

# BCMA CAR-T induces complete and durable remission in refractory plasmablastic lymphoma

Sharmila Raghunandan <sup>1,2</sup>, Melinda Pauly,<sup>1,2</sup> William G Blum,<sup>3</sup> Muna Qayed,<sup>1,2</sup> Madhav V Dhodapkar,<sup>1,3</sup> Mohamed Elkhailifa,<sup>1,2</sup> Benjamin Watkins,<sup>1,2</sup> Michelle Schoettler,<sup>1,2</sup> Edwin Horwitz,<sup>1,2</sup> Suhag Parikh,<sup>1,2</sup> Shanmuganathan Chandrakasan,<sup>1,2</sup> Kathryn Leung,<sup>1,2</sup> Elyse Bryson,<sup>1,2</sup> Laura Deeb,<sup>1,2</sup> Jonathan L Kaufman,<sup>3</sup> Diana Worthington-White,<sup>1,2</sup> Adina Alazraki,<sup>1,2</sup> Jordan M Schecter,<sup>4</sup> Deepu Madduri,<sup>4</sup> Carolyn C Jackson,<sup>4</sup> Enrique Zudaire,<sup>5</sup> Agne Taraseviciute-Morris,<sup>4</sup> Alexander Babich,<sup>5</sup> Tonia Nesheiwat,<sup>6</sup> Martin Vogel,<sup>7</sup> Nikoletta Lendvai,<sup>4</sup> Lida Pacaud,<sup>6</sup> Kirsten M Williams<sup>1,2</sup>

**To cite:** Raghunandan S, Pauly M, Blum WG, *et al.* BCMA CAR-T induces complete and durable remission in refractory plasmablastic lymphoma. *Journal for ImmunoTherapy of Cancer* 2023;**11**:e006684. doi:10.1136/jitc-2023-006684

SR and MP are joint first authors.

Accepted 30 March 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA

<sup>2</sup>Children's Healthcare of Atlanta, Atlanta, Georgia, USA

<sup>3</sup>Winship Cancer Institute, Emory University, Atlanta, Georgia, USA

<sup>4</sup>Janssen Research and Development LLC, Raritan, New Jersey, USA

<sup>5</sup>Janssen R&D, Spring House, Pennsylvania, USA

<sup>6</sup>Legend Biotech USA Inc, Piscataway, New Jersey, USA

<sup>7</sup>Janssen Global Services LLC, Raritan, New Jersey, USA

## Correspondence to

Dr Sharmila Raghunandan; sraghu2@emory.edu

## ABSTRACT

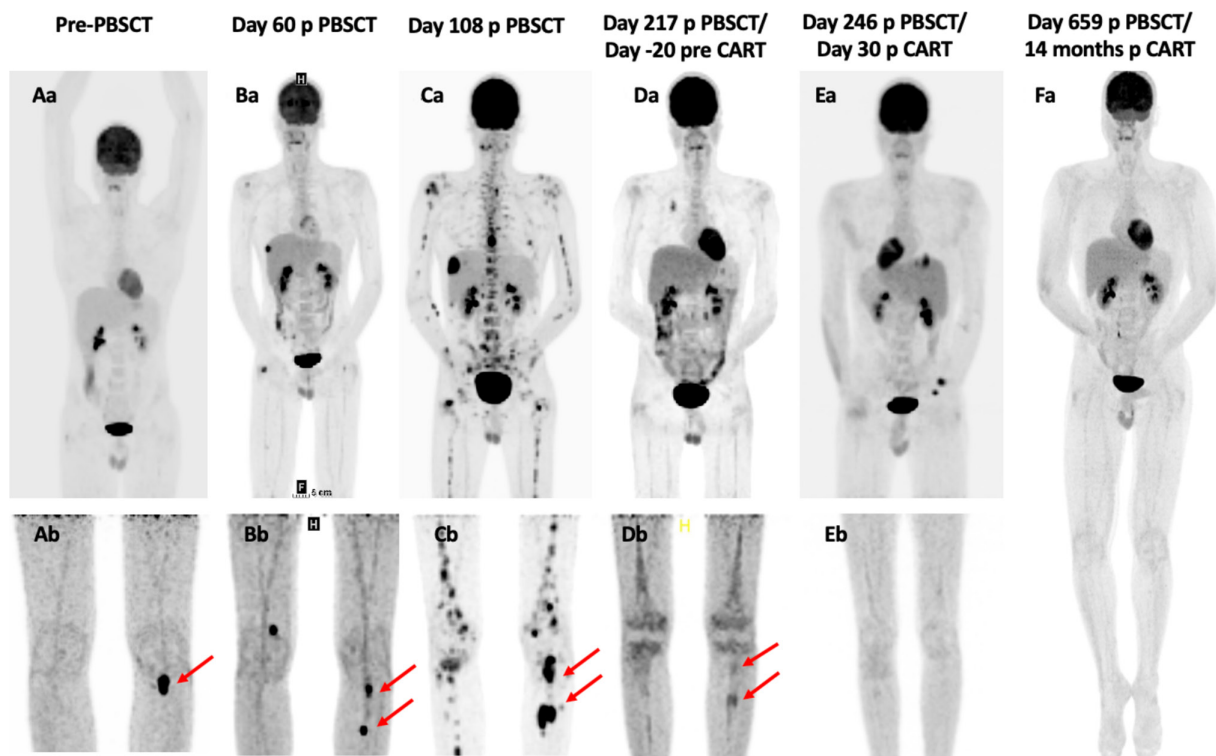
Plasmablastic lymphoma (PBL) is a rare subtype of aggressive large B-cell lymphoma, with a dismal prognosis despite aggressive therapies. New approaches are needed for those with refractory disease. PBL expresses antigens similar to multiple myeloma (MM), including B-cell maturation antigen (BCMA). Chimeric antigen receptor T-cell (CAR-T) therapy directed against BCMA has shown efficacy for the treatment of heavily pretreated MM with low rates of grades 3 and 4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in a phase Ib/II trial (A Study of JNJ-68284528, a CAR-T Directed Against BCMA in Participants With Relapsed or Refractory Multiple Myeloma (CARTITUDE-1), NCT03548207). However, data for the use of BCMA CAR-T for treating PBL are lacking.

