AIBT Associazione Italiana di Immunogenetica e Biologia dei Trapianti
XXX Congresso Nazionale
Napoli, 10/12 ottobre 2024
"The programme of this event has been approved by the EFI Education Committee"

Linfociti T citotossici nel controllo delle infezioni nel paziente trapiantato

PATRIZIA COMOLI
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Fondazione IRCCS Policlinico San Matteo
Sistema Socio Sanitario
Regione Lombardia

Il sottoscritto *Patrizia Comoli*
in qualità di relatore al

XXX CONGRESSO NAZIONALE AIBT
NAPOLI, 10/12 OTTOBRE 2024

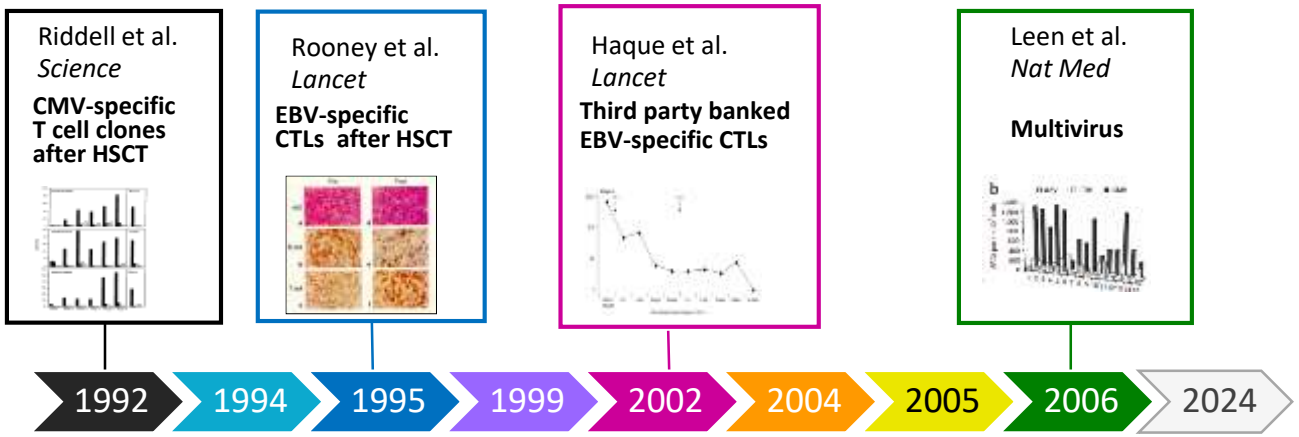
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 dell'Accordo Stato-Regione del 19 aprile 2012, per conto di Planning Congressi srl

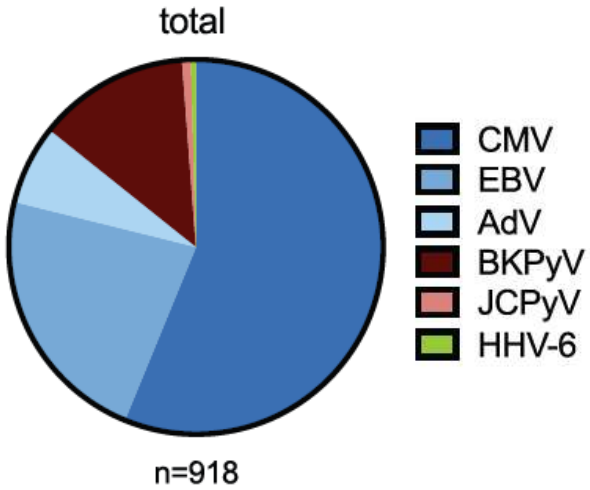
dichiara

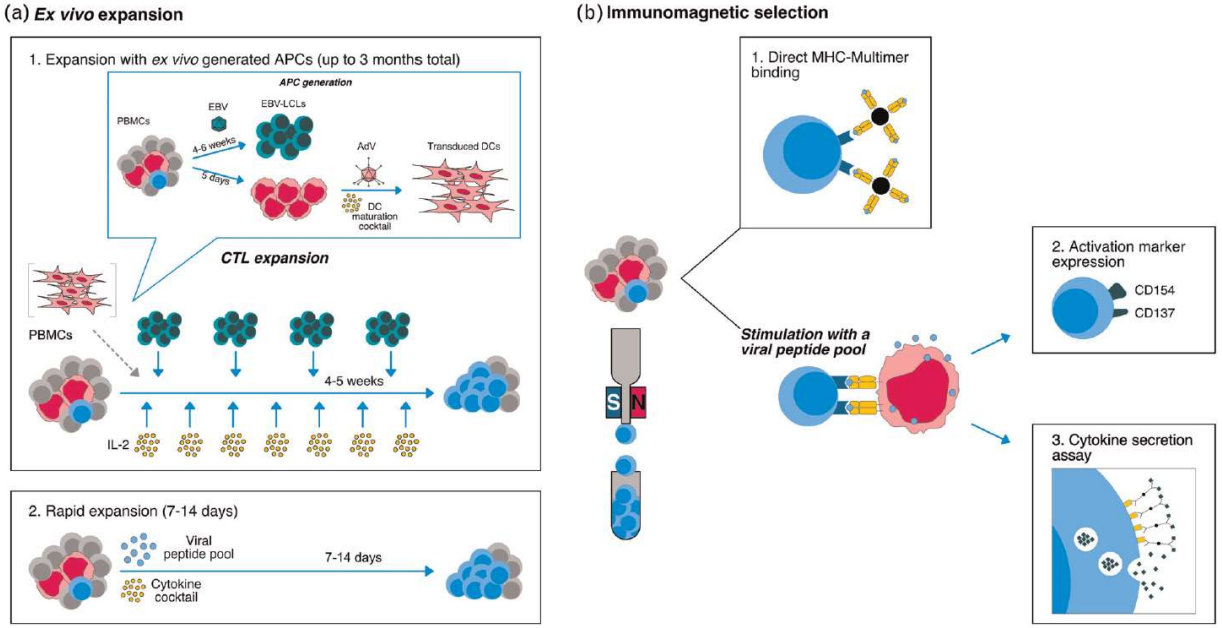
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Atara Biotherapeutics: consultancy/advisory role*
- *Pierre Fabre Pharma: consultancy/advisory role*

Cell therapy for viral infections after HSCT: historical data







Basso et al. Front Immunol 2020
Walti *et al*. *Curr Opin Infect Dis 2022*

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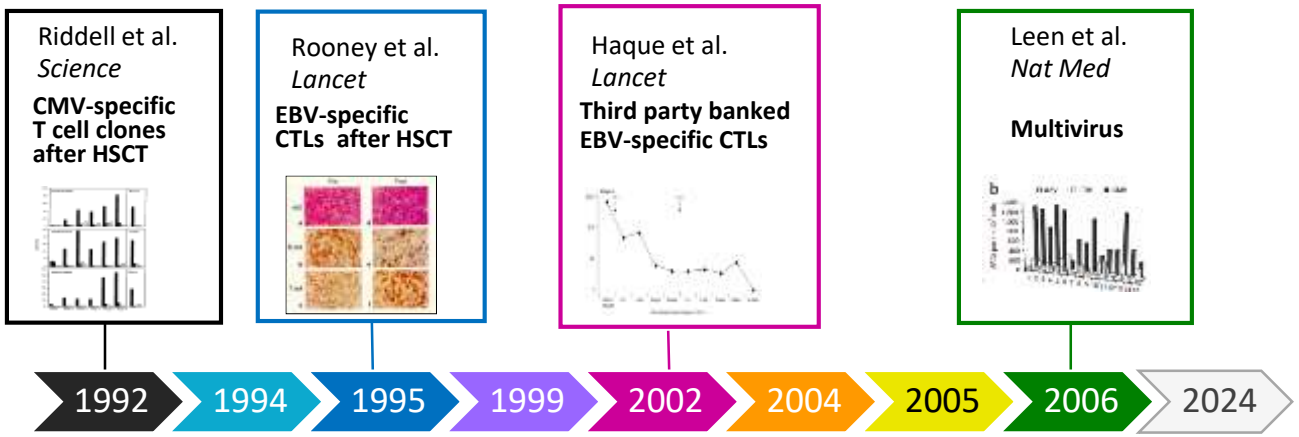
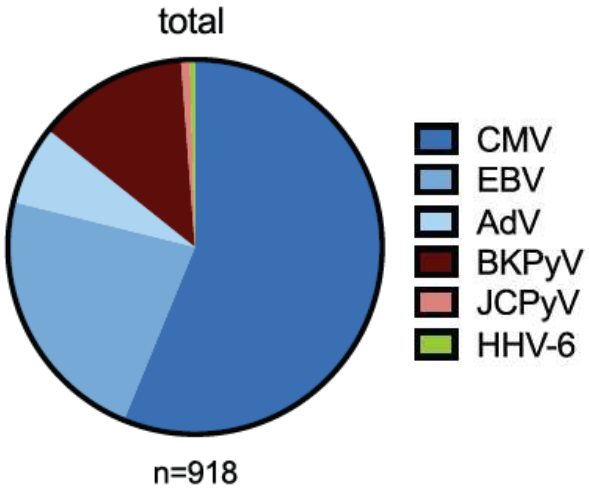
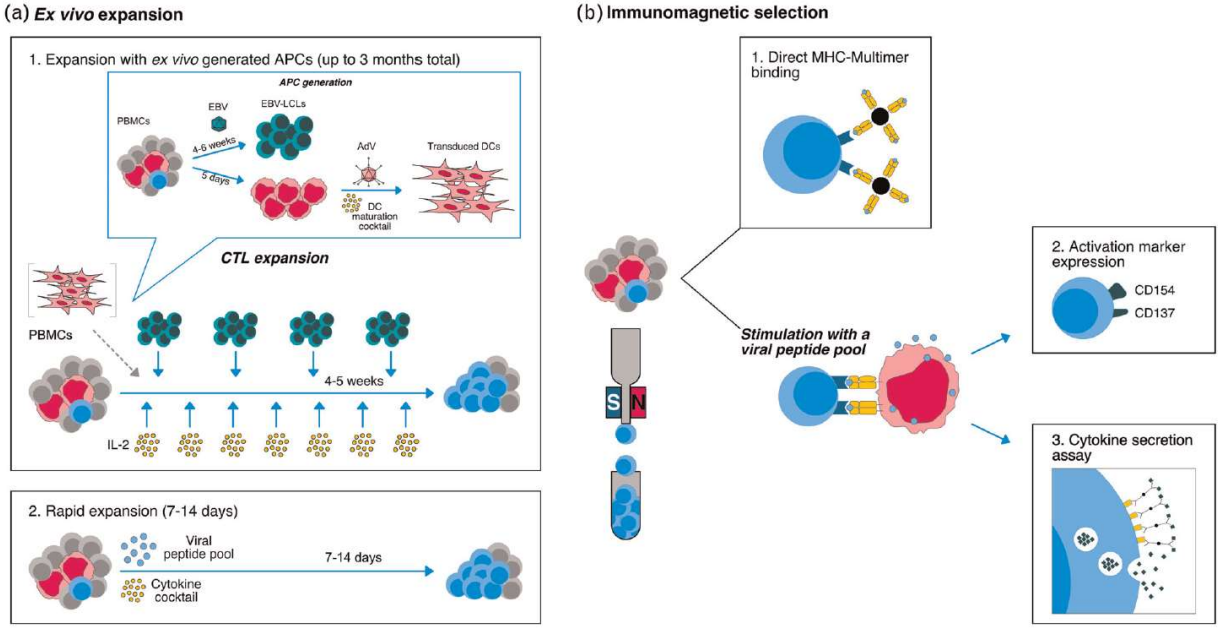




