ALLO-316 in Patients With Advanced or Metastatic Clear Cell Renal Cell Carcinoma (ccRCC): Updated Safety and Efficacy From the Phase 1 TRAVERSE Multicenter Study

Poster 322

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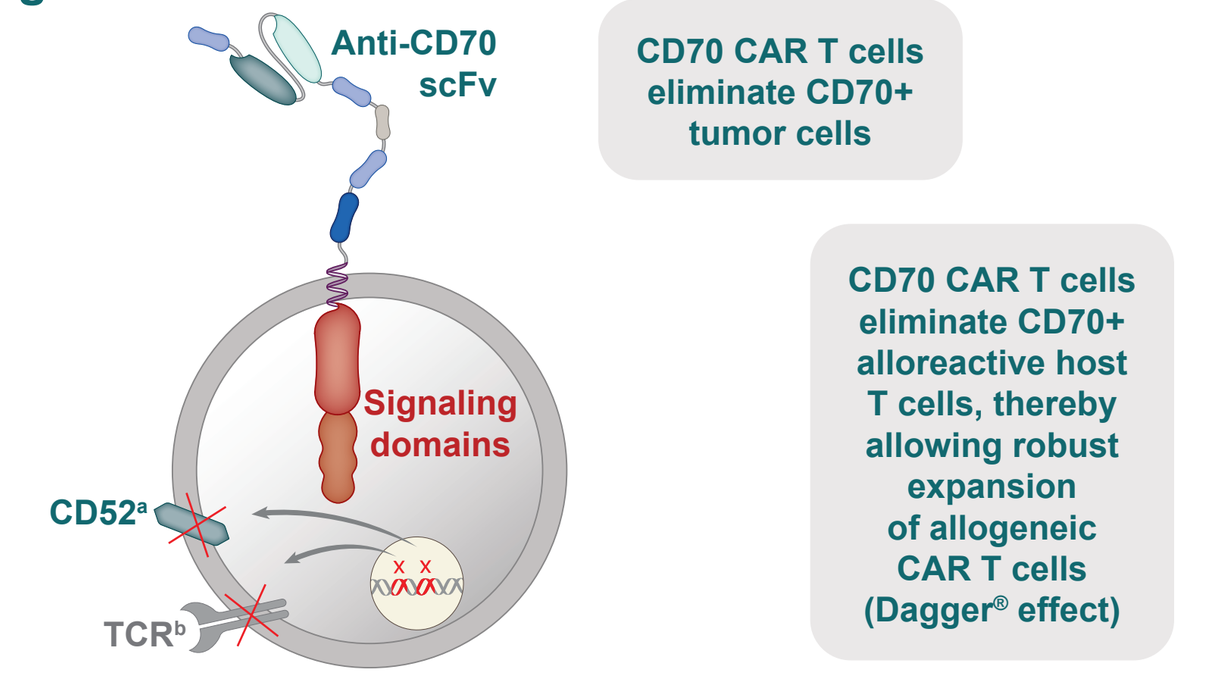
BACKGROUND

- Approximately 80,000 new cases of kidney cancer are diagnosed each year in the United States, of which, nearly 30% are locally advanced or metastatic renal cell carcinoma (mRCC)[1,2]
- Patients with relapsed/refractory RCC have limited therapeutic options after failure of immune checkpoint inhibitors (ICI) and vascular endothelial growth factor–targeting tyrosine kinase inhibitors (TKIs), with low response rates (~5% to 20%) and short median progression-free survival[3,4]
- CD70 is highly expressed on the surface of clear cell RCC (ccRCC), with restricted expression in normal tissues[5,6]; importantly, ~80% of patients with ccRCC have high CD70 expression[7]
- ALLO-316 is an investigational, off-the-shelf, allogeneic CD70 chimeric antigen receptor (CAR) T cell product designed to recognize and kill both CD70+ tumor cells and CD70+ host T cells that cause allorejection (**Figure 1**)
- Here, we present updated safety and efficacy data from the phase 1 TRAVERSE study

Figure 1. ALLO-316



[a] CD52 knockout enables lymphodepletion with ALLO-647.
[b] Knockout performed using TALEN® gene editing technology helps prevent GvHD.
CAR, chimeric antigen receptor; GvHD, graft-versus-host disease; scFv, single chain fragment variable; TCR, T-cell receptor.

METHODS

- TRAVERSE (NCT04696731) is a phase 1a/1b multicenter study evaluating the safety and efficacy of ALLO-316 in patients with advanced or metastatic ccRCC (**Figure 2**)

Figure 2. TRAVERSE Treatment Schema

Prescreening, Screening, & Enrollment → LD (D-5 to D-3) and ALLO-316 (D0) → Follow-Up: Response and Safety Assessments Through M60

Prescreening: CD70 assessed by IHC on **archival or fresh tumor tissue**

Key screening criteria
- Age >18 years with progressive advanced or metastatic ccRCC after an ICI and VEGF-targeted therapy
- ECOG PS 0-1
- Adequate organ function
- Untreated CNS metastases (excluded)

Primary Endpoints/Objectives

Phase 1a
- Dose-limiting toxicities
- Incidence of AEs (TEAEs, SAEs, AESI)

