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Anti-CD19 CAR T cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: phase 2 trial interim results

Jae H. Park[*,1,2,3,4], **Karthik Nath**[*,1], **Sean M. Devlin**[5], **Craig S. Sauter**[1,4,6], **M. Lia Palomba**[1,3,7], **Gunjan Shah**[1,3,8], **Parastoo Dahi**[1,3,8], **Richard J. Lin**[1,3,8], **Michael Scordo**[1,3,8], **Miguel-Angel Perales**[1,3,8], **Roni Shouval**[1,3,8], **Ana Alarcon Tomas**[8,9], **Elizabeth Cathcart**[1], **Elena Mead**[1,10], **Bianca Santomasso**[1,11], **Andrei Holodny**[12], **Renier J. Brentjens**[1,4,13], **Isabelle Riviere**[4,14], **Michel Sadelain**[4]

[1]Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[2]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Corresponding Author: Jae H. Park, MD, Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, parkj6@mskcc.org.

[*]These authors (J.H.P. and K.N.) contributed equally.

Author Contributions

J.H.P. designed the initial study protocol, and R.J.B., I.R., and M.S. provided support for the overall trial design. J.H.P., K.N., C.S., M.L.P., G.S., P.D., R.J.L., M.S., M.P., R.S., A.A.T., E.M., and B.S. provided clinical care for the patients enrolled to the study. E.C. provided support for clinical operation of the study, and E.C. R.S. and A.A.T provided support for data entry. A.H. performed tumor volume assessment. J.H.P., K.N. and S.D. performed the clinical data analysis, and S.D. did the statistical analysis. J.H.P. and K.N. drafted the manuscript, and all authors have reviewed and participated in the revisions of the manuscripts.

Competing Interests

J.H.P. received consulting fees from Affyimmune Therapeutics, Amgen, Autolus, Be Biopharma, Beigene, Bright Pharmaceutical Services, Inc., Curocel, Kite, Medpace, Minerva Biotechnologies, Pfizer, Servier, Sobi, and Takeda; received honoraria from OncLive, Physician Education Resource, and MJH Life Sciences; serves on scientific advisory board of Allogene Therapeutics and Artiva Biotherapeutics; and received institutional research funding from Autolus, Genentech, Fate Therapeutics, InCyte, Servier, and Takeda. **C.S.S.** has served as a paid consultant to Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite/a Gilead Company, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics and GSK; serves on DSMBs for Ono Pharmaceuticals and CRISPR Therapeutics; has received research funds for clinical trials from Juno Therapeutics, Celgene/BMS, Bristol-Myers Squibb, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme and NKARTA. **M.L.P.** received consulting fees from BMS, Cellectar, Kite, Mustang Bio and Synthekine. **G.S.** received consulting fees from Amgen, BMS, Beyond Spring, Janssen and serves on DSMB for Arcellx. **P.D.** received consulting fees from Kite. **R.J.L.** received consulting fees from Kite and Priothera. **M.S.** served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., Kite, and Omeros Corporation; received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, and Amgen, Inc.; and has received honoraria from i3Health and Medscape for CME-related activity. **M.-A. P.** reports personal fees from Adicet, Allovir, Caribou Biosciences, Celgene, BMS, Equilium, Exevir, Karyopharm, Merck, MorphoSys, Omeros, Syncopation, VectivBio AG, Vor Biopharma, Cidara Therapeutics, Medigene, Sellas Life Sciences, and NexImmune; personal fees and other support from Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis; and other support from OrcaBio outside the submitted work. **B.S.** is an inventor on United States Provisional Patent Application No.: US20210181179A1 “Diagnosis and treatment of immunotherapy-induced neurotoxicity” filed by Memorial Sloan Kettering Cancer Center, and served in a consulting or advisory role for Celgene, Janssen, Legend Biotech, Incyte, Kite/Gilead, and In8bio. **A.H.** is an owner/president of fMRI Consultants, LLC. **R.J.B.** has licensed intellectual property to and collect royalties from BMS, Caribou and Sanofi; received research funding from BMS; is a consultant to BMS, Atara Biotherapeutics Inc, CoImmune, Triumvira and was a consultant for Gracell Biotechnologies Inc but ended employment in the past 30 months; and is a member of the scientific advisory board for CoImmune and Triumvira. **I.R.** reports grants from Takeda Pharmaceuticals and Atara, personal fees from Mnemo Therapeutics, Akron, the Centre for Commercialization of Cancer, and Oribiotech, and other support from Bristol Myers Squibb outside the submitted work. **M. S.** reports grants from Atara Biotherapeutics outside the submitted work, as well as patent 8389282 issued and licensed to Juno Therapeutics, patent 11242375 issued and licensed to Atara Biotherapeutics, patent 10370452 issued, licensed, and with royalties paid from Fate Therapeutics, patent 11377637 issued and licensed to Takeda Pharmaceuticals, patent 11377637 issued and licensed to Mnemo Therapeutics, and patent 11377637 issued and licensed to Minerva Biotechnologies. **K.N., S.D., A.A.T., E.C., R.S., and E.M.** have no conflicts to declare.

[3]Department of Medicine, Weill Cornell Medicine, New York, NY

[4]Center for Cell Engineering, Sloan Kettering Institute, New York, NY

[5]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

[6]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH (new address)

[7]Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[8]Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[9]Division of Hematology and Hemotherapy, Hospital General Universitario Gregorio Maranon, Spain (new address)

[10]Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[11]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY

[12]Radiology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center

[13]Roswell Park Comprehensive Cancer Center, Buffalo, NY (new address)

[14]Michael G. Harris Cell Therapy and Cell Engineering Facility, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

In preclinical models, anakinra, an IL-1 receptor antagonist (IL-1Ra), reduced immune effector-cell associated neurotoxicity syndrome (ICANS) without compromising anti-CD19 CAR T-cell efficacy. We initiated a phase 2 clinical trial of anakinra in patients with relapsed/refractory large B-cell lymphoma and mantle cell lymphoma treated with commercial anti-CD19 CAR T-cell therapy. Here we report a non-prespecified interim analysis reporting the final results from Cohort 1 in which patients received subcutaneous anakinra from day 2 until at least day 10 post CAR T-cell infusion. The primary endpoint was the rate of severe (grade ≥3) ICANS. Key secondary endpoints included the rates of all grade cytokine release syndrome (CRS) and ICANS and overall disease response. Amongst 31 treated patients, 74% received axicabtagene ciloleucel, 13% brexucabtagene ciloleucel and 4% tisagenlecleucel. All grade ICANS occurred in 19% and severe ICANS in 9.7% patients. There were no grade 4 or 5 ICANS events. All grade CRS occurred in 74% and severe CRS in 6.4% patients. The overall disease response rate was 77% with 65% complete response rate. These initial results show that prophylactic anakinra resulted in a low incidence of ICANS in patients with lymphoma receiving anti-CD19 CAR T-cell therapy, and support further study of anakinra in immune-related neurotoxicity syndromes. ClinicalTrials.gov registration: NCT04148430.

Introduction

CD19-directed chimeric antigen receptor (CAR) T-cell therapy can be associated with significant toxicities such as cytokine release syndrome (CRS) and immune effector-cell associated neurotoxicity syndrome (ICANS)[1–8]. Both CRS and ICANS require stringent patient monitoring and result in increased morbidity, prolonged hospitalization and intensive care unit admission.

Given the crucial role of IL-6 in mediating CRS, the IL-6 receptor antagonist tocilizumab is approved for the treatment of moderate to severe CRS[9,10]. It has markedly reduced the incidence of severe CRS, but tocilizumab is not effective for ICANS and real-world data continues to demonstrate >30% rates of severe ICANS with axicabtagene ciloleucel (axi-cel) in patients with lymphoma[11–13]. Furthermore, tocilizumab may worsen ICANS[14]. Despite some concerns that nonspecific immune suppression may compromise antitumor activity, the mainstay of current ICANS management is corticosteroids as targeted therapies are currently lacking[8,10,15]. Some studies have examined prophylactic corticosteroid use and reported trends towards lower rates of severe ICANS but all grade neurotoxicity rates remained high at 58–61%[16,17].

Murine models established to investigate CAR T-cell toxicities have demonstrated that CAR T-cells activate tumor-associated macrophages resulting in increased secretions of IL-1 and IL-6[18,19]. IL-1 is a pleiotropic cytokine mainly produced by monocytes and macrophages, and the ubiquitously expressed IL-1 receptor is responsible for pro-inflammatory signalling[20]. Our own preclinical studies providing IL-1 receptor antagonist (IL-1Ra) from engineered CAR T-cells or administering IL-1Ra have demonstrated that prophylactic administration of anakinra abrogated CAR T-cell mediated immune toxicities without compromising efficacy[18]. Based on these studies, we initiated a phase 2 clinical trial to evaluate the efficacy of prophylactic anakinra in preventing severe ICANS in patients receiving CD19-directed CAR T-cell therapy for B-cell lymphoma.

Results

Patients

From November 11, 2019, to April 5, 2021, a total of 34 patients were screened and 31 patients were enrolled; 3 patients did not proceed to the study for not meeting eligibly criteria or to pursue alternative lymphoma treatment (Fig. 1). This was a single-arm, phase II trial conducted at Memorial Sloan Kettering Cancer Center (ClinicalTrials.gov registration: NCT04148430). Eligible patients were ≥18 years of age with a diagnosis of relapsed/refractory large B-cell lymphoma (LBCL) or mantle cell lymphoma (MCL). Patients must have been receiving commercial CD19-directed CAR T-cell therapy (axi-cel, brexucabtagene autoleucel [brexu-cel], lisocabtagene maraleucel [liso-cel], tisagenlecleucel [tisa-cel]) for the approved indications. Patients with a prior neurotoxicity history or active central nervous system (CNS) disease were not excluded. Further details of the study design and eligibility requirements are provided in the study protocol, which can be found in the Supplementary Information.

The study included two independent cohorts with sequential enrollment to cohort 1 followed by enrollment in cohort 2. In cohort 1, patients received subcutaneous anakinra at a dose of 100mg every 12 hours commencing either on day 2 post-infusion or after 2 documented fevers ≥ 38.5°C, whichever occurred first, for a minimum of 10 days. In cohort 2, patients receive subcutaneous anakinra 100mg daily on day 0 of CAR T cell infusion for a minimum of 7 days. Cohort 2 will enroll 31 patients and enrollment is ongoing. Enrollment to cohort 1 is complete, and herein we report the findings from the completed cohort 1 analysis. In this cohort, no patient received prophylactic dexamethasone or tocilizumab. Anakinra was continued for at least 10 days, but the frequency and duration of anakinra could be increased to 100mg every 6 hours or beyond 10 days in the setting of persistent and/or progressing CRS and ICANS. Anakinra was stopped upon complete resolution of CRS or ICANS. Patients could receive tocilizumab and/or corticosteroids after anakinra initiation for persistent or worsening CRS/ICANS at the discretion of treating investigators. The details of anakinra dose escalation guidelines are available in the study protocol; the institutional anti-microbial prophylaxis guidelines and ICANS monitoring strategies are included in the Methods and Extended Data Table 1. A baseline and day 5 post-CAR T-cell infusion lumbar puncture was performed to allow for cerebrospinal fluid (CSF) analysis. Disease response was assessed by positron emission tomography/computerized tomography (PET/CT) scan at month 1, 3 and 6, and as clinically indicated thereafter.

