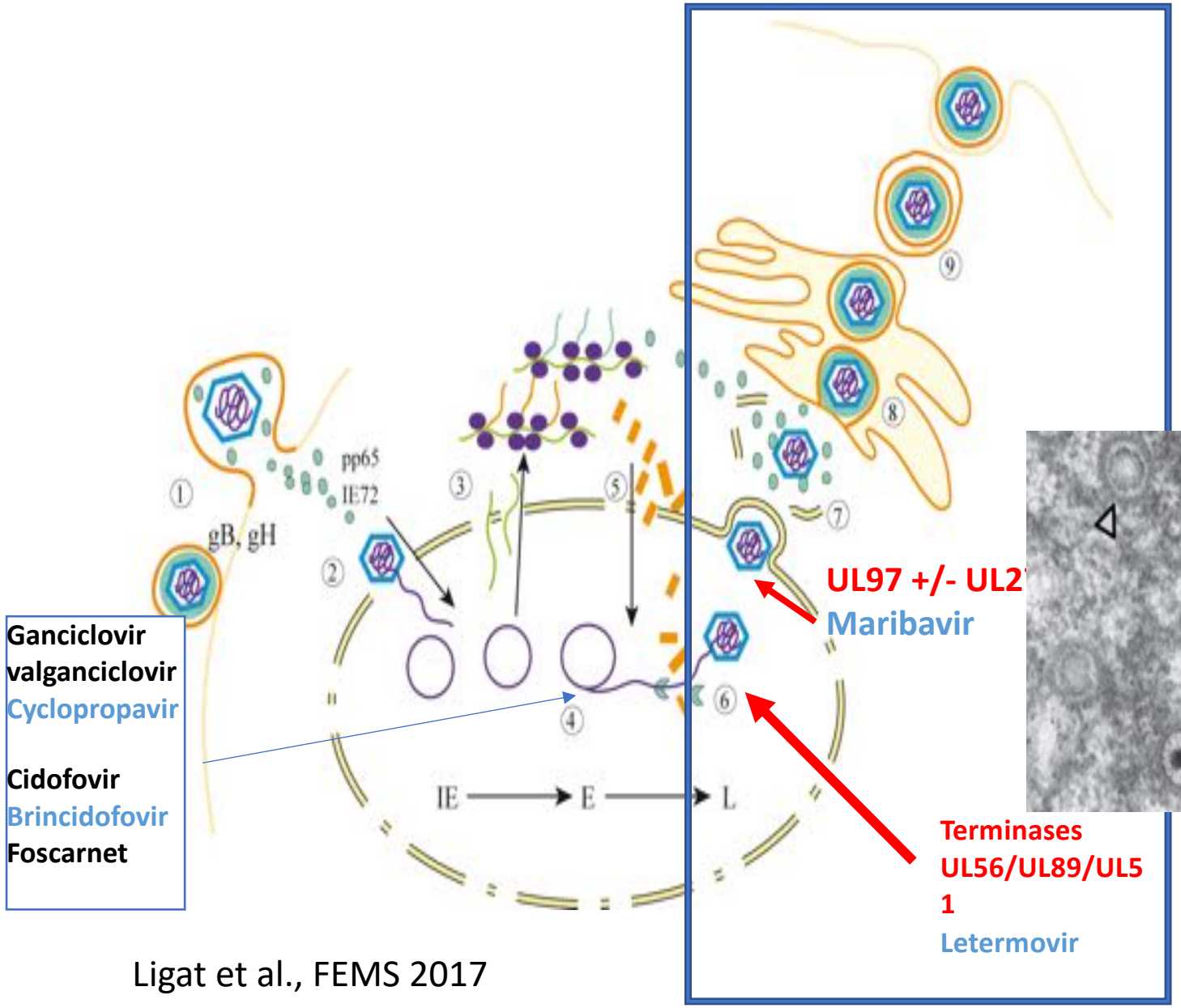
COVID-19 and Allo-SCT outcome

NO IMPACT of COVID-19 on Allo-SCT outcomes



TransCOVID GITMO Survey *Data unpublished*

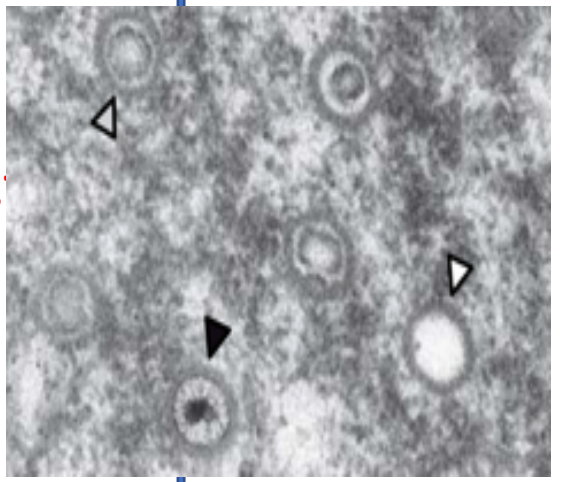
OLD and NEW
Anti-CMV molecules target the late stages of viral replication



