Posoleucel as Preemptive Therapy for BKV Infection in Kidney Transplant Recipients: Safety and Tolerability in a Phase 2 Trial

Ravinder K. Wali[1], Manpreet Singh[2], David Wojciechowski[3], Mohammed J. Ansari[4], Bonnie Lonze[5], Vinay Nair[6], Akhil Sharma[7], Stuart Knechtle[8], Francesca Cardarelli[9], Anil Chandraker[10]

[1]Inova Transplant Center, Falls Church, VA; [2]U. of Pittsburgh Medical Center, Harrisburg, PA; [3]U.T. Southwestern Medical Center, Dallas, TX; [4]Northwestern U. Feinberg School of Medicine, Chicago, IL; [5]NYU Langone Transplant Institute, New York, NY; [6]Northwell Health, Manhasset, NY; [7]U. of Pittsburgh Medical Center, Pittsburgh, PA; [8]Duke U. School of Medicine, Durham, NC; [9]AlloVir, Waltham, MA; [10]Brigham & Women's Hospital, Boston, MA

Anil Chandraker, MD
Director of Renal Transplant Medicine
Brigham and Women's Hospital
Boston, Massachusetts, USA

I have financial relationship(s) with:

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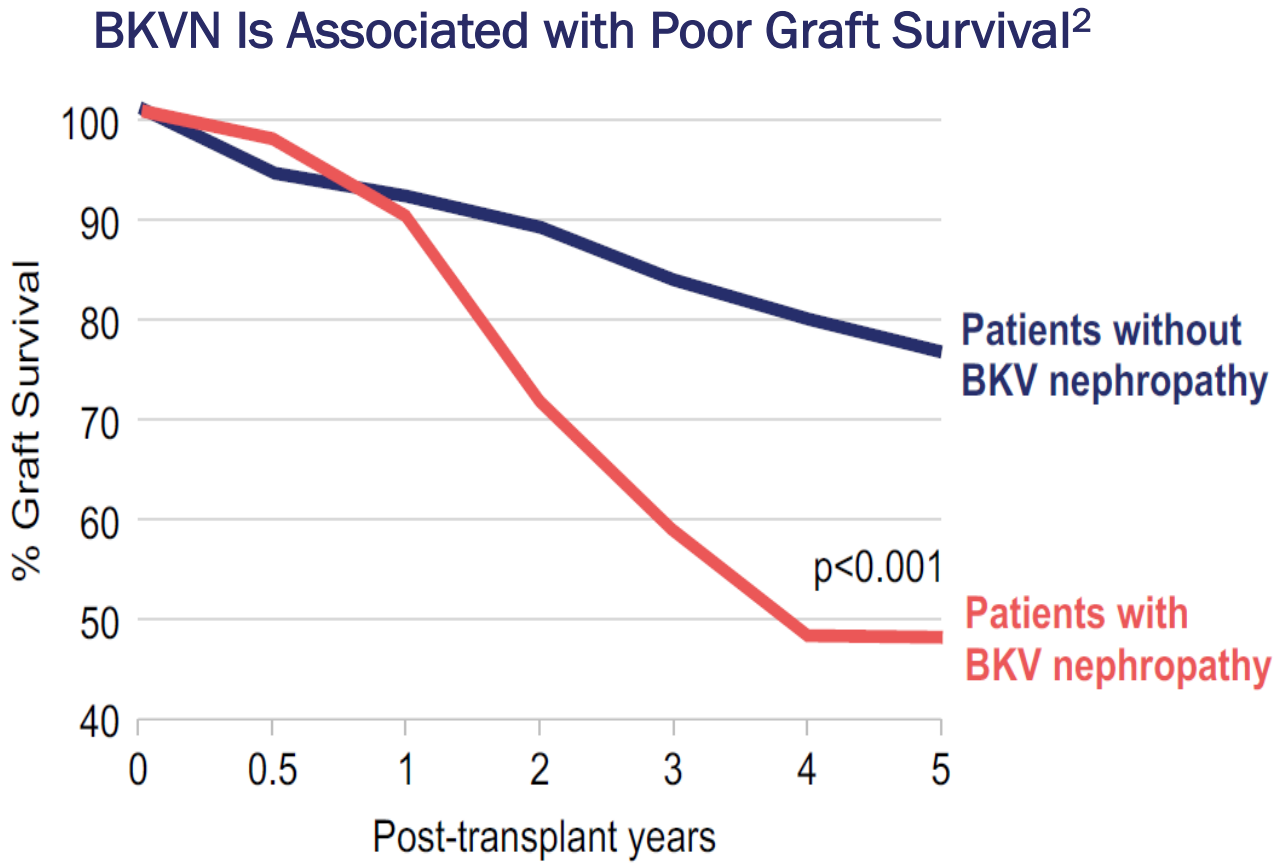
This presentation includes discussion of investigational use of posoleucel, a multivirus-specific T cell therapy

