Posoleucel, an Allogeneic, Off-the-Shelf Multivirus-Specific T-Cell Therapy, for the Treatment of Refractory Viral Infections in the Post-HCT Setting

Thomas Pfeiffer[1,2], Ifigeneia Tzannou[2], Mengfen Wu[2,3], Carlos Ramos[2], Ghadir Sasa[2], Caridad Martinez[2], Premal Lulla[2], Robert A. Krance[2], Lauren Scherer[2], Daniel Ruderfer[4], Swati Naik[2], Claire Bocchini[4], Iain P. Fraser[5], Badrish Patel[5], Dany Ward[5], Tao Wang[2,3], Helen E. Heslop[2], Ann M. Leen[2,5], and Bilal Omer[2]

ABSTRACT

Purpose: Viral infections are a major cause of morbidity and mortality following allogeneic hematopoietic cell transplantation (allo-HCT). In the absence of safe and effective antiviral treatments, virus-specific T cells have emerged as a promising therapeutic option. Posoleucel is a multivirus-specific T-cell therapy for off-the-shelf use against six viral infections that commonly occur in allo-HCT recipients: adenovirus, BK virus (BKV), cytomegalovirus, Epstein–Barr virus, human herpes virus-6, and JC virus.

Patients and Methods: We conducted an open-label, phase II trial to determine the feasibility and safety of posoleucel in allo-HCT recipients infected with one or more of these viruses. Infections were either unresponsive to or patients were unable to tolerate standard antiviral therapies. Fifty-eight adult and pediatric patients were enrolled and treated.

Results: Posoleucel was well tolerated, with no cytokine release syndrome or other infusion-related toxicities; two patients (3.4%) developed Grade 2 and one patient (1.7%) Grade 3 GvHD during the trial. The overall response rate 6 weeks after the first posoleucel infusion was 95%, with a median plasma viral load reduction of 97%. Of the 12 patients who had two or more target viral infections identified at study entry, 10 (83%) had a clinical response for all evaluable viruses. Of the 23 patients treated for refractory BKV-associated hemorrhagic cystitis, 74% had resolution of symptoms and macroscopic hematuria by 6 weeks post-infusion.

Conclusions: In this open-label trial, treatment of refractory viral infections/disease in allo-HCT recipients with posoleucel was feasible, safe, and effective.

Introduction

Viral infections remain a major cause of morbidity and mortality for patients undergoing hematopoietic cell transplantation (HCT). The use of traditional antiviral agents for the treatment of these infections is limited by suboptimal efficacy, development of drug resistance, and frequent toxicity (1). Donor-derived virus-specific T cells (VST) have emerged as a promising therapeutic option for refractory viral infections (2–4). However, this approach is often complicated by the lack of immune memory to target viruses in some donors (e.g., cord blood), donor availability, and the time required for manufacture and release testing.

One way to overcome these limitations is through the prospective creation of banks of third-party VSTs from healthy, seropositive donors for off-the-shelf administration (5, 6). Posoleucel (previously ALVR105) is an off-the-shelf multi-VST designed for administration as a partially HLA-matched product for the treatment or prevention of viral infections or disease due to adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpes virus-6 (HHV-6), and JC virus (JCV) in immunocompromised patients. This phase II trial was the first to evaluate an off-the-shelf multi-VST that simultaneously targets six viruses. Interim results on the first 38 patients who received posoleucel were published previously (7). We now report results for the entire cohort of 58 patients treated in this trial.

Patients and Methods

This open-label, single-arm, phase II study, which was approved by the FDA and the Baylor College of Medicine institutional review board, was open to patients who had undergone allo-HCT from any donor source from day 28 after transplant. Written informed consent was obtained from all patients and the studies were conducted in accordance with recognized ethical guidelines (Declaration of Helsinki, US Common Rule). The 59 posoleucel lines used in this phase II study were manufactured as previously described (3). If eligibility criteria were met and a suitable, partially HLA-matched posoleucel line was identified, patients could consent to treatment. A full list of inclusion and exclusion criteria is available on clinicaltrials.gov (NCT02108522). Treatment consisted of a single intravenous infusion of $2 \times 10^7/\text{m}^2$ of posoleucel with the option to receive a second infusion after four weeks and additional infusions at biweekly intervals thereafter. Therapy with standard antiviral medications could be continued at the discretion of the treating physician. Immune monitoring was performed weekly for 6 weeks post-infusion using IFNγ ELIspot analysis as described

[1]Division of Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri. [2]Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, Houston Methodist Hospital, Houston, Texas. [3]Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas. [4]Section of Pediatric Infectious Disease, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas. [5]AlloVir, Waltham, Massachusetts.