Ganciclovir
valganciclovir
Cyclopropavir

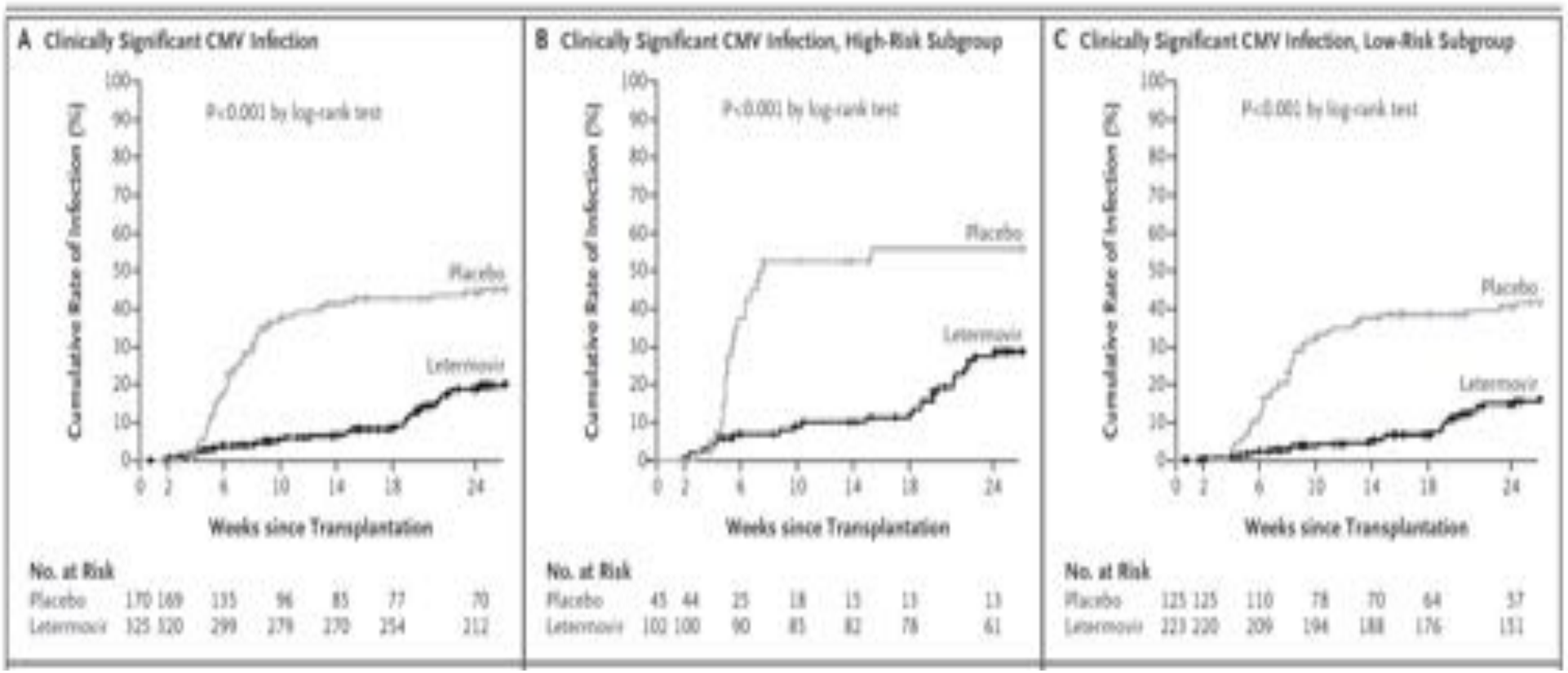
Cidofovir
Brincidofovir
Foscarnet

Ligat et al., FEMS 2017



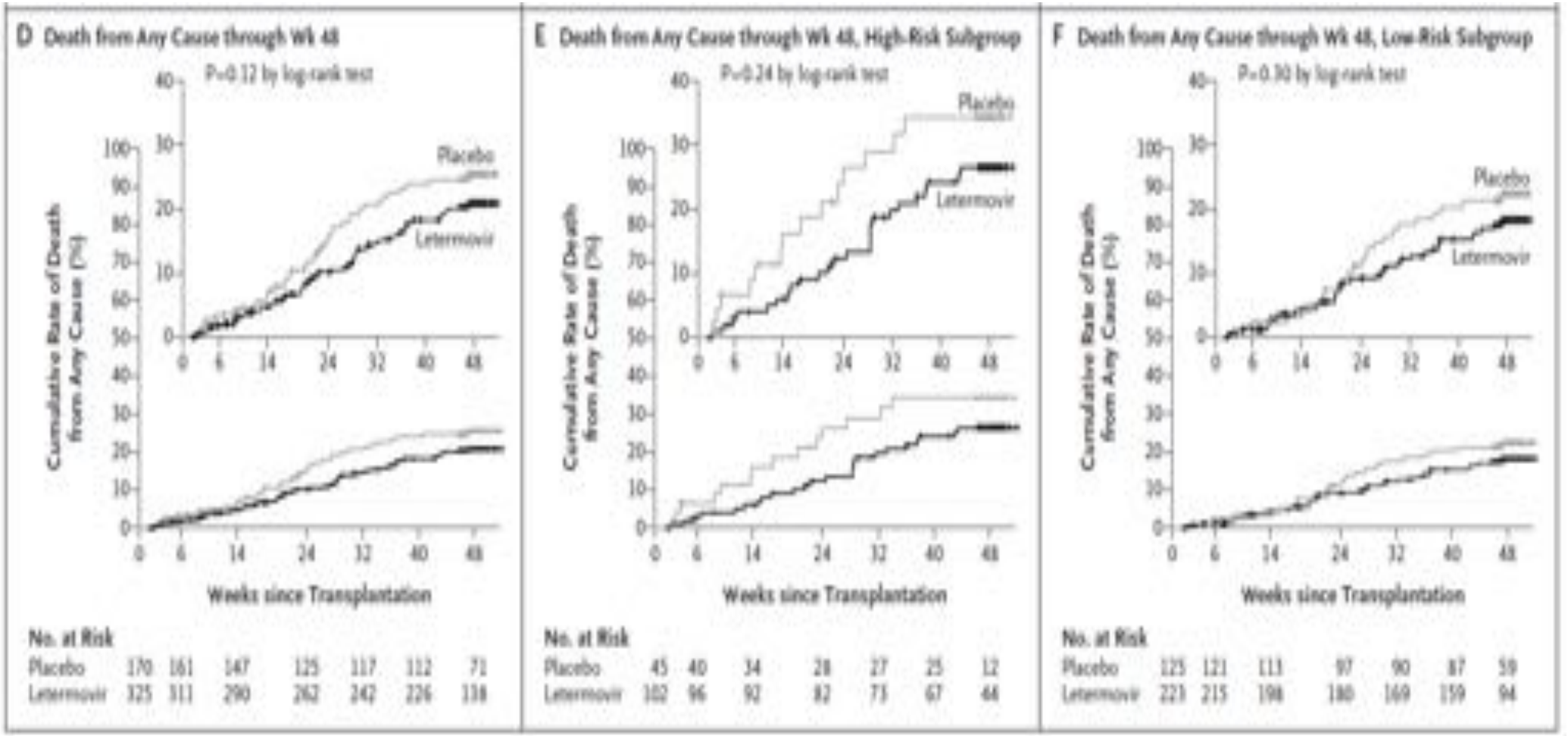
Borst et al., 2016