BK Viremia and Nephropathy in Kidney Transplantation

- 10-20% of kidney transplant (KT) recipients develop BK viremia[1]
- 50% of patients with high-level BK viremia develop BKV nephropathy (BKVN), which is associated with reduced graft survival
- No approved therapies for BKV
- Reduction of immunosuppression can lead to rejection and donor-specific antibodies



1. Hirsch et al. *Am J Transplant*. 2013; 2. Vasudev et al. *Kidney Int. 2005.*

BKV Infection Is Associated with T Cell Deficits

- BKV-specific T-cell immunity correlates with protection from, and resolution of, BKVN[1,2]
  - KT patients without BKVN had ~10-fold higher BKV-specific T-cell responses than KT patients with BKVN
  - Among KT patients with BKV, those who develop robust BKV-specific T cell responses cleared BKV without intervention as compared with those who progressed to BKVN

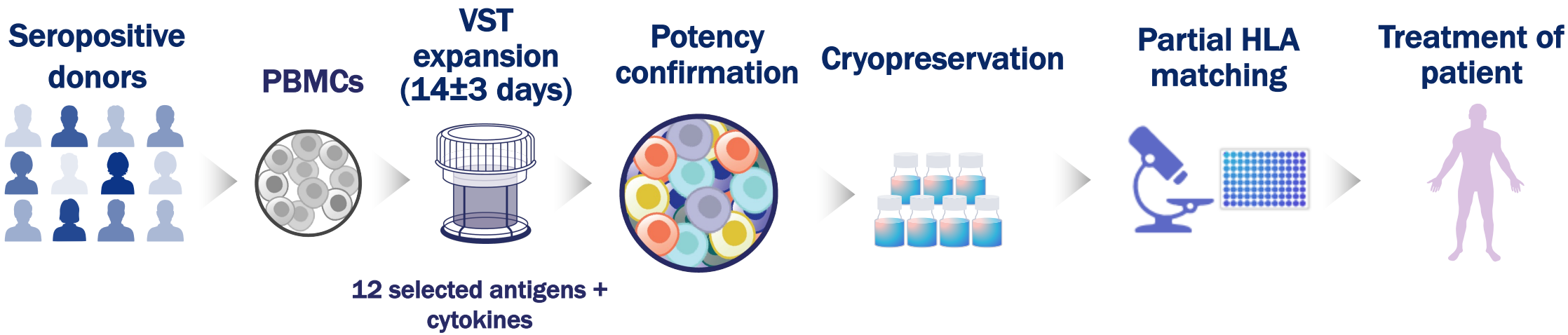
- The presence of anti-BKV antibodies does not correlate with resolution of BKV

Thus, virus-specific T cell therapy may be effective in managing BKV viremia and BKVN

1. Schachtner et al. *Am J Transplant.* 2011; 2. Bae et al. *KJIM.* 2020.

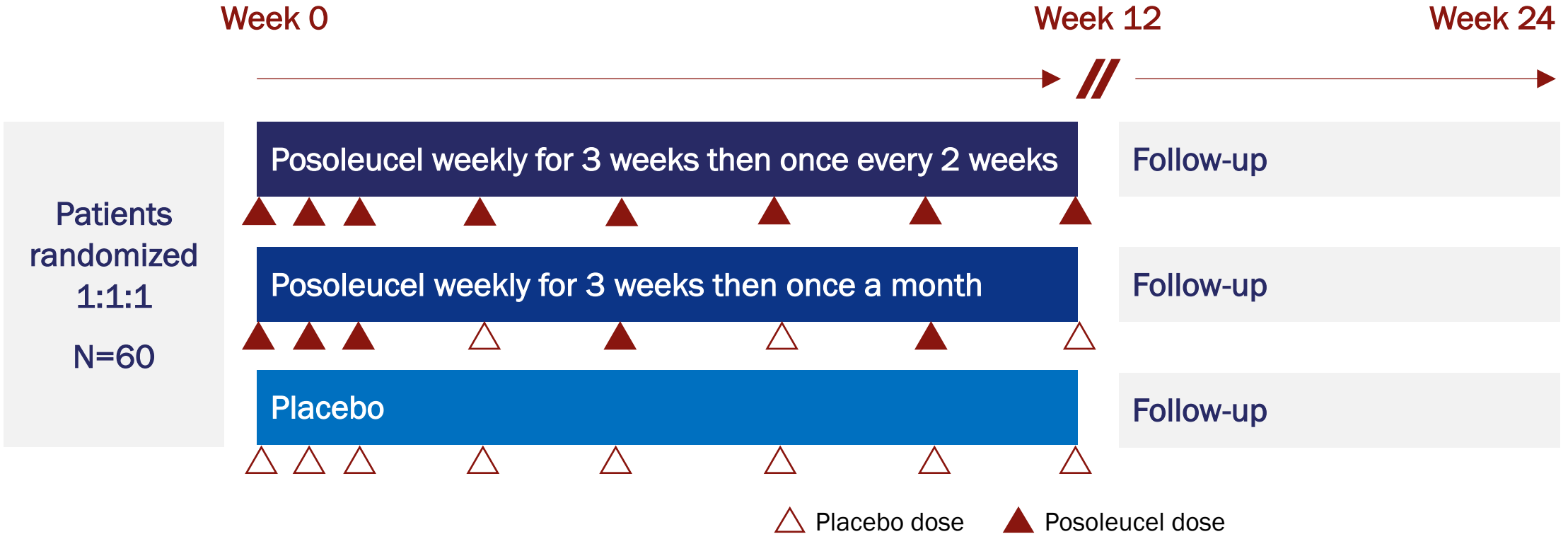
Posoleucel (ALVR105)

