REGULAR ARTICLE

blood advances

Transient responses and significant toxicities of anti-CD30 CAR T cells for CD30$^+$ lymphomas: results of a phase 1 trial

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Key Points

- Anti-CD30 CAR T cells had low efficacy in patients with CD30-expressing lymphoma.
- Rashes and prolonged cytopenias were frequent and severe in some cases, leading to the early closure of the trial.

New treatments are needed for relapsed and refractory CD30-expressing lymphomas. We developed a novel anti-CD30 chimeric antigen receptor (CAR), designated 5F11-28Z. Safety and feasibility of 5F11-28Z–transduced T cells (5F11-Ts) were evaluated in a phase 1 dose escalation clinical trial. Patients with CD30-expressing lymphomas received 300 mg/m^2 or 500 mg/m^2 of cyclophosphamide and 30 mg/m^2 of fludarabine on days −5 to −3, followed by infusion of 5F11-Ts on day 0. Twenty-one patients received 5F11-T infusions. Twenty patients had classical Hodgkin lymphoma, and 1 had anaplastic large-cell lymphoma. Patients were heavily pretreated, with a median of 7 prior lines of therapy and substantial tumor burden, with a median metabolic tumor volume of 66.1 mL (range, 6.4-486.7 mL). The overall response rate was 43%; 1 patient achieved a complete remission. Median event-free survival was 13 weeks. Eleven patients had cytokine release syndrome (CRS; 52%). One patient had grade 3 CRS, and there was no grade 4/5 CRS. Neurologic toxicity was minimal. Nine patients (43%) had new-onset rashes. Two patients (9.5%) received extended courses of corticosteroids for prolonged severe rashes. Five patients (24%) had grade 3/4 cytopenias, with recovery time of ≥30 days, and 2 of these patients (9.5%) had prolonged cytopenias with courses complicated by life-threatening sepsis. The trial was halted early because of toxicity. Median peak blood CAR$^+$ cells per μL was 26 (range, 1-513 cells per μL), but no infiltration of CAR$^+$ cells was detected in lymph node biopsies. 5F11-Ts had low efficacy and substantial toxicities, which limit further development of 5F11-Ts. This trial was registered at www.clinicaltrials.gov as #NCT03049449.

Introduction

Although classical Hodgkin lymphoma (cHL) is frequently curable with first-line therapy even in advanced stages,[1] relapsed and chemotherapy-refractory cHL carries a less favorable prognosis. Brentuximab vedotin (BV) and immune checkpoint inhibitor therapies have impressive antimalignancy activity in cHL, yet a small minority of patients are cured with these therapies.[2-5] T-cell lymphomas, including anaplastic

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large-cell lymphoma (ALCL), have poor prognoses in the relapsed and refractory setting.[6,7] Although BV has some efficacy for T-cell lymphomas, especially in ALCL, the majority of patients eventually relapse, with many succumbing to malignancy.[8,9]

Chimeric antigen receptor (CAR) T-cell therapy has established efficacy in B-cell malignancies[10-17] and multiple myeloma.[18,19] Anti-CD30 CAR T-cell therapy has demonstrated promising anti-malignancy activity in early clinical trials in patients with cHL and T-cell lymphoma who are heavily pretreated.[20-24] We developed a novel anti-CD30 CAR, designated 5F11-28Z, with a human antibody–derived binding domain, CD28 hinge, transmembrane, and costimulatory domains, and a CD3-ζ domain.[25] T cells transduced with 5F11-28Z are hereafter denoted 5F11-Ts. 5F11-Ts exhibited a full range of T-cell functions in vitro and eradicated tumors from mice.[25] Here, we present results of a single center, phase 1 clinical trial of 5F11-Ts for CD30-expressing lymphomas.

Methods

Trial design

We conducted a phase 1 clinical trial of 5F11-Ts for refractory CD30-expressing lymphomas (ClinicalTrials.gov identifier: NCT03049449). This clinical trial was approved by the National Institutes of Health Institutional Review Board. All patients provided written informed consent. Eligible patients had CD30-expressing lymphomas with uniform CD30 expression confirmed by the on-site pathology laboratory. Study participants were required to be aged ≥18 years, and to have measurable malignancy after at least 2 prior lines of therapy, no central nervous system involvement with malignancy, adequate organ function including no baseline grade 3-4 cytopenias, and an Eastern Cooperative Oncology Group performance status score of 0 to 2. Patients who had received prior allogeneic hematopoietic stem cell transplantation (allo-HSCT) were required to have no greater than grade 0 to 1 acute graft-versus-host disease (GVHD) and no greater than mild global score chronic GVHD.

New or worsening GVHD has occurred after autologous CAR T-cell products,[26,27] raising the possibility of alloreactive T-cell clones causing GVHD. For this reason, we divided patients into 2 cohorts with independent dose escalation based on prior allo-HSCT status. Cohort 1 included patients who had not had a prior allo-HSCT; cohort 2 included patients who had received a prior allo-HSCT. Patients received 1 of 4 dose levels of 5F11-Ts (0.3×10^6 CAR^+ T cells per kg, 1×10^6 CAR^+ T cells per kg, 3×10^6 CAR^+ T cells per kg, or 9×10^6 CAR^+ T cells per kg) as a single infusion. Patients received cyclophosphamide at a dose of either 300 or 500 mg/m^2 and fludarabine 30 mg/m^2 daily on days −5 to −3 before 5F11-T infusion on day 0. The cyclophosphamide dose was increased to 500 mg/m^2 for subsequent patients receiving the 3×10^6 CAR^+ T cells per kg and 9×10^6 CAR^+ T cells per kg doses in an attempt to improve 5F11-T expansion and efficacy.

Lymphoma responses were evaluated per Cheson et al.[28] Cytokine release syndrome (CRS) was graded according to the American Society for Transplantation and Cellular Therapy criteria.[29] Because of a lack of immune effector cell–associated encephalopathy scoring data available for patients treated before publication of immune effector cell–associated neurotoxicity syndrome (ICANS) criteria,[29] neurologic adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events version 5.0. All other AEs were graded according to the Common Terminology Criteria for Adverse Events version 5.0. Time to hematologic recovery (TTHR) was defined as the number of days until grade 3 to 4 anemia, thrombocytopenia, and neutropenia had resolved to grade 2 or less with no transfusion support or growth factors for at least 7 days, starting from the date of cell infusion, as previously described.[30] Overall survival data were obtained from patients participating in a long-term follow-up protocol for individuals who have received CAR T-cell therapy on prior clinical trials (ClinicalTrials.gov identifier: NCT02473757).

Production of 5F11-Ts

5F11-Ts were produced by stimulating peripheral blood mononuclear cells with an anti-CD3 monoclonal antibody and interleukin-2 (IL-2) and then transducing the cells with a lentiviral vector encoding 5F11-Ts. This process is described in supplemental Methods.

Determination of baseline metabolic tumor volume (MTV)

Baseline ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scans were performed for all patients within 14 days of conditioning chemotherapy. Baseline PET/CT scans were evaluated using MIM 7.2.8 (MIM Software, Cleveland, OH). Within each lesion, a threshold of 41% of its maximal standardized uptake value was used for segmentation and volume determination using the MIM threshold tool, as previously described.[31]

Immunohistochemical (IHC) staining for CAR^+ cells

A chromogenic IHC stain for the CAR was developed using an anti-CAR antibody, provided by Kite, as further described in supplemental Methods.