Time-to-Event Analyses of Clinically Significant CMV Infection



Marty FM, et al. N Eng J Med 2017;377:2433-44

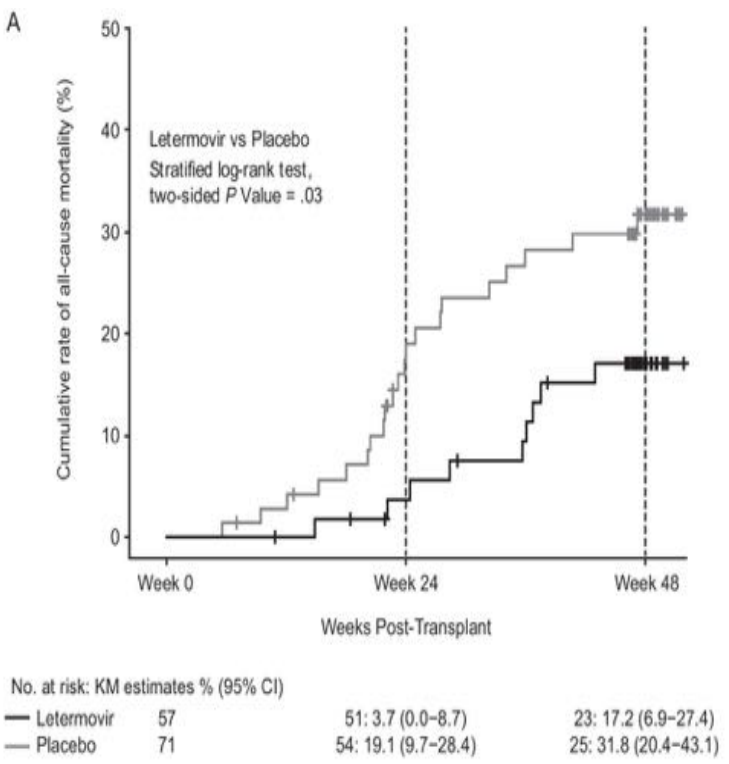
Mortality in the Primary Efficacy Population and According to Risk Subgroup