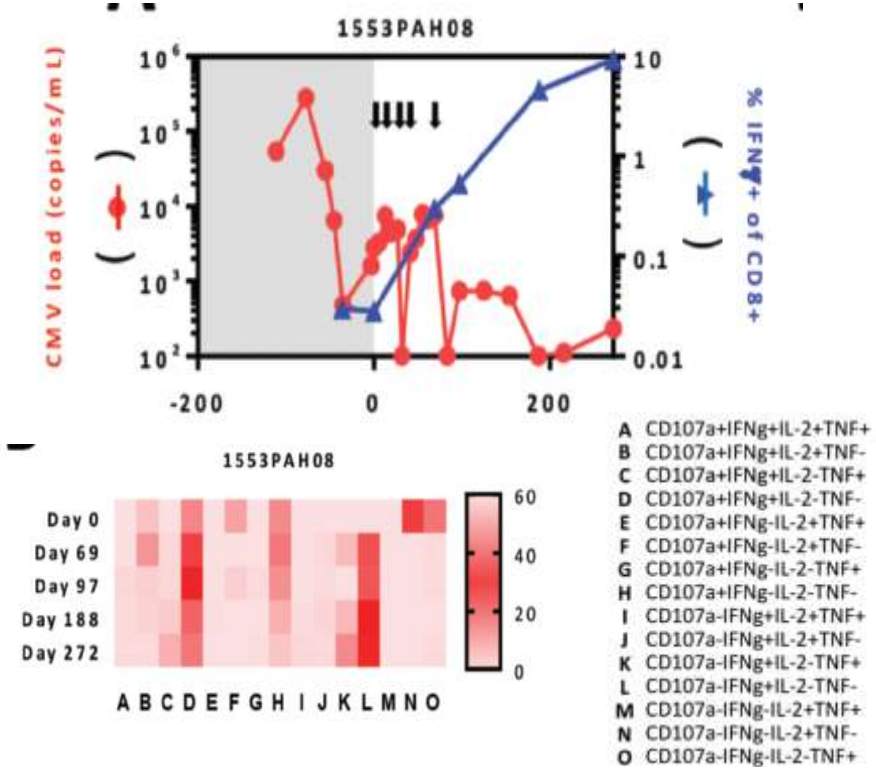


Response rate (%)

	Prophylaxis	Therapy
EBV	99	77
CMV	81	86
ADV	-	77

Basso et al. Front Immunol 2020
Walti *et al*. *Curr Opin Infect Dis 2022*

Cell therapy for viral infections after SOT: CMV



CMV

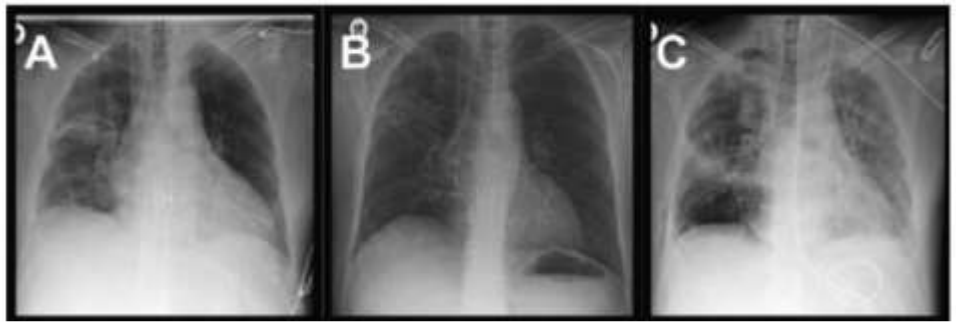
17 pts (refractory CMV infection/disease):

15 clear CMV viremia/disease

2 progression CMV disease

88%

1 acute rejection leading to death from graft failure in a lung Tx recipient



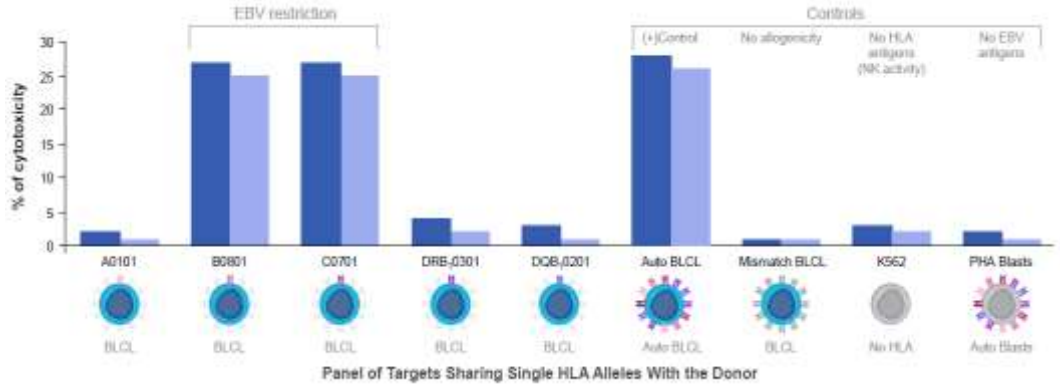
1. Brestrich et al. *Am J Transplant* 2008
2. Holmes-Liew et al. *Clin Transl Immunol* 2015
3. Macesic et al. *Am J Transplant* 2015
4. Smith et al. *Clin Infect Dis* 2019
5. Miele et al. *Microorganisms* 2021

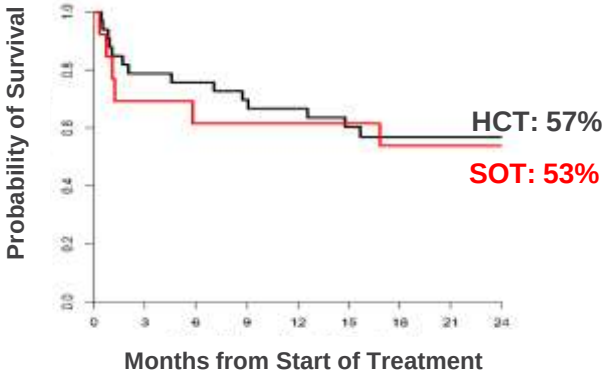
Cell therapy for viral infections: limitations of dedicated VST