The primary endpoint of the study was the rate of severe (grade ≥3) ICANS within the first 28 days after CAR T-cell infusion. Key secondary endpoints included the rates of severe CRS; all grade CRS and ICANS; tocilizumab and corticosteroid use; overall response rate; rates of severe infections; and levels of serum and CSF cytokines at baseline and post-anakinra. CRS and ICANS were graded according to the criteria of the American Society for Transplantation and Cellular Therapy (ASTCT) [8] and disease response was assessed per the Lugano Criteria [21].

Patient characteristics at baseline are summarized in Table 1. The median age of the overall cohort was 62 years (range, 25 to 77). The median time between diagnosis and CAR T-cell infusion was 15 months (range, 3 to 85). Nineteen patients (61%) had stage III or IV disease, and 12 (39%) had elevated pre-lymphodepletion lactate dehydrogenase (LDH). Patients received a median of 3 previous lines of therapy (range, 2 to 5). Twenty-two (71%) patients were refractory to their immediate prior therapy, including 20 patients with progressive disease and 1 patient with stable disease to the last line of treatment. Patients had a histological diagnosis of relapsed/refractory LBCL (58%), high-grade B-cell lymphoma (HGBCL) (19%), MCL (13%) and primary mediastinal B-cell lymphoma (PMBCL) (10%). Twenty-three patients received axi-cel (74%), 4 brexu-cel (13%) and 4 tisa-cel (13%). Twenty-six (84%) patients received bridging therapy prior to CAR T-cell infusion. All tumor volume assessments were performed following bridging therapy and prior to conditioning chemotherapy and CAR T-cell infusion (Table 1). Additional detailed individual patient and disease characteristics including modified EASIX scores[22] are listed in Extended Data Table 2.

Anakinra Administration

All patients started subcutaneous anakinra at 100mg every 12 hours. Twenty-five patients (81%) started anakinra on day 2 post-CAR T-cell infusion and 6 (19%) started prior to day 2 for grade 1 CRS per the protocol (Extended Data Table 3). Anakinra dosing was increased to 100mg every 6 hours in 15 patients (48%) for persistent grade 1 CRS (n=5), grade 2 CRS with hypotension (n=7), grade 2 CRS with hypoxia (n=1) and grade 2 CRS with both hypotension and hypoxia (n=2) (Extended Data Table 4).

The median duration of anakinra administration was 11 days (range, 10 to 27). Six patients (19%) completed anakinra as an outpatient following discharge from the initial hospitalization and all received anakinra at 100mg every 12-hour dosing without dose escalation during their 10-day treatment course (Extended Data Table 4). In all patients, anakinra was discontinued either after the 10-day course (n=15) or upon complete resolution of CRS or ICANS (n=16). All patients tolerated the treatment and completed the minimum 10-day course of anakinra per the protocol. No patient stopped the treatment due to any adverse event.

ICANS, CRS and Infection Incidence

A total of 3 patients (9.7%) experienced severe (grade ≥3) ICANS. Six patients (19%) experienced any grade ICANS; 3 patients (9.7%) experienced grade 1 and the other 3 (9.7%) grade 3 ICANS. No grade 2, 4 or 5 ICANS occurred in the study (Fig. 2A). To align with the two-stage study design, the 90% upper bound for the 9.6% with grade ≥3 ICANS is 20.3% and the associated p-value is 0.0014[23,24]. Of the 27 patients who received CD28 containing CARs, i.e., axi-cel and brexu-cel, all grade and severe ICANS rate was 22% (6 of 27) and 11% (3 of 27), respectively; all 4 patients who received tisa-cel did not experience any ICANS (Fig. 2B). The median time to ICANS onset was 4.5 days (range, 3 to 11) after CAR T-cell infusion, and the median duration was 4 days (range, 1 to 15). The individual neurological symptoms and their respective grading per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria are listed in Extended Data Table 5 and included decreased level of consciousness (n=6), confusion (n=3), expressive dysphasia or dysarthria (n=2), hand tremors (n=2), paraesthesia (n=1), and headache (n=1). Five (16%) patients received dexamethasone for treatment of ICANS and none received dexamethasone for prophylaxis; 2 (6%) patients required transfer to intensive care (but did not require intubation) for grade 3 ICANS (Extended Data Table 6). The median steroid duration was 4 days (range, 2 – 25) and the median total cumulative dose of dexamethasone used for ICANS management was 75mg (range, 0 – 364) (Extended Data Table 6). No patient required high dose methylprednisolone for ICANS management.

All grade CRS occurred in 23 patients (74%). Most CRS events were grade 1 or 2, except for 1 grade 3 and 1 grade 4 event (Fig. 2A and C). Of the patients who received CD28 containing CARs (n=27), i.e., axi-cel and brexu-cel, all grade and severe CRS rate was 78% (21 of 27) and 7% (2 of 27), respectively (Fig. 2C). The median time to CRS onset was 1 day (range, 1 – 8) and the median duration was 7 days (range, 1 – 15). Supportive measures for CRS management included tocilizumab (n=11, 35%), dexamethasone (n=4, 13%), and transfer to intensive care for vasopressor support (n=2, 6%). Tocilizumab was

administered for grade 1 (n=2), grade 2 (n=8), and grade 3 CRS (n=1) management, and none for prophylaxis (Extended Data Table 6). Tocilizumab was started at the same time or within 24 hours of anakinra dose escalation in 8 patients and 2 days later in 2 patients; 1 patient received tocilizumab before anakinra dose escalation for grade 1 CRS. Of the 4 patients who received steroids for CRS, the median duration of steroid was 1 day (range, 1 – 14) and the median total cumulative dose of dexamethasone was 15mg (range, 10 – 380) (Extended Data Table 6).

Five patients (16%) had a documented infection occurring within 30 days post CAR T-cell infusion with a median onset on day 12 (range, 4 to 20 days) (Extended Data Table 7). The 5 infections were *Escherichia* coli and *Pseudomonas* aeruginosa bacteremia, *Escherichia* coli and *Clostridium* difficile stool infections, and bacterial pneumonia. All infections resolved and no patients required hospital readmission for infectious complications. Patients with infectious complications beyond day 30 with corresponding severity and infectious organisms are included in Extended Data Table 7.

CAR T-Cell Efficacy

The median follow-up duration among survivors was 16 months (range, 1 to 24 months). A best overall response of a partial response or better occurred in 24 of 31 patients by day 100 (77%; 95% confidence interval [CI] 59 to 90). Complete responses occurred in 20 patients (65%) and a partial response in 4 (13%) (Fig. 3A). One patient died of COVID-19 pneumonia at day 47 and did not have a day 30 response assessment; this patient is included in the no response category in Fig. 3A. The overall response rates by LBCL histology were 78%, 67% and 67% for DLBCL, HGBCL and PMBCL, respectively (Fig. 3B); overall response rates for axi-cel, tisa-cel and brexu-cel were 78%, 50% and 100%, respectively (Extended Data Fig. 1A). The Kaplan-Meier estimate of response duration for at least 3 months was 83% (95% CI, 69 to 99). The median progression-free survival (PFS) was 16 months (95% CI, 9.2 to not reached) (Fig. 3C). Overall survival (OS) at 1-year was 68% (95% CI: 53–88); the median OS was not reached (Fig. 3D). For the 27 LBCL patients, the estimated 1-year OS was 63% (95% CI: 44–83) and 1-year PFS was 52% (95% CI: 30–73). Among the 4 MCL patients, all remain alive and one progressed 9 months after infusion (Extended Data Fig. 1B–C).

Biomarker Analysis

Previous studies of CD19 CAR T cells in lymphoma demonstrated a significant association between ICANS and elevated levels of serum cytokines, including IFNγ, IL-2, IL-6, IL-8, IL-10, IL-15, MCP-1, GM-CSF, and TNFα[2,16,17,25,26]. In our study, we observed a transient early increase of CRP, IL-15 and MCP-1, which normalized within one week of infusion and minimal changes for other serum cytokines in all patients regardless of the severity of ICANS (Fig. 4A; Extended Data Fig. 2). Importantly, we observed no significant increase in IL-1 downstream cytokines including IL-1α, IL-1β, IL-6, and IL-8 in all patients, but found a dramatic and sustained increase in the levels of serum IL-1Ra for the entire duration of anakinra administration (Fig. 4A), indicating that the measured IL-1Ra levels represent anakinra concentration as opposed to endogenous IL-1Ra production.

Next, based on our prior finding that linked severe ICANS and increased CSF protein as a surrogate marker of blood-CSF barrier disruption[25], we measured CSF protein levels at baseline and day 5 post CAR T-cell infusion and observed no significant increase (Fig. 4B). In addition, we measured CSF cytokine levels at baseline and post CAR T cell infusion and selected the day 5 timepoint to provide comparisons to the levels published in the prior study of axi-cel with prophylactic corticosteroid use[17]. Similar to our findings of the serum cytokine analysis, we observed a significant and dramatic increase of IL-1Ra in the CSF at day 5, supporting the previous published observation that anakinra can cross the blood-brain barrier[17,27]. Most gratifyingly, we did not find a significant change of cytokines previously found to be associated with ICANS including IL-1α, IL-2, IL-6, IL-8, IL-10, IL-15, TNFα and IFNγ, with the exception of G-CSF [25] (Fig. 4C).

Discussion

In this phase 2 study, we found that prophylactic subcutaneous administration of anakinra at 100mg every 12 hours with step-up dosing reduced rates of high-grade ICANS in patients receiving CD19-directed CAR T-cell therapy, findings that are consistent with results of preclinical studies[18,19]. To the best of our knowledge, this is the first and largest prospective clinical trial of prophylactic anakinra for prevention of ICANS associated with CD19-directed CAR T-cell therapy. Overall, all grade ICANS occurred in 19% of patients and ≥ grade 3 ICANS in 9.7%. Of the patients receiving axi-cel and brexu-cel, all grade ICANS occurred in 22% and ≥ grade 3 ICANS in 11% in the study, as compared with 55–69% all grade and 31–38% ≥ grade 3 ICANS reported with axi-cel and brexu-cel in prior clinical trials and real-world data[4,11–13]. Importantly, we found rapid biodistribution of anakinra into both the serum and CSF with subsequent suppression of IL-1 associated cytokines, including in the CSF. Lastly, administration of anakinra did not impact the efficacy of CAR T-cells, corroborating our earlier findings in animal models[18]. At a median follow-up of 16 months, responses occurred in 77% of patients with a median PFS and OS of 16 months and not reached, respectively.

ICANS associated with CD19 CAR T-cell therapy remains one of its most troublesome toxicities with limited and no targeted treatment options. IL-1 is produced by recipient monocytes and macrophages and demonstrated to be an actionable target to mitigate CAR T-cell mediated immune toxicities in two separate animal models without affecting CAR efficacy[10,18,19]. In both models, prophylactic anakinra reduced macrophage activation and infiltration to the brain. In addition, our prior analysis of CSF cytokines from patients with severe ICANS demonstrated marked elevation of IL-1α along with IL-6, IL-8, IP-10, and MCP-1 in the CSF and suggested these locally produced cytokines secreted by activated microglia, macrophages or astrocytes as a potential mechanism of neurotoxicity[25]. To date, clinical experience of anakinra has been limited to case reports and as a treatment of refractory CRS/ICANS rather than as a preventive strategy[28–30]. However, our preclinical data suggests IL-1 inhibition would be most effective when applied early to abate macrophage activation before high-grade CRS and ICANS developed[18,19].