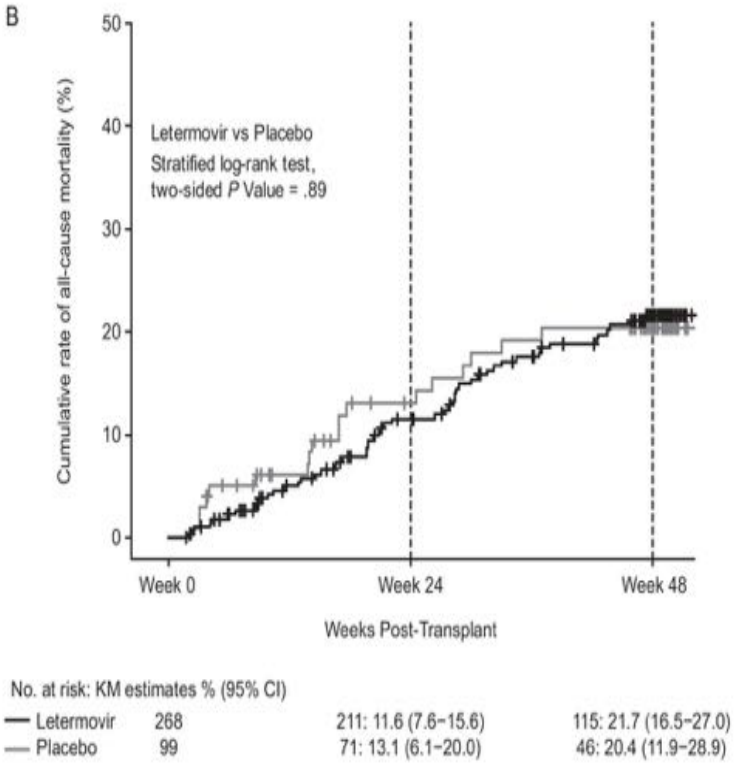
Marty FM, et al. N Eng J Med 2017;377:2433-44

Letermovir may reduce mortality by preventing or delaying clinically significant CMV infections in HCT recipients.