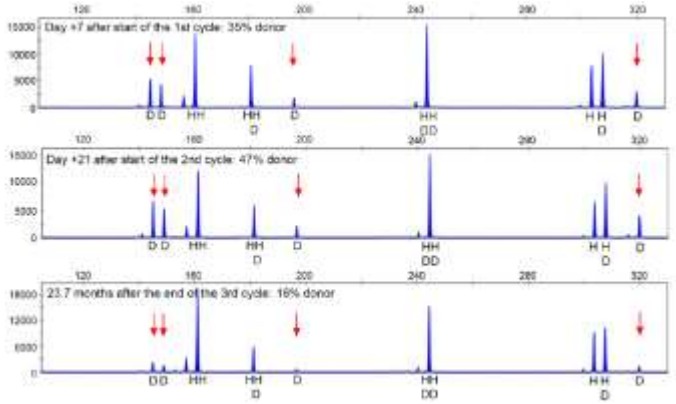
- Urgency of treatment in some patients:
  - shorten the time needed for VST production (>15 days)
- Technical difficulties in selecting/expanding VSTs from virus-seronegative individuals:
  - dedicated VSTs unavailable for virus-seronegative recipients or HSCT recipients of virus-seronegative donors
- Restricted access to cellular therapies:
  - production in few GMP facilities with limited ability for widespread distribution
  - limited commercialization

Implementing cell therapy for viral infections: 3° party S-VST banking

- Third-party donor-derived EBV-CTLs in 46 HSCT or SOT recipients with rituximab-refractory lymphomas
- Attribution: HLA typing + restriction







Prockop et al. *J Clin Invest.* 2020

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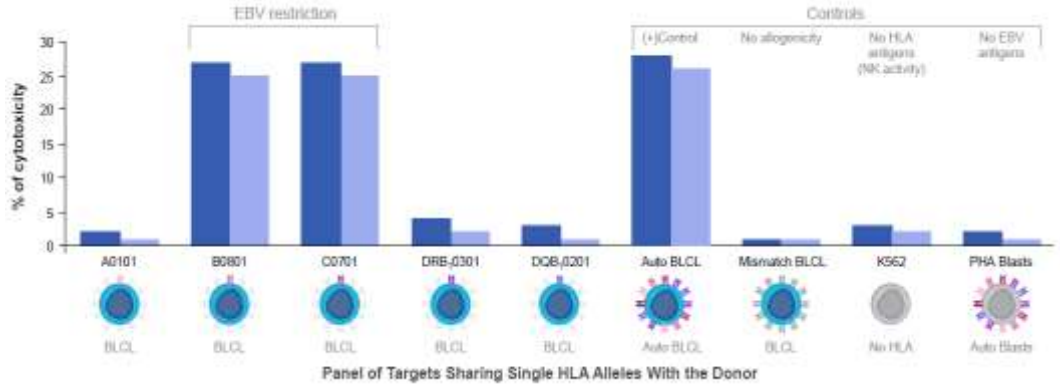
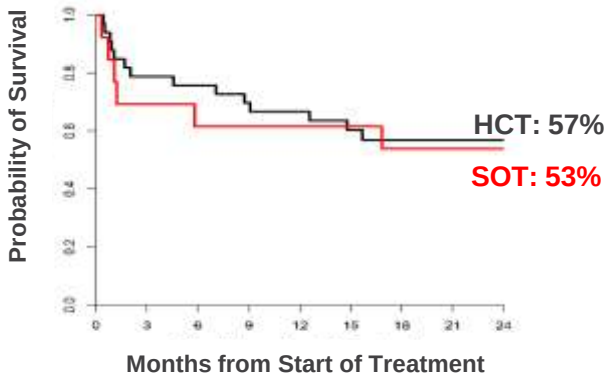
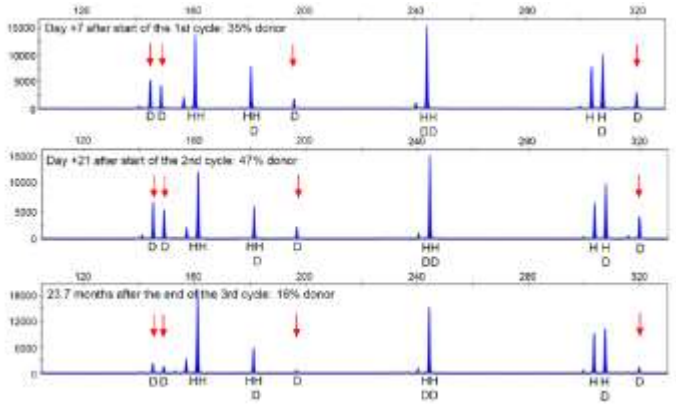
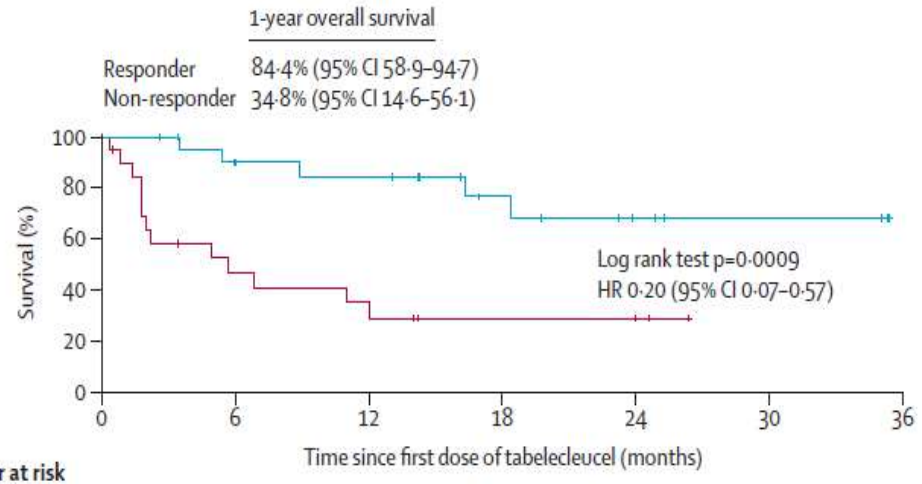






Prockop et al. *J Clin Invest.* 2020

Phase III trial



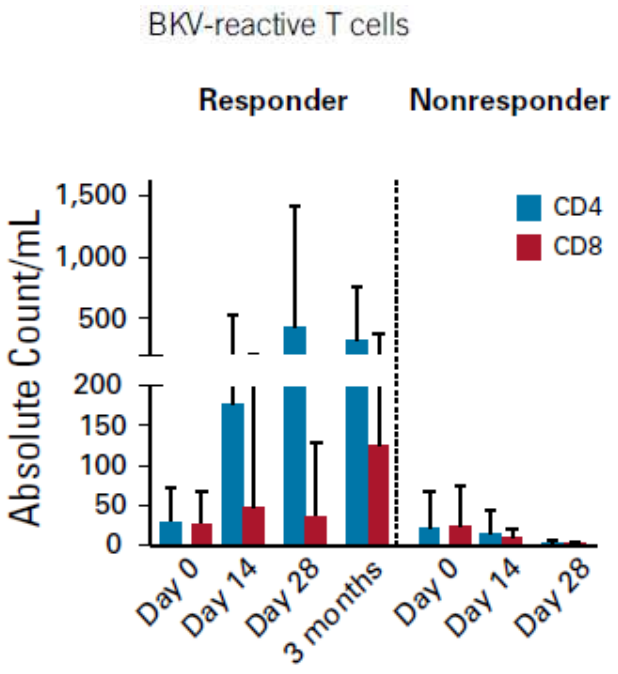
Number at risk (number censored)							
Responder	22 (0)	17 (3)	15 (4)	9 (9)	5 (12)	3 (14)	0 (17)
Non-responder	21 (0)	8 (3)	6 (3)	3 (5)	3 (5)	0 (8)	.. ..