Quantification of blood and bone marrow (BM) CAR^+ cells and infusion cell flow cytometry

Real-time quantitative polymerase chain reaction (PCR) analysis was used to quantify CAR-expressing cells from blood samples collected at baseline and at multiple posttreatment time points, using methods as previously reported.[32] Briefly, DNA was extracted from peripheral blood mononuclear cells with the Qiagen DNeasy Blood and Tissue kit, and extracted DNA was amplified with a primer and probe set specific to 5F11-28Z (Eurofins Genomics). Real-time PCR was performed with a Roche Light Cycler 480 real-time PCR system. Flow cytometry for CAR-expressing cells was performed on BM aspirate, as described in supplemental Methods. Flow cytometry on infusion cells was conducted by standard methods, as previously described.[32]

Quantification of serum cytokines

Ten serum cytokines were assessed in patient samples collected at baseline and at multiple posttreatment timepoints with the V-PLEX Proinflammatory Panel 1 Human kit (Meso Scale Diagnostics, Rockville, MD).

Statistics

Statistical analyses were performed with Mann-Whitney *U* tests to compare 2 groups of continuous variables, the Kruskal-Wallis test

Table 1. Patient characteristics

	Median (range), n = 21
Age, y	33 (18-64)
Prior lines of therapy	7 (4-15)
Baseline LDH*	181 (112-469)
	Number of patients (%)
Male	15 (71)
Female	6 (29)
cHL	20 (95)
Nodular sclerosis	10 (48)
Histologic subtype not determined	6 (29)
Mixed cellularity	2 (9.5)
Lymphocyte rich	2 (9.5)
Anaplastic large-cell lymphoma, ALK-negative	1 (4.8)
Prior autologous stem cell transplantation	14 (67)
Prior BV	21 (100)
Prior immune checkpoint inhibitor	18 (86)
Prior allogeneic stem cell transplantation	3 (14)
Chemotherapy refractory†	8 (40)
Refractory to BV‡	17 (94)
Cyclophosphamide dose (mg/m^2) and CAR T-cell dose (CAR$^+$ T cells per kg)§	
Cyclophosphamide 300 mg/m^2 + 0.3 × 10^6 CAR$^+$ T cells per kg	3 (14)
Cyclophosphamide 300 mg/m^2 + 1.0 × 10^6 CAR$^+$ T cells per kg	6 (29)
Cyclophosphamide 300 mg/m^2 + 3.0 × 10^6 CAR$^+$ T cells per kg	3 (14)
Cyclophosphamide 500 mg/m^2 + 3.0 × 10^6 CAR$^+$ T cells per kg	4 (19)
Cyclophosphamide 500 mg/m^2 + 9.0 × 10^6 CAR$^+$ T cells per kg	5 (24)
	Median (range), n = 21
Baseline MTV	66.1 (6.4 - 486.7)
	Number of patients (%)
MTV > 60 mL	11 (52)

ALK, anaplastic lymphoma kinase; LDH, lactate dehydrogenase.

*Most recent LDH before start of conditioning chemotherapy. Units are international units/L. The institutional upper limit of normal is 226 U/L.

†Chemotherapy refractory is defined as best response to last therapy being SD or PD, or PD while receiving last therapy. Percentage calculated based on 20 evaluable patients. One patient had unknown response to last cytotoxic chemotherapy.

‡Refractory to BV was defined as best response to the last regimen containing BV being SD or PD. In addition, PD while receiving the last regimen containing BV was counted as refractory. Percentage calculated based on 18 evaluable patients. Three patients had unknown response to BV.

§Because of low toxicity observed at the 0.3 × 10^6 CAR$^+$ T cells per kg dose level, the protocol was amended to allow patients in cohort 2 to start dose escalation at the 1 × 10^6 CAR$^+$ T cells per kg dose. Because of limited durability of responses observed on the first 3 dose levels, the protocol was amended to increase the dose of cyclophosphamide from 300 to 500 mg/m^2, so that 3 patients received 3 × 10^6 CAR$^+$ T cells per kg and cyclophosphamide 300 mg/m^2, and 3 patients received 3 × 10^6 CAR$^+$ T cells per kg and cyclophosphamide 500 mg/m^2.

to compare ≥3 groups of continuous variables, Fisher exact test to compare categorical outcomes in 2 groups, and with Kaplan-Meier log-rank test and Cox proportional hazards (CPH) regression for time-to-event analyses. The software used was RStudio 2023.03.0 for time-to-event analyses, and Prism 9.3.1 for all other analyses.

Table 2. Antimalignancy responses

Response	Number of patients (%)
ORR	9 (43)
CR	1 (4.8)
PR	8 (38)
SD	11 (52)
PD	1 (4.8)
	Median (95% CI)
Duration of response, weeks*	8.9 (8.7-NE)
EFS, weeks†	13 (11-17)
Overall survival, weeks‡	134 (81-NE)

CI, confidence interval; NE, cannot be estimated.

*Duration of response for patients achieving PR or CR, defined as time from achieving first response of PR or CR until lymphoma progression, start of additional therapy, or death.

†EFS, defined as time from CAR T-cell infusion until lymphoma progression, start of additional therapy, or death.

‡Overall survival was defined as time from CAR T-cell infusion until death; 11 patients were still surviving at last follow-up.

Results

Patient characteristics

In total, 24 patients enrolled; 21 patients received conditioning chemotherapy and CAR T-cell infusion (Table 1; supplemental Table 1). Two patients did not proceed to conditioning chemotherapy and CAR T-cell infusion: 1 because of progression of malignancy, and 1 because of a thromboembolic event. One patient received conditioning chemotherapy but did not proceed to CAR T-cell infusion because of the development of grade 3 encephalopathy (supplemental Table 2), likely a result of polypharmacy of pain medications.

Patients who received CAR T-cell infusion had a median age of 33 years and were predominantly male (Table 1). Twenty patients had cHL, and 1 patient had anaplastic lymphoma kinase–negative ALCL. Patients were heavily pretreated, with a median of 7 prior lines of therapy (Table 1). All patients had received prior BV, with 94% of evaluable patients having lymphoma refractory to BV. Forty percent of evaluable patients had chemotherapy-refractory lymphoma, defined as best response to last cytotoxic therapy being stable disease (SD) or progressive disease (PD), or PD while receiving last cytotoxic therapy. Baseline tumor volume as assessed by MTV was 66.1 mL (range, 6.4-486.7 mL; Table 1). Two patients received bridging therapy between leukapheresis and 5F11-T infusion. The median time from enrollment to 5F11-T infusion was 20 days (range, 12-63 days).

Limited efficacy of 5F11-Ts

The overall response rate (ORR) was 43%, with 8 patients (38%) achieving a partial remission (PR) and 1 patient (4.8%) achieving a complete remission (CR; Table 2). PRs were achieved in patients with heavily pretreated cHL, including patient 10 and patient 15 in cohort 1, as pictured in Figure 1A-D. Two patients with previously chemotherapy-refractory cHL achieved a PR. All but 2 patients experienced reduction in tumor burden as assessed by percent change in the sum of the products of the diameters of target lymph nodes (Figure 1E; supplemental Table 1).