CS-CMVi

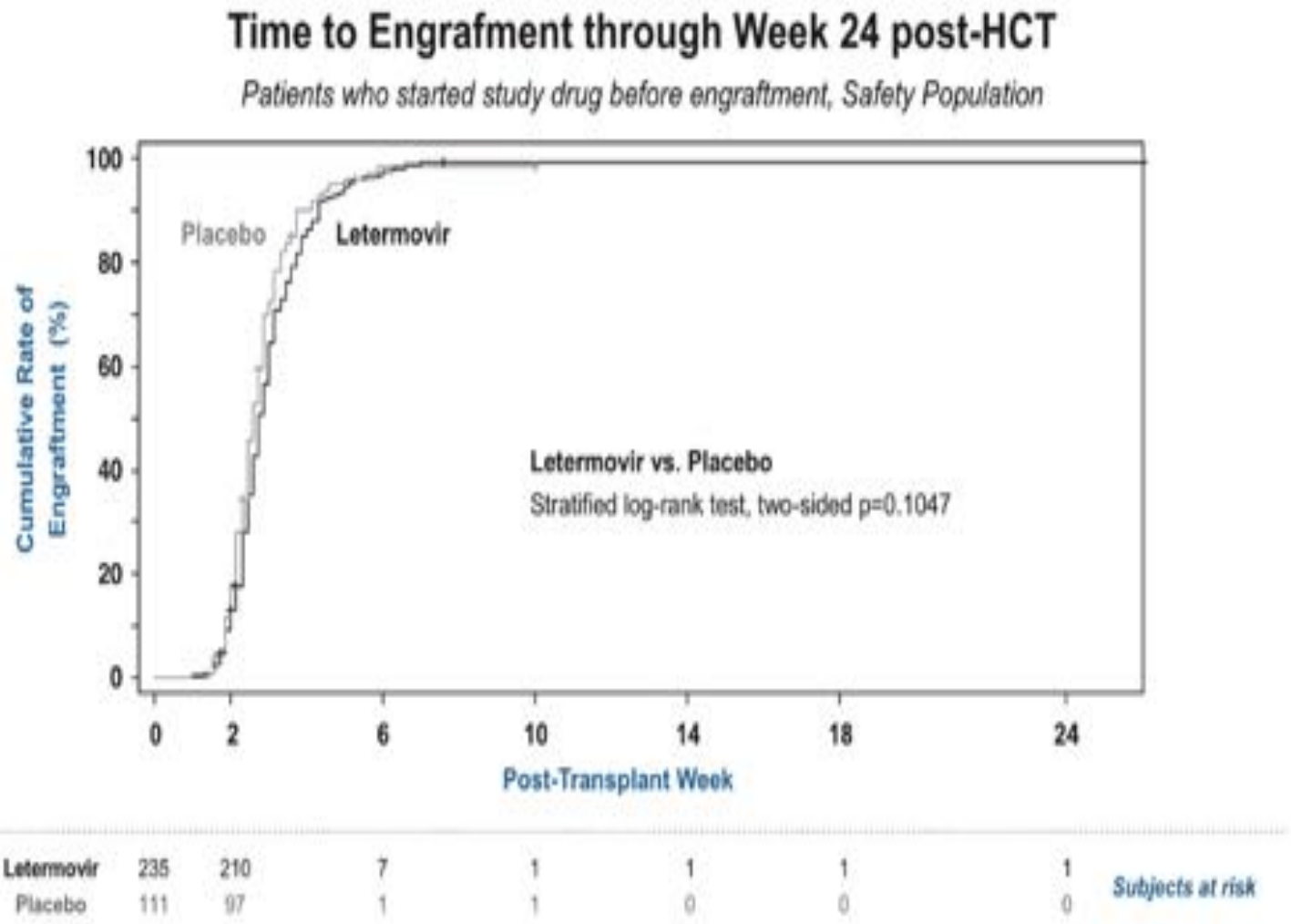


No CS-CMVi



Ljungman P et al, Clinical Infectious Diseases 2019

Figure S6. Time to neutrophil engraftment through Week 24 post-HCT among patients who started study drug before engraftment, Safety Population.



Marty FM, et al. N Eng J Med 2017;377:2433-44

frontiers in Cell and Developmental Biology

ORIGINAL RESEARCH
published: xx October 2020
doi: 10.3389/fcell.2020.594068

Advances in CMV Management: A Single Center Real-Life Experience

Michele Malagola[1]*, Caterina Poiara[2], Nicola Polverelli[1], Tatiana Zollner[1], Daria Beffoni[3], Lisa Gandolfi[1], Doriana Gramegna[3], Enrico Morello[1], Alessandro Turra[1], Silvia Corbellini[3], Liana Signorini[4], Giovanni Moioli[4], Simona Bernardi[1,5], Camilla Zanaglio[1,5], Mirko Farina[1], Tullio Ella Testa[1], Arnaldo Caruso[2] and Domenico Russo[1]

[1] Chair of Hematology, Bone Marrow Transplant Unit, ASST-Spedali Civili Brescia, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [2] ASST-Spedali Civili, Section of Microbiology, Department of Experimental and Applied Medicine, University of Brescia, Brescia, Italy, [3] UO Farmacia Aziendale, ASST Spedali Civili of Brescia, Italy, [4] UOC Malattie Infettive, ASST Spedali Civili, Brescia, Italy, [5] CREA Laboratory (Hematological Research All. Centre), ASST-Spedali Civili Brescia, Brescia, Italy