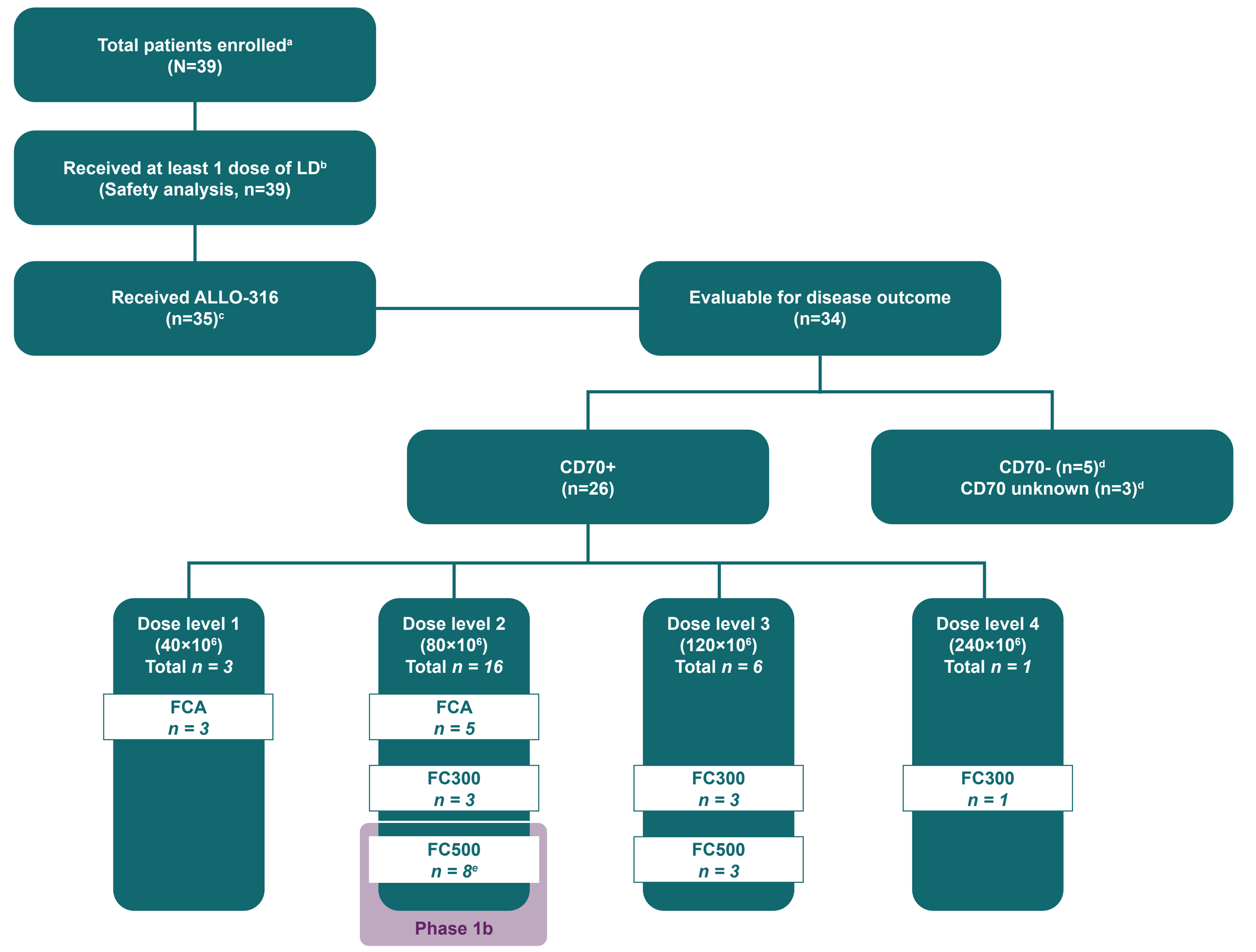
Phase 1b
- Identify RP2D and establish CD70 TPS cutoff
- Incidence of AEs (TEAEs, SAEs, AESI)

Secondary Endpoints
- ORR and CR (investigator assessment)
- DOR, TTR, PFS
- CAR expansion kinetics
- Expression of CD70 target on tumor cells (IHC)

AE, adverse event; AESI, adverse event of special interest; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; LD, lymphodepletion; M, month; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TPS, tumor proportion score; TTR, time to response; VEGF, vascular endothelial growth factor.

RESULTS

Figure 3. Patient Disposition


Total patients enrolled[a] (N=39)
Received at least 1 dose of LD[b] (Safety analysis, n=39)
Received ALLO-316 (n=35)[c]
Evaluable for disease outcome (n=34)
CD70+ (n=26)
CD70- (n=5)[d] CD70 unknown (n=3)[d]
Dose level 1 (40×10⁶) Total n = 3
FCA n = 3
Dose level 2 (80×10⁶) Total n = 16
FCA n = 5
FC300 n = 3
FC500 n = 8[e]
Phase 1b
Dose level 3 (120×10⁶) Total n = 6
FC300 n = 3
FC500 n = 3
Dose level 4 (240×10⁶) Total n = 1
FC300 n = 1