We observed that IL-1Ra levels dramatically increased immediately following anakinra administration, suggesting a rapid biodistribution of anakinra and suppression of its

downstream IL-1 related cytokines. The marked elevation of CSF IL-1Ra after anakinra administration is consistent with anakinra's ability to cross the blood-brain-barrier and directly exert its effects within the central nervous system [27,31]. In contrast, tocilizumab is unable to cross the blood-brain-barrier, and this may partly explain its minimal activity on ICANS. Secondly, only modest increases of other cytokines typically associated with ICANS were seen in both the serum and CSF, suggesting that IL-1 inhibition exerts a broader downstream effect to reduce other pro-inflammatory cytokines[10]. In a study of prophylactic corticosteroid use in patients treated with axi-cel, CSF cytokines measured at day 5 post-CAR T-cell infusion demonstrated higher levels of IL-2Rα, IL-6, IL-8, IL-15 and IFN-γ in patients who had grade ≥3 neurotoxicity[17]. In contrast, we did not observe significant increases of these cytokines at day 5. Our findings underscore the usefulness and effectiveness of agents that unlike monoclonal antibodies can cross the blood-brain barrier.

It is important to put the results of this study in context with ICANS rates from other CD19-directed CAR T-cell studies. Prior to the establishment of the ASTCT ICANS grading criteria[8], neurotoxicity was reported per the CTCAE grading. Although cross-trial comparisons are challenging owing to various grading systems for neurotoxicity, we have previously reported a high concordance between ASTCT and CTCAE grades[12]. Furthermore, the most recent real-world data analysed neurotoxicity using the ASTCT criteria and reported 56% all grade and 38% ≥ grade 3 ICANS rate in 168 patients receiving axi-cel[13]. In the present study, we observed all grade and ≥ grade 3 ICANS rates of 22% and 9%, respectively, in patients who were treated with axi-cel. These rates compare favorably with those from prior trials and real-world data with axi-cel that reported the higher all grade and ≥ grade 3 neurotoxicity rates of 56–64% and 28–38%, respectively[2,12,13]. When compared to prior studies using early intervention or prophylactic corticosteroids with axi-cel, our data shows lower all grade (22% vs. 58–61%) and ≥ grade 3 ICANS rates (9% vs. 13–17%) noting the similar pre-treatment disease burdens (median sum of the product of diameters [SPD] in our cohort of 1609.5mm^2 vs. 1184 and 2100mm^2 in prior studies)[16,17].

In addition, we did not observe a delayed onset of either CRS or ICANS with prophylactic anakinra. The median onset of CRS and ICANS in the study was 1 and 4.5 days, respectively, and is comparable to the 2 and 5 days reported with axi-cel[2,11]. Importantly, anakinra prophylaxis does not seem to impact CAR T-cell efficacy. We observed 61% complete response rate and 1-year PFS estimate of 52% in patients treated with axi-cel, comparable to 54–64% complete repones rates and 44–45% 1-year PFS reported in prior studies of axi-cel at a similar median duration of follow-up[2,11].

Our study also indicates that the dose and timing of anakinra are important to maximize its efficacy. While anakinra has been used for management of refractory CRS and ICANS[28–30,32,33], the optimal dose when used as prophylaxis remains unknown. Preliminary results from a study that used 200mg daily of prophylactic anakinra did not see a reduction in severe ICANS[34], and another retrospective study concluded that a higher dose and a shorter time to initiate anakinra was associated with improvement of CRS/ICANS[32]. In the present study, we started anakinra at 100mg every 12 hours and allowed a prompt dose escalation to 100mg every 6 hours (400mg daily) for persistent grade 1 CRS or progression to grade 2 CRS. This design of risk-adapted anakinra dose adjustment in response to toxicity likely led

to more effective early inhibition of IL-1. Our data suggest that starting with 100mg every 6 hour-dosing may also be considered in future clinical trials.

This trial has some limitations. Because the validated assay to measure commercial CAR T-cell products was not available during the study period, we were unable to analyse for CAR T-cell expansion although the overall response rates of 77% is comparable to the published data[2–4,11]. In another study, preliminary results demonstrated that prophylactic anakinra did not impact the peak expansion and antitumor efficacy of axi-cel compared to the ZUMA-1 cohort [34]. Our study was non-randomized and therefore might have introduced a selection bias. Unlike the ZUMA-1 cohort 1 and 2, our study allowed bridging therapy as did the subsequent ZUMA-1 cohort 4 and 6 and ZUMA-2 studies. Baseline pre-treatment tumor volume in our study as measured by SPD (median 1609.5mm^2) was comparable to those reported in the ZUMA-1 cohort 4 and 6; it was numerically higher than the value reported in ZUMA-1 cohort 6 (median 1184mm^2)[16] but lower than ZUMA-1 cohort 4 (median 2100mm^2)[16,17]. Future randomized studies will be useful to formally address any unforeseen potential selection bias. Lastly, the current cohort evaluated the efficacy of starting anakinra on day 2 or after the onset of early CRS; the ongoing cohort 2 is investigating starting anakinra on day 0 to assess whether we can prevent CRS and further reduce lower severe CRS and ICANS rates with the earlier use of anakinra.

In conclusion, this phase 2 study demonstrates that prophylactic anakinra has a promising activity in reducing rates of both severe and all grade ICANS for patients treated with CD19-directed CAR T-cell therapy and provides strong support for further investigation of its role in neurotoxicity associated not only with CAR T cell therapies but also with other immunotherapies that expose patients to ICANS.

Methods

Study Design and Patients

Study Oversight—The clinical trial (NCT04148430) was approved by the MSK Institutional Review Board and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice. Written informed consent was obtained from patients before start of the treatment. All authors had access to the data and were involved in the analysis of the results and vouch for the data and adherence to the protocol.

Endpoints and Assessments—The primary endpoint of the study was the rate of severe (grade ≥ 3) ICANS within the first 28 days after CAR T-cell infusion. Key secondary endpoints included the rates of severe CRS; all grade CRS and ICANS; tocilizumab and corticosteroid use; overall response rate; rates of severe infections; and levels of serum and CSF cytokines at baseline and post-anakinra. CRS and ICANS were graded according to the criteria of the American Society for Transplantation and Cellular Therapy (ASTCT) [8] and disease response was assessed per the Lugano Criteria [21]. All other toxicities were assessed per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria.

Neurotoxicity Assessment—Patients on the study were followed according to the institutional standard. During the hospitalization, patients were assessed for Immune Effector Cell-Associated Encephalopathy (ICE)[8] at least twice a day by treating nurses and the score was documented in the flow chart. Following discharge from the hospital, patients were followed daily as outpatient until day 14 (day 0 being the day of T cell infusion) and then 2–3 times weekly as indicated for the remaining 14 days.

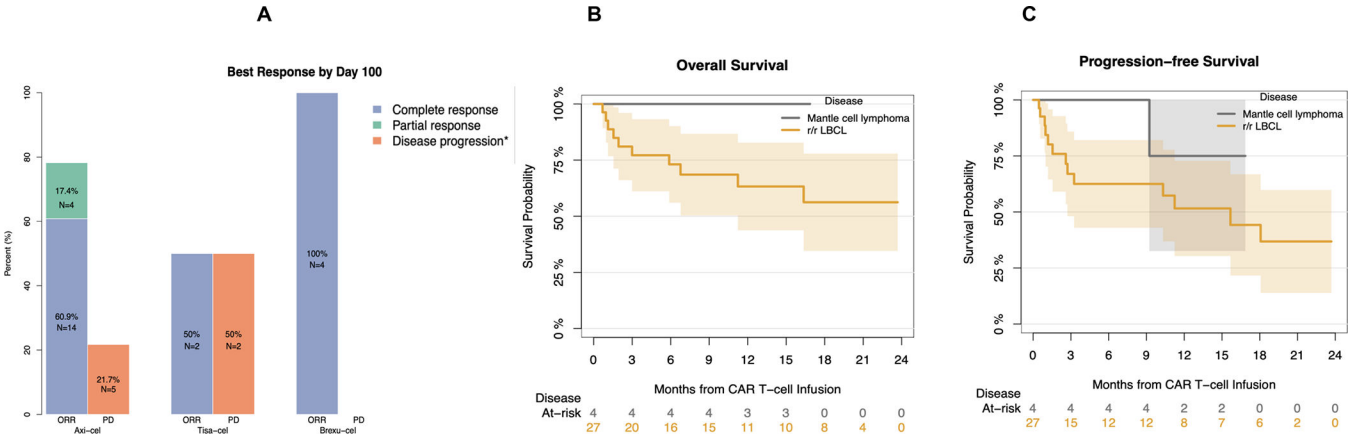
Statistical Analysis

For the primary endpoint of grade ≥ 3 ICANS, the study implemented a Simon's two-stage minimax design aiming to reduce ICANS to 15% or less compared to a historical rate of ≥ 35%. An interim analysis for futility occurred after 13 patients, and the overall study would be considered promising if at least 24 out of 31 patients were free of grade ≥ 3 ICANS at 28 days post-infusion. The type I and type II errors were both set to 0.10. We have selected 35% as the expected grade 3 or higher ICANS rate based on the reported neurotoxicity rates of the commercial CD19 CAR products. Clinical trials and real-world data reported ≥ grade 3 neurotoxicity rate of 28% to 38% for axi-cel and brexu-cel[2,4,11–13] and 12% for tisa-cel in lymphoma[3]. Because we were predominantly using axi-cel for lymphoma patients at study initiation, we estimated the expected rate based more on the axi-cel trials and real-world data.

Summary statistics described the grade, onset, and resolution of ICANS and CRS of study participants. Kaplan-Meier survival curves were used to estimate overall survival (OS) and progression-free survival (PFS) from the time of CAR T-cell infusion.

The longitudinal evaluation of inflammatory markers and cytokines over the first 28 days was plotted with a locally weighted scatterplot smoother to visualize trends over time. CSF white blood cell counts and protein levels were compared between the pre-infusion timepoint and day 5 using a Wilcoxon signed-rank statistic. For CSF cytokines, a partially matched Wilcoxon test was used as pre- and post-infusion paired evaluations were not available on all patients[1]. All statistical analyses were conducted in R v4.2.2.