We report a challenging case of multiple refractory PBL that emerged from B-cell acute lymphoblastic leukemia in an adolescent who failed to respond to an allogeneic hematopoietic cell transplant. The patient developed rapidly advancing disease despite withdrawal of immunosuppression, treatment with etoposide, ibrutinib, and daratumumab, prompting consideration of BCMA CAR-T (under emergency investigational new drug (eIND)). The patient achieved a complete remission (CR), without recurrent acute graft versus host disease (GVHD), CRS or ICANS after BCMA CAR-T therapy. BCMA CAR-T expansion was detected *in vivo*, peaking on day 15. The patient remains in CR for more than a year post CAR-T therapy, supporting consideration of immunotherapy for future patients with refractory PBL, a disease with few treatment options.

Plasmablastic lymphoma (PBL) is a rare subtype of aggressive large B-cell lymphoma associated with immunodeficiency and confers a dismal prognosis despite aggressive therapies.<sup>1–5</sup> Thus, new approaches are needed for those with refractory disease. PBL expresses similar antigens as multiple

myeloma (MM), including B-cell maturation antigen (BCMA). While there are limited data in the literature, the one study showed that seven of seven PBLs demonstrated strong and diffuse BCMA expression.<sup>6</sup> Ciltacabtagene autoleucel (cilta-cel) is a second-generation chimeric antigen receptor T cell (CAR-T) with two BCMA-binding single domains, the CD3 $\zeta$  T-cell activation domain and a 4-1BB costimulatory domain. Cilta-cel has shown efficacy for the treatment of heavily pretreated MM with low rates of grades 3 and 4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in a phase Ib/II trial (CARTITUDE-1, NCT03548207).<sup>7,8</sup> Cilta-cel has shown an excellent overall response rate of 98% at 28 months with 83% of patients achieving a complete remission (CR).<sup>8</sup> Given the aggressiveness of PBL and limited treatment options, we hypothesized that cilta-cel would have efficacy against BCMA+ refractory PBL that arose from B-cell acute lymphoblastic leukemia (B-ALL) with manageable toxicity.

An adolescent patient was diagnosed with B-ALL (National Cancer Institute (NCI) high-risk by age), expressing CD10+, CD19+, partial CD20, partial CD22, partial CD34, CD38, partial CD200 (dim), HLA-DR, and partial CD45 (dim) by flow cytometry. The patient's disease was refractory to high-risk ALL induction therapy but achieved CR following CD22 antibody–drug conjugate treatment (inotuzumab ozogamicin) combined with chemotherapy. Without evidence of marrow or central nervous system disease, but with a lung lesion of uncertain etiology identified