NOVEMBER 2017 – APRIL 2020

101 allo-SCT

41 patients (41%)
NO LETERMOVIR ERA
November 2017 – November 2018

60 patients (59%)
LETERMOVIR ERA
December 2018 – April 2020

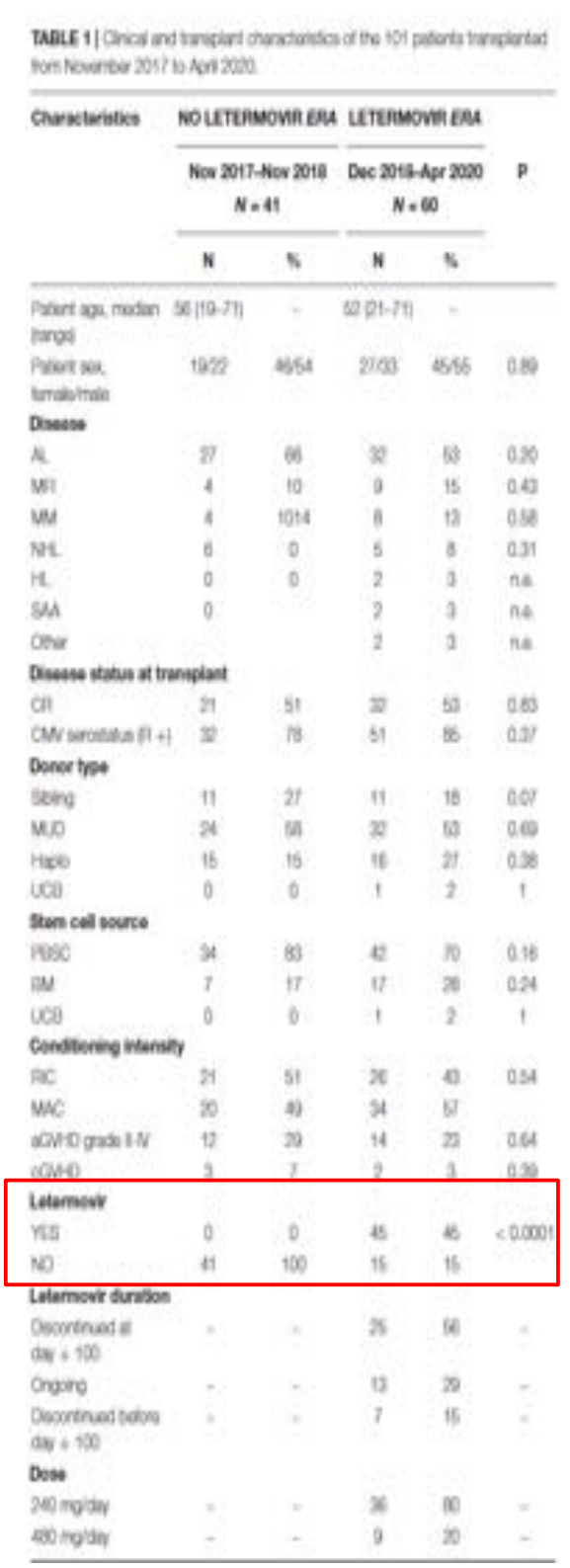


TABLE 1 | Clinical and transplant characteristics of the 101 patients transplanted from November 2017 to April 2020.

Characteristics	NO LETERMOVIR ERA		LETERMOVIR ERA		
	Nov 2017–Nov 2018 N = 41		Dec 2018–Apr 2020 N = 60		P
	N	%	N	%	
Patient age, median (range)	56 (19–71)	-	52 (21–71)	-	
Patient sex, female/male	19/22	46/54	27/33	45/55	0.89
Disease					
AL	27	66	32	53	0.20
MS	4	10	9	15	0.43
MM	4	10/4	8	13	0.58
NHL	6	0	5	8	0.31
HL	0	0	2	3	n.a.
SAA	0		2	3	n.a.
Other			2	3	n.a.
Disease status at transplant					
CR	21	51	32	53	0.83
CMV serostatus (R +)	32	78	51	85	0.37
Donor type					
Sibling	11	27	11	18	0.07
MUD	24	58	32	53	0.69
Haplo	15	15	16	27	0.38
UCB	0	0	1	2	1
Stem cell source					
PBSC	34	83	42	70	0.16
BM	7	17	17	28	0.24
UCB	0	0	1	2	1
Conditioning intensity					
RIC	21	51	26	43	0.54
MAC	20	49	34	57	
aGVHD grade II-IV	12	29	14	23	0.64
cGVHD	3	7	2	3	0.39
Letermovir					
YES	0	0	45	45	< 0.0001
NO	41	100	15	15	
Letermovir duration					
Discontinued at day + 100	-	-	25	56	-
Ongoing	-	-	13	29	-
Discontinued before day + 100	-	-	7	15	-
Dose					
240 mg/day	-	-	36	80	-
480 mg/day	-	-	9	20	-

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RESULTS (1)

TABLE 3 | Impact of letermovir on the management of patients undergoing allo-SCT.