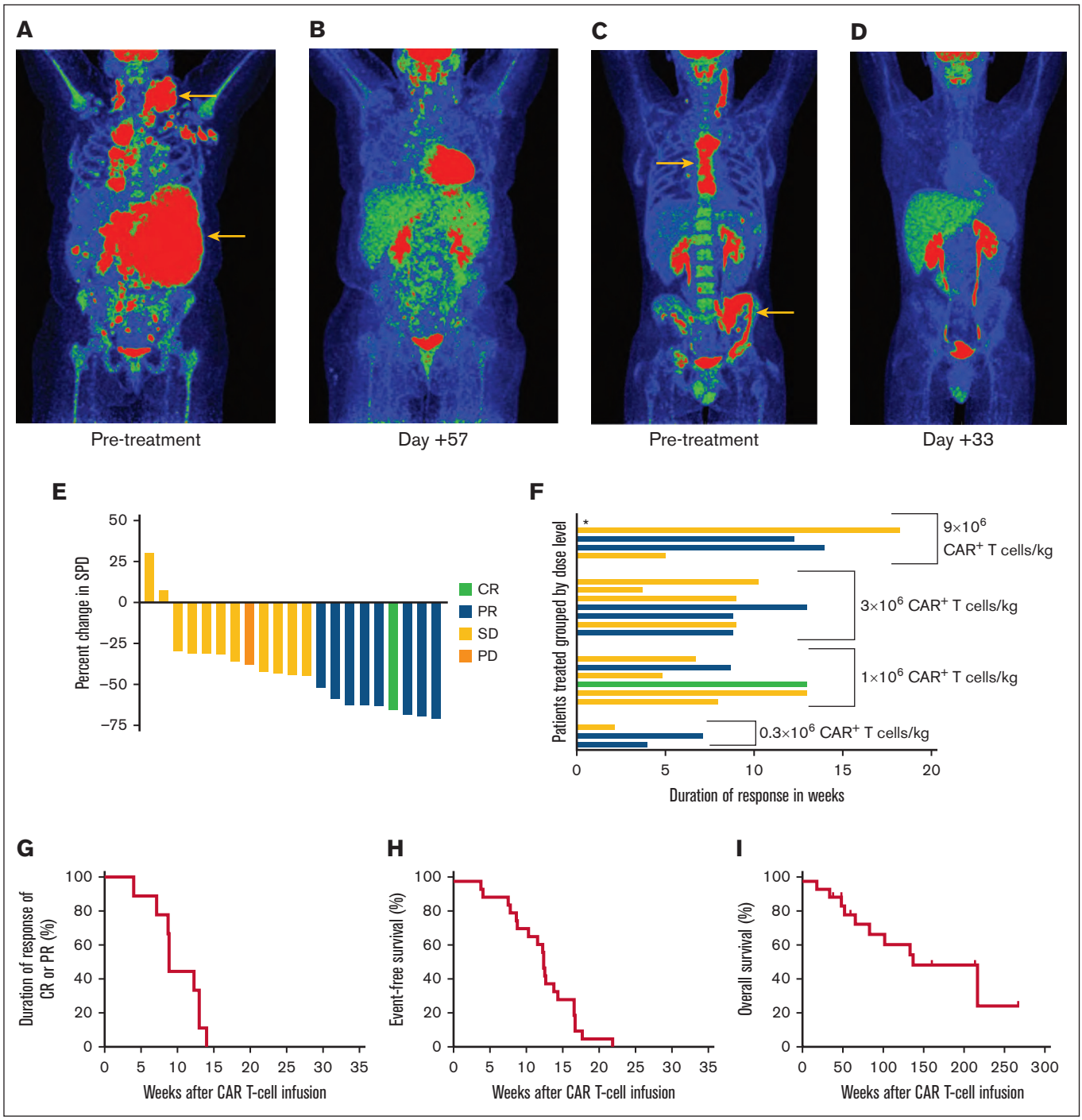

Figure 1. Efficacy of 5F11-Ts. (A) Patient 10 in cohort 1 had high-burden (baseline MTV, 486.7 mL), chemotherapy-refractory cHL before 5F11-T treatment, including involvement of the left cervical lymph nodes and an enlarged hypermetabolic spleen (yellow arrows), as indicated on the pretreatment positron emission tomography-computed tomography (PET-CT) scan. (B) At day +57 after 5F11-T infusion, Patient 10's posttreatment PET-CT scan demonstrated substantial reductions in fluorodeoxyglucose (FDG) avidity, with residual avidity present in the cervical, supraclavicular, and mediastinal nodes, and the spleen, retroperitoneum, and right pelvic wall. FDG avidity in the heart and bladder is an artifact of the test due to isotope accumulation. Patient 10 was in PR by CT criteria at this time. Lymphoma progression occurred 4 months after 5F11-T treatment. (C) Patient 15 on cohort 1 had extensive involvement of cHL before 5F11-T treatment (baseline MTV, 180.1 mL), including the sternal and left pelvic bones (yellow arrows), as shown on pretreatment PET-CT scan. (D) On day +33 after 5F11-T infusion, Patient 15 had resolution of most areas of FDG avidity, with residual avidity present in the left ilium. FDG avidity in the kidneys and bladder is an artifact of the test due to isotope accumulation. Patient 15 was in PR by CT criteria at this time. Lymphoma progression occurred 4 months after 5F11-T treatment. (E) Maximum percent change in sum of the products of the diameters (SPD) of the target lymph nodes achieved after 5F11-T infusion for each patient. The first response assessment took place 1 month after CAR T-cell infusion. The maximum percent change in SPD was achieved in all patients by 3 months after CAR T-cell infusion, or earlier. The patient with response of PD had reduction of target lesions but developed new lesions after 5F11-T infusion. (F) Duration of response in weeks of

Table 3. Selected AEs*

AE	Grade 1, number of patients (%)	Grade 2, number of patients (%)	Grade 3, number of patients (%)	Grade 4, number of patients (%)
CRS				
Any CRS	4 (19)	6 (29)	1 (4.8)†	–
Tocilizumab for CRS	1 (4.8)	1 (4.8)	–	–
Corticosteroids for CRS	–	–	–	–
Neurologic toxicity				
Neurologic toxicity‡	NR	5 (24)	–	–
Dizziness	NR	2 (9.5)	–	–
Confusion	NR	1 (4.8)	–	–
Headache	NR	1 (4.8)	–	–
Hallucinations	NR	1 (4.8)	–	–
Corticosteroids for neurologic toxicity	NR	–	–	–
Rash				
Rash, maculopapular, pustular, or eczematous	NR	6 (29)	3 (14)	–
Systemic corticosteroids for rash	NR	–	2 (9.5)	–
Hematologic				
Neutropenia	NR	2 (9.5)	7 (33)	12 (57)
Thrombocytopenia	NR	4 (19)	1 (4.8)	4 (19)
Anemia	NR	4 (19)	6 (29)	–
TTHR and interventions for hematologic toxicity				
TTHR ≥ 30 days§		5 (24)		
TTHR ≥ 90 days§		2 (9.5)		
Delayed grade 3/4 cytopenias after day +30‖		4 (21)		
Eltrombopag for cytopenias		3 (14)		
Corticosteroids for cytopenias		2 (9.5)		

NR, not recorded, as grade 1 AEs were not recorded on this trial, except for CRS grading; (–) no AEs of the indicated category and grade occurred on the trial.

*The highest grade alone recorded for each patient. AEs were recorded according to the Common Terminology Criteria for Adverse Events version 5.0. CRS was graded according to Lee et al.[29] No grade 5 events occurred on trial.

†One patient had grade 3 CRS due to hypotension lasting 34 hours requiring intermittent low-dose vasopressor support. This patient did not receive tocilizumab because of the transient nature of the vasopressor support required, per institutional guidelines at the time of CAR T-cell infusion.

‡Attributed to CAR T cells.

§TTHR defined as number of days until grade 3 or 4 anemia, thrombocytopenia, and neutropenia are resolved with no transfusion support or growth factors for at least 7 days, starting from the date of cell infusion.

‖ Delayed grade 3 or 4 cytopenias occurring after hematologic recovery was previously achieved and after day +30. Two patients with TTHR of >30 days achieved hematologic recovery and later developed delayed cytopenias. Two patients were not evaluable because of cytopenias beginning within 30 days of CAR T-cell infusion and lasting >90 days (patients 15 and 18 of cohort 1).