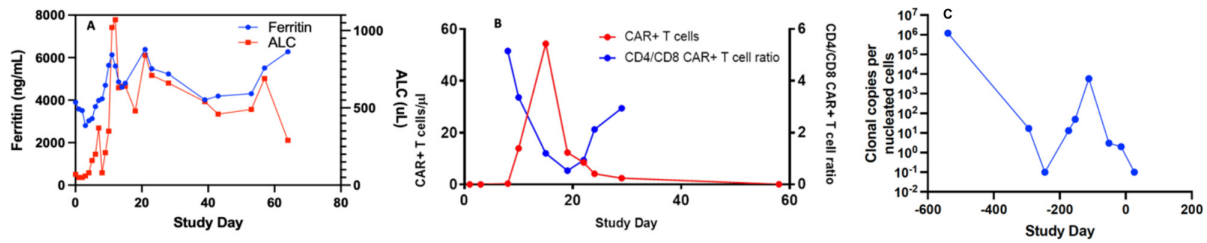


**Figure 1** PET whole body and lower extremity. (Aa) Pre-PBSCT. Minimal FDG of pleural-based lesion, SUV <2. (Ab) Hypermetabolic lesion in proximal left tibia, SUV 14. (Ba) Relapse at day 60 post PBSCT. No abnormal FDG uptake in chest. New uptake in liver, SUV 15.6. (Bb) Numerous areas of abnormal intake including right humerus, right sacrum and ilium, right proximal femur, right distal femur, and left mid-tibia. (Ca) Day 108 post PBSCT. Increase in size of hepatic lesion, two new hepatic lesions. (Cb) Innumerable, multifocal, hypermetabolic lesions throughout the axial and appendicular skeleton including proximal left tibial lesion; SUV 14.5. (Da) Pre-BCMA CAR-T. New patchy ground-glass opacities in the right upper lobe, SUV 4.4; no abnormal FDG in the abdomen/pelvis. (Db) Persistent residual disease in the left tibia. (Ea) Post-BCMA CAR-T: no abnormal FDG uptake in the chest/abdomen/pelvis. (Eb) Near complete resolution of FDG uptake in the left proximal tibia. (Fa) Fourteen months post-BCMA CAR-T: normal PET/CT. CAR-T, chimeric antigen receptor T cell; PBSCT, peripheral blood stem cell transplant; PET, positron emission tomography; FDG, fluorodeoxyglucose; SUV, standardized uptake value; Red arrows, identify certain hypermetabolic lesions.

on MRI for back pain, the patient subsequently received investigational humanized CD19 CAR-T therapy with 41BB costimulatory domain 5 months after diagnosis (NCT03792633). The patient relapsed 60 days later. Flow cytometry at the time of relapse was similar to that at diagnosis with addition of CD9+, partial CD58, partial CD123, and dimterminal deoxynucleotidyl transferase (TdT), retaining CD19 expression. Cytogenetics revealed t(14;18), der(4)t(1;4), and focal loss of IKZF1 and PAX5 on microarray. Reinduction with idarubicin–fludarabine, cytarabine, and venetoclax achieved CR of B-ALL. However, a chest mass, first identified directly prior to CD19 CAR-T infusion, worsened, accompanied by a new tibial lesion. Biopsies of each lesion revealed PBL with a t(14;18) translocation. Immunohistochemistry (IHC) showed CD138+, MUM1+, CD43 majorly, CD56 majorly, vimentin majorly, INI1 retained, negative for CD19, CD20, HHV8, and EBV-EBER, confirming the diagnosis of PBL. Extensive testing for underlying immunodeficiency was negative. PBL-directed therapy with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and bortezomib achieved resolution of the chest mass and reduced but persistent tibial uptake on imaging

(figure 1Aa,b). With PBL in partial remission and B-ALL in CR3, the patient underwent myeloablative total body irradiation-based matched sibling peripheral blood stem cell transplant (PBSCT) with boosts to the tibia (20 Gy), lungs (200 cGy), and brain (600 cGy). Full donor chimerism was achieved, but unfortunately, the patient relapsed with PBL 60 days after PBSCT with progression at the prior tibial disease site and abundant liver and bone lesions (figure 1Ba,b). Tibial and liver IHC showed CD138+ and MUM-1+, variable CD45, focal positivity for lambda light chain with Ki-67 of >70%, t(8;14) fusion, and gain of Myc. Targeted testing showed CD38+ and BCMA variably positive. Despite acute calcineurin inhibitor withdrawal and treatment with etoposide, ibrutinib, and daratumumab, the disease progressed (figure 1Ca,b).