- Allogeneic, off-the-shelf, multivirus-specific T-cell (VST) therapy targeting adenovirus, BK virus, cytomegalovirus, Epstein Barr virus, human herpesvirus-6, and JC virus
- 93% response rate treating stem cell transplant patients with refractory viral disease with one or more target viruses in Phase 2 CHARMS study[1]
  - 75% of patients with BK virus-associated hemorrhagic cystitis resolved by Week 6[2]
- No clinically significant infections due to BKV occurred in the open-label cohort of the Prevent study[3]



[1]Tzannou et al. *Blood.* 2020; [2]Tzannou et al. *Transplant Cell Ther.* 2021;[3]Dadwal et al. *EMBT.* 2022.

Study Design



- Double-blind, placebo-controlled
- Key inclusion criteria: KT recipients with BK viremia 350-10,000,000 copies/mL
- Consensus immunosuppression reduction guidelines used to harmonize immunosuppression reduction across sites
- Dosing discontinued if BKV <LLOQ at 2 consecutive measurements

Endpoints

Primary endpoint

Safety and tolerability of posoleucel compared to placebo

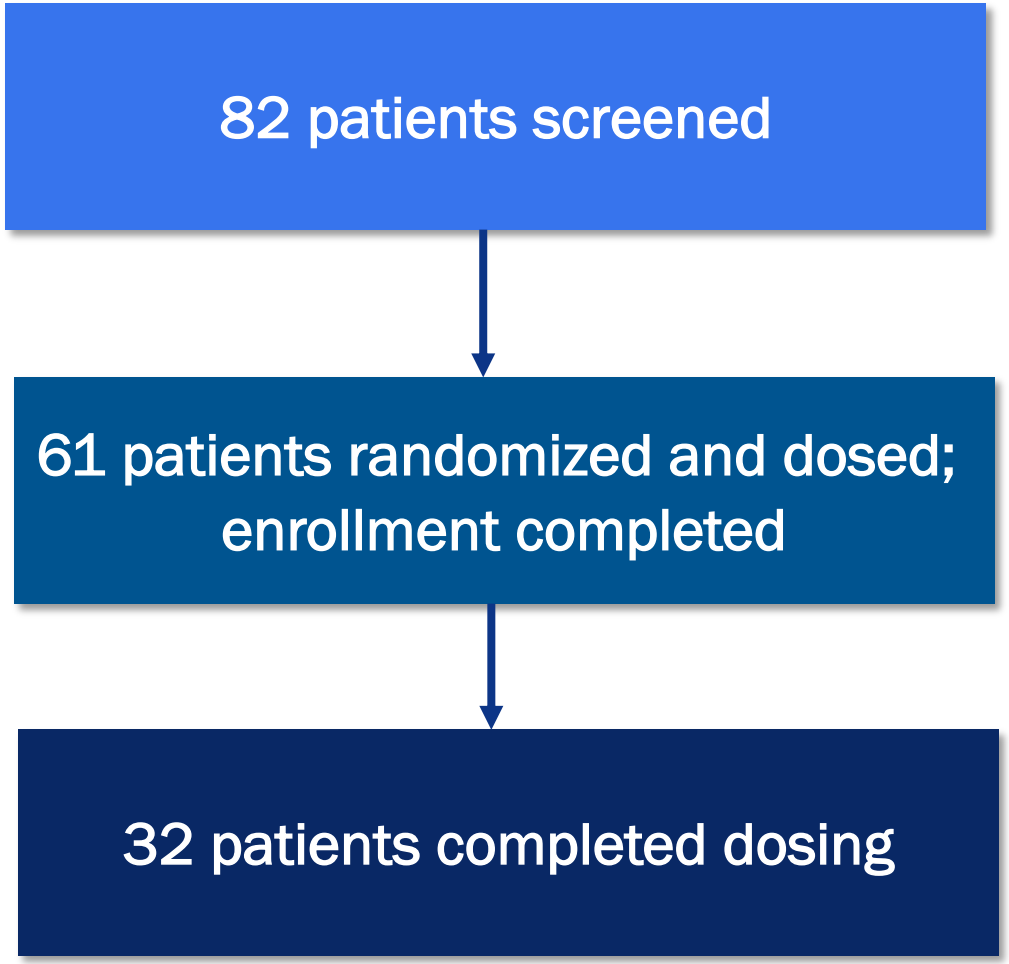
Secondary endpoint

Change in BK viremia in patients receiving posoleucel compared to placebo

Selected exploratory endpoints

- Change in eGFR
- Assessment of T cell expansion by ELISpot
- Assessment of posoleucel persistence by T cell receptor (TCR)-beta sequencing

Patient Disposition as of Data Cutoff for Blinded Interim Analysis



- 100% matching cell-line coverage

- 34 BK VL 350 to <10,000 cps/mL
- 27 BK VL 10,000 to 10,000,000 cps/mL
- 1st dose administered a median of 458 days post transplant

- 28 completed 8 blinded doses
- 4 discontinued dosing due to resolution of BK viremia
- 12 have completed 12 weeks of dosing and 12 weeks of follow up

Data as of 16 May 2022

Demographics

Demographics	N=61
Median age, years (range)	59 (21–75)
Female, n (%)	12 (20%)
Latino or non-Caucasian, n (%)	38 (62%)
Median day 1 eGFR, mL/min/1.73 m^2 (range)	44 (19–61)
Median day 1 BK VL, copies/mL (range)	6,670 (242–7,837,086)
Immunosuppression at baseline, n (%)	
• Calcineurin inhibitor	54 (89%)
• Mycophenolate or mycophenolic acid	21 (34%)
• mTOR inhibitor	4 (7%)
• Corticosteroids	42 (69%)
• Dual	39 (64%)
• Triple	14 (23%)