[a] Enrolled includes all patients who signed informed consent, were screened, and determined to be eligible for study treatment. [b] Four patients received at least 1 dose of fludarabine, cyclophosphamide, and/or ALLO-647, but were not dosed with ALLO-316 due to (i) becoming COVID-19 positive, (ii) rising creatinine and transaminase levels above eligibility criteria for ALLO-316 administration, (iii) altered mental status diagnosed as CNS metastases before ALLO-316 administration, and (iv) after becoming COVID-19 positive, patient withdrew consent before ALLO-316 was dosed. [c] One patient received ALLO-316 but has not yet reached Day 28 for tumor assessment. [d] The 5 CD70 negative patients were enrolled and treated in the 40×10⁶ FCA (n=3), 80×10⁶ FCA (n=1) and 40×10⁶ FC300 (n=1) dose groups. The 3 patients with CD70 status unknown were enrolled and treated in the 40×10⁶ FCA (n=1), 40×10⁶ FC300 (n=1) and 80×10⁶ FC300 (n=1) dose groups. [e] Within the DL2 FC500 group, 8 patients were evaluable for efficacy (received ALLO-316 and had the opportunity to be followed to the first disease assessment or died prior to assessment) and 11 patients were evaluable for safety (received at least 1 dose of protocol therapy).
CNS, central nervous system; DL, dose level; FC300, fludarabine 30 mg/m² and cyclophosphamide 300 mg/m²; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; FCA, fludarabine, cyclophosphamide, and ALLO-647; LD, lymphodepletion.

RESULTS

PATIENTS

Table 1. Patient Baseline Characteristics

Characteristic	All Patients (N=39)
Median age (range), years	60 (35-70)
Gender: male/female, %	90/10
ECOG PS: 0/1, %	56/44
Disease stage IV, n (%)	38 (97)
Previous nephrectomy, n (%)	32 (82)
CD70 positive, m (%)	31 (79)
High TPS (≥50), n/m (%)	24 (77)
Low TPS (<50), n/m (%)	7 (23)
CD70 negative or unknown, n (%)	8 (21)
Median time since original diagnosis, months (range)	43 (12-216)
Median lines of prior therapy (range)	3 (1-8)
Prior therapies, n (%)	
Anti–PD-1 therapy	39 (100)
Anti–PD-L1 therapy	1 (3)
Anti–CTLA-4 therapy	25 (64)
Belzutifan	5 (13)
Cabozantinib	31 (79)
≥1 TKI	39 (100)
≥2 TKIs	23 (59)
≥3 TKIs	11 (28)
Progressive disease despite anti–CTLA-4, anti–PD-1, TKI, and belzutifan, n (%)	3 (8)
IMDC category at screening	
Favorable risk	13 (33)
Intermediate risk	20 (51)
Poor risk	4 (10)
Median time from enrollment to lymphodepletion, days (range)	5 (1-10)
Median follow-up, months (range)	6.8 (0.4-36.8)

Data cutoff: October 14, 2024.
CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score.

SAFETY

- Dose-limiting toxicities (DLTs) were seen in 2 patients, both of whom received fludarabine, cyclophosphamide, and ALLO-647 (FCA) lymphodepletion (LD) and ALLO-316 dose level (DL) 2 (80×10⁶ CAR cells)
  - DLTs were autoimmune hepatitis and cardiogenic shock in the setting of multiorgan failure (n=1 each)
- All patients experienced treatment-emergent adverse events, of which 81% were grade ≥3
  - Cytokine release syndrome (CRS) in 62% of patients, of which 3% were grade ≥3
  - Immune effector cell-associated neurotoxicity syndrome (ICANS) in 8% of patients, of which 0% were grade ≥3
  - Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) in 13% of patients, of which 3% were grade ≥3
- Fatal treatment-related adverse events were due to the following reasons:
  - Cardiogenic shock (DLT)
  - Sepsis from multidrug-resistant *Klebsiella pneumoniae* in a patient with evidence of hyperinflammation treated with dexamethasone and anakinra; notably, the same organism was recovered during an episode of muscle abscess and bacteremia 2 years prior
  - Failure to thrive in a patient 16 months after last treatment (persistent RCC at 12 months after last treatment, with no interval scans to evaluate disease status prior to death)

Table 2. Safety: Most Prevalent TEAEs (>40% Any Grade Incidence) and AESI

	All Patients (N=39)		DL2 FC500 (N=11)	
Preferred Term, n (%)	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Any TEAE	39 (100)	29 (81)	11 (100)	8 (73)
CRS	24 (62)	1 (3)	8 (73)	0
Fatigue	23 (59)	1 (3)	2 (18)	0
Neutropenia	22 (56)	20 (51)	7 (64)	7 (64)
White blood cell count decreased	21 (54)	19 (49)	8 (73)	8 (73)
Anemia	20 (51)	13 (33)	7 (64)	5 (46)
Nausea	20 (51)	0	3 (27)	0
Thrombocytopenia	18 (46)	10 (26)	7 (64)	3 (27)
Pyrexia	16 (41)	2 (5)	4 (36)	0
AESIs	**Any Grades**	**Grade ≥3**	**Any Grades**	**Grade ≥3**
Infection[a]	24 (62)	12 (31)	5 (46)	2 (18)
Viral infections	13 (33)	2 (5)	2 (18)	0
Neurotoxicity[b]	17 (44)	3 (8)	4 (36)	0
Headache	8 (21)	0	2 (18)	0
IEC-HS	5 (13)	1 (3)	2 (18)	0
ICANS	3 (8)	0	3 (27)	0
Graft-versus-host disease	0	0	0	0