Durations of responses of CR, PR, and SD are shown in Figure 1F. The median duration of response of CR or PR was 8.9 weeks (Table 2; Figure 1G). The median event-free survival (EFS) was 13 weeks (Table 2; Figure 1H). All patients experienced malignancy progression or received new antimalignancy therapy within 6 months after 5F11-Ts. The median OS was 134 weeks (Table 2; Figure 1I). Higher baseline MTV was associated with worse EFS in a CPH regression model in both unadjusted analysis ($P = .0152$) and analysis adjusted for 5F11-T dose ($P = .0206$).

Low rates of CRS and neurologic toxicity

AEs experienced by the patient who underwent conditioning chemotherapy but did not receive 5F11-Ts are presented in supplemental Table 2. Selected AEs for all patients who received 5F11-T infusions are presented hereafter, and in Table 3. No patients experienced new or worsening GVHD.

Eleven patients (52%) experienced any grade of CRS; 4 patients (19%) had grade 1 CRS, 6 (29%) had grade 2 CRS, and 1 patient

Figure 1 (continued) each patient, grouped by dose level. Duration of response was defined as the time from first documentation of response, including CR, PR, or SD (for patients whose best response was SD) until progression, start of new treatment, or death. Asterisks (*) denotes a patient with response of PD. (G) Duration of response in weeks after 5F11-T infusion for patients achieving a response of PR or CR. (H) EFS in weeks after 5F11-T infusion for all patients. EFS was defined as the time from 5F11-T infusion until progression, start of new treatment, or death. (I) Overall survival in weeks after 5F11-T infusion. Overall survival was defined as the time from 5F11-T infusion until death or last follow-up.

had grade 3 CRS, with no patients experiencing grade 4 or 5 CRS (Table 3). For patients experiencing CRS, the median time of CRS onset was 6 days (range, 0-10 days) after 5F11-T infusion, with the median CRS duration being 6 days (range, 1-12 days). Two patients (9.5%) received tocilizumab for CRS management. No patients received corticosteroids for CRS management. Patients with CRS received higher doses of 5F11-Ts per kilogram than patients without CRS (Mann-Whitney *U* test, $P = .0423$).

To further contextualize the temporal patterns of CRS in this trial, the proportion of patients experiencing CRS after 5F11-T infusion was compared with the proportion of patients with B-cell non-HL who experienced CRS after CAR T-cell treatment with Hu19-CD828Z T cells (Hu19-CD828Z-Ts) on a phase 1 trial at our center.[32] Participants in both trials were followed-up by the same clinical team and received similar supportive care. A lower proportion of patients experienced CRS after 5F11-T (52%) than the proportion experiencing CRS after Hu19-CD828Z-Ts (85%; Fisher exact test, $P = .043$; Figure 2A). The cumulative incidence of patients having CRS over time significantly differed between patients receiving 5F11-Ts vs Hu19-CD828Z-Ts (Kaplan-Meier log-rank test, $P < .0001$), with patients tending to have later onset CRS after 5F11-Ts (Figure 2B).

Grade 2 neurologic toxicity occurred in 5 patients (24%; Table 3). No grade 3 to 5 neurologic toxicity was observed. No patients

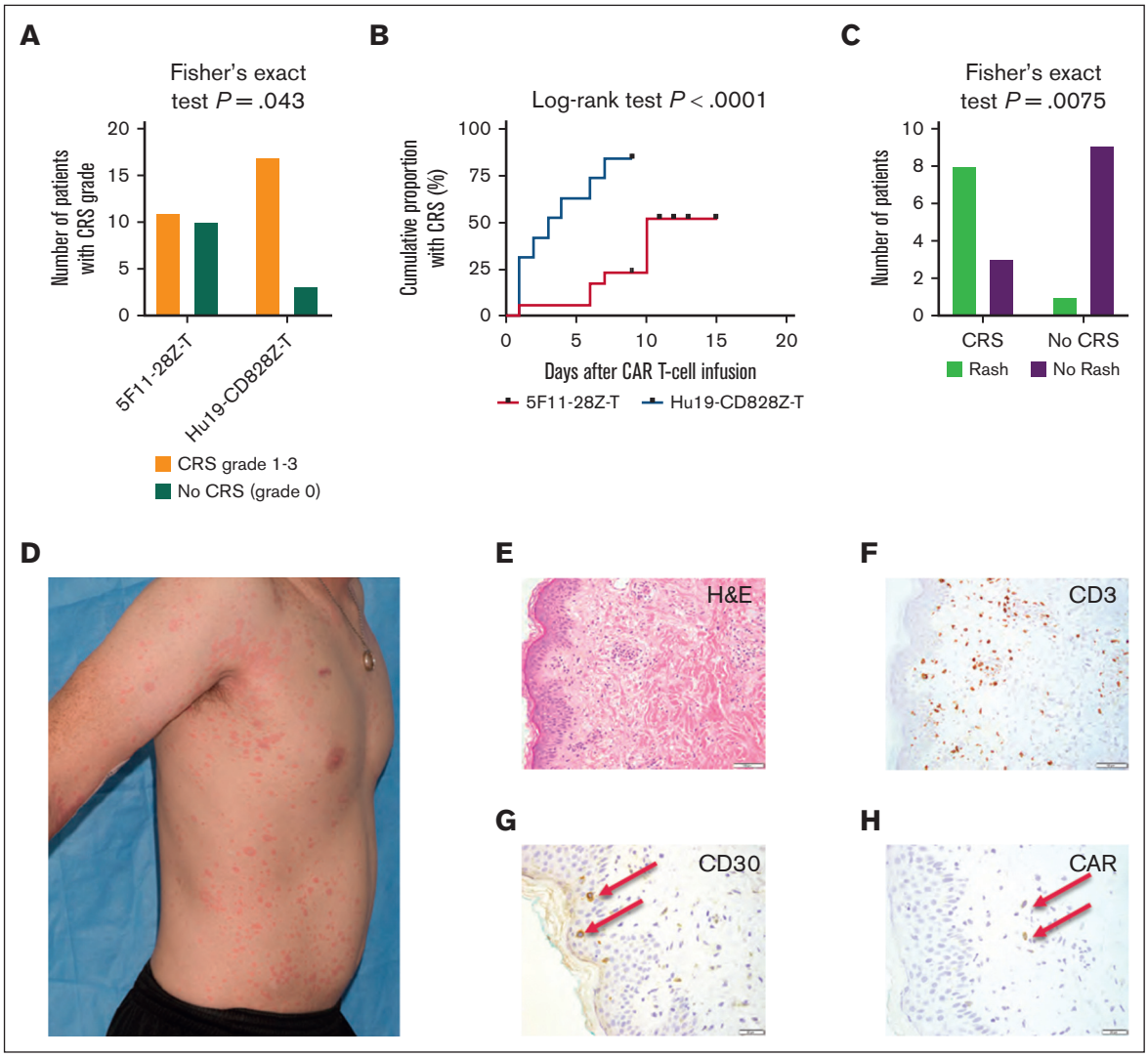

Figure 2. CRS and rashes after 5F11-T. (A) A significantly lower proportion of patients experienced CRS after receiving 5F11-T than those in a prior trial of Hu19-CD828Z-Ts for patients with B-cell non-HL. (Fisher exact test, $P = .043$). (B) Patients receiving 5F11-T had lower rates of CRS, and CRS tended to start later, than in our prior experience with Hu19-CD828Z-Ts (log-rank test, $P < .0001$). (C) Of the patients receiving 5F11-T, a greater proportion of patients who had CRS also developed a rash than patients without CRS (Fisher exact test, $P = .0075$). (D) Patient 16 in cohort 1 developed a diffuse, grade 3 maculopapular rash starting on day +7 after 5F11-T infusion. The photo was taken on day +8. (E) Patient 16 in cohort 1 underwent a skin biopsy of the rash on day +7. Hematoxylin and eosin (H&E) staining at 20× original magnification reveals a spongiotic dermatitis with a lymphohistiocytic infiltrate and perivascular inflammation. (F) CD3 staining at 20× original magnification demonstrates superficial and deep perivascular T cells. (G) CD30 staining at 40× original magnification shows CD30-expressing lymphocytes in the dermis. No keratinocytes were found to be $CD30^+$. (H) IHC staining for the CAR at 40× original magnification reveals scattered CAR^+ cells in the dermis.

received corticosteroids or other immunosuppressive therapies for management of neurologic toxicity (Table 3).