Corresponding Authors: Bilal Omer, Baylor College of Medicine, 1102 Bates Street, Suite 1640.16, Houston, TX 77030. Phone: 183-2824-6855; and Fax: 183-2825-4732; E-mail: bomer@bcm.edu; and Thomas Pfeiffer, pthomas@wustl.edu

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Translational Relevance

Viral infections are a major cause of morbidity and mortality following allogeneic hematopoietic cell transplantation (allo-HCT). In the absence of safe and effective antiviral treatments, virus-specific T cells have emerged as a promising therapeutic option. Posoleucel is a multivirus-specific T-cell therapy for off-the-shelf use against six viral infections that commonly complicate allo-HCT. Fifty-eight allo-HCT recipients with refractory viral infections were enrolled in a phase II clinical trial evaluating the safety and efficacy of posoleucel. Posoleucel proved to be highly effective with clinical responses observed in 95% of patients. These efficacy data combined with a favorable safety profile and immediate product availability suggest that posoleucel is a promising therapeutic option in this context. Therefore, posoleucel is currently being investigated in three randomized phase 3 clinical trials for therapeutic and preventative indications.

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previously (3). A positive response was defined as an increase in virus-specific, IFNγ-producing spot forming cells (SFC) or the detection of ≥10 SFC in patients with a previously negative result to antigen stimulation.

Safety endpoints

Acute grade 3 to 4 GVHD within 42 days of the last dose of posoleucel, and grade 3 to 5 non-hematologic adverse events related to posoleucel within 28 days of the last infusion. Patients were also monitored for chronic GVHD for 12 months. Toxicities were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.

Efficacy endpoints

Antiviral response was assessed six weeks after the first dose of posoleucel. Complete response (CR) was defined as return of viral load to normal range as defined by the specific assay used (Q-PCR in all reported patients) as well as resolution of clinical signs and symptoms. Partial response (PR) was defined as a viral load reduction of ≥50% by Q-PCR or a 50% improvement of clinical signs and symptoms in patients with assessable symptomatic disease (NCI-CTCAE v4.0 criteria). Stable disease was defined as changes insufficient to qualify as PR or progression. Progressive disease (PD) was defined as an increase in viral load of at least 50% from baseline or dissemination to other sites of disease.

Statistical analysis

Descriptive statistics were calculated to summarize clinical characteristics. One patient was enrolled twice for treatment of AdV and JCV. Both infusions for this patient were included in the safety and efficacy analyses. The proportion of clinical responses (i.e., PR or CR) was calculated and presented by virus type. In addition, the exact 95% confidence intervals (CI) for the binomial proportions were presented. Viral response was presented both as separate endpoints for each virus (i.e., as a proportion of patients with a given virus at baseline who had a PR or CR at time of assessment) and as one cumulative response endpoint (proportions of the total population with PR or CR in at least one virus at the time of assessment). Comparisons between groups were made using Fisher's exact tests for categorical variables. Overall response was defined as achieving CR/PR by 6 weeks post-infusion and summarized along with exact 95% binomial CIs. The percentage of

change over time from baseline in viral load was calculated. Boxplots were generated to visually show viral reduction over time.

Data availability

Data were generated by the authors and available on request. Please contact Bilal Omer, bomer@bcm.edu

Results

Patient enrollment and disposition

Of the 82 allogeneic HCT recipients screened for study participation, a suitable VST line was identified for 80 (98%) recipients. Six patients did not require treatment and 16 patients were ineligible for trial participation, leaving a total of 58 patients who were ultimately enrolled. **Figure 1** schematically represents the screening and exclusion process. One patient was enrolled twice, once for treatment of AdV and once for JCV (310 days after the first enrollment). This patient was counted twice in efficacy analyses ($n = 59$) and once in safety analyses ($n = 58$).