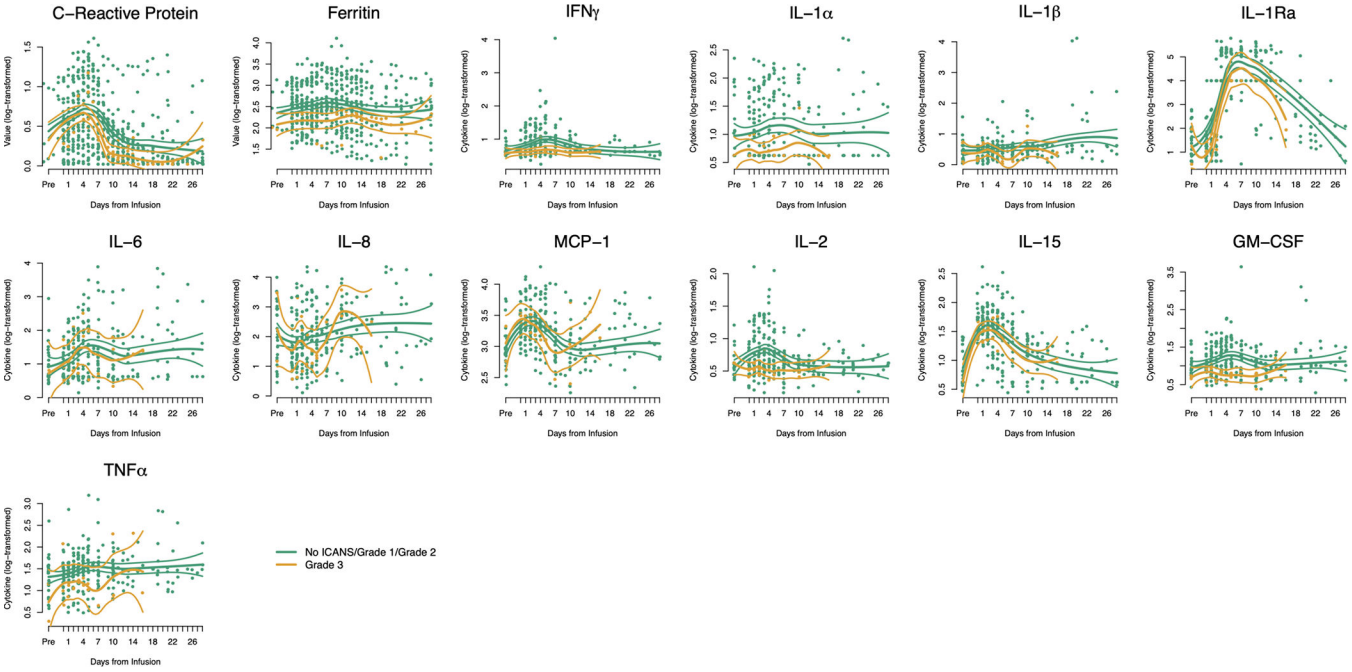
Extended Data



Extended Data Figure 1: Response of patients with relapsed and refractory lymphoma

(1A) Best response by day 100 post CAR T-cell infusion displayed by the cell products received. (1B) Overall survival (1C) progression free survival of the study patients separated by LBCL vs. MCL. The shaded region represents the pointwise 95% confidence interval of the survival estimate.

CAR denotes chimeric antigen receptor; ORR denotes overall response rate; PD denotes progressive disease; LBCL denotes large B-cell lymphoma; MCL denotes mantle cell lymphoma; *One patient died of COVID-19 pneumonia at day 47 and did not have day 30 response assessment - this patient is included in the PD category.



Extended Data Figure 2: Serum cytokine changes over time on study

Changes in the level of serum cytokines after anakinra administration separated by grade 0-2 ICANS vs. grade 3-4 ICANS. The smoothed solid lines over time in each plot represent a locally weighted scatterplot smoother, and the dashed lines represent the corresponding 95% confidence interval.

Extended Data Table 1:

Antimicrobial Prophylaxis Guidelines

	Clinical Scenario	Recommended Agent and Dose	Comments
Antibacterial prophylaxis	Neutropenic (ANC ≤0.5) patients being followed outpatient	Levofloxacin 500mg po q24h	Discontinue upon neutrophil recovery or initiation of broad-spectrum antibiotics for neutropenic fever
Antiviral prophylaxis	Any patients receiving LDC	Acyclovir 400mg po q12h	Commence with LDC and continue for 6 months post-CAR T infusion. Consider extending duration beyond 6 months with persistent lymphopenia (i.e. CD4<200)

	Clinical Scenario	Recommended Agent and Dose	Comments
Hepatitis B antiviral prophylaxis	Hep BsAg+ or HBV DNA PCR+, or Hep BcAb+ plus prior history of rituximab or HSCT	Entecavir 0.5mg po q24h	Continue through active chemotherapy and for a minimum of 6 months post CAR T cell infusion or minimum of 12 months if prior history of anti-CD20 directed mAbs or HSCT.
Anti-PJP prophylaxis	Any patients receiving LDC	TMP/SMX 1DS tab po three times weekly or pentamidine 300mg inh monthly or Dapsone 100mg po q24h (rule out G6PD deficiency)	Commence with LDC and continue for 6 months post-CAR T infusion. Consider extending duration beyond 6 months with persistent lymphopenia (i.e. CD4<200)

LDC: lymphodepleting chemotherapy

Extended Data Table 2:

Baseline Patient and Disease Characteristics

Patient ID	Age	Gender	Disease Histology	Cell Product	# of Prior Tx	Primary Ref.	Ref. to Prior Tx	Performance Status (KPS)	Prior Auto HCT	Bulky Disease	Prior CNS Disease	Active CNS Disease	Bridging Therapy	Baseline LDH (U/l)	Baseline CRP (mg/dL)	Baseline Ferritin (ng/mL)	Baseline PLT ($x10^3$µl)	Baseline SPD (mm^2)	mEASIX
1	55	M	DLBCL	Tisa-cel	3	N	Y	100	N	N	N	N	Y	164	0.91	60	159	6605	0.94
2	25	F	DLBCL	Axi-cel	3	Y	Y	80	N	N	N	N	Y	249	1.5	80	247	924	1.51
3	56	F	DLBCL	Axi-cel	2	N	N	80	N	N	N	N	Y	374	8.05	191	330	9140	9.12
4	58	F	DLBCL	Axi-cel	3	N	Y	90	N	N	N	N	N	278	0.34	37	169	2608	0.56
5	77	M	DLBCL	Axi-cel	2	Y	Y	70	N	N	Y	Y	Y	356	0.08	128	182	598	0.16
6	73	F	DLBCL	Axi-cel	2	N	Y	70	N	N	N	N	Y	182	0.09	72	236	299	0.07
7	72	M	DLBCL	Axi-cel	4	N	N	80	N	N	N	N	Y	204	0.88	19	211	1868	0.85
8	44	M	DLBCL	Axi-cel	2	Y	Y	80	N	Y	N	N	Y	159	0.36	217	188	1566	0.30
9	62	M	DLBCL	Axi-cel	2	Y	Y	90	N	N	N	N	Y	203	0.08	106	221	2929	0.07
10	58	M	DLBCL	Axi-cel	4	N	N	90	N	N	N	N	Y	163	0.81	105	215	1207	0.61
11	73	F	DLBCL	Tisa-cel	4	N	Y	80	N	N	Y	N	N	180	0.18	18	87	452	0.37
12	69	F	HGBCL	Tisa-cel	3	N	Y	80	Y	N	N	N	Y	154	0.13	310	184	1044	0.11
13	43	F	HGBCL	Axi-cel	3	Y	Y	50	N	N	N	Y	Y	453	11.14	626	56	1003	90.1
14	62	M	DLBCL	Axi-cel	5	N	N	90	N	N	N	N	Y	416	3.2	854	30	UN	44.4
15	71	M	DLBCL	Axi-cel	5	N	Y	80	N	N	N	N	Y	184	8.58	237	247	9154	6.4
16	73	F	MCL	Brexu-cel	2	Y	Y	80	N	N	N	N	Y	298	0.31	326	411	1048	0.22
17	58	M	HGBCL	Axi-cel	4	Y	Y	70	N	Y	N	N	Y	1255	7.34	1372	272	11178	33.9
18	56	F	MCL	Brexu-cel	3	N	UN	80	N	N	Y	N	Y	147	0.05	255	167	336	0.04
19	75	F	MCL	Brexu-cel	4	N	N	80	Y	N	N	N	Y	1041	6.8	1059	49	130	144.5
20	73	M	DLBCL	Axi-cel	2	N	Y	80	N	N	N	N	Y	239	5.28	33	136	2372	9.28
21	73	M	DLBCL	Tisa-cel	3	N	Y	70	N	N	Y	Y	Y	659	0.11	143	237	7054	0.31
22	75	M	HGBCL	Axi-cel	2	N	N	90	N	N	N	N	Y	189	0.15	851	191	0	0.15
23	65	F	HGBCL	Axi-cel	3	Y	Y	80	N	Y	N	Y	Y	738	1.83	2309	601	885	2.25
24	69	F	HGBCL	Axi-cel	3	Y	Y	80	N	N	N	N	Y	206	2.1	325	52	780	8.32
25	69	F	PMBCL	Axi-cel	4	N	Y	90	Y	Y	N	N	N	158	19.44	282	240	4026	12.8
26	62	M	MCL	Brexu-cel	2	Y	Y	80	N	N	N	Y	Y	248	18.67	72	64	2099	72.3

Patient ID	Age	Gender	Disease Histology	Cell Product	# of Prior Tx	Primary Ref.	Ref. to Prior Tx	Performance Status (KPS)	Prior Auto HCT	Bulky Disease	Prior CNS Disease	Active CNS Disease	Bridging Therapy	Baseline LDH (U/l)	Baseline CRP (mg/dL)	Baseline Ferritin (ng/mL)	Baseline PLT ($x10^3$µl)	Baseline SPD (mm^2)	mEASIX
27	75	M	DLBCL	Axi-cel	2	N	N	80	N	N	N	N	N	253	0.07	267	181	84	0.10
28	56	M	DLBCL	Axi-cel	3	N	N	80	Y	N	N	N	Y	205	0.96	258	227	2524	0.87
29	52	M	DLBCL	Axi-cel	4	N	Y	80	Y	N	N	N	Y	301	0.2	380	222	3046	0.27
30	30	M	PMBCL	Axi-cel	2	N	Y	90	Y	N	N	N	N	139	0.62	69	154	1653	0.56
31	31	M	PMBCL	Axi-cel	2	Y	y	90	N	Y	N	N	Y	187	0.29	77	143	4575	0.38

Tx: treatment; Ref.: refractory; SPD: sum of the products of diameters; mEASIX: modified EASIX score; M: male; F: female: DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; KPS: Karnofsky Performance Score; Auto HCT: autologous hematopoietic stem cell transplant; Axi-cel: axicabtagene; Brexu-cel: brexucabtagene; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; CR: complete response; PR: partial response; NR: no response; N/A: not applicable; UN: unknown; Y: yes; N: No; UN: unknown

Extended Data Table 3:

Baseline Characteristics, Toxicity Management and Clinical Outcomes of All Patients

Patient ID	Age	Gender	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Anakinra Duration (d)	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)	Best ORR	Relapse (Y/N)
1	55	M	DLBCL	Tisa-cel	N	N	11	0	0	N	N	NR	N/A
2	25	F	DLBCL	Axi-cel	Y	Y	10	2	0	N	N	PR	N
3	56	F	DLBCL	Axi-cel	N	N	11	2	0	N	N	PR	Y
4	58	F	DLBCL	Axi-cel	N	Y	11	1	0	N	N	CR	Y
5	77	M	DLBCL	Axi-cel	N	N	11	1	0	N	N	NR	N/A
6	73	F	DLBCL	Axi-cel	N	Y	11	2	0	Y	N	NR	N/A
7	72	M	DLBCL	Axi-cel	Y	Y	17	2	0	Y	Y	CR	N
8	44	M	DLBCL	Axi-cel	N	Y	11	1	0	N	N	CR	N
9	62	M	DLBCL	Axi-cel	N	N	12	1	0	N	N	CR	Y
10	58	M	DLBCL	Axi-cel	N	N	10	1	0	N	N	CR	N
11	73	F	DLBCL	Tisa-cel	N	N	10	1	0	N	N	CR	N
12	69	F	HGBCL	Tisa-cel	N	N	10	0	0	N	N	CR	Y
13	43	F	HGBCL	Axi-cel	Y	Y	11	1	1	N	N	CR	Y
14	62	M	DLBCL	Axi-cel	N	N	10	2	0	N	N	CR	N
15	71	M	DLBCL	Axi-cel	N	Y	10	2	0	Y	N	CR	N
16	73	F	MCL	Brexu-cel	N	N	10	0	0	N	N	CR	N
17	58	M	HGBCL	Axi-cel	N	N	11	0	0	N	N	NR	N/A
4	56	F	MCL	Brexu-cel	N	Y	11	2	3	Y	Y	CR	N
19	75	F	MCL	Brexu-cel	Y	Y	10	2	0	Y	Y	CR	Y
20	73	M	DLBCL	Axi-cel	N	N	10	0	1	N	Y	PR	Y
21	73	M	DLBCL	Tisa-cel	N	Y	10	2	0	Y	Y	NR	N/A
22	75	M	HGBCL	Axi-cel	Y	Y	10	2	0	Y	N	CR	N
23	65	F	HGBCL	Axi-cel	N	N	11	0	0	N	N	NR	N/A
24	69	F	HGBCL	Axi-cel	Y	Y	11	3	1	Y	Y	CR	N
25	69	F	PMBCL	Axi-cel	N	N	11	1	0	N	N	NR	N/A
26	62	M	MCL	Brexu-cel	N	Y	27	4	0	Y	Y	CR	N