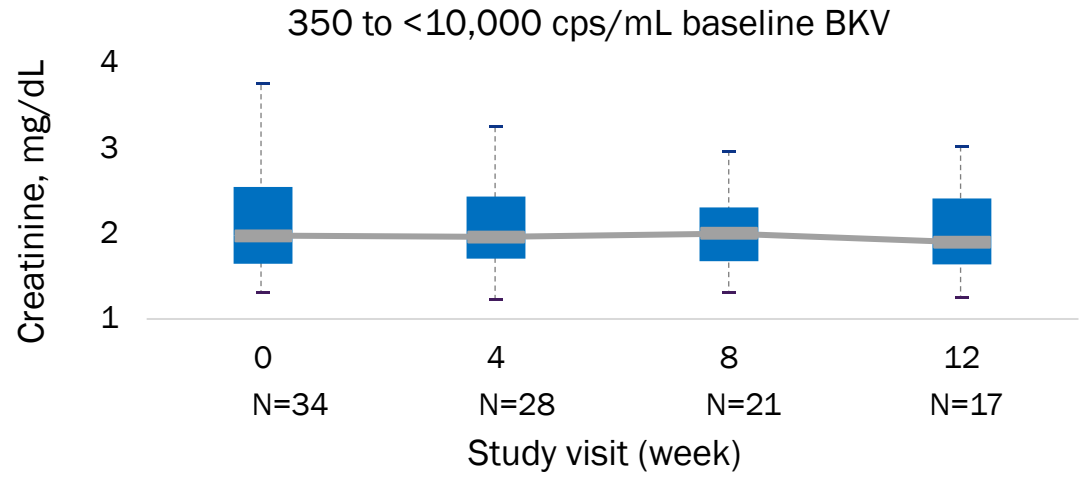
Posoleucel Safety and Tolerability

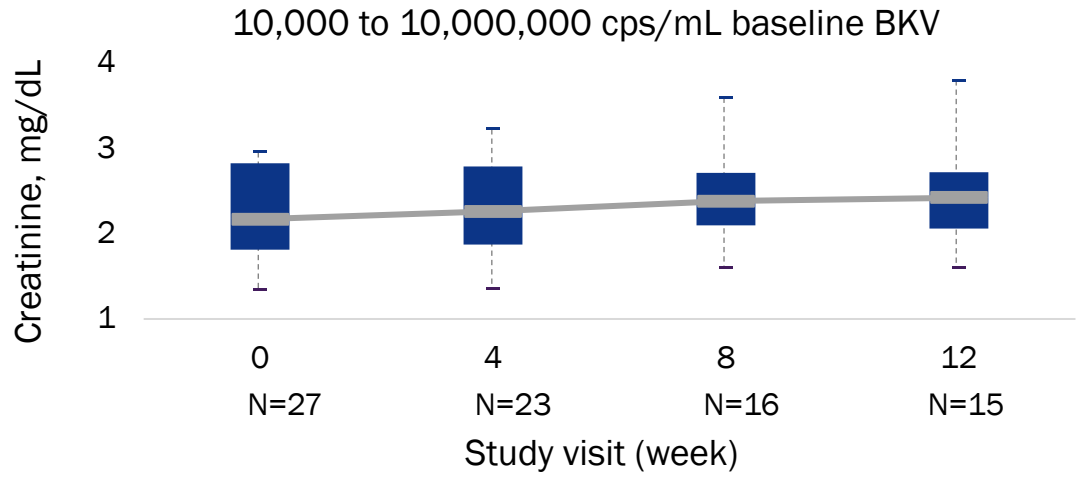
Patients, n (%)	Posoleucel or placebo (n=61)
Adverse events (AEs) related to study drug[1]	13 (21%)
Related AEs in ≥5% of patients	
• Headache	6 (10%)
Grade 3-4 AEs	0
Serious AEs related to study drug	0
Treatment D/C due to AEs	0
Graft-vs-host disease	0
Cytokine release syndrome	0
Death	0
De novo donor specific antibodies (not against posoleucel)	1 (2%)
AE of increased creatinine related to study drug[2]	1 (2%)