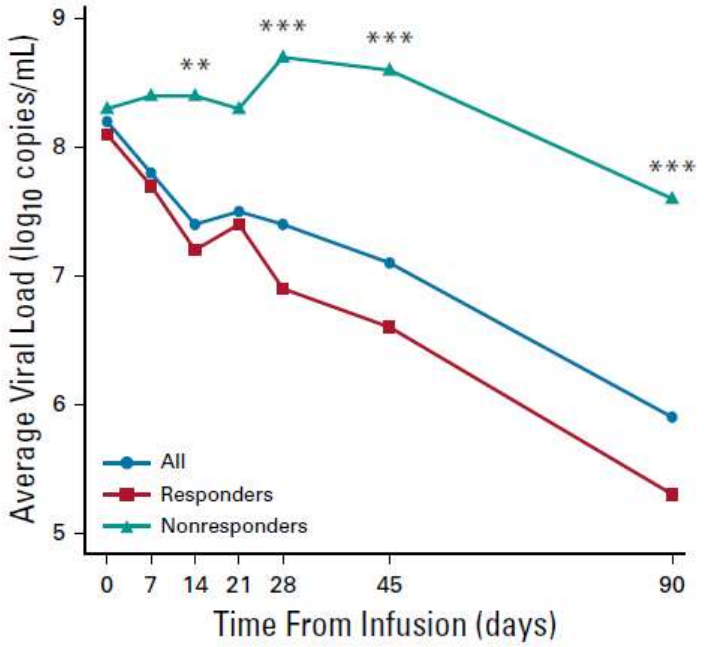
Mahadeo et al. *Lancet Oncol 2024*

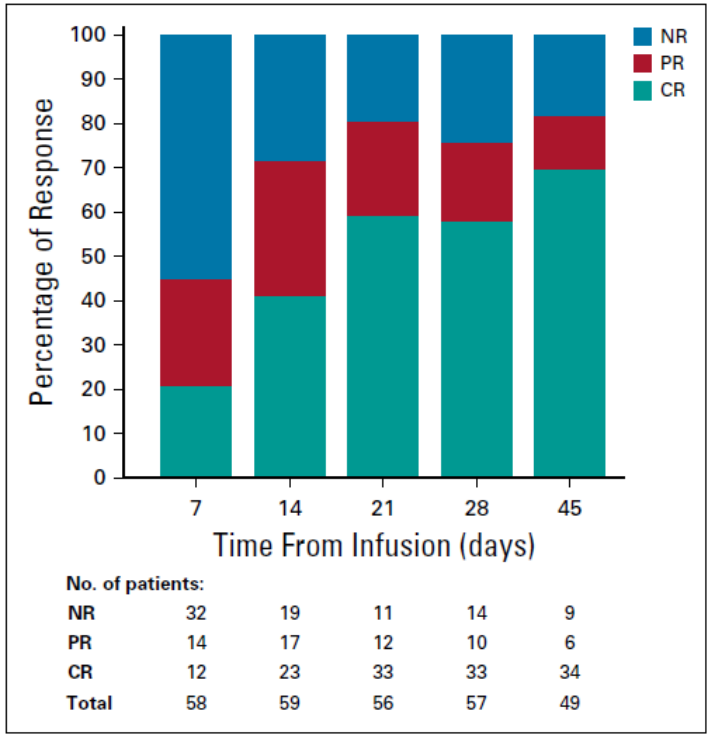
Cell therapy for viral infections: 3rd party BKV-CTLs

Open-label, single arm, phase II study:

- 59 allo HSCT recipients with BKV-related HC
- cell dose: 1 x 10^5 CTLs/kg for the phase I and 2 x 10^5 CTLs/kg for the phase II
- primary end-point: response as decrease in HC grade and viral load





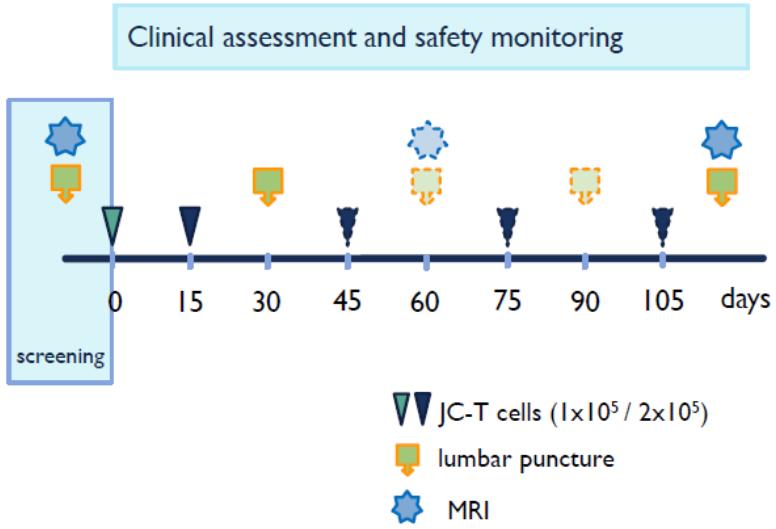


Olson *et al*. *J Clin Oncol* 2021

Cell therapy for viral infections: 3rd party VST- JCPyV

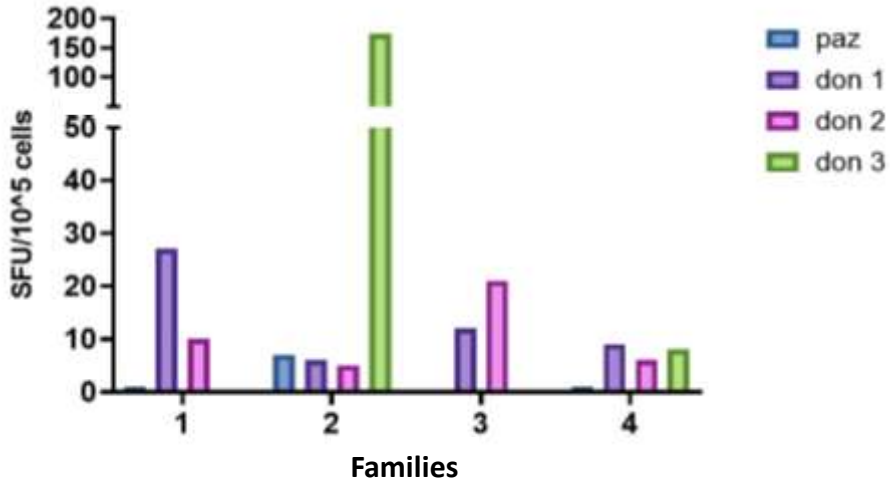
Between 2014 and 2024

- 27 patients treated for PML
- underlying condition:
  - hematologic malignancy treated with biologicals
  - Tx recipients
  - PIDs or AIDS



Cell product

- autologous
- allogeneic:
  - HSCT donor (if available)
  - HLA-haploidentical family donor
  - HLA-partially matched third-party donor



Balduzzi et al. Bone Marrow Transplant 2011
Berzero et al. Ann Neurol 2021
Peghin et al. J Heart Lung Transplant 2022

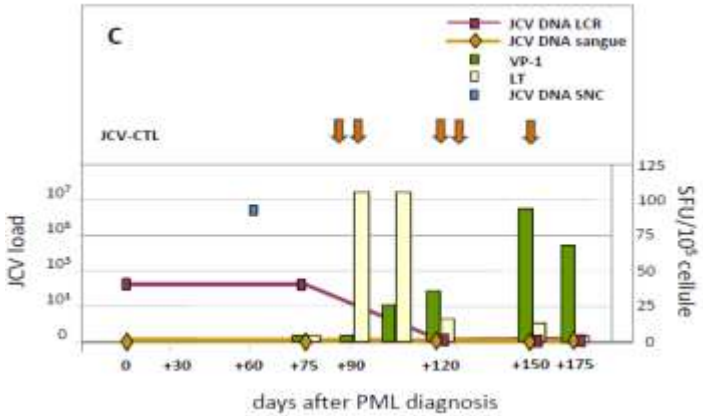
Cell therapy for viral infections: 3rd party VST- JCPyV

Clinical results

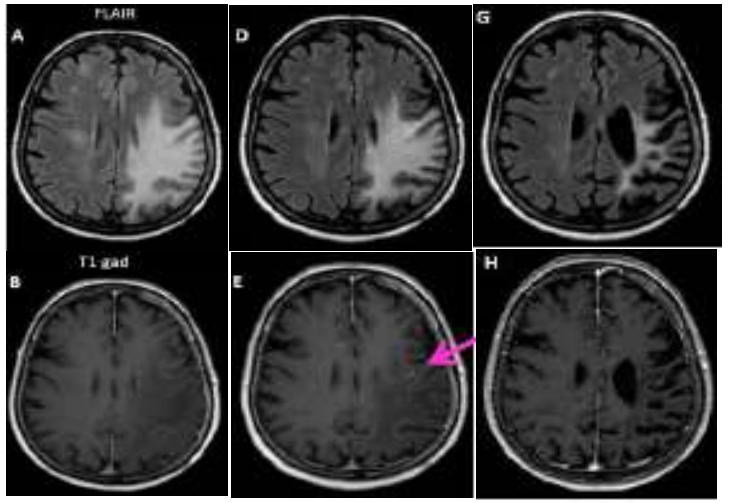
- 14/27 pts reached PML control (52%)
  - 11 are alive in remission
  - 3 died of complications related to baseline disease
- 13 patients had PML progression and died of PML or disease-related causes
- AE/SAE
  - grade 3 or >: 1 infection (VZV reactivation: encephalitis)*
  - no hematologic AEs
  - 1 clinical IRIS, treated with steroids
- Main factor related to failure
  - time to intervention: early treatment is crucial for CR

*unrelated to cell therapy

JCPyV immune recovery

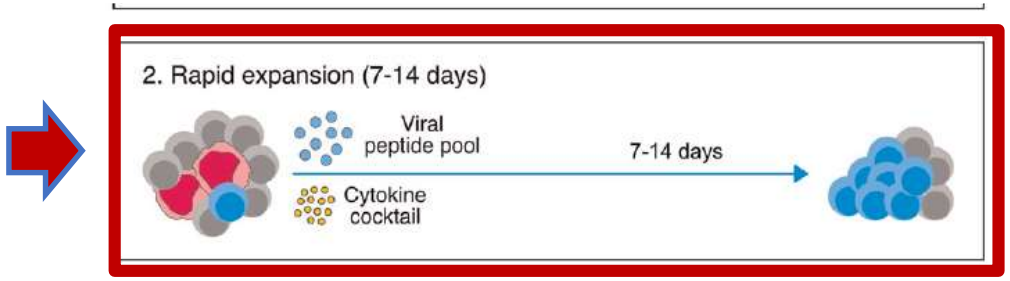


MRI: small areas of punctate enhancement



Balduzzi et al. Bone Marrow Transplant 2011
Berzero et al. Ann Neurol 2021
Peghin et al. J Heart Lung Transplant 2022

Implementing cell therapy for viral infections: rapid expansion and multi-VST



Specificities:

CMV pp65
EBV EBNA-1, LMP2, BZLF
ADV penton, hexon
BKV VP1, LT
HHV6 U11, U14 and U90