Patient characteristics

Of the 58 treated patients, 18 (31%) were <18 years of age at the time of enrollment (**Table 1**). Thirty (52%) patients were male and 28 (48%) were female. Transplant donor sources included matched unrelated ($n = 28$, 48%), cord blood ($n = 9$, 16%), mismatched unrelated ($n = 9$, 16%), haploidentical ($n = 6$, 10%), and matched related ($n = 6$, 10%).
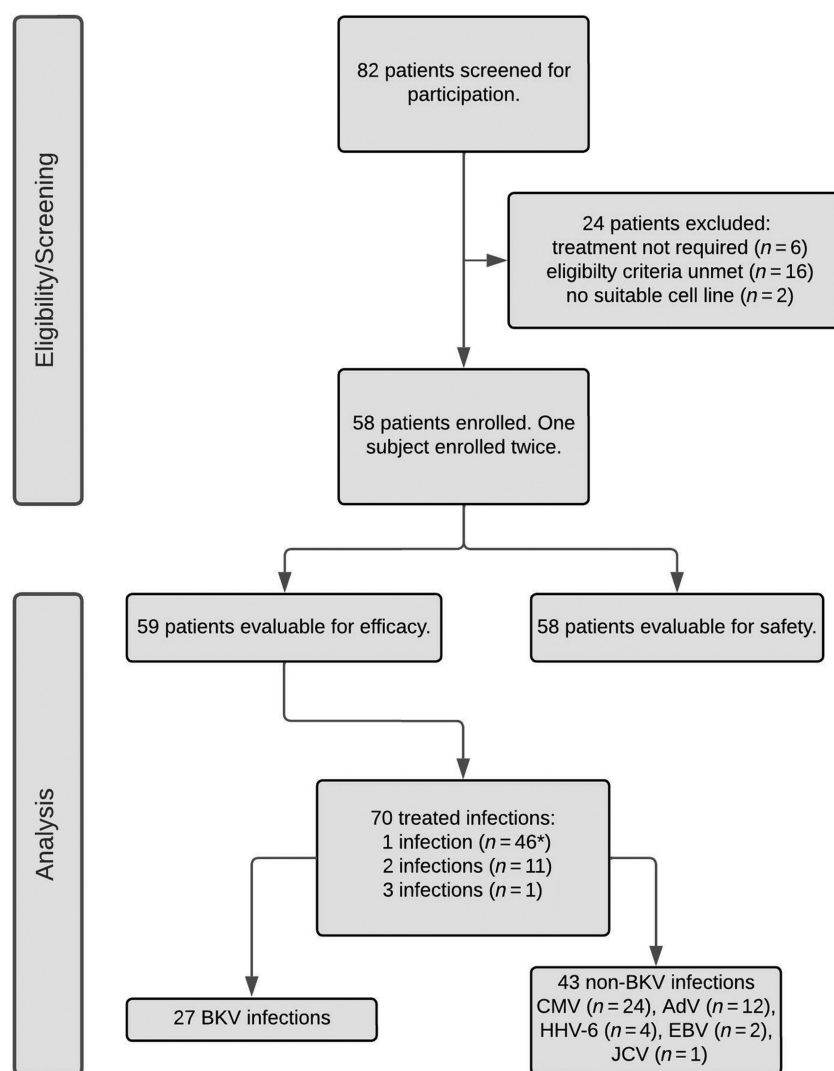
Of the 70 total evaluable infections treated, the majority were caused by BKV (27, 39%) and CMV (24, 34%). Forty-six patients (79%; including patient 4183 who was enrolled twice) were treated for a single virus at study entry, eleven (19%) were treated for two concurrent viral infections and one (2%) was treated for infections with three different viruses at study entry.

Clinical response

Overall, 55 of all 58 patients (95%; 95% CI, 85.6%–98.9%) experienced a PR or CR by week 6 after their initial posoleucel infusion. Of the 46 patients with a single-target virus identified at study entry, 45 (98%) were reported to have either a PR or CR by the week 6 assessment. One patient was reported to have PD at this assessment. Of the 12 patients with more than 1 target virus identified at study entry, 10 (83%) were reported to have either a PR or CR for all evaluable target viruses by 6 weeks post-infusion.

CMV

Twenty-four patients with evaluable refractory CMV infections received a total of 35 posoleucel infusions. Although CMV resistance testing was not routinely performed, 11 of these patients (44%) were resistant to conventional antiviral medications as confirmed by CMV gene sequencing. The overall response rate of patients with CMV infection to posoleucel by 6 weeks post-infusion was 96% (95% CI, 78.9%–99.3%) with a PR in 12/24 (50%) and CR in 11/24 of evaluable patients (46%). The median plasma viral load reduction at 2, 4, and 6 weeks was 55%, 83%, and 94%, respectively (**Fig. 2**). One patient, who had CMV encephalitis in the absence of viremia, was excluded from this analysis. However, in this patient, cerebrospinal fluid (CSF) CMV viral load decreased from 22,700 copies/mL at baseline to 255 copies/mL at 6 weeks. An additional three patients had CMV end-organ disease at the time of VST treatment: CMV colitis ($n = 2$) and CMV pneumonia ($n = 1$). All three patients experienced improvement of both disease symptoms and viral load by week 6 (CR = 1 and PR = 2).