Patient ID	Age	Gender	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Anakinra Duration (d)	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)	Best ORR	Relapse (Y/N)
27	75	M	DLBCL	Axi-cel	N	N	10	1	0	N	N	CR	N
28	56	M	DLBCL	Axi-cel	N	N	10	0	0	N	N	CR	N
29	52	M	DLBCL	Axi-cel	N	Y	10	1	3	Y	Y	CR	Y
30	30	M	PMBCL	Axi-cel	N	Y	10	2	3	Y	Y	CR	N
31	31	M	PMBCL	Axi-cel	N	N	11	0	0	N	N	PR	N

M: male; F: female: DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; Auto HCT: autologous hematopoietic stem cell transplant; Axi-cel: axicabtagene; Brexu-cel: brexucabtagene; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; CR: complete response; PR: partial response; NR: no response; N/A: not applicable

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Extended Data Table 4:

Anakinra Administration Schedules and Dose Escalation Indication

Patient ID	Age	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Day of Anakinra Dose Escalation	Anakinra Dose Escalation Indication	Anakinra Duration (d)	Anakinra Completed as Outpatient	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)
1	55	DLBCL	Tisa-cel	N	N	N/A		11	N	0	0	N	N
2	25	DLBCL	Axi-cel	Y	Y	D3	Gr2 CRS (hypotension)	10	N	2	0	N	N
3	56	DLBCL	Axi-cel	N	N	N/A		11	N	2	0	N	N
4	58	DLBCL	Axi-cel	N	Y	D9	Prolonged Gr1 CRS	11	N	1	0	N	N
5	77	DLBCL	Axi-cel	N	N	N/A		11	N	1	0	N	N
6	73	DLBCL	Axi-cel	N	Y	D5	Gr2 CRS (hypotension)	11	N	2	0	Y	N
7	72	DLBCL	Axi-cel	Y	Y	D3	Prolonged Gr1 CRS	17	N	2	0	Y	Y
8	44	DLBCL	Axi-cel	N	Y	D6	Prolonged Gr1 CRS	11	N	1	0	N	N
9	62	DLBCL	Axi-cel	N	N	N/A		12	N	1	0	N	N
10	58	DLBCL	Axi-cel	N	N	N/A		10	Y	1	0	N	N
11	73	DLBCL	Tisa-cel	N	N	N/A		10	N	1	0	N	N
12	69	HGBCL	Tisa-cel	N	N	N/A		10	Y	0	0	N	N
13	43	HGBCL	Axi-cel	Y	Y	D5	Prolonged Gr1 CRS	11	N	1	1	N	N
14	62	DLBCL	Axi-cel	N	N	N/A		10	N	2	0	N	N
15	71	DLBCL	Axi-cel	N	Y	D7	Gr2 CRS (hypotension, Afib RVR)	10	N	2	0	Y	N
16	73	MCL	Brexu-cel	N	N	N/A		10	Y	0	0	N	N
17	58	HGBCL	Axi-cel	N	N	N/A		11	N	0	0	N	N
18	56	MCL	Brexu-cel	N	Y	D4	Gr2 CRS (hypotension)	11	N	2	3	Y	Y
19	75	MCL	Brexu-cel	Y	Y	D2	Gr2 CRS (hypotension & hypoxia)	10	N	2	0	Y	Y

Patient ID	Age	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Day of Anakinra Dose Escalation	Anakinra Dose Escalation Indication	Anakinra Duration (d)	Anakinra Completed as Outpatient	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)
20	73	DLBCL	Axi-cel	N	N	N/A		10	Y	0	1	N	Y
21	73	DLBCL	Tisa-cel	N	Y	D4	Gr2 CRS (hypotension)	10	N	2	0	Y	Y
22	75	HGBCL	Axi-cel	Y	Y	D3	Gr2 CRS (hypotension & hypoxia)	10	N	2	0	Y	N
23	65	HGBCL	Axi-cel	N	N	N/A		11	N	0	0	N	N
24	69	HGBCL	Axi-cel	Y	Y	D3	Gr2 CRS (hypoxia)	11	N	3	1	Y	Y
25	69	PMBCL	Axi-cel	N	N	N/A		11	Y	1	0	N	N
26	62	MCL	Brexu-cel	N	Y	D5	Gr2 CRS (hypotension)	27	N	4	0	Y	Y
27	75	DLBCL	Axi-cel	N	N	N/A		10	N	1	0	N	N
28	56	DLBCL	Axi-cel	N	N	N/A		10	N	0	0	N	N
29	52	DLBCL	Axi-cel	N	Y	D3	Prolonged Gr1 CRS	10	N	1	3	Y	Y
30	30	PMBCL	Axi-cel	N	Y	D4	Gr2 CRS (hypotension)	10	N	2	3	Y	Y
31	31	PMBCL	Axi-cel	N	N	N/A		11	Y	0	0	N	N

DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; Axi-cel: axicabtagene ciloleucel; Brexu-cel: brexucabtagene autoleucel; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; N/A: not applicable

Extended Data Table 5:

Neurological Symptoms Observed in the Study and CTCAE Grading

Patient ID	Neurological Symptoms	CTCAE v.5.0 Grade
13	Confusion	2
	Decreased level of consciousness	2
18	Decreased level of consciousness	3
20	Decreased level of consciousness	1
	Bilateral hand tremors	1
	Expressive dysphasia	2
	Right upper limb paresthesia	1
24	Decreased level of consciousness	3
	Bilateral hand tremors	1
29	Confusion	1
	Dysarthria	1
	Expressive Dysphasia	2
	Decreased level of consciousness	3
30	Decreased level of consciousness	3
	Confusion	2
	Headache	2

Extended Data Table 6:

Tocilizumab and Corticosteroid Use and Indications

Patient ID	Age	Disease Histology	Cell Product	Anakinra Dose Escalation	Max CRS Grade	Max ICANS Grade	# of Toci Administration	Toci Indication	Steroid (Y/N)	Steroid Duration (d)	Total Steroid Dose (mg)	Steroid Indication
6	73	DLBCL	Axi-cel	Y	2	0	1	Gr2 CRS (hypotension)	N	N/A	N/A	N/A
7	72	DLBCL	Axi-cel	Y	2	0	1	Gr2 CRS (hypotension)	Y	1	10	Gr2 CRS (hypotension)
15	71	DLBCL	Axi-cel	Y	2	0	1	Gr1 CRS	N	N/A	N/A	N/A
18	56	MCL	Brexu-cel	Y	2	3	1	Gr2 CRS (hypotension)	Y	19	364	Gr2 ICANS
19	75	MCL	Brexu-cel	Y	2	0	3	Gr2 CRS (hypotension & hypoxia)	Y	1	20	Gr2 CRS (hypoxia)
20	73	DLBCL	Axi-cel	N	0	1	0	N/A	Y	3	40	Gr1 ICANS (aphasia)
21	73	DLBCL	Tisa-cel	Y	2	0	1	Gr2 CRS (hypotension)	Y	1	10	Gr2 CRS (hypotension)
22	75	HGBCL	Axi-cel	Y	2	0	1	Gr2 CRS (hypotension & hypoxia)	N	N/A	N/A	N/A
24	69	HGBCL	Axi-cel	Y	3	1	2	Gr3 CRS	Y	2	30	Gr1 ICANS
26	62	MCL	Brexu-cel	Y	4	0	3	Gr2 CRS (hypotension)	Y	14	380	Gr3 CRS
29	52	DLBCL	Axi-cel	Y	1	3	1	Prolonged Gr1 CRS	Y	4	110	Gr3 ICANS
30	30	PMBCL	Axi-cel	Y	2	3	2	Gr2 CRS (hypotension)	Y	25	190	Gr3 ICANS

DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; Axi-cel: axicabtagene; Brexu-cel: brexucabtagene; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; N/A: not applicable

Extended Data Table 7.

Infectious Complications after CAR T-cell Infusion in All Patients

Patient ID	Documented infection after CAR infusion[a]	Infection onset (days post CAR infusion)	Infection type	Infectious organism	CTCAE grade	Hospital readmission for infection	Duration of hospital readmission (days)	ICU admission for infection
1	No	-	-	-	-	-	-	-
2	Yes	20	Bacteremia	Pseudomonas aeruginosa	3	Yes	7	No
		250	URTI	Rhinovirus	1	No	-	-
		357	Skin	Staph. lugdunesis & Klebsiella pneumoniae	2	No	-	-
		593	URTI	Parainfluenza III	1	No	-	-
		988	URTI	Rhinovirus	1	No	-	-
3	Yes	12	Enterocolitis	Escherichia coli	1	Already admitted	-	No
4	No	-	-	-	-	-	-	-
5	Yes	4	Bacteremia	Escherichia coli	3	Already admitted		No
6	Yes	42	Lung	COVID-19	5	Yes	6	No
7	Yes	167	URTI	N/A	2	No	-	-
		670	URTI	COVID-19	2	No	-	-
		819	Shingles	Herpes zoster	2	No	-	-
		819	UTI	N/A	2	No	-	-
8	Yes	629	Lung	COVID-19	3	Yes	8	No
9	No	-	-	-	-	-	-	-
10	Yes	527	Lung	COVID-19	2	No	-	-
		696	URIT	COVID-19	2	No	-	-
11	Yes	70	Enterocolitis	Clostridium difficile	2	No	-	-
		270	URTI	COVID-19	2	No	-	-
		543	URTI	COVID-19	2	No	-	-
		724	URTI	COVID-19	2	No	-	-
12	No	-	-	-	-	-	-	-
13	No	-	-	-	-	-	-	-

Patient ID	Documented infection after CAR infusion[a]	Infection onset (days post CAR infusion)	Infection type	Infectious organism	CTCAE grade	Hospital readmission for infection	Duration of hospital readmission (days)	ICU admission for infection
14	Yes	45	Bacteremia	Pseudomonas putida	3	Yes	5	-
		182	Lung	COVID-19	2	No	-	-
		307	URTI	N/A	2	No	-	-
15	Yes	3	Enterocolitis	Clostridium difficile	2	Already admitted	-	-
16	No	-	-	-	-	-	-	-
17	Yes	435	URTI	COVID-19	2	No	-	-
18	Yes	419	Sepsis	Staphylococcus aureus	3	Yes	39	-
19	No	-	-	-	-	-	-	-
20	No	-	-	-	-	-	-	-
21	No	-	-	-	-	-	-	-
22	No	-	-	-	-	-	-	-
23	No	-	-	-	-	-	-	-
24	Yes	31	Skin	Fungal infection	1	No	-	-
		92	Skin	Bacterial infection	1	No	-	-
		562	URTI	COVID-19	2	No	-	-
25	Yes	17	Lung	N/A	2	No	-	-
26	No	-	-	-	-	-	-	-
27	No	-	-	-	-	-	-	-
28	No	-	-	-	-	-	-	-
29	No	-	-	-	-	-	-	-
30	No	-	-	-	-	-	-	-
31	Yes	397	URTI	COVID-19	2	No	-	-

CAR: chimeric antigen receptor; CTCAE: Common Terminology Criteria for Adverse Events; ICU; intensive care unit: URTI; upper respiratory tract infection: -; not applicable: N/A; not available.