9-11 days

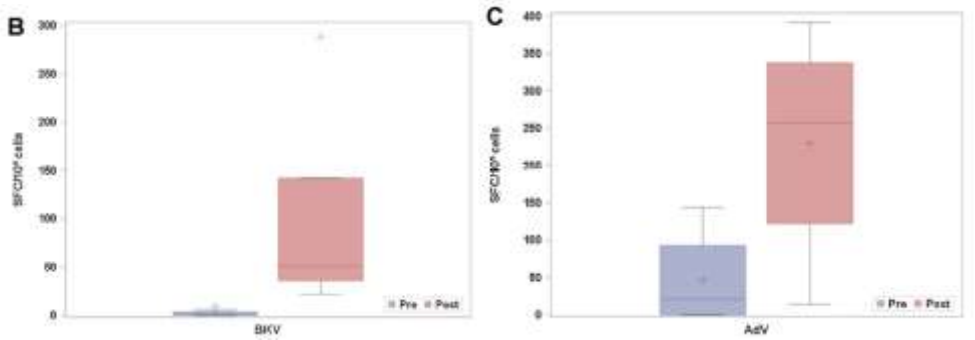
AdV	CMV	EBV	BKV	HHV6	control
1863	1105	1328	1251	418	8
1821	5355	489	313	303	1
951	3335	1338	303	248	0
206	855	395	11	178	0
425	851	32	6	130	0
21	2580	68	39	67	0
303	2	305	36	8	0
150	184	59	9	0	0
37	119	86	3	12	0
43	891	11	1	4	1
26	2	179	5	53	2
61	174	23	3	2	0
1170	16	21	21	25	10

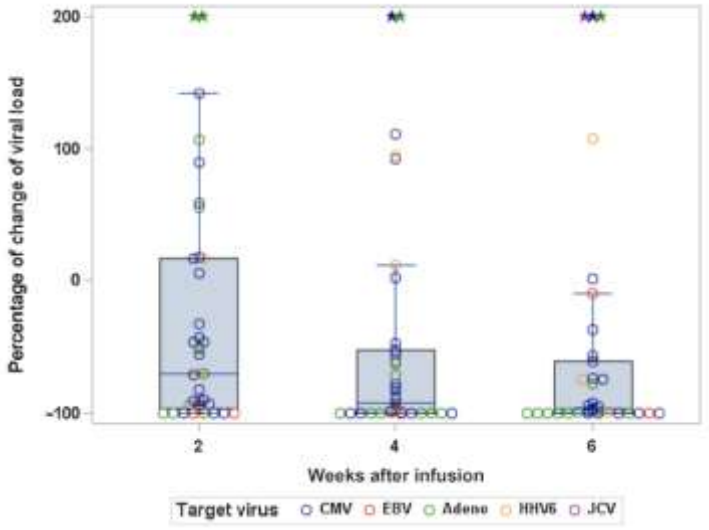
Tzannou *et al*. *J Clin Oncol 2017*

Cell therapy for viral infections: rapid 3rd party MVST

Open-label, single arm, phase II study- curative treatment:

- 58 pts with CMV, EBV, AdV, BKV-JCV, HHV6 DNAemia or disease
- cell dose: 1 x (2 x 10^7 VST/m^2), repeatable every 2 weeks if PR
- 23 pts received single infusion, 11 two infusions, and 4 three infusions of MVST





	Pt n.	Response	GVHD/toxicity
Multi 3rd party VST	58		17% aGVHD after treatment 1 grade III GI tract aGVHD 2 grade II skin aGVHD 7 grade I skin GVHD (4 de novo) Toxicity: 1 secondary graft failure
CMV	24	96% (11/24 CR and 12/24 PR)	
EBV	2	100% (2/2 CR)	
ADV	12	83% (6/12 CR and 4/12 PR)	
HHV6	3	100% (3/3 achieved PR)	
BKV	27	100% (27/27 PR: 74% resolved HC, 50% nephropathy)	

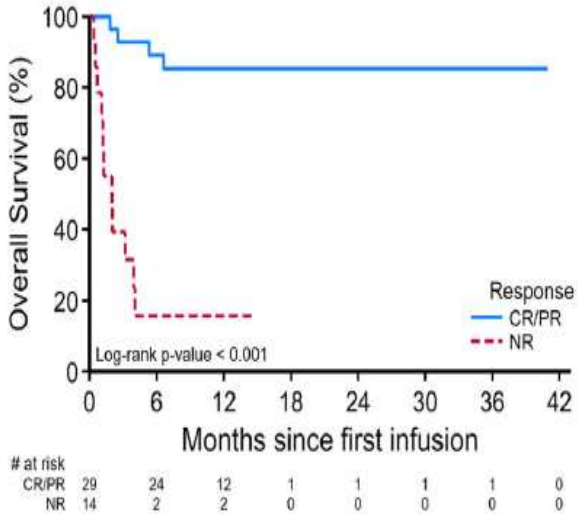
Pfeiffer *et al*. *Clin Cancer Res* 2023

*No difference in response when low ≤2/8 allele vs high ≥ 3/8 allele matching was considered (p=0.08)

Cell therapy for viral infections: rapid 3rd party MVST

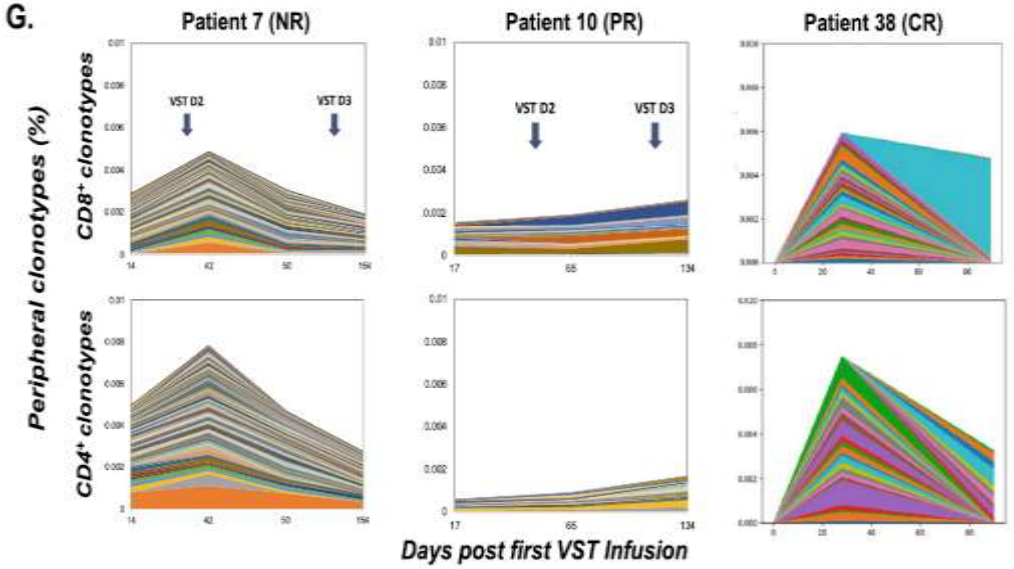
Multicenter phase II study: 51 pediatric pts, 47 treated post-HSCT with MVST vs EBV, CMV, and ADV

- cell allocation: HLA typing + restriction + activity
- cell dose: 1 x (2 x 10^7 VST/m^2), repeatable if PR or NR
- clinical results: 29/47 CR/PR: 62%



SAE	N	Grade
aGVHD (flares) + cGVHD	5	
Graft rejection	1	4
Cytopenia	2	4
Respiratory distress	1	4
CRS	1	3
ICANS	2	5