82 patients screened for participation.

24 patients excluded:
treatment not required ($n = 6$)
eligibilty criteria unmet ($n = 16$)
no suitable cell line ($n = 2$)

58 patients enrolled. One subject enrolled twice.

Eligibility/Screening

59 patients evaluable for efficacy.

58 patients evaluable for safety.

Analysis

70 treated infections:
1 infection ($n = 46*$)
2 infections ($n = 11$)
3 infections ($n = 1$)

27 BKV infections

43 non-BKV infections
CMV ($n = 24$), AdV ($n = 12$),
HHV-6 ($n = 4$), EBV ($n = 2$),
JCV ($n = 1$)

Figure 1.
Patient disposition. Schematic representation of eligibility screening, patient inclusion, and efficacy analysis. *, includes patient 4183, who was enrolled twice for 2 separate infections.

Adenovirus

Twelve patients with refractory AdV received 19 VST infusions. Overall, a response by week 6 was observed in 10 of 12 patients (83%; 95% CI, 51.6%–97.9%), with a PR or CR achieved in four (33%) and six (50%) patients, respectively, and a median time to response of 13 days. All but two patients (83%) with AdV viremia had end-organ disease at the time of infusion. A combination of upper and lower respiratory infections and diarrhea from enteritis was a common observation. Adenovirus-associated hemorrhagic cystitis was present in three patients. Eight of the 10 patients with AdV end organ disease responded to VST treatment by week 6 (PR = 4 and CR = 4). The median plasma viral load reduction at 2, 4, and 6 weeks was 51.1%, 100%, and 100%, respectively (**Fig. 2**).

HHV-6

Four patients with HHV-6 infections received a total of seven VST infusions. One patient received two VST infusions to treat persistently elevated HHV-6 levels in the absence of symptoms. Chromosomal integration of HHV-6 (8) was subsequently discovered in this patient that led to their exclusion from further efficacy analyses. A PR was observed in all three evaluable patients. One patient had resolution of symptoms but no virological response. The remaining two patients had an 83.5- and 3.8-fold reduction in plasma viral load, respectively (**Fig. 2**). HHV-6 encephalitis was confirmed in one patient; following administration of posoleucel, this patient's level of alertness and mental status promptly improved with subsequent return to neurological baseline.

EBV

Two patients with refractory EBV-associated PTLD received a total of three infusions of posoleucel. By 2 weeks following infusion, significant reduction in viral load was observed: Viral titers decreased from 19,707 to 41 copies/mL, and 280,319 to 391 copies/mL, respectively (**Fig. 2**). By six weeks after the first infusion, both patients (100%) had a PR. Both patients subsequently experienced gradual resolution of PTLD-associated symptoms.

JC virus

One patient developed JC virus–associated progressive multifocal leukoencephalopathy (PML) 10 months following HCT. The patient had initial stabilization of neurological symptoms after a single infusion of posoleucel with a corresponding reduction of viremia at

Table 1. Patient demographics.

Characteristic	Value (%)
Sex	
Male	30 (52)
Female	28 (48)
Race/ethnicity	
White	51 (88)
Black/African American	3 (5)
Asian	3 (5)
Unknown	1 (2)
Age	
Adult (≥18 years)	40 (69)
Pediatric (<18 years)	18 (31)
Diagnosis	
AML/MDS	24 (41)
ALL/MPAL	17 (29)
Nonmalignant	12 (21)
Lymphoma/MM/CML	5 (9)
Transplant type	
MUD	28 (48)
MMUD	9 (16)
Cord blood	9 (16)
Haploidentical	6 (10)
MRD	6 (10)
HLA match	
Low (≤2/8 alleles)	31 (53)
High (≥3/8 alleles)	27 (47)
Evaluable infections treated ($n = 70$)	
CMV	24 (34)
BKV	27 (39)
AdV	12 (16)
HHV-6	4 (6)
EBV	2 (3)
JCV	1 (1)
#Infections/patient at study entry	
1[a]	46 (79)
2	11 (19)
3	1 (2)
#Infusions/patient	
1	39 (67)
2[a]	15 (26)
3	4 (7)

[a]Includes patient 4183, who was enrolled twice for 2 separate infections.