	Nov 2017–Nov 2018 NO LET "ERA"	Dec 2018–APR 2020 LET "ERA"	P
No. of allo-SCT	41	60	–
Letermovir prophylaxis day 0 → + 100	0	45	–
Clinically significant CMV infection (≤ 100 days)	18 (44%)	5* (8%)	0.0006
Clinically significant CMV infection (≤ 180 days)	28 (68%)	10 (17%)	<0.00001
CMV disease (≤100 days)	5 (12%)	1** (2%)	0.02
CMV disease (≤180 days)	5 (12%)	1 (2%)	0.02
Bacterial infections (≤100 days)	23 (56%)	22 (37%)	0.05
Bacterial infections (≤180 days)	32 (78%)	27 (45%)	0.009
Fungal infections (probable/proven) (≤100 days)	8 (19%)	5 (8%)	0.09
Fungal infections (probable/proven) (≤180 days)	9 (22%)	5 (8%)	0.05
aGVHD grade ≥ 2	12 (29%)	14 (23%)	0.5
Hospital re-admission (≤100 days)	16 (39%)	14 (23%)	0.09
Hospital re-admission (≤180 days)	27 (66%)	24 (40%)	0.01
Cumulative cost for ITC†	Euro 38,000	Euro 10,000	–
Letermovir costs			
–240 mg day 0 → + 100	–	Euro 13,700/pt	–
–480 mg day 0 → + 100	–	Euro 29,000/pt	–

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RESULTS (2)

TABLE 3 | Impact of letermovir on the management of patients undergoing allo-SCT.

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–240 mg day 0 → + 100	–	Euro 13,700/pt	–
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RESULTS (3)

TABLE 3 | Impact of letermovir on the management of patients undergoing allo-SCT.

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Cumulative cost for ITC†	Euro 38,000	Euro 10,000	–
Letermovir costs			
–240 mg day 0 → + 100	–	Euro 13,700/pt	–
–480 mg day 0 → + 100	–	Euro 29,000/pt	–

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RESULTS (4)

TABLE 3 | Impact of letermovir on the management of patients undergoing allo-SCT.

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Fungal infections (probable/proven) (≤180 days)	9 (22%)	5 (8%)	0.05
aGVHD grade ≥ 2	12 (29%)	14 (23%)	0.5
Hospital re-admission (≤100 days)	16 (39%)	14 (23%)	0.09
Hospital re-admission (≤180 days)	27 (66%)	24 (40%)	0.01
Cumulative cost for ICT[#]	Euro 38,000	Euro 10,000	–
Letermovir costs			
–240 mg day 0 → + 100	–	Euro 13,700/pt	–
–480 mg day 0 → + 100	–	Euro 29,000/pt	–

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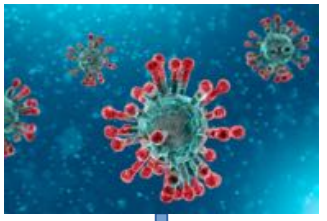
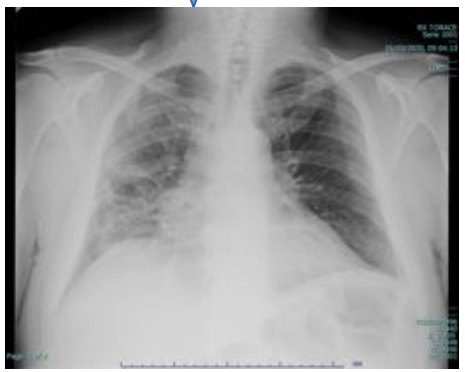
EFFECTS OF SARS CoV-2 INFECTION