[a]This includes any infection from the time of CAR infusion until last follow-up or progressive of disease, whichever occurred earlier.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data Availability

This trial is currently ongoing. Subject to patient privacy and confidentiality obligations, access to patient-level data and supporting clinical documents will be available upon request and subject to review by the study sponsor and/or the corresponding author on completion of the trial. Such requests can be made to the corresponding author by email at parkj6@mskcc.org. Any data and materials that can be shared will be released via a material transfer agreement and/or data access agreement.

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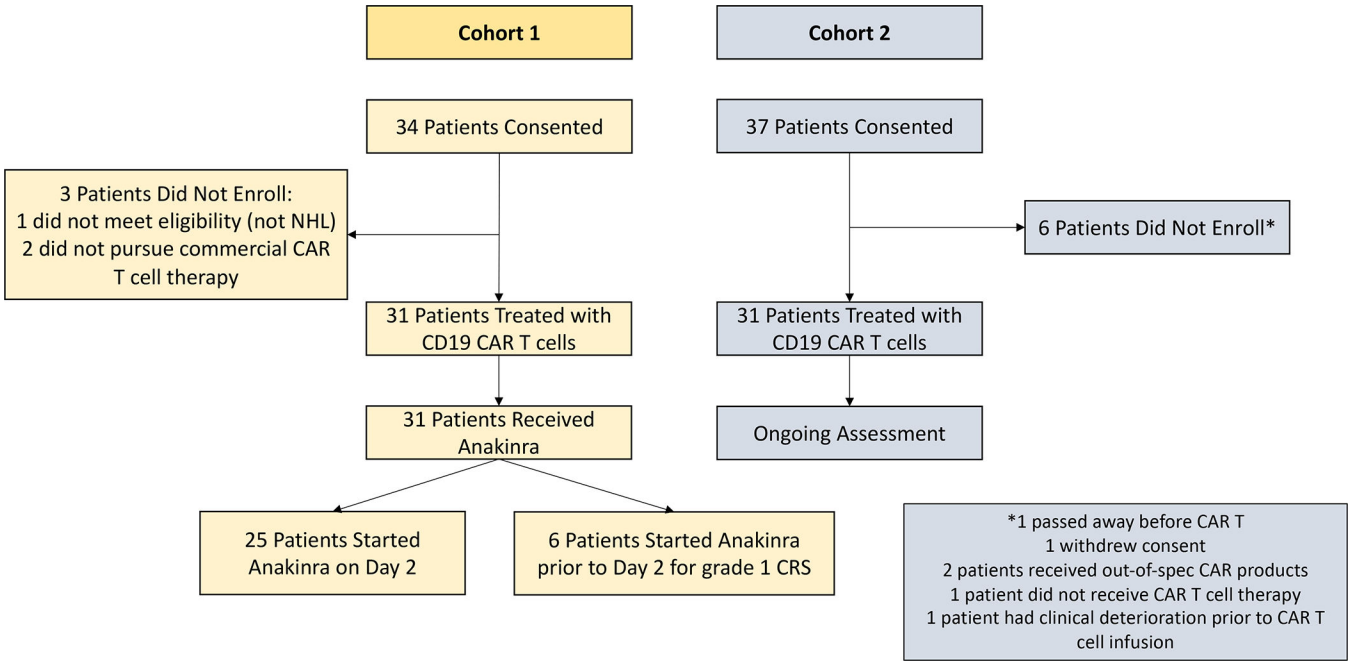

Figure 1.
Consort Diagram

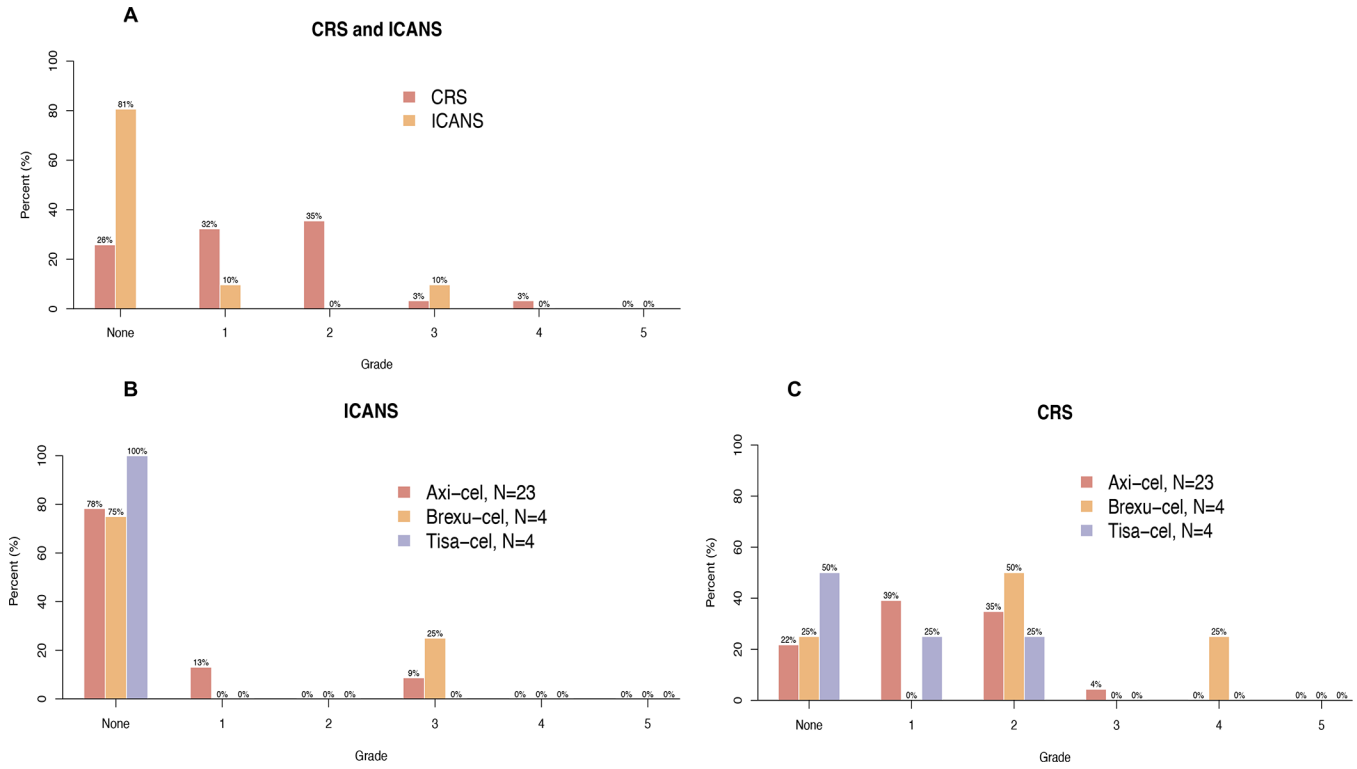

Figure 2. Rates of CRS and ICANS in the 31 patients treated with prophylactic anakinra.

(2A) Overall rate of CRS and ICANS. (2B) Rate of ICANS by grade and CD19-directed CAR T-cell product. (2C) Rate of CRS by grade and CD19-directed CAR T-cell product CRS denotes cytokine release syndrome; ICANS denotes immune effector-cell mediated neurotoxicity syndrome; axi-cel denotes axicabtagene ciloleucel; brexu-cel denotes brexucabtagene; tisa-cel denotes tisagenlecleucel.

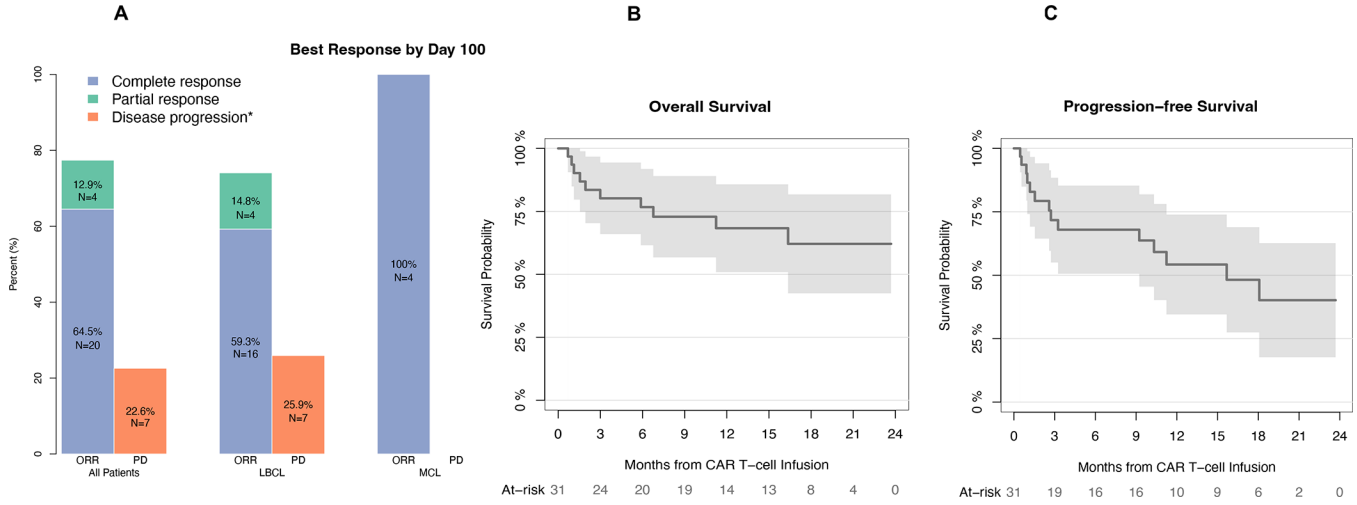

Figure 3. Response of patients with relapsed and refractory lymphoma.

(3A) Best response by day 100 post CAR T-cell infusion in the 31 patients treated with prophylactic anakinra by diseae subtype. (3B) Overall survival and (3C) progression free survial of the study patients. The shaded resion represents the pointwise 95% confidence interval of the survival estimate.