2 weeks (1,100 to 106 copies/mL; **Fig. 2**) and viral load in CSF at 4 weeks (7,700 to 423 copies/mL). Despite this initial response, the patient ultimately died of progressive PML six weeks after posoleucel.

BKV infections

Twenty-seven patients with BKV-associated disease [hemorrhagic cystitis ($n = 25$), nephritis ($n = 2$)] received a total of 34 posoleucel infusions. All 27 evaluable patients (100%; 95% CI, 87.2–100) had a PR at 6 weeks.

BKV-associated nephritis. Of the two patients with BKV-associated nephritis, one had a modest improvement in creatinine, and one patient with end-stage kidney disease failed to recover clinically despite an initial decrease in viral load.

BKV-HC. The relationship between BK viremia and viruria and the duration of BKV-HC is not well established and asymptomatic BK viruria is widely reported in allo-HCT patients (9–11). In a *post hoc* analysis, we therefore monitored response to VST treatment through serial HC grading focused on clinical symptoms (using CTCAE criteria), which was performed in 23/25 of evaluable patients with BKV-HC who at baseline were not dialysis-dependent and had not undergone surgical intervention (i.e., nephrostomy placement). In these 23 patients, all of whom had a PR, complete resolution of macroscopic hematuria and symptoms was observed in 43%, 61%, and 74% of patients at 2, 4, and 6 weeks post-infusion, respectively. The cystitis grade improved from median 3.0 (range, 2–4) pre-infusion to 1.00 (range, 0–3) at 6 weeks.

Repeat infusions

Nineteen patients received more than one infusion of posoleucel. One of these patients received two infusions over two separate enrollments for different infections, and another received two infusions but was diagnosed with chromosomal integration of HHV-6 after the second infusion and was subsequently not evaluated further for efficacy. Seventeen patients receiving more than one infusion were, therefore, evaluable for efficacy. In these patients, the reasons for repeat infusions were diverse, but usually due to incomplete response or recurrence after initial response. Depending on the response to the first posoleucel infusion, evaluable patients received a cell line from the same donor ($n = 9$) or a different donor ($n = 8$) for the second infusion at a median of 42 days (IQR 28–75 days) following the first infusion. In response to the second infusion, we observed a CR in four patients and PR in 10 patients. Three patients had further progression of their infections after the second infusion. In these three patients, we observed a PR following a third infusion administered at a median of 48 days (IQR 36–68 days) after the first infusion.

Clinical safety

All infusions were well tolerated and no patient developed cytokine release syndrome. Thirteen of 58 patients (22%) evaluated for safety reported acute GVHD. At study entry, four of these 13 patients had no prior history of GVHD and no GVHD present, six patients had a history of grade 1–3 GVHD that had become quiescent, and three patients, all with a prior history of GVHD, had active, low-grade GVHD (**Table 2**). Post-infusion, grade 1 skin GVHD flares were observed in 10 patients and most resolved with topical therapy only. Grade 2 skin GVHD flares were observed in two patients and resolved with administration of systemic glucocorticoids. One patient had a history of grade 3 lower GI GVHD and developed a grade 3 gastrointestinal GVHD flare post-infusion that resolved after a brief intravenous steroid pulse.

Secondary graft failure was observed in one patient, who exhibited transient rash, fevers, and elevated liver enzymes. However, even preceding posoleucel administration, this patient exhibited poor graft function requiring G-CSF administration. Notably, the patient had also been receiving rifampin, isoniazid, pyrazinamide, and ethambutol for disseminated mycobacterium tuberculosis infection with bone marrow involvement, which may have further contributed to graft failure.