Direct Effects



CMV re-activation

Bacterial
Fungal Infections

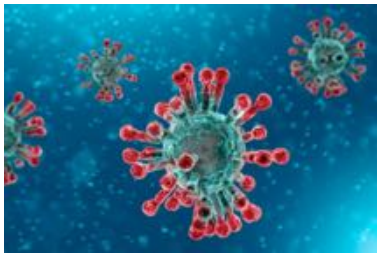
SARS CoV-2 treatment

Alterated Immune
response

GVHD

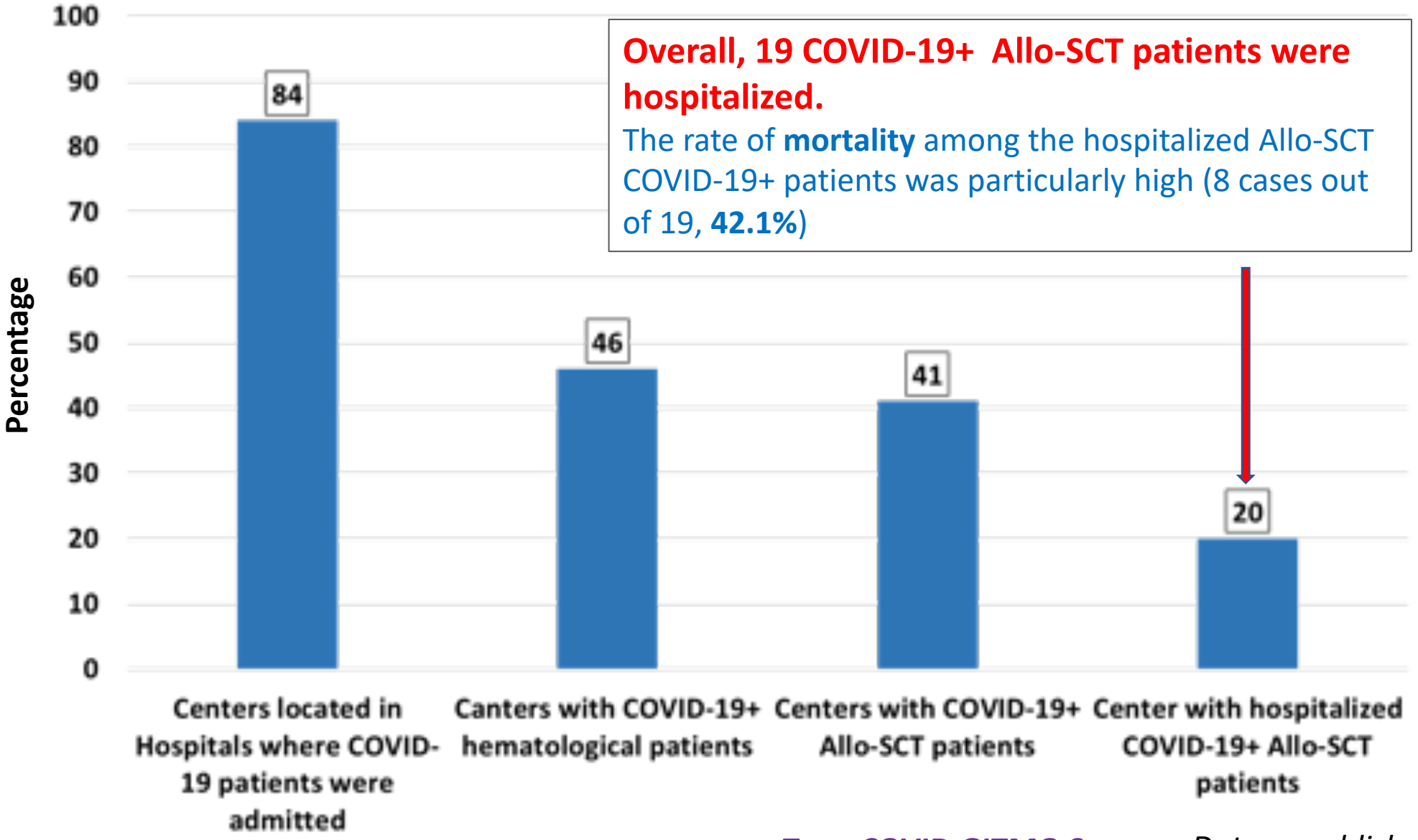
Immunosuppressive drugs

COVID-19 and Allo-SCT



Overall, 19 COVID-19+ Allo-SCT patients were hospitalized.

The rate of **mortality** among the hospitalized Allo-SCT COVID-19+ patients was particularly high (8 cases out of 19, **42.1%**)



TransCOVID GITMO Survey *Data unpublished*