An emergency use of investigation drug was obtained, and the patient was enrolled on a single patient protocol using cilta-cel. Following apheresis, rapid disease progression including multiple skin nodules and cachexia led to the addition of lenalidomide to daratumumab and ibrutinib 150 days post PBSCT, resulting in a dramatic reduction in disease burden (figure 1Da,b) but also grade III acute graft versus host disease (GVHD) of the liver (stage



**Figure 2** (A) Ferritin and ALC following BCMA CAR-T demonstrate a moderate elevation in ferritin following CAR-T and a robust response in ALC with a peak on day 12, demonstrating successful CAR-T expansion. (B) BCMA directed CAR-Ts expanded in vivo, peaking on day 15, and were detectable until day 29 by flow cytometry. At the time of peak expansion, the CD4:CD8 ratio was 1.2 and CD8 cells were effector memory phenotype. (C) Minimal residual disease by next-generation sequencing of B-cell receptor clones throughout his clinical course, showing no residual sequences detected since BCMA CAR-T. ALC, absolute leukocyte count; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell.

3), skin (stage 3), and lower gastrointestinal tract (stage 3). GVHD became quiescent with steroids and tacrolimus. Two weeks after cessation of steroids, the patient began fludarabine and cyclophosphamide lymphodepletion and 3 days later received  $0.75 \times 10^6$  cilta-cel chimeric antigen receptor (CAR)+ T cells/kg, 217 days post PBSCT while on tacrolimus. CAR+ T cells expanded postinfusion peaking on day 15 and were detectable peripherally until day 29 (figure 2A,B). At the time of peak expansion CAR+ T-cell CD4:CD8 ratio was 1.2 with CAR+ CD8 T cells being mainly effector memory phenotype. The course was uncomplicated, without GVHD flare, CRS (figure 2B), nor ICANS, though with expected brief grade 2 neutropenia, grade 3 gamma-glutamyl transferase (GGT) increase and grade 1 alkaline phosphatase and aspartate aminotransferase increase, grade 2 lymphopenia, grade 1 thrombocytopenia, grade 1 adrenal insufficiency possibly attributed to CAR-T, all of which resolved. Positron emission tomography/CT demonstrated remission 28 days post CAR-T. At the time of this report, the patient remains in CR by imaging (figure 1Fa,b) 14 months following cilta-cel. The same B-cell receptor clone that identified B-ALL and PBL by next-generation sequencing was not detected after cilta-cel (figure 2C).

This case demonstrates response to cilta-cel in an adolescent with refractory PBL, an aggressive B-cell malignancy with an overall survival of 6–9 months.<sup>3,4</sup> Our patient had already received the most effective first-line regimens including EPOCH, ALL regimens<sup>2,3</sup> and second-line approaches, such as bortezomib and lenalidomide,<sup>2,9–13</sup> as well as an intensive radiation-based allogeneic PBSCT with refractory PBL. Acute GVHD prior to relapse and severe acute GVHD after lenalidomide precluded the use of checkpoint inhibitors which have shown some benefit in PBL.<sup>14</sup> While CD19 CAR-T has been used to treat PBL, lack of CD19 expression also excluded this therapy for our patient.<sup>15</sup> Given the dearth of treatment options in our multiple refractory patient whose PBL expressed BCMA, we trialed cilta-cel based on the promising results in myeloma. While our patient experienced neutropenia, common in the patients who received cilta-cel for myeloma, our patient did not develop ICANS nor CRS. This is surprising, given the patient's risk factors

for these complications, residual disease burden and prior ICANS and CRS with a CD19 CAR-T. We hypothesize that the exposure to tacrolimus (target level 6–8 ng/mL) throughout the CAR-T infusion and expansion may have mitigated these inflammatory syndromes. The patient's ferritin peaked at 6129 ng/mL (reference range 22–275 ng/mL), 11 days post CAR-T infusion, concurrent with peak CAR-T expansion (figure 2A,B). However, cilta-cel appears to have had anti-PBL activity despite the tacrolimus exposure, with remission recently documented 14 months post infusion on a tacrolimus wean.

In summary, we describe a challenging case of multiple refractory PBL in an adolescent who achieved CR after cilta-cel infusion. It was well tolerated despite acute GVHD that occurred prior to the cilta-cel infusion. This case shows PBL CR despite tacrolimus coadministration, with BCMA CAR-T expansion detected in vivo, peaking on day 15. Our data support the consideration of immunotherapy for refractory PBL, a disease with few treatment options.