Rejection	0
Immunosuppression reduction[3]	6 (10%)

1. Patients with multiple events are counted once. 2. Renal biopsy performed at week 7 (reported as consistent with BKVN). 3. Immunosuppression changes were standardized per protocol and were CNI reduction, MPA reduction, MPA discontinuation, everolimus reduction, and/or leflunomide discontinuation.

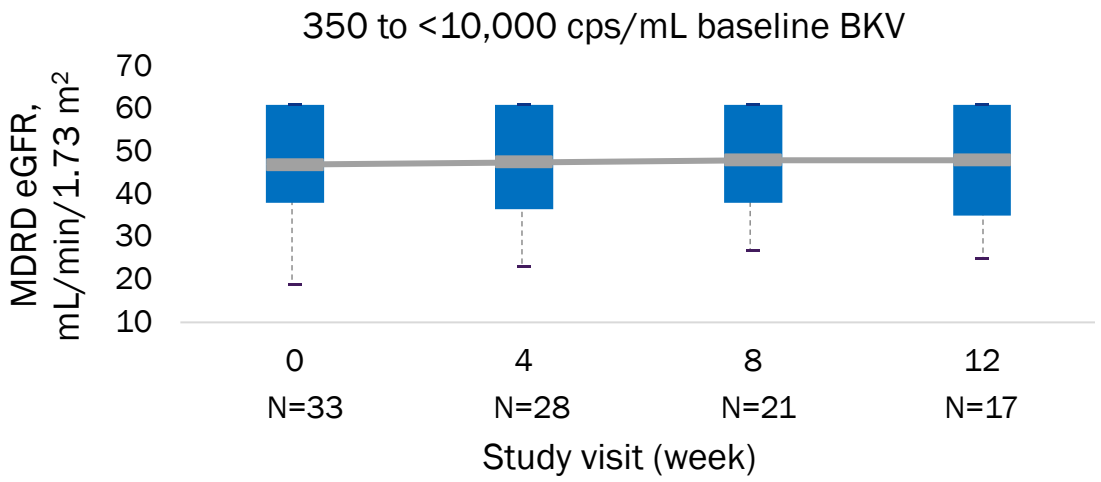
Creatinine and eGFR

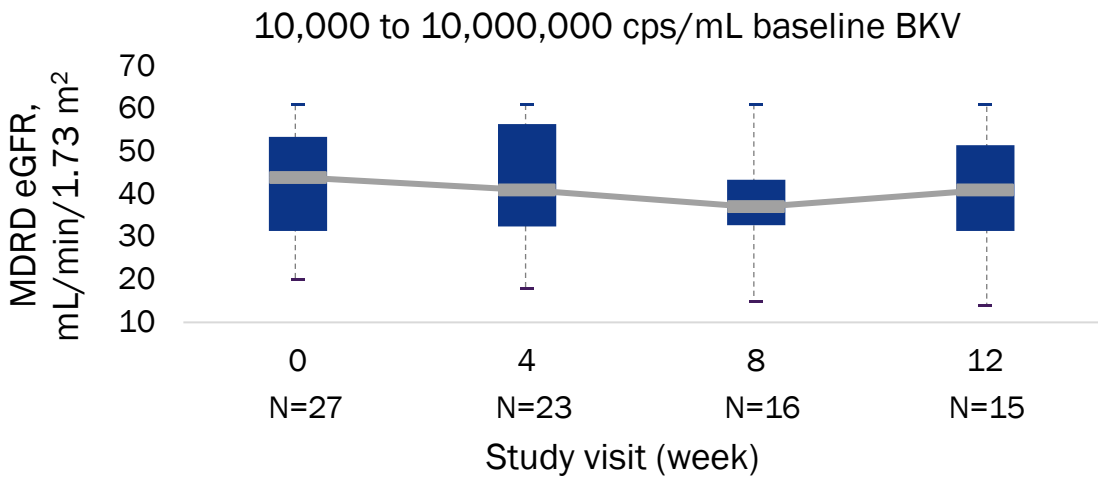
Creatinine over time (mg/dL)