Frequent rashes with slow resolution in 2 patients

Nine patients (43%) developed new maculopapular, pustular, or eczematous rashes after 5F11-Ts (Table 3). Six patients (29%) had grade 2 rashes; 3 patients (14%) had grade 3 rashes; and no patients had grade 4 or 5 rashes. Rashes occurred a median of 11 days (range, 7-55 days) after 5F11-T infusion and lasted at grade ≥2 for a median of 7 (3-39) days. Two patients (9.5%) with grade 3 rashes lasting 29 and 39 days, respectively, received systemic corticosteroids for management of rash (Table 3); 1 of these patients additionally received phototherapy. A higher proportion of patients with CRS also had rashes (73%) than the proportion of patients without CRS who developed rashes (10%; Fisher exact test, $P = .0075$; Figure 2C). Patients with rashes received higher doses of 5F11-Ts per kilogram than patients without rashes (Mann-Whitney U test, $P = .0379$). Patients with rashes did not have greater baseline sum of the products of the diameters or MTV than patients without rashes (data not shown).

Patient 16 on cohort 1 developed a grade 3 rash starting on day +7. A photo taken on day +8 is shown in Figure 2D. A skin biopsy revealed a spongiotic dermatitis (Figure 2E), $CD3^+$ T cells infiltrating the dermis (Figure 2F), few $CD30^+$ lymphocytes extending to the epidermis (Figure 2G), and scattered dermal CAR^+ cells (Figure 2H). This patient received a prolonged course of systemic corticosteroids for management of the rash. He developed a new Epstein-Barr virus–positive lymphoproliferative disorder on day +36, likely due to immunosuppression because of extended corticosteroid exposure. This resolved with a rapid taper of corticosteroids. One patient with a prior allo-HSCT developed a rash. He declined a skin biopsy, but the rash resolved in 6 days without intervention, making GVHD unlikely.

Four patients with rashes underwent a total of 6 skin biopsies for evaluation of rashes. Biopsies showed a similar nonspecific pattern of spongiotic dermatitis with T-cell infiltrates in the perivascular areas in the upper dermis, infiltrating the epidermis in some places. No skin biopsies were consistent with GVHD. CD30 was not detected on keratinocytes. Biopsies from 3 patients were evaluable for IHC staining of CAR^+ cells. Of these, only the day +7 biopsy of patient 16 showed few CAR^+ cells. Skin biopsies performed for 2 other patients at later time points did not have detectable CAR^+ cells (not shown).

Prolonged hematologic toxicity

Patients had expected cytopenias after conditioning chemotherapy. Nineteen patients (91%) experienced grade 3 or 4 neutropenia; 6 patients (29%) had grade 3 anemia, with no grade 4 events; and 5 patients (24%) had grade 3 or 4 thrombocytopenia (Table 3; supplemental Table 3).

A subset of patients experienced prolonged myelosuppression. Five patients (24%) experienced TTHR of ≥30 days, and 2 (9.5%) patients had TTHR lasting ≥90 days (Table 3). Twenty-one percent of evaluable patients had delayed grade 3 or 4 cytopenias after day +30. Three patients (14%; patients 4, 15, and 18; cohort 1) received eltrombopag, and 2 patients (9.5%; patients 15 and 18; cohort 1) received corticosteroids for management of prolonged cytopenias (Table 3). No patients received stem cell boost or transplantation for management of cytopenias. Patient 15 and Patient 18 on cohort 1 experienced prolonged thrombocytopenia and neutropenia (Figure 3A-D). Both patients had severe infections necessitating intensive care while neutropenic and receiving systemic corticosteroids: pneumonia in patient 15 and methicillin-resistant *Staphylococcus aureus* bacteremia in patient 18. Patient 15 achieved full hematologic recovery after a course of corticosteroids and eltrombopag, but patient 18 had ongoing grade 3/4 cytopenias when she discontinued trial participation because of PD, despite having received 69 days of corticosteroids and 51 days of eltrombopag.

Five patients, 4 with prolonged TTHR and 1 with delayed neutropenia, underwent a total of 11 posttreatment BM biopsies for evaluation of cytopenias (supplemental Table 4). Pretreatment BM biopsies had varying degrees of hypocellularity. All patients had posttreatment hypocellular marrows; the majority (4 of 5) had posttreatment trilineage hypoplasia (supplemental Table 4). Three patients had marrow fibrosis with increased scattered lymphocytes, most of which were T cells (supplemental Table 4; Figure 3E-H). No patients had baseline BM involvement with malignancy; all patients had few or no $CD30^+$ lymphocytes detectable on pretreatment or posttreatment core biopsy. No significant dysplasia or progression of BM $CD30^+$ lymphoma was observed. All 5 patients, except patient 12 in cohort 1, who had isolated delayed neutropenia, had available posttreatment cytogenetics, none of which revealed clonal abnormalities (supplemental Table 4). Three patients had 5 BM biopsies evaluable for CAR^+ cells by flow cytometry. Of those, q patient had 2 posttreatment BM biopsies with detectable CAR^+ cells (supplemental Table 4). Five patients had 7 BM biopsies evaluable for CAR^+ cells by IHC. Of these, only the day +16 BM biopsy of patient 15, which was the earliest time point of all the samples, had detectable CAR^+ cells.

To investigate whether hematologic recovery on this clinical trial was atypically delayed when compared with our prior experience with CAR T-cell therapy for lymphoma, TTHR for 5F11-Ts was compared with TTHR for Hu19-CD828Z-Ts (Figure 3I). The criteria for transfusion and growth factor support were the same for both trials. In a univariable CPH regression model, the 5F11-T trial had a trend toward longer TTHR than that for Hu19-CD828Z-Ts, with a hazard ratio for achieving recovery of 0.550 and a P value of .0909 (supplemental Table 5). A multivariable CPH regression analysis was performed using forward selection (supplemental Tables 5 and 6). In the multivariable model, the 5F11-T trial had significantly longer TTHR than the Hu19-CD828Z-T trial, with a hazard ratio for achieving recovery of 0.480 and a P value of .0499 (supplemental Table 5).

Dose limiting toxicities and grade 4 AEs

There were 2 dose limiting toxicities at the 9.0×10^6 CAR^+ T cells per kg dose level. These were prolonged transfusion-dependent thrombocytopenia experienced by patient 15 in cohort 1, and grade 4 elevated creatine phosphokinase lasting >72 hours in the setting of CRS experienced by patient 17 in cohort 1. The 3.0×10^6 CAR^+ T cells per kg dose level was determined to be the maximum tolerated dose. In addition to cytopenias, other grade 4 AEs were sepsis and hypotension experienced by Patient 15 in cohort 1, and sepsis due to methicillin-resistant *S aureus* bacteremia affecting patient 18 in cohort 1 (supplemental Table 3), as discussed earlier.