Data cutoff: October 14, 2024.
TEAE included all AEs that started from the first dose date of study drug in each treatment period up to start of another treatment period, death, or the date prior to initiation of another anti-cancer agent, whichever occurred first. IEC-HS includes preferred terms Immune effector cell-associated HLH-like syndrome and Haemophagocytic lymphohistiocytosis. Two patients developed an inflammatory syndrome prior to the existence of IEC-HS as a term in MedDRA, which has been updated as of September 2023.
[a] Infection events (62%) were primarily low grade; the most common was viral infections (33%) with cytomegalovirus infection and COVID-19 (any grade, 18% and 15%; grade ≥3, 0% and 5%, respectively). [b] Neurotoxicity includes system organ class of nervous system disorders and psychiatric disorders with onset date up to study Day 30 post ALLO-316 infusion.
AE, adverse event; AESI, adverse event of special interest; CRS, cytokine release syndrome; DL, dose level; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

EFFICACY

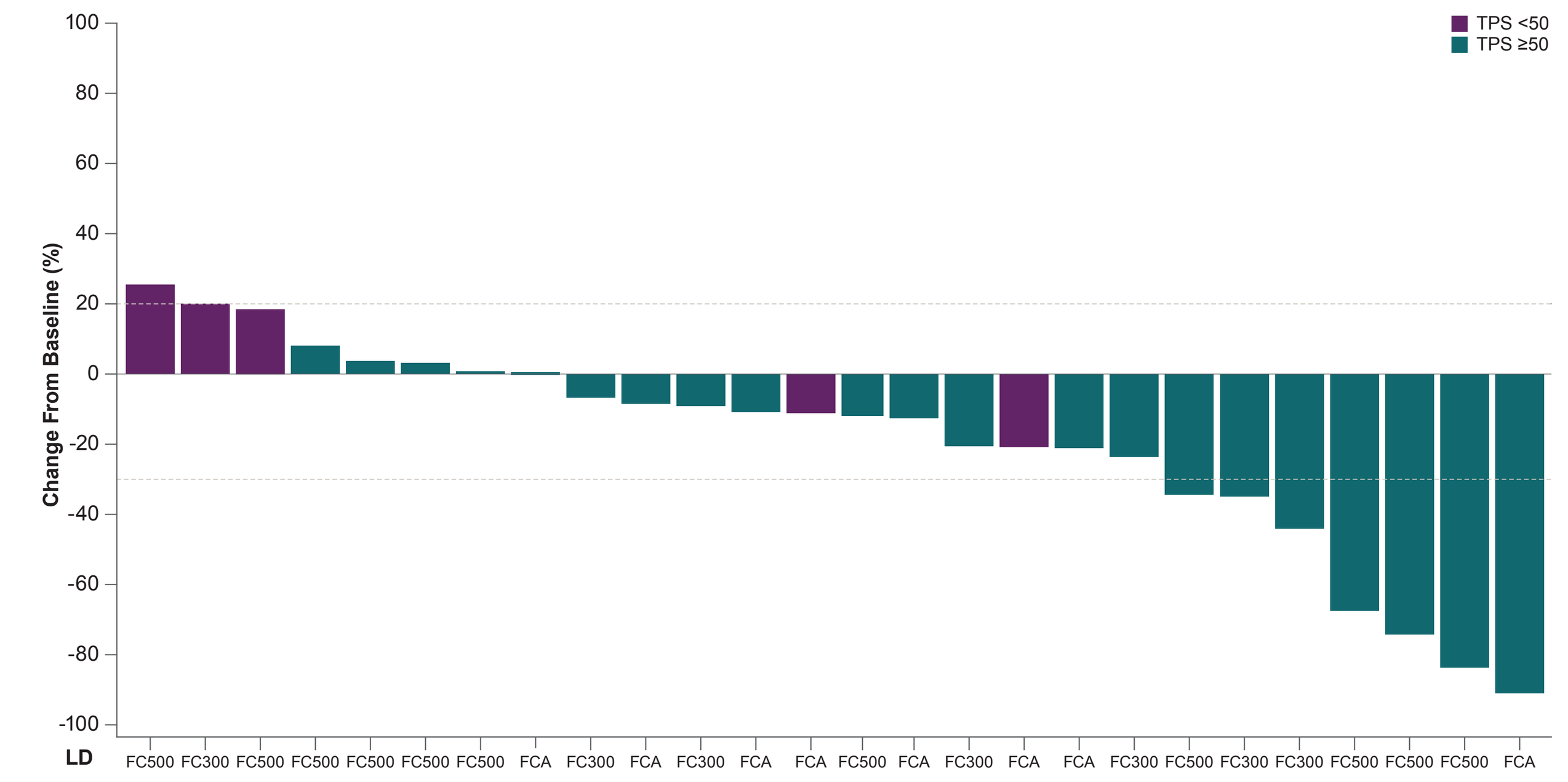
- Responses were seen with either FCA or standard fludarabine and cyclophosphamide (FC) LD (**Table 3**)
- Of those with tumor proportion score (TPS) ≥50, 76% (16/21) experienced a reduction in tumor burden and 33% (7/21) experienced >30% reduction (**Figure 4**)
- Two of 8 patients (25%) who received DL2 of ALLO-316 and fludarabine 30 mg/m² and cyclophosphamide 500 mg/m² (FC500) LD showed durable responses ongoing at ≥4 months (**Figure 5**)