Cell line matching

From the bank of 59 posoleucel VST lines, 27 were administered to one to 10 patients, matched at 1 to 5 of 8 HLA antigens. There was no significant difference in clinical response and the degree of HLA matching between patients who received "low" (one to two matching alleles, $n = 31$) versus "high" (three to five matching alleles, $n = 27$) matched VST lines ($P = 0.084$). Clinical responses (CR/PR) were observed in 100% of low HLA match patients and 88.5% of high HLA match patients.
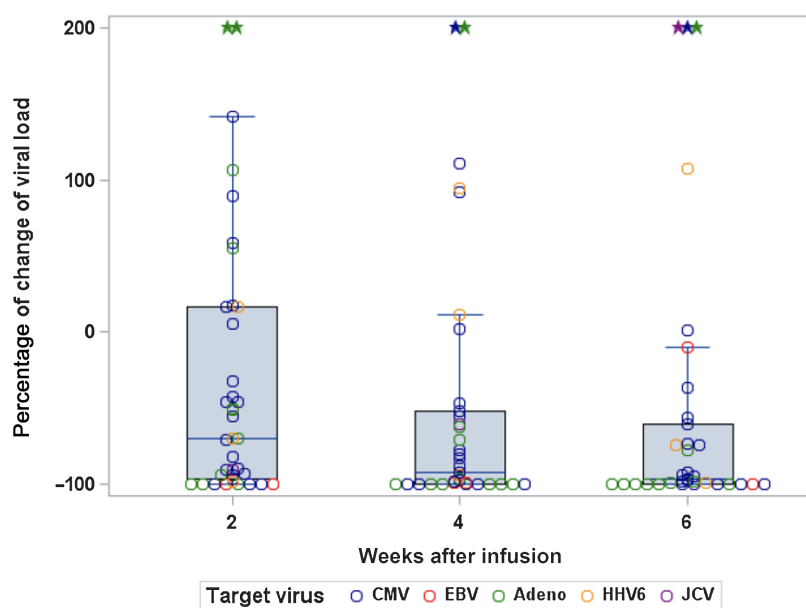
Figure 2.
Viral loads. Plasma viral load reduction at 2, 4, and 6 weeks following posoleucel infusion. Extreme outliers exceeding the cutoff value of 200% are marked with an asterisk (*) on the boxplot.

Immune monitoring

IFNγ ELISpot analysis was performed weekly for the first 6 weeks post-infusion to determine the frequency of circulating T cells with specificity against viral antigens. Of patients with sufficient ELISpot data, 13/23 infected with CMV (56.5%), 9/24 (37.5%) infected with BKV, and 4/9 (44.4%) infected with AdV developed detectable spots post-infusion or had an increase in spot counts from baseline (**Fig. 3**). The highest SFC measurements were detected at a median of 4 weeks post-infusion. In the three infections (CMV, $n = 1$; AdV, $n = 2$) without clinical response, ELISpot remained negative during follow-up testing.

In vivo T-cell persistence

Endogenous cells and circulating VSTs were distinguished on the basis of peptide–epitope specificity. As previously reported, the persistence of circulating third-party VSTs for up to 12 weeks could be demonstrated in 11 of the 16 patients (69%) with adequate sample availability.

Discussion

For patients who undergo allo-HCT, the months between pre-transplant conditioning and reconstitution of immune function are a period of great risk. Despite advances in prophylaxis, up to 90% of allo-HCT patients experience reactivation of at least one virus and almost two thirds of patients develop infections with more than one virus, further increasing their risk for morbidity and mortality (12).

In this Phase II trial, we administered posoleucel to 58 allo-HCT recipients suffering from refractory viral infections. To our knowledge, this is the largest study to date using a third-party, off-the-shelf, multi-VST product and the only study using a VST product designed to target the six most commonly identified viruses in this setting simultaneously. Our data suggest promising clinical efficacy of posoleucel with the vast majority of patients (95%) experiencing clinical benefit by the sixth week post-infusion. The high rate of response (83%) among the 12 patients with more than one viral infection at baseline suggests

Table 2. GVHD.