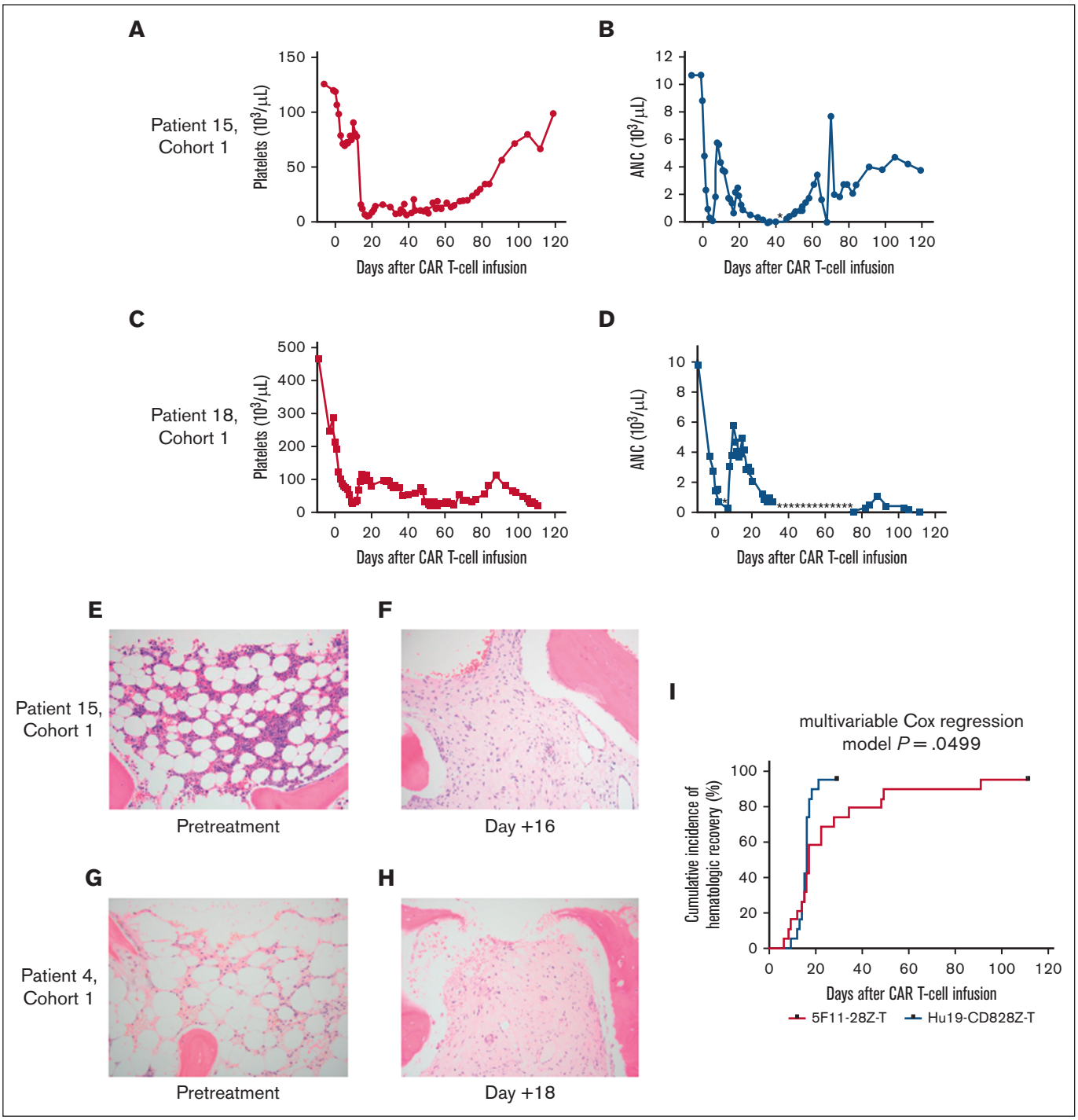

Figure 3. Hematologic toxicity after 5F11-Ts. (A) Patient 15 in cohort 1 experienced expected acute thrombocytopenia after CAR T-cell infusion, with initial partial recovery by day +10. He then experienced an abrupt decrease in platelet count on day +14, followed by progressive pancytopenia. (B) His absolute neutrophil count (ANC) was 0 (10^3/μL) on day +40. His ANC values were <0.2 (10^3/μL) on days +43 to +44, as denoted by the asterisk. He required platelet transfusions and growth factor support with filgrastim until day +58 and day +70, respectively. (C) Patient 18 in cohort 1 had elevated platelets of 467 (10^3/μL) before conditioning chemotherapy. Her platelet count decreased to 31 (10^3/μL) on day +10. (D) Patient 18 experienced an expected acute neutrophil decrease, with ANC <0.2 (10^3/μL) on days +3 to +6, as indicated by the asterisk. After initial recovery with growth factor support with filgrastim and pegfilgrastim, her ANC again decreased to values of ≤0.5 (10^3/μL) on days +32 to +72, as denoted by the line of asterisks, and with values of ≤0.2 (10^3/μL) on days +40 to +70. (E) The baseline BM biopsy for patient 15 is shown. H&E staining at 20× original magnification shows mildly hypocellular marrow for age at 40% overall cellularity with trilineage hematopoiesis. (F) H&E staining at 20× original magnification of patient 15's day +16 BM biopsy demonstrates markedly hypocellular marrow with <5% overall cellularity, trilineage hypoplasia, and fibrosis. (G) The baseline BM biopsy for patient 4 in cohort 1 is shown. H&E staining at 20× original magnification shows baseline hypocellularity and trilineage hypoplasia. (H) H&E staining at 20× magnification of patient 4's day +18 BM biopsy demonstrates ongoing hypocellularity and

Lack of infiltration of CAR$^+$ cells observed in posttreatment lymph node biopsies

Of 10 patients who underwent tumor biopsies at progression, all retained CD30 expression. Seven patients had tumor biopsies performed for research purposes within 30 days after 5F11-Ts that were technically adequate for CAR staining. At the time of biopsy, 6 patients had detectable CAR$^+$ cells in their blood. Infiltrating CAR$^+$ cells were not detected in any of these biopsies by IHC. In comparison, 33% (2 of 6) of evaluable patients with B-cell non-Hodgkin lymphoma had ≥1 tumor biopsies within 30 days of Hu19-CD828Z-T infusion with detectable CAR$^+$ cells.

Robust 5F11-T blood levels with low-level cytokine production

5F11-Ts were manufactured successfully for all patients. Percentages of CD45$^+$ CD4$^+$ and CD45$^+$ CD8$^+$ cells, as well as CD4:CD8 ratio at day 7 of culture are shown in supplemental Table 7. CAR T cells were detectable in the blood of all patients, with a median of 26 peak blood CAR$^+$ cells per μL (range, 1-513 peak blood CAR$^+$ cells per μL). Blood CAR$^+$ cell levels peaked a median of 11 days (range, 5-19 days) after 5F11-T infusion. The median time 5F11-Ts were detectable in blood at ≥1 CAR$^+$ cell per μL, or last follow-up before progression, was 27 days (range, 8-138 days). There was a trend toward higher peak blood CAR$^+$ cells per μL at higher dose levels (Kruskal-Wallis test, $P = .056$; Figure 4A). Neither peak nor area under the curve blood CAR$^+$ cells per μL significantly differed between patients with a lymphoma response of SD or PD vs response of CR or PR (Figure 4B-C). However, patients with CRS had significantly higher peak blood CAR$^+$ cells/μL than patients with no CRS (Mann-Whitney *U* test, $P = .0095$; Figure 4D). Similarly, patients with rashes had significantly higher peak blood CAR$^+$ cells per μL than patients without rashes (Mann-Whitney *U* test, $P = .0014$; Figure 4E).

Peak levels of 10 serum cytokines are shown in Figure 4F. Patients with CRS had significantly higher peak serum levels of interferon-γ, IL-10, IL-2, IL-6, and tumor necrosis factor α than patients without CRS (supplemental Table 8; Figure 4G-K). For patients with rashes, only peak serum IL-6 was significantly higher than peak serum levels for patients not experiencing rashes (Mann-Whitney *U* test, $P = .0005$; supplemental Table 9; Figure 4L).