Infused clonotypes do not persist in vivo

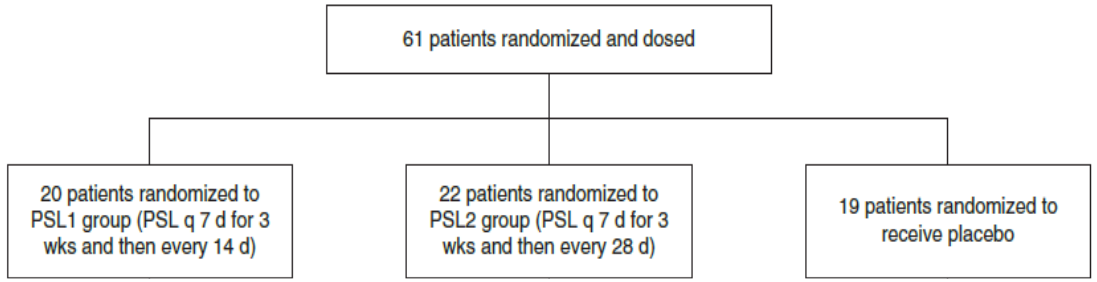


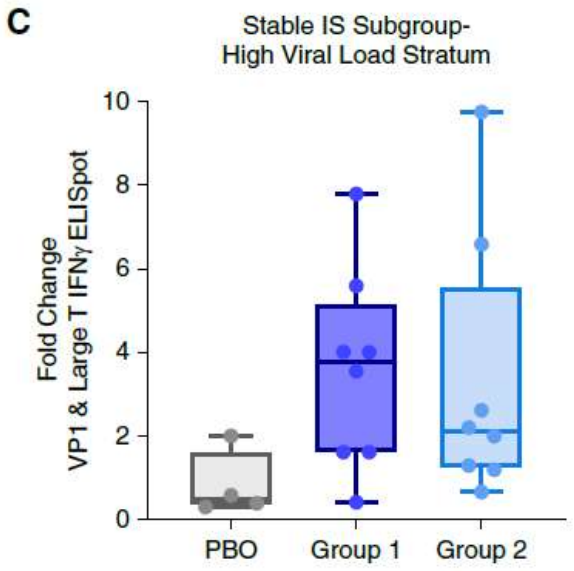
Keller *et al*. *Nat Commun* 2024

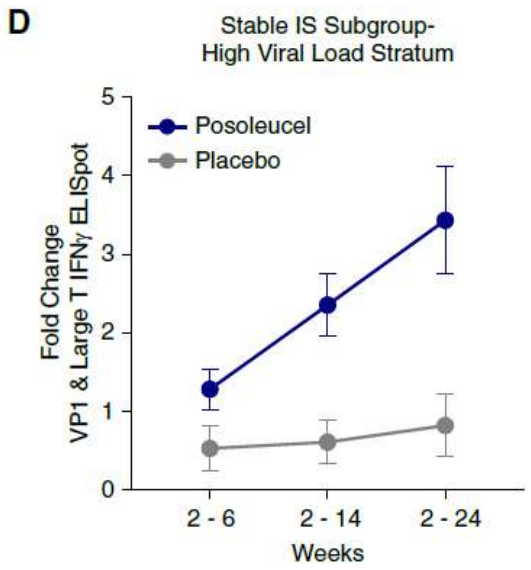
Cell therapy for viral infections: rapid 3rd party MVST

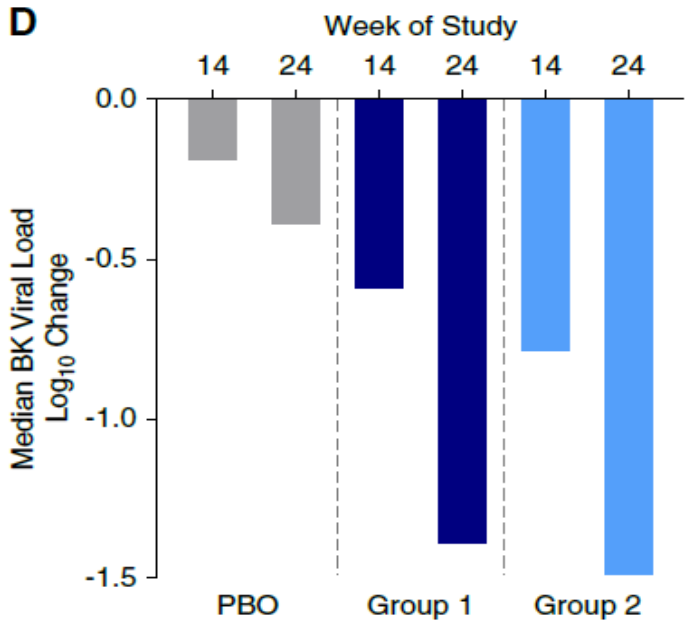
Phase II, multicenter, randomized study:

- 61 KTx recipients with BKPyV infection (any viremia)
- cell dose: 4 x 10^7 VST (3 weekly doses + 6 biweekly or 3 monthly)
- Results:
  - good safety
  - virological and immunological responses







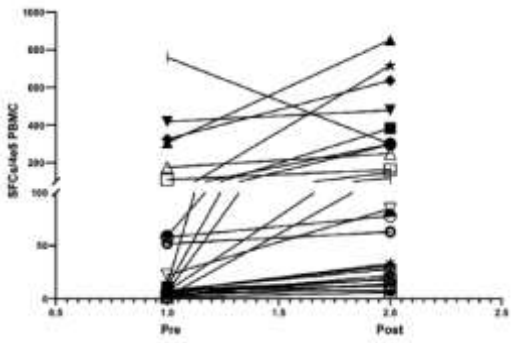


Chandraker *et al*. *JASN* 2024

Cell therapy for viral infections: rapid 3rd party MVST

Open-label phase II study:

- 98 pts with refractory viral reactivation/infection that failed SoC management, which included reduction of immune suppression (for all viruses), antivirals (for CMV and ADV), and intravenous immunoglobulin for BKPyV
- cell product: VST specific for EBV, CMV, ADV, PyVBK
- cell dose: 1 x (5 x 10^7 VST/m^2), repeatable
- product allocation: at least 2 HLA class I Ag-matches for EBV and CMV; at least 2 HLA class II Ag-matches for ADV and PyVBK
- 55 pts received single infusion, 43 ≥ 2 infusions: 52 KTx, 18 OLTx, 16 HR, 8 LTx, 4 multivisceral recipients



	Pt n.	Response	rejection/toxicity
Single or multiple infections			3% acute organ rejection no graft loss No infusion reactions or CRS
CMV	25	68% (13/25 CR and 4/25 PR)	
EBV	24	58% (4/24 CR; 10/24 PR)	
ADV	15	68% (9/16 CR and 2/16 PR)	
PyVBK	40	42% (14% CR, 28% GPR)* + (39% PPR,19% NR) * Only DNAemia, no PyVBKN	

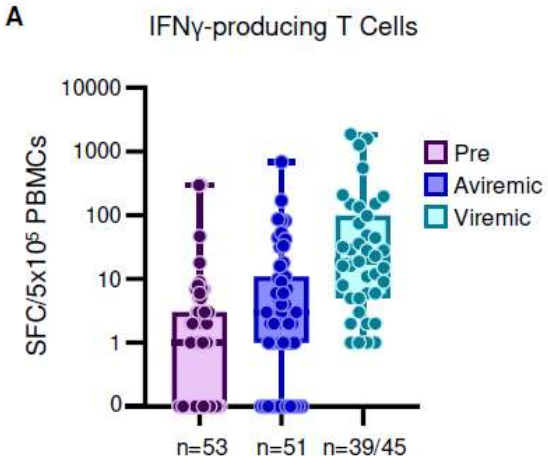
* No difference in response when allele matching was considered