Age	Sex	Prior GVHD	GVHD at infusion	GVHD prophylaxis or treatment at time of infusion	aGVHD by Week 6
4	F	Grade 1 (skin)	Quiescent	None	Grade 1 skin (topicals, resolved)
9	M	Grade 1 (skin)	Yes	Top. steroid, top. tacrolimus	Grade 1 skin GVHD (IV hydrocort., resolved)
12	M	Grade 2 (skin)	Quiescent	Top. steroid, top. tacrolimus	Grade 1 skin (topicals, improved)
12	F	No	No	None	Grade 1 skin (IV hydrocort., resolved)
15	F	Grade 3 (LGI)	Quiescent	Budesonide, solumedrol	Grade 3 LGI (IV steroid pulse, resolved)
25	M	Grade 3 (skin)	Quiescent	Tacrolimus, prednisone	Grade 1 skin (increased prednisone, improved)
34	F	Grade 1 (skin)	Quiescent	Tacrolimus, prednisone	Grade 2 skin (topicals, prednisone, unchanged)
48	F	Grade 1 (skin)	Yes	Tacrolimus, prednisone	Grade 1 skin (increased prednisone, improved)
49	M	No	No	None	Grade 1 skin (top. steroids, IV hydrocort., resolved)
55	M	No	No	None	Grade 1 skin (topicals, resolved)
58	M	Grade 2 (skin)	Quiescent	Tacrolimus, prednisone	Grade 2 skin (prednisone, resolved)
59	M	Grade 1 (skin)	Yes	Tacrolimus, prednisone, top.	Grade 1 skin (increased prednisone, improved)
65	F	No	No	None	Grade 1 skin (topicals, resolved)
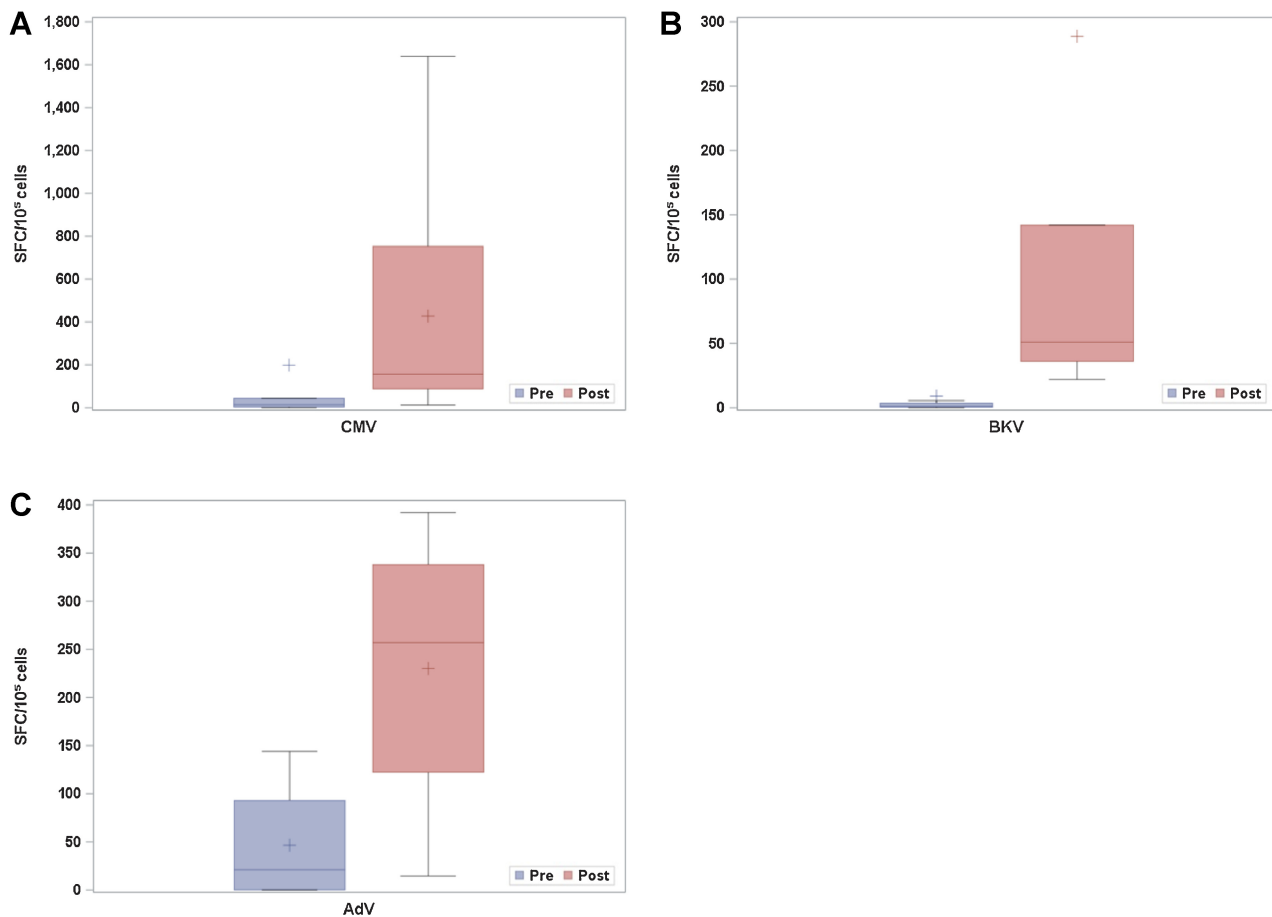
Figure 3.
ELISpot data. Frequency of VSTs *in vivo* in the peripheral blood before (pre) and after (post) infusion, as measured by IFNγ enzyme-linked immunospot (ELISpot). Only patients with positive ELISpot response are shown. Results are expressed as spot-forming cells (SFC) per 5×10^5 input cells with specificity for patients with (**A**) CMV, (**B**) BKV, and (**C**) AdV. The box is drawn from Q1 to Q3 (25th percentile–75th percentile interquartile range), with a horizontal line drawn at the median value. A marker "+" is used to display the mean value

that posoleucel has the potential to treat multiple viruses that occur in immunocompromised patients.