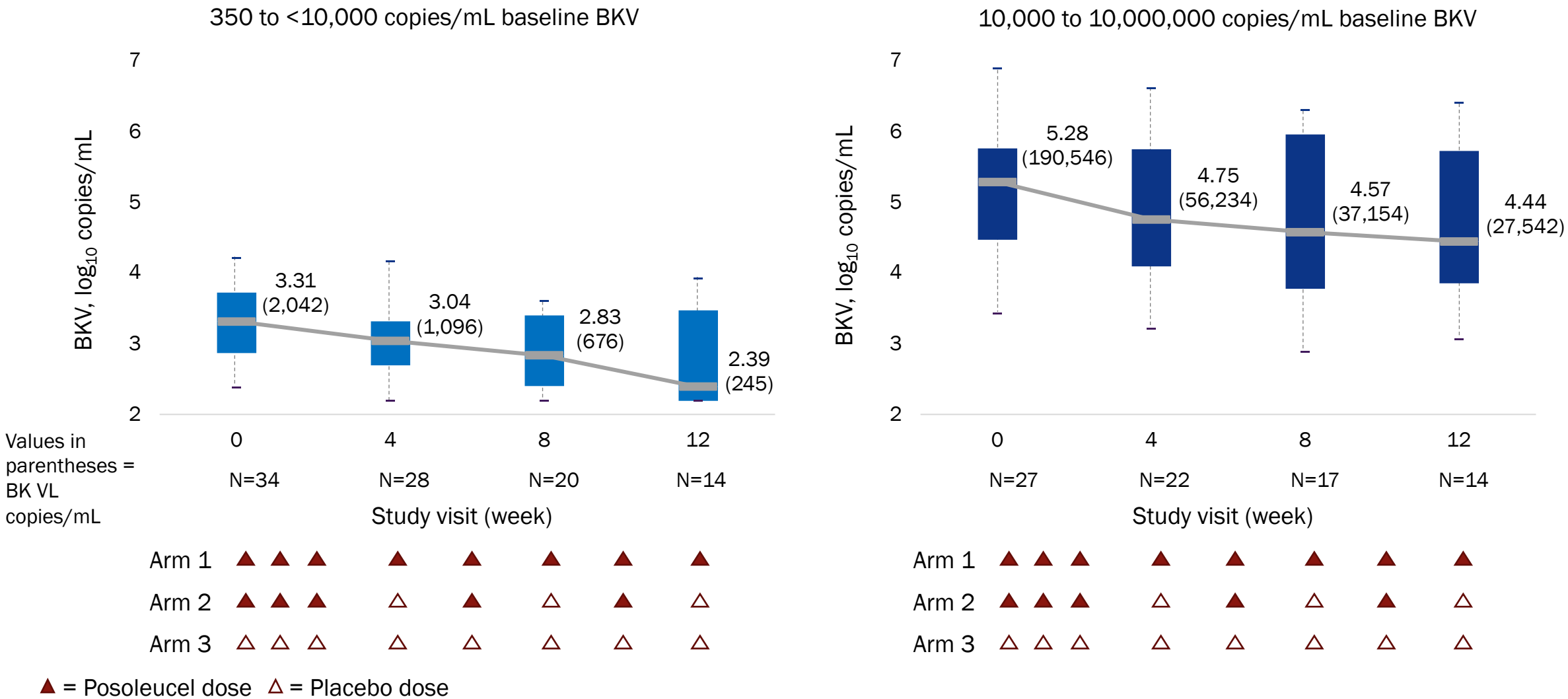
MDRD eGFR over time (mL/min/1.73 m^2)





Secondary Endpoint: BK Viral Load

BK viral load over time (log_{10} copies/mL)



Posoleucel Persists in vivo

- Posoleucel VSTs detected in all seven of the patients with complete TCR sequencing data during infusion period and for up to 12 weeks after last infusion

- Functional T cells (BK-reactive interferon-γ-positive) confirmed in six of these seven patients by means of ELISpot

Conclusions

In this blinded analysis of the first cellular therapy treatment trial for BK virus