Table 3. Response Rates by CD70 Status and by Dose

	Patients Evaluable for Disease Outcomes[a] (N=34)				
	CD70 Positive (N=26)				CD70 Negative or Unknown (N=8)
	All (N=26)	FCA (N=8)	FC (N=18)	DL2[b] FC500 (Phase 1b) (N=8)	
Best overall response,[c] n/N (%)	7/26 (27)	1/8 (13)	6/18 (33)	3/8 (38)	0/8 (0)
High TPS (≥50)	7/21 (33)	1/6 (17)	6/15 (40)	3/6 (50)	–
Low TPS (<50)	0/5 (0)	0/2 (0)	0/3 (0)	0/2 (0)	–
Confirmed ORR,[d] n/N (%)	5/26 (19)	1/8 (13)	4/18 (22)	2/8 (25)	0/8 (0)
High TPS (≥50)	5/21 (24)	1/6 (17)	4/15 (27)	2/6 (33)	–
Low TPS (<50)	0/5 (0)	0/2 (0)	0/3 (0)	0/2 (0)	–

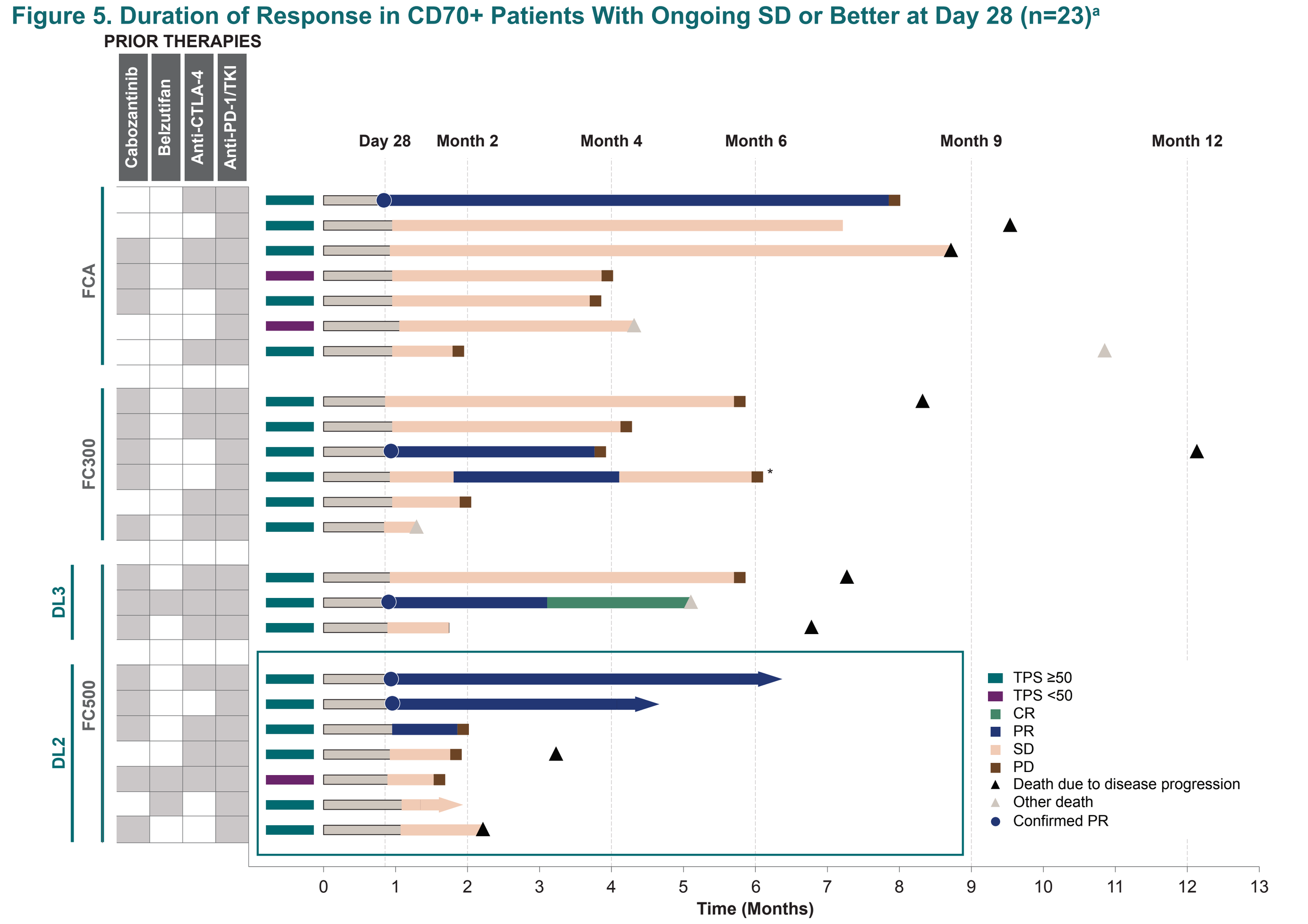
Data cutoff: October 14, 2024.
[a] Patients evaluable for disease outcome includes those who received ALLO-316 and had at least one tumor assessment. [b] 80×10⁶ dose of CD70 CAR+ cells (DL2). Three patients were in the DL2 FC500 Safety Analysis Set but were not included in the efficacy analysis for DL2 FC500 (2 patients received lymphodepletion but not ALLO-316; 1 patient received ALLO-316 but has not yet reached Day 28 for tumor assessment). [c] Best overall response across visits did not require confirmation for CR/PR or minimum duration for SD. [d] Confirmed best overall response of CR/PR required confirmation at the subsequent visit.
CR, complete response; DL, dose level; FC, fludarabine and cyclophosphamide; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; FCA, fludarabine, cyclophosphamide, and ALLO-647; ORR, overall response rate; PR, partial response; TPS, tumor proportion score.