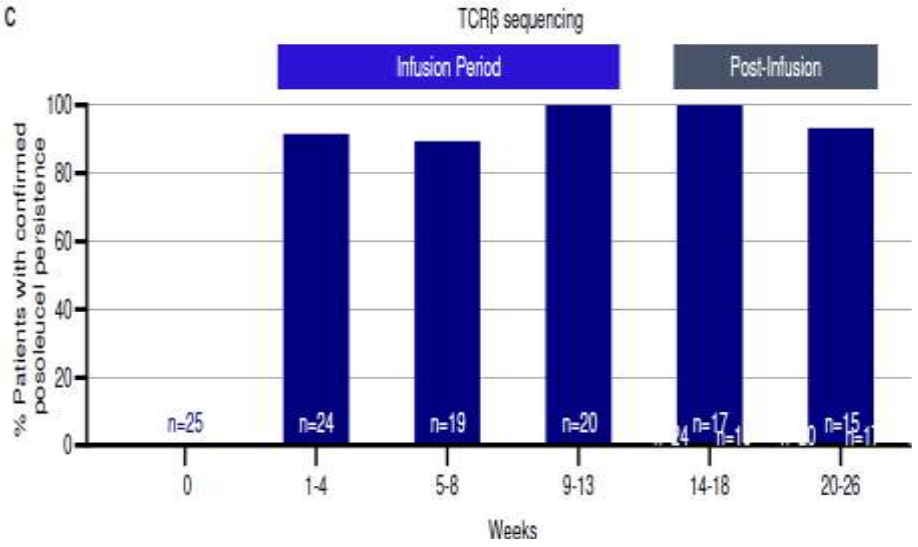
Khouri *et al*. *Am J Transplant* 2024

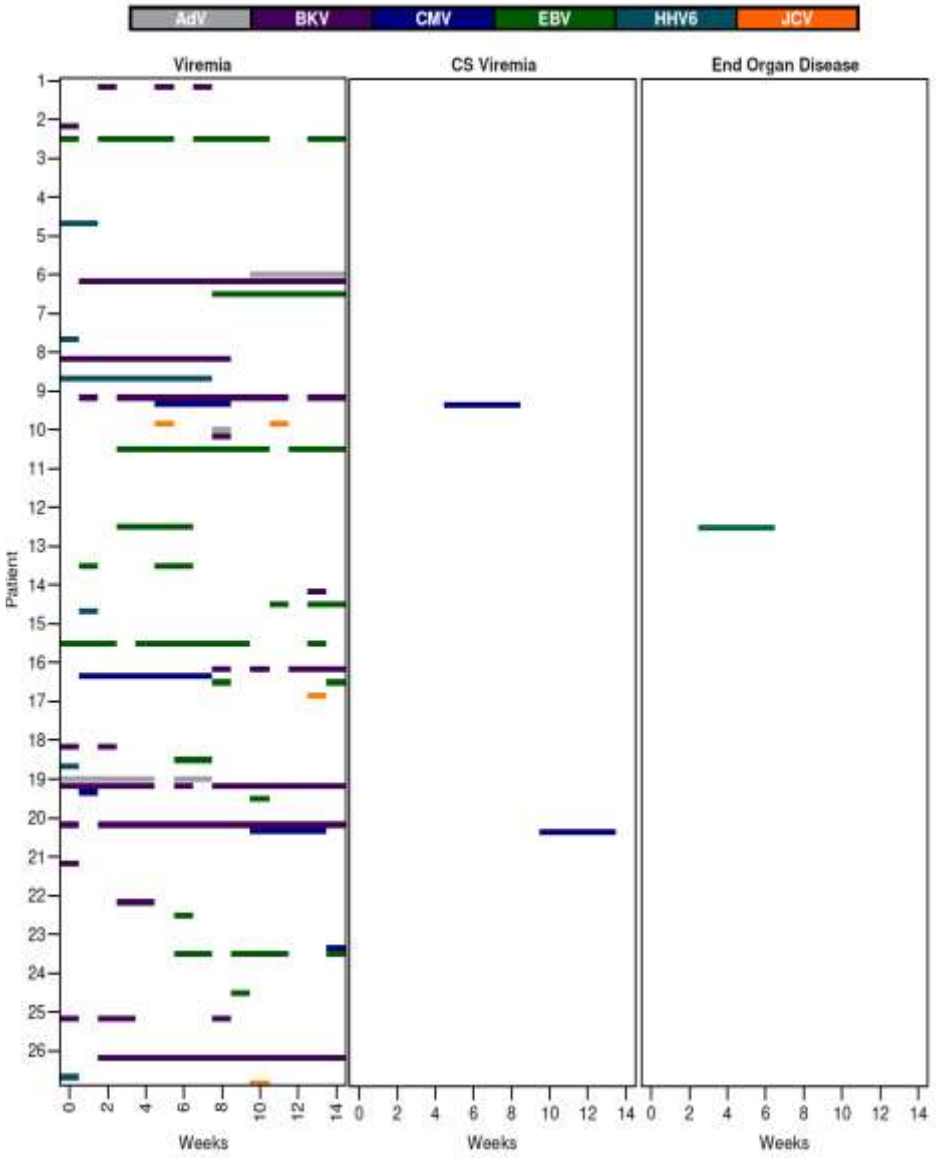
Cell therapy for viral infections: rapid 3rd party MVST

Open-label, single arm, phase II study- preventive treatment:

- 26 high-risk HSCT recipients
- cell dose: (2 x 10^7 VST if < 40kg, 4 x 10^7 VST if > 40kg), repeated every 2 weeks up to 7 times
- primary end-point: number of viremias requiring treatment or end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV through week 14







Dadwal *et al*. *Blood Adv* 2024

Cell therapy for viral infections: rapid 3rd party MVST

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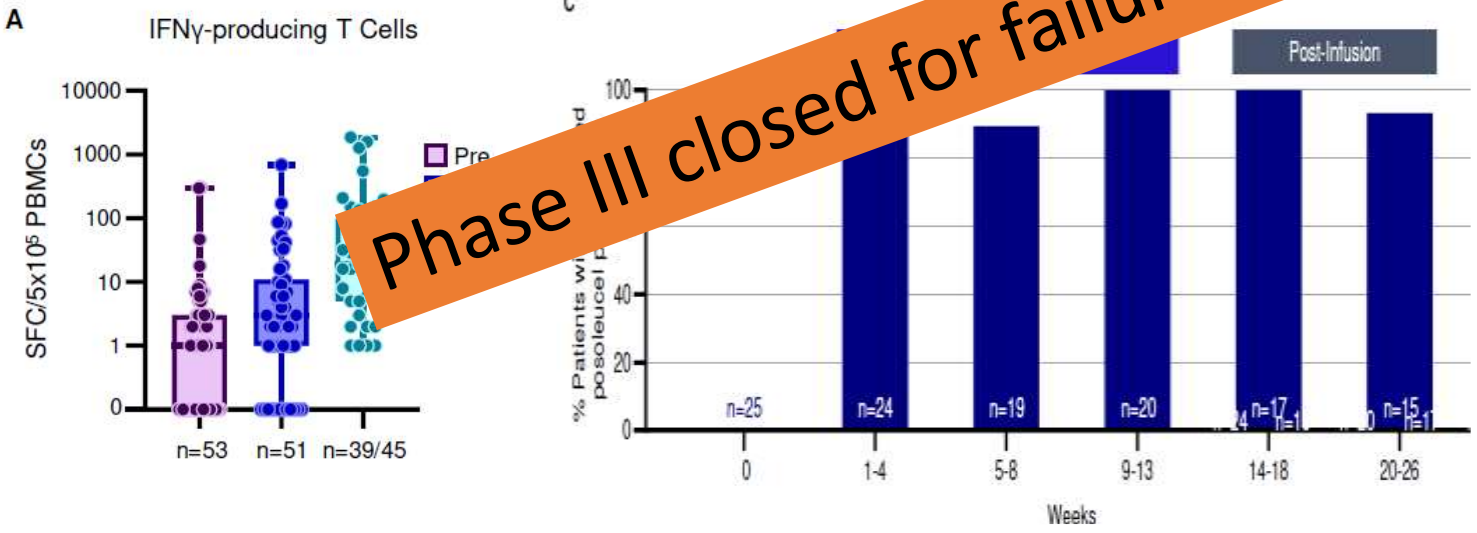
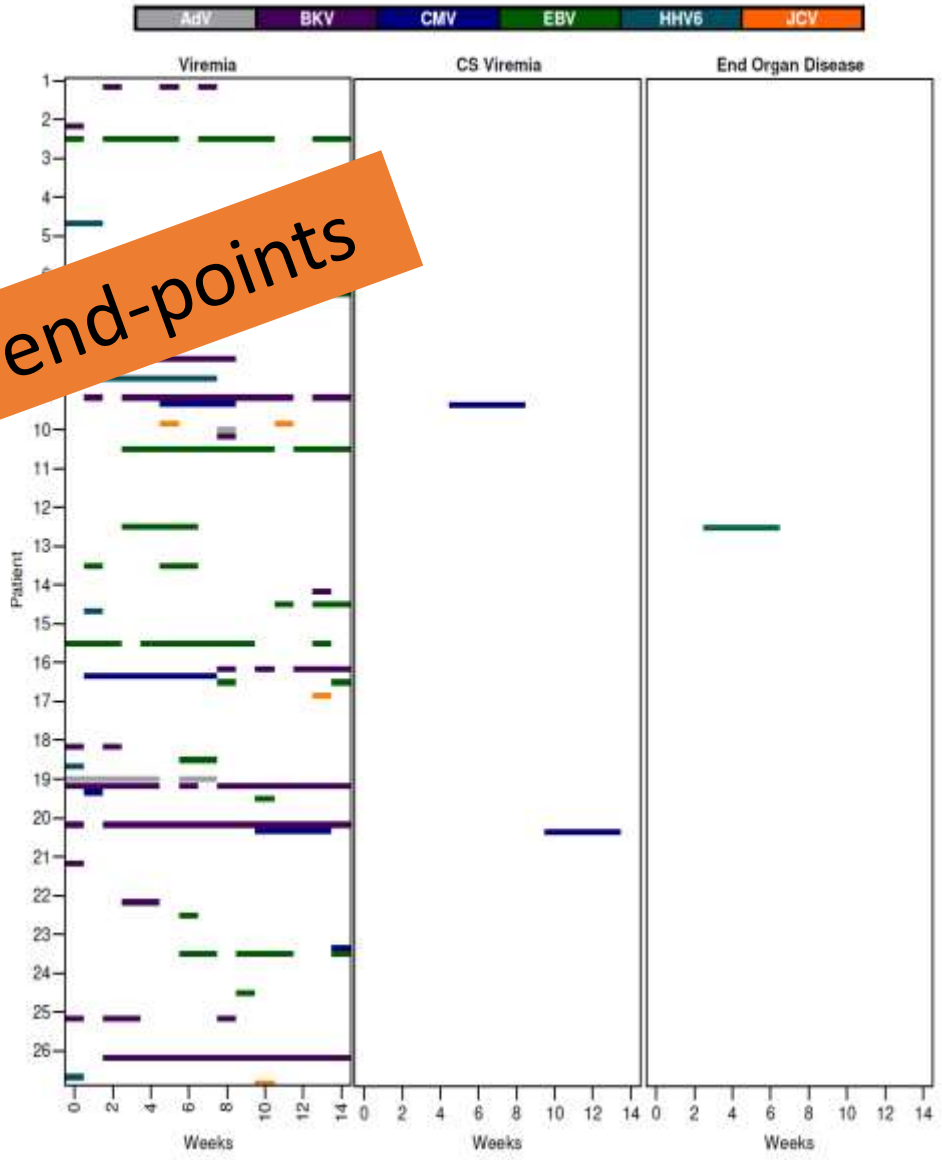
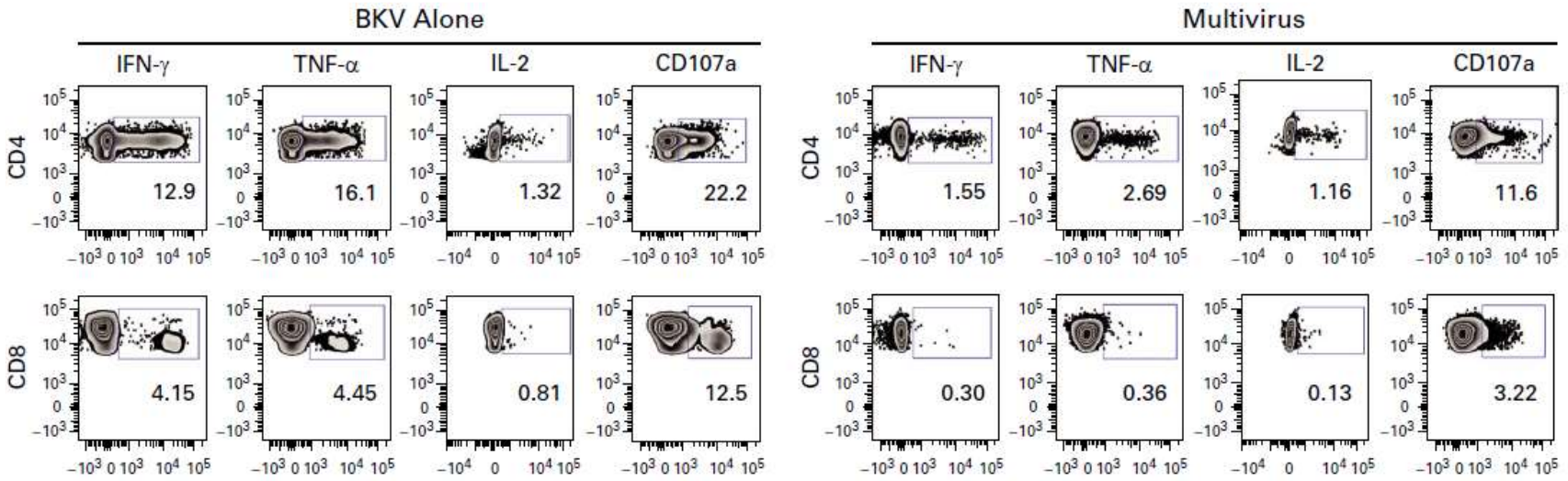
Phase III closed for failure to reach end-points