CAR denotes chimeric antigen receptor; ORR denotes overall response rate; PD denotes progressive disease; LBCL denotes large B-cell lymphoma; MCL denotes mantle cell lymphoma; * One patient died of COVID-19 pneumonia at day 47 and did not have day 30 response assessment - this patient is included in the PD category

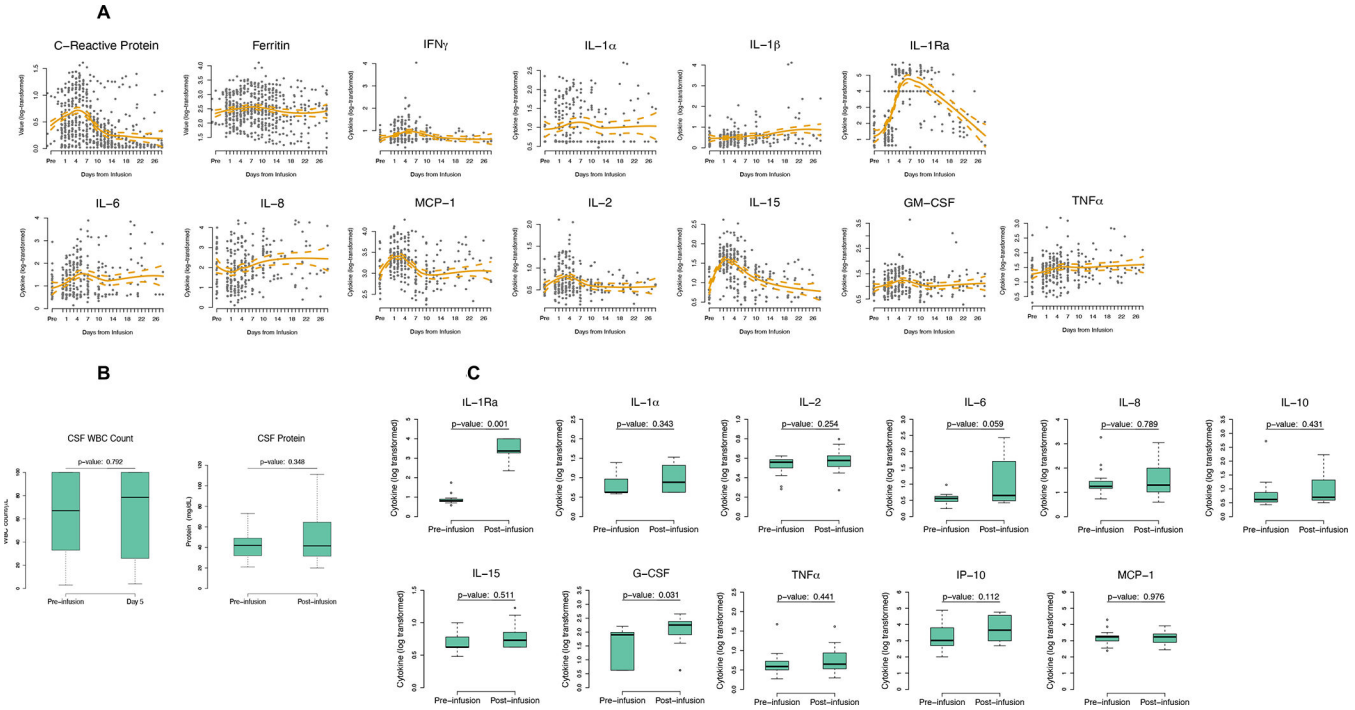

Figure 4: Serum and CSF cytokine changes over time on study.

(4A) Change in the level of serum cytokines after anakinra adminstration (n=31). The orange smoothed solid lines over time in each plot represent a locally weighted scatterplot smoother, and the dashed lines represent the corresponding 95% confidence interval. All 31 patients contributed at least one cytokine value in each figure. **(4B) Levels of CSF white blood cell (WBC) counts, and CSF protein counts before and after anakinra administration.** For WBC and CSF protein counts, a total of 27 patients had an available pre-infusion value and 24 had a post-infusion value. **(4C) Levels of cytokines in the CSF at baseline and 5-days after the adminstration of anakinra.** A total of 15 patients had available pre-infusion cytokine value, and 15 patients had post-infusion values. For 4B and 4C, the black center line within the box represents the median, and the lower and upper edges of the box represent the 25% (Q1) and 75% (Q3) quantiles of the measurements. The upper whisker represents the minimum of either the highest count or 1.5 times the interquartile range (IQR) above Q3 (i.e., Q3+1.5*IQR). The lower whisker is defined similarly. Significance was assessed using a two-sided, partially matched Wilcoxon test. There was no adjustment for multiple comparisons.

CSF denotes cerebrospinal fluid; WBC denotes white blood cell

Extended Data Table 2:

Baseline Patient and Disease Characteristics

Patient ID	Age	Gender	Disease Histology	Cell Product	# of Prior Tx	Primary Ref.	Ref. to Prior Tx	Performance Status (KPS)	Prior Auto HCT	Bulky Disease	Prior CNS Disease	Active CNS Disease	Bridging Therapy	Baseline LDH (U/l)	Baseline CRP (mg/dL)	Baseline Ferritin (ng/mL)	Baseline PLT ($x10^3$µl)	Baseline SPD (mm^2)	mEASIX
1	55	M	DLBCL	Tisa-cel	3	N	Y	100	N	N	N	N	Y	164	0.91	60	159	6605	0.94
2	25	F	DLBCL	Axi-cel	3	Y	Y	80	N	N	N	N	Y	249	1.5	80	247	924	1.51
3	56	F	DLBCL	Axi-cel	2	N	N	80	N	N	N	N	Y	374	8.05	191	330	9140	9.12
4	58	F	DLBCL	Axi-cel	3	N	Y	90	N	N	N	N	N	278	0.34	37	169	2608	0.56
5	77	M	DLBCL	Axi-cel	2	Y	Y	70	N	N	Y	Y	Y	356	0.08	128	182	598	0.16
6	73	F	DLBCL	Axi-cel	2	N	Y	70	N	N	N	N	Y	182	0.09	72	236	299	0.07
7	72	M	DLBCL	Axi-cel	4	N	N	80	N	N	N	N	Y	204	0.88	19	211	1868	0.85
8	44	M	DLBCL	Axi-cel	2	Y	Y	80	N	Y	N	N	Y	159	0.36	217	188	1566	0.30
9	62	M	DLBCL	Axi-cel	2	Y	Y	90	N	N	N	N	Y	203	0.08	106	221	2929	0.07
10	58	M	DLBCL	Axi-cel	4	N	N	90	N	N	N	N	Y	163	0.81	105	215	1207	0.61
11	73	F	DLBCL	Tisa-cel	4	N	Y	80	N	N	Y	N	N	180	0.18	18	87	452	0.37
12	69	F	HGBCL	Tisa-cel	3	N	Y	80	Y	N	N	N	Y	154	0.13	310	184	1044	0.11
13	43	F	HGBCL	Axi-cel	3	Y	Y	50	N	N	N	Y	Y	453	11.14	626	56	1003	90.1
14	62	M	DLBCL	Axi-cel	5	N	N	90	N	N	N	N	Y	416	3.2	854	30	UN	44.4
15	71	M	DLBCL	Axi-cel	5	N	Y	80	N	N	N	N	Y	184	8.58	237	247	9154	6.4
16	73	F	MCL	Brexu-cel	2	Y	Y	80	N	N	N	N	Y	298	0.31	326	411	1048	0.22
17	58	M	HGBCL	Axi-cel	4	Y	Y	70	N	Y	N	N	Y	1255	7.34	1372	272	11178	33.9
18	56	F	MCL	Brexu-cel	3	N	UN	80	N	N	Y	N	Y	147	0.05	255	167	336	0.04
19	75	F	MCL	Brexu-cel	4	N	N	80	Y	N	N	N	Y	1041	6.8	1059	49	130	144.5
20	73	M	DLBCL	Axi-cel	2	N	Y	80	N	N	N	N	Y	239	5.28	33	136	2372	9.28
21	73	M	DLBCL	Tisa-cel	3	N	Y	70	N	N	Y	Y	Y	659	0.11	143	237	7054	0.31
22	75	M	HGBCL	Axi-cel	2	N	N	90	N	N	N	N	Y	189	0.15	851	191	0	0.15
23	65	F	HGBCL	Axi-cel	3	Y	Y	80	N	Y	N	Y	Y	738	1.83	2309	601	885	2.25
24	69	F	HGBCL	Axi-cel	3	Y	Y	80	N	N	N	N	Y	206	2.1	325	52	780	8.32
25	69	F	PMBCL	Axi-cel	4	N	Y	90	Y	Y	N	N	N	158	19.44	282	240	4026	12.8
26	62	M	MCL	Brexu-cel	2	Y	Y	80	N	N	N	Y	Y	248	18.67	72	64	2099	72.3
27	75	M	DLBCL	Axi-cel	2	N	N	80	N	N	N	N	N	253	0.07	267	181	84	0.10
28	56	M	DLBCL	Axi-cel	3	N	N	80	Y	N	N	N	Y	205	0.96	258	227	2524	0.87

Patient ID	Age	Gender	Disease Histology	Cell Product	# of Prior Tx	Primary Ref.	Ref. to Prior Tx	Performance Status (KPS)	Prior Auto HCT	Bulky Disease	Prior CNS Disease	Active CNS Disease	Bridging Therapy	Baseline LDH (U/l)	Baseline CRP (mg/dL)	Baseline Ferritin (ng/mL)	Baseline PLT ($x10^3$µl)	Baseline SPD (mm^2)	mEASIX
29	52	M	DLBCL	Axi-cel	4	N	Y	80	Y	N	N	N	Y	301	0.2	380	222	3046	0.27
30	30	M	PMBCL	Axi-cel	2	N	Y	90	Y	N	N	N	N	139	0.62	69	154	1653	0.56
31	31	M	PMBCL	Axi-cel	2	Y	y	90	N	Y	N	N	Y	187	0.29	77	143	4575	0.38

Tx: treatment; Ref.: refractory; SPD: sum of the products of diameters; mEASIX: modified EASIX score; M: male; F: female: DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; KPS: Karnofsky Performance Score; Auto HCT: autologous hematopoietic stem cell transplant; Axi-cel: axicabtagene; Brexu-cel: brexucabtagene; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; CR: complete response; PR: partial response; NR: no response; N/A: not applicable; UN: unknown; Y: yes; N: No; UN: unknown

Extended Data Table 3:

Baseline Characteristics, Toxicity Management and Clinical Outcomes of All Patients