Discussion

5F11-Ts demonstrated evidence of antimalignancy activity in patients with heavily pretreated CD30-expressing lymphomas, a sample group in which all but 1 patient had cHL. There were responses of PR in 2 patients with previously chemotherapy-refractory cHL, suggesting that some portion of the efficacy was related to the CAR T cells and not the conditioning chemotherapy alone. However, the ORR of 43% and CR rate of 4.8% were low compared with previous clinical results with CD30-targeting CAR T cells in which ORR and CR rates have been reported as 67% to 100% and 36% to 59%, respectively.[20,22-24] Likewise, responses to 5F11-Ts were transient, with a median EFS of 13 weeks. In contrast, a prior clinical trial of anti-CD30 CAR T cells resulted in progression-free survival of 36% at 1 year in patients with measurable cHL, demonstrating durability in a subset of patients.[20]

5F11-Ts were detectable in the blood of all patients, with median peak blood CAR$^+$ cells per μL of 26 (range, 1-513 cells per μL); thus, absence of 5F11-Ts in vivo was not the cause of the low response rates observed; in addition, there was no difference in either peak or area under the curve blood CAR$^+$ cells per μL between patients with and without a lymphoma response. This finding was similar to prior results of other investigations.[20] There was no clear evidence of antigen escape being the cause of treatment failure, as all tumor biopsies at lymphoma progression showed retained expression of CD30. However, there could be cleavages in the target molecule that include the epitope to which the CAR is directed or conformational changes that allow antigenic escape. Participants in this trial had heavily pretreated lymphoma that may have innately been more resistant to therapy, but prior experience by other investigators has shown greater efficacy in similarly heavily pretreated samples.[20] However, patients who received 5F11-Ts had relatively high baseline tumor burden. Of 21 patients who received 5F11-Ts, 11 had an MTV of ≥60 mL, compared with 7 of 27 patients in a prior report of anti-CD30 CAR T cells[31] (Fisher exact test, $P = .077$). Patients with pretreatment MTV of ≥60 mL before 5F11-T infusion had a median EFS of 63 days. In the prior report of Voorhees et al,[31] patients with pretreatment MTV of ≥60 mL had a median progression-free survival of 129 days.[31] In both trials, no patients with pretreatment MTV of ≥60 mL achieved durable remissions beyond 500 days, demonstrating limited efficacy of anti-CD30 CAR T cells in treating high-burden cHL. Patients with higher baseline MTV before 5F11-T treatment had worse EFS in a CPH regression model. This finding is consistent with results with anti-CD19 CAR T cells targeting B-cell malignancies in which higher malignancy burden is associated with lack of response.[33,34]

An additional possible reason for low efficacy of 5F11-Ts is poor penetration of CAR T cells into the especially immunosuppressive microenvironment of cHL lymphoma masses. CAR$^+$ cell infiltration was not evident in any of 7 evaluable lymph node biopsies within 30 days of 5F11-T infusion. Finally, the fact that CD30$^+$ Reed Sternberg cells make up an average of <1% of the cells in a HL mass[35] might be another reason for the lesser antilymphoma efficacy of 5F11-Ts compared with our prior experience with anti-CD19 CAR T cells.[11,32] Potential strategies for overcoming an immunosuppressive tumor microenvironment and increasing anti-CD30 CAR T-cell efficacy for cHL include the design of CAR T-cell products that coexpress CCR4[22]; and the use of immune checkpoint inhibitor agents after, or in combination with, anti-CD30 CAR T cells.[36,37]

5F11-Ts caused low rates of CRS and neurologic toxicity. Similarly, low rates of these toxicities were observed in other clinical trials of anti-CD30 CAR T cells.[20,22-24] Higher 5F11-T doses may promote CRS. Patients experiencing CRS had higher peak blood CAR$^+$ cells per μL and higher levels of multiple serum cytokines than patients with no CRS; however, peak serum cytokine levels were generally low. A possible reason for this is that because of the low numbers of CD30$^+$ cells in the tumor mass, the antigen stimulation

Figure 3 (continued) hypoplasia, as well as fibrosis. (I) Kaplan-Meier curve showing cumulative incidence of hematologic recovery (TTHR) for patients who received 5F11-Ts compared with patients who received Hu19-CD828Z-Ts. Multivariable CPH regression, $P = .0499$.

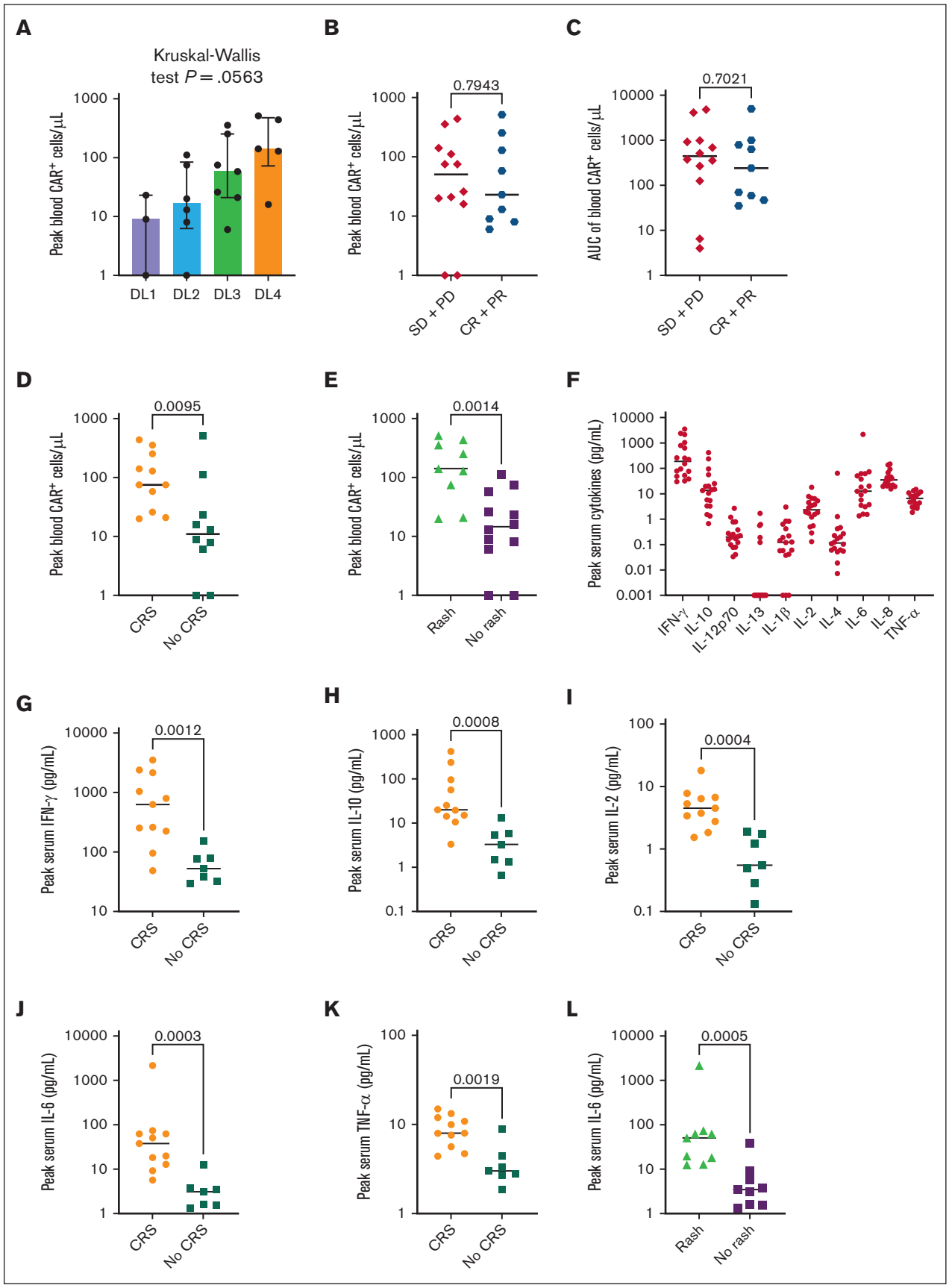

Figure 4.

of CAR T cells and subsequent cytokine release may be limited. Although some neurologic AEs occurring after 5F11-T infusion were attributed as possibly due to CAR T cells, all neurologic AEs had possible other etiologies. Typical manifestations of ICANS, such as tremors, dysphasias, and excessive somnolence were not observed. Whether 5F11-Ts cause ICANS is not known.