Figure 4. Tumor Reduction From Baseline in CD70+ Patients[a] (N=26)



[a] Fresh biopsies were not required; responses were observed in patients deemed CD70+ with fresh and archival tissues.
FC300, fludarabine 30 mg/m² and cyclophosphamide 300 mg/m²; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; FCA, fludarabine, cyclophosphamide, and ALLO-647; LD, lymphodepletion; TPS, tumor proportion score.

Figure 5. Duration of Response in CD70+ Patients With Ongoing SD or Better at Day 28 (n=23)[a]

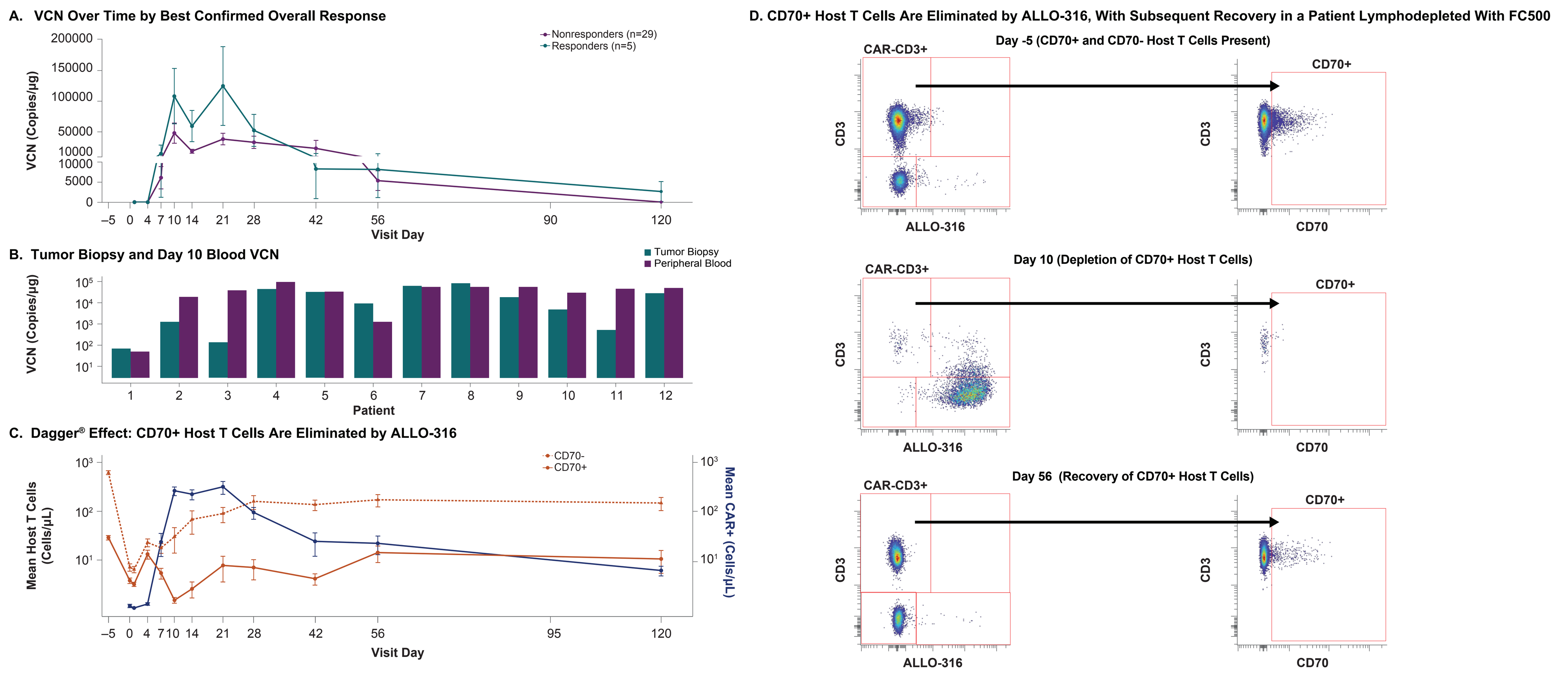


Two patients who progressed after achieving PRs received retreatment and achieved additional time in response. One patient with SD had target lesions that were not measurable at Month 4 due to poor image quality, but were measurable again at Month 6 and deemed as SD.
* Deepening response from day 28 (27% reduction from baseline) to day 56 (35% reduction from baseline). Unconfirmed response at month 4 with 17% increase from nadir. PD at month 6. Follow-up ongoing post retreatment.
[a] DOR is for patients who achieved best overall response of SD or better only.
CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; DL, dose level; FC300, fludarabine 30 mg/m² and cyclophosphamide 300 mg/m²; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; FCA, fludarabine, cyclophosphamide, and ALLO-647; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score.