**Acknowledgements** The authors gratefully acknowledge the patient, family, staff, and caregivers.

**Contributors** KMW initiated the investigational new drug (IND) that led to this case report. SR, MP, and KW wrote the manuscript. SR and MP are both cofirst authors. SR, MP, WGB, MQ, MVD, ME, BW, MS, EH, SP, SC, KL, EB, LD, JLK, DW-W, and AA cared for the patient, reviewed the data, and edited the manuscript. JMS, DM, CCJ, EZ, AT-M, AB, TN, MV, NL, and LP contributed to the IND and protocol, generated the chimeric antigen receptor T-cell therapy, contributed and analyzed the data, and edited the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** MQ reports honoraria from Vertex and Novartis. MVD is on the advisory board for Janssen, Sanofi, and Lava Therapeutics. SC is on the science advisory board of SOBI. JLK reports consulting for Abbvie, BMS, and DSnc for Incyte. JMS reports employment, equity and stock options at Janssen. DM reports employment at Janssen Research & Development, being adjunct assistant professor at Mount Sinai Hospital, Icahn School of Medicine, and being on the consultancy/advisory board at Takeda, Celgene, BMS, GlaxoSmithKline, Legend, Janssen, Kinevant, and Foundation Medicine. CCJ is an employee of Janssen Research & Development and physician consultant at Memorial Sloan Kettering Cancer Center. EZ is an employee of Janssen Research & Development. AT-M is an employee of Janssen Research & Development and an adjunct assistant professor at Los Angeles County/University of Southern California. AB is an employee of Janssen Research & Development. MV is an employee of Janssen-Cilag GmbH. TN reports being an employee of Caribou Biosciences, Inc., in Berkeley, California. NL reports being a full-time employee of Janssen. LP is an employee at Legend Biotech.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Children's Healthcare of Atlanta institutional review board (ID: study00000928). The participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Sharmila Raghunandan <http://orcid.org/0000-0002-1149-8524>

## REFERENCES

- Delecluse HJ, Anagnostopoulos I, Dallenbach F, *et al.* Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood* 1997;89:1413–20.
- Makady NF, Ramzy D, Ghaly R, *et al.* The emerging treatment options of plasmablastic lymphoma: analysis of 173 individual patient outcomes. *Clin Lymphoma Myeloma Leuk* 2021;21:e255–63.
- Lopez A, Abrisqueta P. Plasmablastic lymphoma: current perspectives. *Blood Lymphat Cancer* 2018;8:63–70.
- Pretschner D, Kalisch A, Wilhelm M, *et al.* Refractory plasmablastic lymphoma—a review of treatment options beyond standard therapy. *Ann Hematol* 2017;96:967–70.
- Castillo JJ, Bibas M, Miranda RN. The biology and treatment of plasmablastic lymphoma. *Blood* 2015;125:2323–30.
- Dogan A, Siegel D, Tran N, *et al.* B-cell maturation antigen expression across hematologic cancers: a systematic literature review. *Blood Cancer J* 2020;10:73.
- Berdeja JG, Madduri D, Usmani SZ, *et al.* Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *The Lancet* 2021;398:314–24.
- Martin T, Usmani SZ, Berdeja JG, *et al.* Ciltacabtagene autoleucel, an anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. *J Clin Oncol* 2023;41:1265–74.
- Castillo JJ, Guerrero-Garcia T, Baldini F, *et al.* Bortezomib plus epoch is effective as frontline treatment in patients with plasmablastic lymphoma. *Br J Haematol* 2019;184:679–82. 10.1111/bjh.15156 Available: <https://onlinelibrary.wiley.com/doi/10.1111/bjh.15156>
- Fernandez-Alvarez R, Gonzalez-Rodriguez AP, Rubio-Castro A, *et al.* Bortezomib plus CHOP for the treatment of HIV-associated plasmablastic lymphoma: clinical experience in three patients. *Leuk Lymphoma* 2016;57:463–6.
- Yanamandra U, Sahu KK, Jain N, *et al.* Plasmablastic lymphoma: successful management with CHOP and lenalidomide in resource constraint settings. *Ann Hematol* 2016;95:1715–7.
- Cheng L, Song Q, Liu M, *et al.* Case report: successful management of a refractory plasmablastic lymphoma patient with tislelizumab and lenalidomide. *Front Immunol* 2021;12.
- Ando K, Imaizumi Y, Kobayashi Y, *et al.* Bortezomib- and lenalidomide-based treatment of refractory plasmablastic lymphoma. *Oncol Res Treat* 2020;43:112–6.
- Damlaj M, Alzayed M, Alahmari B, *et al.* Therapeutic potential of checkpoint inhibitors in refractory plasmablastic lymphoma. *Clin Lymphoma Myeloma Leuk* 2019;19:e559–63.
- Raychaudhuri R, Quattieri J, Garfall AL. Axicabtagene ciloleucel for cd19+ plasmablastic lymphoma. *Am J Hematol* 2020;95:E28–30.