Rashes that occurred on this clinical trial were, in some cases, severe. Forty-three percent of patients had rashes, with 3 patients (14%) having grade 3 rashes, and 2 patients (9.5%) having long-duration rashes requiring extended courses of systemic corticosteroids. Rashes have been reported with similar frequencies of 40% to 48% in prior clinical trials of CD30-directed CAR T cells[20,23] but were reportedly transient, with rashes all lasting no more than 10 days and resolving without specific treatment in a prior report.[20] Rashes also occur after treatment with BV, necessitating systemic corticosteroids in 12% of patients with CD30-expressing lymphomas,[38] suggesting that the cutaneous toxicity observed with anti-CD30 CAR T cells is a shared effect of both cellular and noncellular CD30-directed therapies. The mechanism of this cutaneous toxicity is not clear. Like CRS, rashes may be cell dose–dependent. Skin biopsies after 5F11-Ts demonstrated spongiotic dermatitis with T-cell infiltrates in the perivascular areas. Spongiotic dermatitis has similarly been previously reported in skin biopsies of patients with rashes after anti-CD30 CAR T cells[20] and after BV.[38] As reported for a prior clinical trial,[20] CAR^+ cells were detected in the dermis of the patient with the earliest skin biopsy after 5F11-T infusion, suggesting that direct infiltration of CAR^+ cells into the dermis might be involved in the mechanism of toxicity. However, CD30 was observed on lymphocytes in the dermis but not on keratinocytes. CRS and rashes may have shared mechanisms or risk factors because almost all patients with rashes also had CRS.

Prolonged cytopenias are well described AEs after CAR T-cell therapies targeting CD19 or B-cell maturation antigen, with the underlying pathophysiology being poorly understood.[30,39-41] Prolonged thrombocytopenia and neutropenia were also reported for a prior trial of anti-CD30 CAR T cells.[20] Twenty-four percent had TTHR of ≥30 days after 5F11-Ts, with 2 patients having infectious complications during prolonged neutropenia and corticosteroid use. BM biopsies revealed nonspecific findings of hypocellularity and trilineage hypoplasia but also showed new fibrosis in 3 patients, with no evidence of dysplasia or progression of lymphoma. A multivariable CPH regression model of TTHR including patients who received 5F11-Ts and patients who received Hu19-CD828Z-Ts revealed that whether a patient was on the 5F11-T trial or the Hu19-CD828Z trial was an independent predictor of TTHR. This analysis controlled for patient-related factors thought to contribute to the development of prolonged cytopenias, such as prior lines of therapy, baseline blood counts, and baseline CRP,[30,39,41] although, because different patient populations with different prior therapies are being compared, results should be interpreted cautiously in light of these limitations. The model suggests that CD30-directed CAR T-cell products may be particularly myelosuppressive. A potential mechanism for this hematologic toxicity is CAR T-cell mediated killing of $CD34^+$ hematopoietic stem and progenitor cells (HSPCs), which express low levels of CD30 upon cytokine stimulation.[42] However, activated HSPCs may express CD30 at levels below the T-cell activation threshold for some anti-CD30 CAR constructs.[42] We did not detect a high burden of $CD30^+$ cells on either pretreatment or posttreatment BM biopsies, although transient low-level expression of CD30 by cytokine-stimulated HSPCs may not have been captured. The 2 patients with the most severe prolonged cytopenias received both eltrombopag and corticosteroids for management of cytopenias. In our experience, hematologic recovery occurred in most patients after they were given eltrombopag and corticosteroids; of course, we do not know whether these agents caused the hematologic recovery. However, Patient 18 had refractory cytopenias when she discontinued trial participation, demonstrating that not all cases of prolonged cytopenias respond to pharmacologic management.

In conclusion, 5F11-Ts demonstrated a low rate of transient antilymphoma responses in patients with heavily pretreated CD30-expressing lymphomas. Although CRS and neurologic toxicities were relatively mild and manageable, rashes and prolonged hematologic toxicities are barriers to further clinical investigation of this CAR T-cell product. We did not find a relationship between lymphoma burden and toxicity. We also have not determined a structural factor of the 5F11-28Z CAR that might be associated with toxicity. We speculate that the toxicity could be related to the 5F11 single chain variable fragment because this is the first CAR tested in humans to contain this single chain variable fragment. Improved understanding of these atypical toxicities and the development of strategies to prevent or treat them will be critical in the future advancement of anti-CD30 CAR T-cell therapies. The combination of low antilymphoma efficacy and significant hematologic toxicity prompted us to end this clinical trial.

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Figure 4. Associations with efficacy and toxicity: peak blood CAR^+ cells, serum cytokines. (A) There was a trend toward an increase in peak blood CAR^+ cells with increasing dose levels (DL). Bracketed vertical lines represent interquartile range. Horizontal bars represent medians throughout. Blood concentration of CAR^+ cells was determined by real-time quantitative PCR as described in "Methods." (B) There was no significant difference in peak blood CAR^+ cells for patients with SD or PD compared with patients who had CR or PR. (C) There was no difference in the area under the curve (AUC) of blood CAR^+ cells for patients with SD or PD compared with patients who had CR or PR. AUC was calculated including all measures up to, and including, day +30 after CAR T-cell infusion. (D) Patients experiencing CRS had significantly higher peak levels of blood CAR^+ cells than patients who had no CRS. (E) Patients experiencing rashes had a significantly higher peak levels of blood CAR^+ cells than patients who had no rashes. For panels B-E, all statistics were by Mann-Whitney *U* test; $P < .05$ is considered statistically significant. (F) Peak levels of 10 serum cytokines for all patients. Serum levels of the following cytokines were higher in patients experiencing CRS vs patients who had no CRS: (G) IFN-γ, (H) IL-10, (I) IL-2, (J) IL-6, and (K) TNF-α. (L) Patients experiencing rashes had significantly higher peak serum IL-6 levels than patients who had no rashes. For panels G-L, statistical comparisons were by the Mann-Whitney *U* test with Bonferroni correction for multiple comparisons; $P < .005$ is considered statistically significant. IFN-γ, interferon gamma; TNF-α, tumor necrosis factor α.

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Authorship

Contribution: J.N.B. and J.N.K. designed the study, provided patient care, analyzed data, and wrote the manuscript; D.A.N. performed experiments and analyzed data; L.M., J.M., and G.C.F. provided patient care; J.K. and S.P. designed the immunohistochemical stain for the chimeric antigen receptor, processed and analyzed pathology samples, and provided images for figures; N.P. analyzed patient pathology samples and contributed to construction of figures and tables; R.M.-M. performed analysis of metabolic tumor volumes; M.A.A. contributed images for figures; R.P. provided regulatory support; D.F.S. and S.L.H. planned and executed 5F11-T production; and all authors edited the manuscript.

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