CELLULAR KINETICS

- Robust CAR T cell expansion and persistence were observed, which was superior in responders relative to nonresponders (**Figure 6A**)
- The high vector copy number (VCN) levels observed in the tumor samples demonstrates extensive infiltration of ALLO-316 cells into the tumor microenvironment (**Figure 6B**)
- Evidence for the intrinsic Dagger® effect
  - ALLO-316 expansion was seen by Day 10 with elimination of CD70+ host T cells while CD70- host T cells were largely preserved (**Figure 6C**)
  - Effect was observed with standard LD (without ALLO-647)
  - Effect resolved as ALLO-316 contracted, allowing recovery of CD70+ host T cells (**Figure 6D**)

Figure 6. (A) VCN Over Time by Response (B) VCN in Whole Blood and Tumor Biopsy (C) Dagger® Effect, and (D) Flow Cytometry

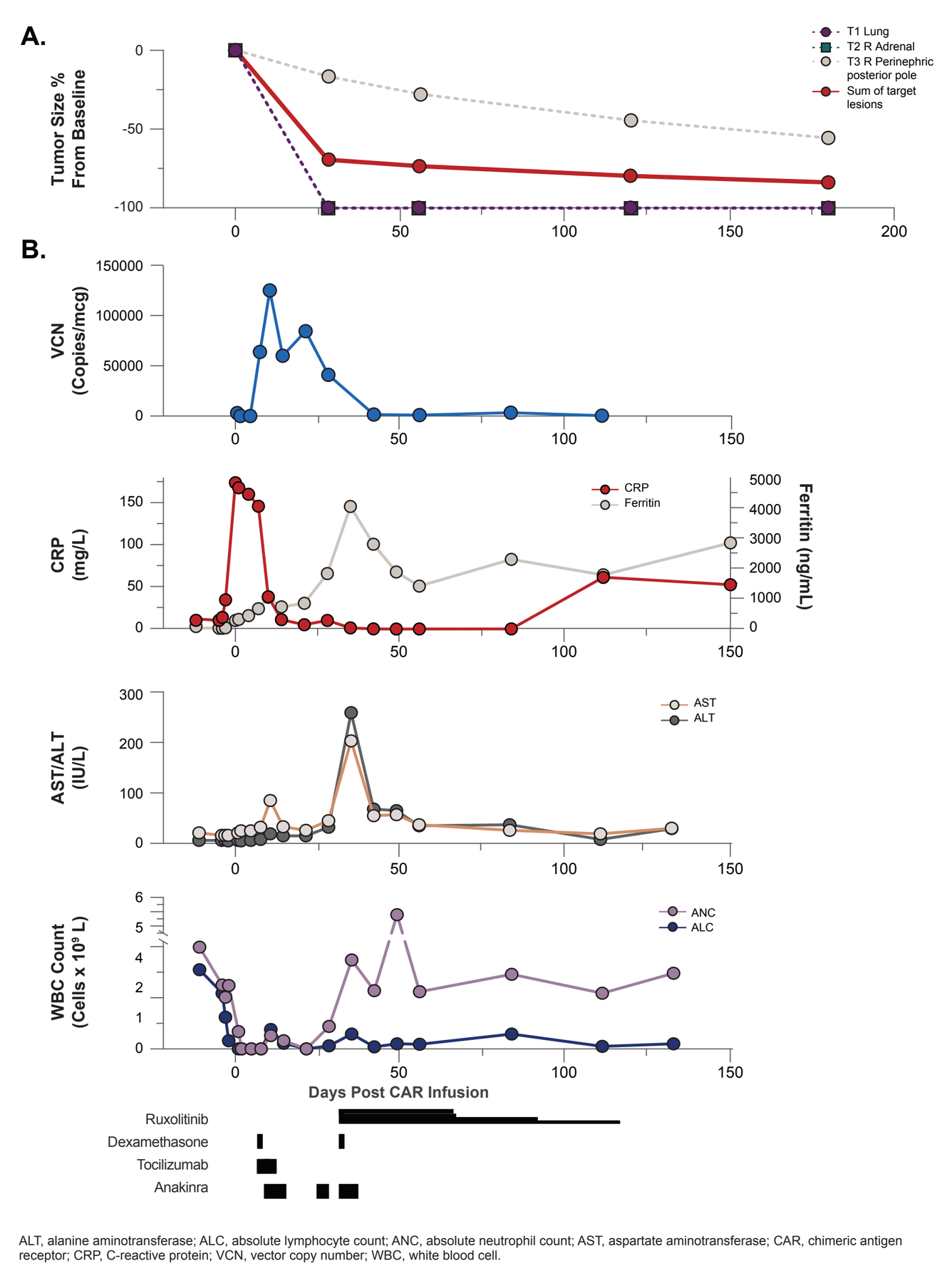

A. VCN Over Time by Best Confirmed Overall Response
Nonresponders (n=29)
Responders (n=5)
VCN (Copies/μg)
Visit Day
B. Tumor Biopsy and Day 10 Blood VCN
Tumor Biopsy
Peripheral Blood
VCN (Copies/μg)
Patient
C. Dagger® Effect: CD70+ Host T Cells Are Eliminated by ALLO-316
CD70-
CD70+
Mean Host T Cells (Cells/μL)
Mean CAR+ (Cells/μL)
Visit Day
D. CD70+ Host T Cells Are Eliminated by ALLO-316, With Subsequent Recovery in a Patient Lymphodepleted With FC500
Day -5 (CD70+ and CD70- Host T Cells Present)
Day 10 (Depletion of CD70+ Host T Cells)
Day 56 (Recovery of CD70+ Host T Cells)
CAR-CD3+
CD70+
CD3
ALLO-316
CD70