- Posoleucel, an allogeneic, off-the-shelf, multi-virus-specific T-cell therapy targeting BK virus as well as 5 other viruses, can be safely administered to kidney transplant recipients with BK viremia
  - No treatment-emergent adverse events leading to discontinuation
  - No SAEs deemed treatment-related
  - No GVHD or CRS
  - No rejection
  - Stable kidney allograft function
- A decline in median BK VL was seen irrespective of the baseline BK VL
- First demonstration of posoleucel persistence associated with expansion of BK-specific T cells in solid organ transplantation

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Posoleucel for EBV & Leiomyosarcoma - poster # 4813

R. Saranu1, S. Nikiforow2, V. Jo3, H. So2, P. Stowe2, S. Tripathi1, R. Anumolu1, R. Vasileiou4, A. Leen4, F. Cardarelli4, A. Chandraker1

1Renal Division, Brigham and Women's Hospital,Boston, MA, 2Dana-Farber Cancer Institute, Boston, MA, 3Pathology, Brigham and Women's Hospital, Boston, MA, 4Allovir, Cambridge, MA

Introduction

- Epstein-Barr virus (EBV)-associated leiomyosarcomas (EBV+LMS) are neoplasms rarely seen in solid organ transplant (SOT) recipients and currently lack effective treatment options.
- We present the case of a kidney transplant recipient (KTR) with EBV+LMS treated with posoleucel (formerly known as ALVR105), an off-the-shelf, investigational T-cell immunotherapy that can target multiple viruses (Adv, BKV, CMV, EBV, HHV-6, and JCV) on a single-patient IND.

Background of EBV+LMS and Rationale for Cell Therapy

EBV Smooth Muscle Neoplasms

- These are rare neoplasms, usually seen in pediatric patients with HIV and other immunodeficiency syndromes. There have been few reported cases worldwide in adult solid organ transplant recipients. EBV-SMTs can arise at any time and in any part of the body after transplantation.
- EBV expresses certain proteins in distinct patterns, known as latency patterns, some of which are recognized more easily by host immune system. Latency pattern III is commonly exhibited by EBV in immunocompromised hosts and literature supports that a majority of EBV+LMS in transplant recipients exhibit latency pattern III (vs. II), but this requires further investigation (Shannon-Lowe C, Front. Onc. (2019)9:713).
- The majority of patients have multifocal disease, postulated secondary to multiple independent primary tumors representing multiple infection events. Some tumors remain indolent and do not progress for years despite being classified as malignant, while others progress rapidly and lead to death.
- These tumors tend to be resistant to radiation and chemotherapy. Management options include surgical resection, mTOR inhibitors, reduction of immunosuppression. However, there is no standardized approach at this time.

Posoleucel

- Posoleucel (formerly known as ALVR105), is an off-the-shelf, investigational T-cell immunotherapy that can target multiple viruses (Adv, BKV, CMV, EBV, HHV-6 and JCV) and is currently in multiple clinical trials targeting hemorrhagic cystitis (NCT05305040), prevention of viral infections/disease (NCT05305040), and adenoviral infections (NCT05179057)---after allogeneic hematopoietic stem cell transplant. An additional study targets BK viremia in kidney transplant patients (NCT04605484), with more trials on the way.
- Donor T cells are exposed, *in vitro*, to multiple viral antigenic peptides and then expanded. They are characterized and evaluated for EBV-specific gamma interferon production, and lack of alloreactivity.
- Posoleucel is expanded against the specific EBV antigens EBNA1 (Latency I, II, III), LMP2 (Latency II and III) and BZLF1 (lytic virus), and in the CHARMS study a complete EBV-specific virologic response was achieved in 2/2 patients with EBV+PTLD or viremia by week 6 post dose (Tzannou, I, JCO, (2017)., 31: 3547. Overall response rate to Posoleucel was 92% for 38 infused patients infected with at least 1 of the 5 target viruses.
- Given the multifocal nature of EBV-SMTs, and potential for differential EBV protein expression, varied response to treatment with a given ALVR105 line may be seen. Off-the-shelf T cells offer the option to switch between multiple cell lines specific to certain epitopes.

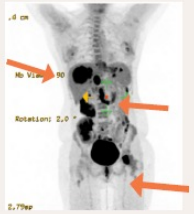
Use Of Targeted T-Cell Therapy (Posoleucel) For The Treatment Of Epstein-Barr Virus Associated Leiomyosarcoma In An Adult Kidney Transplant Recipient: A Case Report

Case Presentation

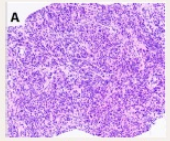
- A 34-year-old female KTR presented 3 years following transplantation with severe hypercalcemia (14.4 mg/dl), elevated creatinine, lymphopenia, EBV viral load of 4128 IU/ml in peripheral blood, and symptoms of fatigue, anorexia, and night sweats.
- Patient immunosuppressive regimen at the time of presentation included Tacrolimus 3mg BID, Azathioprine 100mg QD, and Prednisone 5mg QD.