Patient ID	Age	Gender	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Anakinra Duration (d)	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)	Best ORR	Relapse (Y/N)
1	55	M	DLBCL	Tisa-cel	N	N	11	0	0	N	N	NR	N/A
2	25	F	DLBCL	Axi-cel	Y	Y	10	2	0	N	N	PR	N
3	56	F	DLBCL	Axi-cel	N	N	11	2	0	N	N	PR	Y
4	58	F	DLBCL	Axi-cel	N	Y	11	1	0	N	N	CR	Y
5	77	M	DLBCL	Axi-cel	N	N	11	1	0	N	N	NR	N/A
6	73	F	DLBCL	Axi-cel	N	Y	11	2	0	Y	N	NR	N/A
7	72	M	DLBCL	Axi-cel	Y	Y	17	2	0	Y	Y	CR	N
8	44	M	DLBCL	Axi-cel	N	Y	11	1	0	N	N	CR	N
9	62	M	DLBCL	Axi-cel	N	N	12	1	0	N	N	CR	Y
10	58	M	DLBCL	Axi-cel	N	N	10	1	0	N	N	CR	N
11	73	F	DLBCL	Tisa-cel	N	N	10	1	0	N	N	CR	N
12	69	F	HGBCL	Tisa-cel	N	N	10	0	0	N	N	CR	Y
13	43	F	HGBCL	Axi-cel	Y	Y	11	1	1	N	N	CR	Y
14	62	M	DLBCL	Axi-cel	N	N	10	2	0	N	N	CR	N
15	71	M	DLBCL	Axi-cel	N	Y	10	2	0	Y	N	CR	N
16	73	F	MCL	Brexu-cel	N	N	10	0	0	N	N	CR	N
17	58	M	HGBCL	Axi-cel	N	N	11	0	0	N	N	NR	N/A
4	56	F	MCL	Brexu-cel	N	Y	11	2	3	Y	Y	CR	N
19	75	F	MCL	Brexu-cel	Y	Y	10	2	0	Y	Y	CR	Y
20	73	M	DLBCL	Axi-cel	N	N	10	0	1	N	Y	PR	Y
21	73	M	DLBCL	Tisa-cel	N	Y	10	2	0	Y	Y	NR	N/A
22	75	M	HGBCL	Axi-cel	Y	Y	10	2	0	Y	N	CR	N
23	65	F	HGBCL	Axi-cel	N	N	11	0	0	N	N	NR	N/A
24	69	F	HGBCL	Axi-cel	Y	Y	11	3	1	Y	Y	CR	N
25	69	F	PMBCL	Axi-cel	N	N	11	1	0	N	N	NR	N/A
26	62	M	MCL	Brexu-cel	N	Y	27	4	0	Y	Y	CR	N
27	75	M	DLBCL	Axi-cel	N	N	10	1	0	N	N	CR	N

Patient ID	Age	Gender	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Anakinra Duration (d)	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)	Best ORR	Relapse (Y/N)
28	56	M	DLBCL	Axi-cel	N	N	10	0	0	N	N	CR	N
29	52	M	DLBCL	Axi-cel	N	Y	10	1	3	Y	Y	CR	Y
30	30	M	PMBCL	Axi-cel	N	Y	10	2	3	Y	Y	CR	N
31	31	M	PMBCL	Axi-cel	N	N	11	0	0	N	N	PR	N

M: male; F: female: DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; Auto HCT: autologous hematopoietic stem cell transplant; Axi-cel: axicabtagene; Brexu-cel: brexucabtagene; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; CR: complete response; PR: partial response; NR: no response; N/A: not applicable

Extended Data Table 4:

Anakinra Administration Schedules and Dose Escalation Indication

Patient ID	Age	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Day of Anakinra Dose Escalation	Anakinra Dose Escalation Indication	Anakinra Duration (d)	Anakinra Completed as Outpatient	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)
1	55	DLBCL	Tisa-cel	N	N	N/A		11	N	0	0	N	N
2	25	DLBCL	Axi-cel	Y	Y	D3	Gr2 CRS (hypotension)	10	N	2	0	N	N
3	56	DLBCL	Axi-cel	N	N	N/A		11	N	2	0	N	N
4	58	DLBCL	Axi-cel	N	Y	D9	Prolonged Gr1 CRS	11	N	1	0	N	N
5	77	DLBCL	Axi-cel	N	N	N/A		11	N	1	0	N	N
6	73	DLBCL	Axi-cel	N	Y	D5	Gr2 CRS (hypotension)	11	N	2	0	Y	N
7	72	DLBCL	Axi-cel	Y	Y	D3	Prolonged Gr1 CRS	17	N	2	0	Y	Y
8	44	DLBCL	Axi-cel	N	Y	D6	Prolonged Gr1 CRS	11	N	1	0	N	N
9	62	DLBCL	Axi-cel	N	N	N/A		12	N	1	0	N	N
10	58	DLBCL	Axi-cel	N	N	N/A		10	Y	1	0	N	N
11	73	DLBCL	Tisa-cel	N	N	N/A		10	N	1	0	N	N
12	69	HGBCL	Tisa-cel	N	N	N/A		10	Y	0	0	N	N
13	43	HGBCL	Axi-cel	Y	Y	D5	Prolonged Gr1 CRS	11	N	1	1	N	N
14	62	DLBCL	Axi-cel	N	N	N/A		10	N	2	0	N	N
15	71	DLBCL	Axi-cel	N	Y	D7	Gr2 CRS (hypotension, Afib RVR)	10	N	2	0	Y	N
16	73	MCL	Brexu-cel	N	N	N/A		10	Y	0	0	N	N
17	58	HGBCL	Axi-cel	N	N	N/A		11	N	0	0	N	N
18	56	MCL	Brexu-cel	N	Y	D4	Gr2 CRS (hypotension)	11	N	2	3	Y	Y
19	75	MCL	Brexu-cel	Y	Y	D2	Gr2 CRS (hypotension & hypoxia)	10	N	2	0	Y	Y
20	73	DLBCL	Axi-cel	N	N	N/A		10	Y	0	1	N	Y
21	73	DLBCL	Tisa-cel	N	Y	D4	Gr2 CRS (hypotension)	10	N	2	0	Y	Y
22	75	HGBCL	Axi-cel	Y	Y	D3	Gr2 CRS (hypotension & hypoxia)	10	N	2	0	Y	N
23	65	HGBCL	Axi-cel	N	N	N/A		11	N	0	0	N	N
24	69	HGBCL	Axi-cel	Y	Y	D3	Gr2 CRS (hypoxia)	11	N	3	1	Y	Y

Patient ID	Age	Disease Histology	Cell Product	Anakinra Start Before D2	Anakinra Dose Escalation	Day of Anakinra Dose Escalation	Anakinra Dose Escalation Indication	Anakinra Duration (d)	Anakinra Completed as Outpatient	Max CRS Grade	Max ICANS Grade	Toci (Y/N)	Steroid (Y/N)
25	69	PMBCL	Axi-cel	N	N	N/A		11	Y	1	0	N	N
26	62	MCL	Brexu-cel	N	Y	D5	Gr2 CRS (hypotension)	27	N	4	0	Y	Y
27	75	DLBCL	Axi-cel	N	N	N/A		10	N	1	0	N	N
28	56	DLBCL	Axi-cel	N	N	N/A		10	N	0	0	N	N
29	52	DLBCL	Axi-cel	N	Y	D3	Prolonged Gr1 CRS	10	N	1	3	Y	Y
30	30	PMBCL	Axi-cel	N	Y	D4	Gr2 CRS (hypotension)	10	N	2	3	Y	Y
31	31	PMBCL	Axi-cel	N	N	N/A		11	Y	0	0	N	N

DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; Axi-cel: axicabtagene ciloleucel; Brexu-cel: brexucabtagene autoleucel; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; N/A: not applicable

Extended Data Table 6:

Tocilizumab and Corticosteroid Use and Indications

Patient ID	Age	Disease Histology	Cell Product	Anakinra Dose Escalation	Max CRS Grade	Max ICANS Grade	# of Toci Administration	Toci Indication	Steroid (Y/N)	Steroid Duration (d)	Total Steroid Dose (mg)	Steroid Indication
6	73	DLBCL	Axi-cel	Y	2	0	1	Gr2 CRS (hypotension)	N	N/A	N/A	N/A
7	72	DLBCL	Axi-cel	Y	2	0	1	Gr2 CRS (hypotension)	Y	1	10	Gr2 CRS (hypotension)
15	71	DLBCL	Axi-cel	Y	2	0	1	Gr1 CRS	N	N/A	N/A	N/A
18	56	MCL	Brexu-cel	Y	2	3	1	Gr2 CRS (hypotension)	Y	19	364	Gr2 ICANS
19	75	MCL	Brexu-cel	Y	2	0	3	Gr2 CRS (hypotension & hypoxia)	Y	1	20	Gr2 CRS (hypoxia)
20	73	DLBCL	Axi-cel	N	0	1	0	N/A	Y	3	40	Gr1 ICANS (aphasia)
21	73	DLBCL	Tisa-cel	Y	2	0	1	Gr2 CRS (hypotension)	Y	1	10	Gr2 CRS (hypotension)
22	75	HGBCL	Axi-cel	Y	2	0	1	Gr2 CRS (hypotension & hypoxia)	N	N/A	N/A	N/A
24	69	HGBCL	Axi-cel	Y	3	1	2	Gr3 CRS	Y	2	30	Gr1 ICANS
26	62	MCL	Brexu-cel	Y	4	0	3	Gr2 CRS (hypotension)	Y	14	380	Gr3 CRS
29	52	DLBCL	Axi-cel	Y	1	3	1	Prolonged Gr1 CRS	Y	4	110	Gr3 ICANS
30	30	PMBCL	Axi-cel	Y	2	3	2	Gr2 CRS (hypotension)	Y	25	190	Gr3 ICANS

DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; tFL: transformed follicular lymphoma; Axi-cel: axicabtagene; Brexu-cel: brexucabtagene; Tisa-cel: tisagenlecleucel; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome; Toci: tocilizumab; d: days; N/A: not applicable

Table 1.

Baseline Patient and Disease Characteristics

Characteristic	Number (%)
No. of patients	31
Disease type – no. (%)	
DLBCL	18 (58)
HGBCL	6 (19)
PMBCL	3 (10)
MCL	4 (13)
Age	
Median (range) – yr.	62 (25 – 77)
≥65 yr. – no. (%)	15 (48)
Male sex – no. (%)	18 (58)
International Prognostic Index score – no. (%)	
I - II	12 (39)
III-IV	19 (61)
Prior therapies – no. (%)	
≥3 prior lines of therapy	19 (61)
Refractory to last line of therapy pre-apheresis	22 (71)
Prior autologous SCT	6 (19)
Prior allogeneic SCT	1 (3)
Prior CD19 directed therapy	1 (3)
Bridging therapy	26 (84)
Disease status at CAR T-cell infusion	
CR	1 (3)
PR	9 (29)
SD/PD	21 (67)
Bulky disease at CAR T-cell infusion (≥ 10cm) – no. (%)	5 (16)
Tumor burden by SPD at pre-CAR T-cell infusion * – mm^2	
Median (range)	1,609.5 (0 – 11,178)
LDH > ULN at conditioning chemotherapy – no. (%)	12 (39)
Median LDH (range), U/l	206 (139 – 1,255)
CRP at conditioning chemotherapy	
Median CRP (range), mg/dL	0.81 (0.05 – 19.44)
Ferritin at conditioning chemotherapy	
Median ferritin (range), ng/mL	217 (18 – 2,309)

Characteristic	Number (%)
PLT at conditioning chemotherapy	
Median PLT (range), $x10^3/\mu l$	188 (30 – 601)
CAR T-cell product	
Axi-cel	23 (74)
Brexu-cel	4 (13)
Tisa-cel	4 (13)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; MCL, mantle cell lymphoma; SCT, stem cell transplant; CR, complete remission; PR, partial remission; SD/PD, stable disease/progressive disease; SPD: sum of the products of diameters; LDH: lactate dehydrogenase; ULN, upper limit of normal; CRP, C-reactive protein; Axi-cel, Axicabtagene ciloleucel; Brexu-cel, Brexucabtagene; Tisa-cel, Tisagenlecleucel.

*Restaged after bridging (if administered) and immediately prior to conditioning chemotherapy and prior to CAR T cell infusion. One patient did not have pre-treatment PET/CT but only had CT chest that demonstrated a biopsy proven lymphoma, and therefore, was not able to have the accurate tumor volume assessment and not included in this analysis. One patient was in CR after bridging and is included here as having 0 tumor volume.