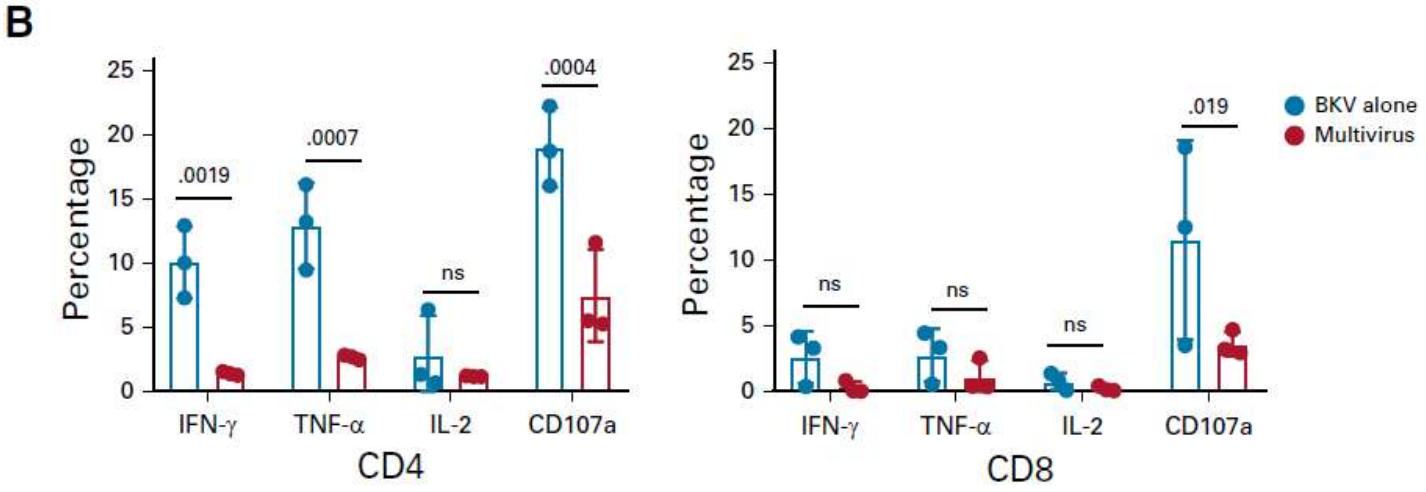


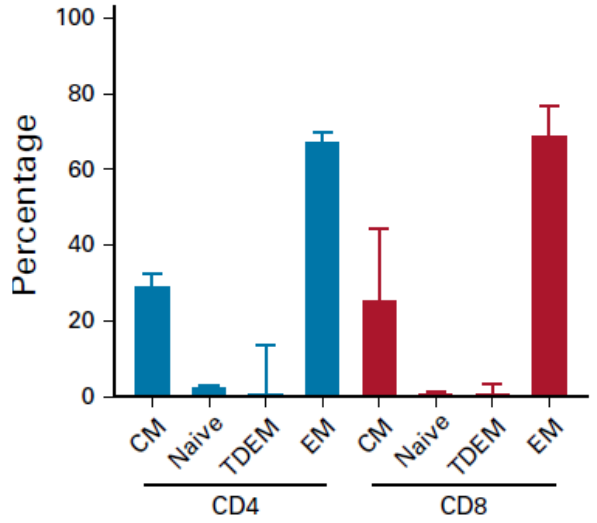


Dadwal *et al*. *Blood Adv* 2024

Cell therapy for viral infections: 3rd party BKV-CTLs





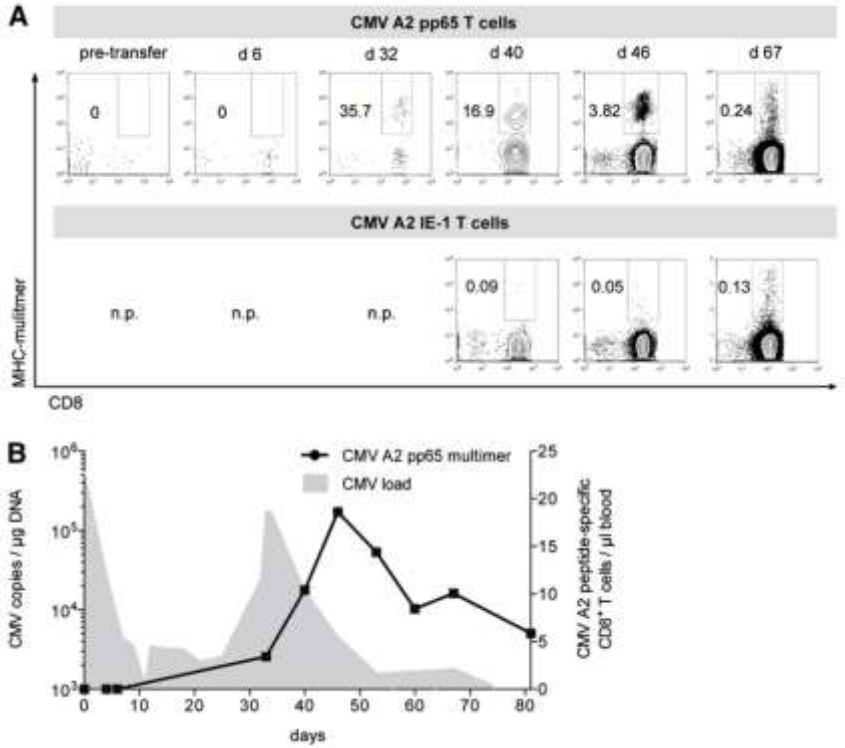


Olson *et al*. *J Clin Oncol* 2021

Cell therapy for viral infections: cell population features

T_{CM}

3000-4000 CD8+ cells/kg are able to reconstitute a HSCT recipient



	T_N	T_{NR}	T_{CNP}	T_{SCM}	T_{CM}	T_{EM}
CD45RO	-	-	-	-	+	+
CD45RA	+	+	+	+	-	-
CCR7	+	+	+	+	+	-
CD62L	+	+	+	+	+	-
CD27	+	+	+	+	+	+/-
CD28	+	?	+	+	+	+/-
CD31	+/-	-	+/-	+	-	-
CD95	-	?	+/-	+	+	+
CD49d	-	?	+	?	+/-	+
CXCR3	-	+/-	+/-	+	+	+
CD11a	-	+/-	?	+	+	+
CD122	-	?	?	+	+	+/-
CD127	+	?	+	+	+	-
TCR diversity	+	+/-	+	+/-	+/-	+/-
Effector functions	-	+	+	+	+	+
Proliferation potential	+/-	+/-	?	+	+/-	-

Neuenhahn *et al*. *Leukemia 2017*

Caccamo *et al*. *Front Immunol 2018*

Cell therapy for viral infections: open issues

- Clinics: most of the studies are phase I/II open-label
  - difficult to find suitable/meaningful endpoints
- The cohorts include both pts with viremia and with disease:
  - requirements in terms of dose and schedule are likely different
- The characteristics of the products are different in the different studies:
  - Donor vs 3° party, MVST vs single antigen, selected vs expanded
  - Even within expanded products, cytokine cocktails and media employed may be different, and this has an impact on cell phenotype characteristics: % of effector memory vs early memory vs central memory

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