Diagnosis

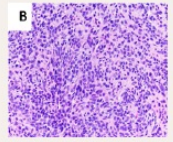
- PET CT scan revealed the following:
  - Multiple FDG-avid liver lesions, a splenic lesion, T6/7 foraminal and S1 vertebral lesions, and a lytic lesion of the left femoral head...among others.



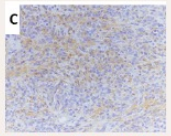
- Liver biopsy revealed the following:



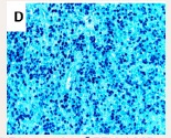
(A) The tumor shows fascicular growth of spindle cells with eosinophilic cytoplasm admixed with a round cell population (core biopsy, 200x).



(B) The round cell component appears primitive with mild-to-moderate cytologic atypia (core biopsy, 400x).

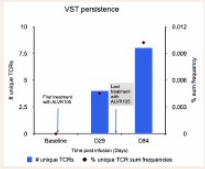


(C) Immunohistochemistry for smooth muscle actin (SMA) is positive, supporting smooth muscle differentiation (400x).



(D) Diagnosis of EBV+LMS was confirmed by in situ hybridization for EBV-encoded RNA (EBER) (400x).

- TCRvβ sequences from posoleucel lot infused in 1st treatment course, patient PBMCs prior to infusion, and circulating PBMCs at 1 month into therapy and 3 months following initiation (1 month after completion of therapy) were analyzed.
- Simpson's Clonality and Downsampled Richness both support increasing T-cell diversity in the patient at 1 and 3 months following treatment initiation.



- After removing TCRvβ sequences found in the patient at baseline, new unique sequences are found at 1 month and in increasing numbers at 3 months following treatment initiation, potentially indicating expansion and persistence of T-cell clones in the posoleucel infusions.

Management

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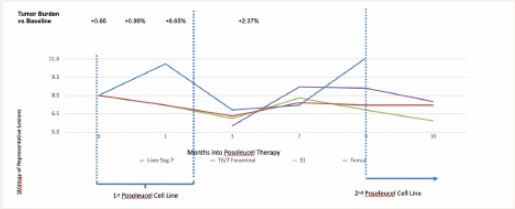
Initial Treatment

- Valacyclovir was initiated to potentially decrease circulating EBV.
- Azathioprine was stopped. Prednisone continued at the same dose, and Tacrolimus was switched to Sirolimus based on case reports demonstrating activation of mTOR/Akt pathways in patients with EBV+LMS.
- The patient received 3 cycles (9 doses) of a different cellular immunotherapy on clinical trial with initial RECIST grading of "stable disease" but clear radiographic improvement and then mild progression prompting transition to Posoleucel.

Treatment with Posoleucel

- The patient received 6 doses of 4x107 cells (3 weekly, then 3 every other week) over a 2-month period during the 1st phase of treatment with a unique Posoleucel line.
- PET-CT at 1 month into therapy and 1 month following completion of therapy (3 months after start) showed RECIST "stable disease (<1% increase in tumor burden) but decreased FDG uptake in multiple areas.
- EBV viral load remained </= 78IU/mL and at times was below level of quantification.
- 4 months following completion of initial therapy course (6 months after start), tumor burden increased by >6% from baseline with SUVmax increasing in representative lesions.
- As of May, 2022, the patient is over 1 month into a 2nd phase of treatment with a different Posoleucel line, currently given every 2 weeks. Tumor burden decreased >4% and FDG avidity in multiple areas was stable to slightly improved.
- The patient tolerated all infusions well. No significant adverse events noted to date.



Discussion

- Cellular therapy targeting viral proteins in viral-driven cancers has entered clinical utilization, through early and late stage clinical trials and in this case single patient INDs.
- Efficacy in typical post-transplant lymphomas secondary to EBV (EBV+ PTLD) has been seen with 50-70% response rates, but EBV+ smooth muscle tumors constitute a unique entity .
- The disease control by RECIST and clinical benefit in symptoms and FDG-avidity seen in this patient while on active therapy with posoleucel supports the premise that allogeneic off-the-shelf EBV-directed cell therapy may be efficacious in EBV+LMS (Kurlander, L, Abstract34O, ESMO IO (2018)).
- Formal clinical trials with posoleucel and other EBV-directed cell therapies in EBV+LMS are now relevant (NCT04554914) .

Footnotes:

1. TCRvB sequencing performed using Adaptive Biotechnologies Immunoseq Platform
2. RECIST Response Evaluation Criteria in Solid Tumor used to provide standard grading

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