One of the most appealing aspects of using third-party, off-the-shelf multi-VSTs, is the rapid product availability, which mitigates any potential delays in treatment of these often life-threatening viral infections. Indeed, from a bank of 59 posoleucel VST lines, we were able to identify a suitable line for 58/60 (97%) of screened and eligible patients, allowing treatment of local patients within 48 hours. Clinical benefit was achieved even with posoleucel matched on a single HLA allele, though the majority of patients received lines matched at a median of two alleles.

Posoleucel is derived from healthy, seropositive third-party donors rather than being an autologous or HLA-matched HCT donor source. Hence, there is theoretically an increased risk of GVHD. However, the incidence of *de novo* or worsening GVHD in our study—beyond the development of mild, transient rashes—was low, in line with comparable studies using third-party VSTs and not higher in incidence or severity than that seen in allogeneic HCT patients not infused with VSTs (13–17). This is likely attributable to the fact that posoleucel is enriched for virus-reactive T cells and consists almost entirely of cells with a central and effector memory

phenotype without overt allo-reactivity. Hence, absent viral peptides, these T cells remain quiescent.

More than one third of patients enrolled in this study received posoleucel for the treatment of BKV-induced HC. In the absence of effective antiviral treatments, BK-HC management has historically relied primarily on supportive care. An effective treatment of BK-HC may positively impact morbidity, including kidney damage, prolonged hospitalization, and increased healthcare costs associated with this complication (18). Our findings of rapid resolution of hemorrhagic cystitis in the vast majority of posoleucel recipients are consistent with recent reports by Nelson and colleagues and Olson and colleagues (14, 13).

Given the unknown rate of spontaneous viral clearance and normal biological fluctuation in the viruses under consideration, the interpretation of the results of this uncontrolled trial is necessarily limited, in particular for EBV, HHV-6, and JCV, where the number of enrolled patients was low.

In summary, results of our trial suggest that posoleucel is a safe and effective therapy for the treatment of severe viral infections following allogeneic HCT. Its use might aid in alleviating the morbidity and mortality associated with post-HCT viral infections and helps avoid

the nephrotoxic and myelosuppressive side effects associated with the use of conventional antiviral medications. On the basis of these promising findings, posoleucel is currently being evaluated in three randomized phase III trials for both treatment and preventive indications.

Authors' Disclosures

Disclaimer

The funding sources had no role in trial design, data collection, interpretation of data, or decision to publish.

Authors' Contributions

T. Pfeiffer: Data curation, formal analysis, writing–original draft, writing–review and editing. **I. Tzannou:** Conceptualization, investigation, writing–original draft, writing–review and editing. **M. Wu:** Software, formal analysis, writing–original draft, writing–review and editing. **C. Ramos:** Investigation, writing–original draft, writing–review and editing. **G. Sasa:** Investigation, writing–original draft, writing–review and editing. **C. Martinez:** Investigation, writing–original draft, writing–review and editing. **P. Lulla:** Formal analysis, investigation, writing–original draft, writing–review and editing. **R.A. Krance:** Investigation, writing–original draft, writing–review and editing. **L. Scherer:** Writing–original draft, writing–review and editing. **D. Ruderfer:** Formal analysis, writing–original draft, writing–review and editing. **S. Naik:** Formal analysis, investigation, writing–original draft, writing–review and editing. **C. Bocchini:** Formal analysis, writing–original draft, writing–review and editing. **I.P. Fraser:** Writing–review and editing. **B. Patel:** Writing–review and editing. **D. Ward:** Writing–review and editing. **T. Wang:** Data curation, software, formal analysis, writing–original draft, writing–review and editing. **H.E. Heslop:** Conceptualization, writing–original draft, writing–review and editing. **A.M. Leen:** Conceptualization, formal analysis, writing–original draft, writing–review and editing. **B. Omer:** Conceptualization, data curation, formal analysis, writing–original draft, writing–review and editing.

Acknowledgments

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