CAR, chimeric antigen receptor; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; VCN, vector copy number.

CASE STUDY: DEEP AND DURABLE REMISSION IN A PATIENT TREATED FOR HYPERINFLAMMATION FOLLOWING ALLO-316

- A 63-year-old patient with mRCC and 4 lines of prior therapy (pembrolizumab/axitinib, nivolumab/ipilimumab, cabozantinib, lenvatinib/everolimus) was treated with DL2 FC500 (**Figure 7**)
  - Patient developed grade 2 CRS on Day 7 that resolved with tocilizumab (interleukin-6 inhibitor)
- High CAR T VCN and rapid tumor regression were observed with achievement of partial response by Day 28
  - IEC-HS grade 2 developed on Day 33 with sudden onset of cytopenias, elevated ferritin, high alanine and aspartate aminotransferases, and normal C-reactive protein
  - IEC-HS was managed under a prespecified diagnostic and treatment algorithm with rapid improvement (**Figure 8**)
  - Patient was discharged home on ruxolitinib taper with eventual discontinuation
- Tumor response continued to deepen during IEC-HS management. Patient is in ongoing PR at 6 months

Figure 7. Response to Early Ruxolitinib in a Patient With IEC-HS. (A) Clinical Response, (B) VCN, CRP, Ferritin, Liver Transaminases, and WBC Count


A.
T1 Lung
T2 R Adrenal
T3 R Perinephric posterior pole
Sum of target lesions
Tumor Size % From Baseline
B.
VCN (Copies/mcg)
CRP
Ferritin
CRP (mg/L)
Ferritin (ng/mL)
AST
ALT
AST/ALT (IU/L)
ANC
ALC
WBC Count (Cells x 10⁹ L)
Days Post CAR Infusion
Ruxolitinib
Dexamethasone
Tocilizumab
Anakinra

ALT, alanine aminotransferase; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CAR, chimeric antigen receptor; CRP, C-reactive protein; VCN, vector copy number; WBC, white blood cell.

Figure 8. Recommended IEC-HS Management Guidance in the TRAVERSE Study

Abbreviated IEC-HS Diagnostic Criteria:
- Elevated and/or rapidly rising ferritin (>2×ULN or baseline)
- Timeframe consistent with IEC-HS: (generally, Day 21 or later, often after resolution of early CRS in first 2 weeks)[a]
- At least 1 of the following:
  - Cytopenias (rapidly decreasing ANC/platelets after prior recovery)
  - Hepatic transaminase elevation (>5×ULN)[b]
  - Rapidly decreasing fibrinogen/hypofibrinogenemia (<150 mg/dL or <LLN)

FIRST-LINE THERAPY
Initiate ruxolitinib, consider dexamethasone +/- anakinra

If insufficient response within 24-48 h:

SECOND-LINE THERAPY
Add dexamethasone +/- anakinra; if no improvement after 24 hours, escalate dosing (maximize ruxolitinib, dexamethasone +/- anakinra)

If insufficient response within 24-48 h, pursue alternative agents:

THIRD-LINE THERAPY
Emapalumab or etoposide and/or "Off-switch" for adoptive cellular therapy

Modified from Hines MR, et al[8] and expert opinion.
[a] IEC-HS may occur before Day 21. [b] More than 5 × baseline if baseline was abnormal.
ANC, absolute neutrophil count; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; h, hour; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; LLN, lower limit of normal; ULN, upper limit of normal.

CONCLUSIONS

- Observed responses (33% [7/21]), including ongoing and deepening responses, in patients with CD70 TPS ≥50%, suggest a single infusion of ALLO-316 could benefit patients with ICI- and TKI-relapsed/refractory RCC
- The CD70 CAR-intrinsic Dagger® effect promotes robust expansion and persistence of ALLO-316 with standard FC LD, highlighting the potential of Dagger® technology as the next-generation allogeneic platform
- A single dose of ALLO-316 demonstrated a manageable safety profile. Newly implemented diagnostic and management algorithm appears highly effective in abating IEC-HS due to CAR T-related expansion to improve tolerance and safety while preserving efficacy
- The phase 1 TRAVERSE study supports further evaluation of ALLO-316 in CD70+ ccRCC and other CD70+ malignancies. Enrollment is ongoing at the phase 1b dose regimen of FC500 and 80×10⁶ CAR T cells

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ACKNOWLEDGMENTS

This research was in part made possible by an award from the California Institute for Regenerative Medicine (Award Number CLIN2-15343).
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Medical writing and editorial assistance were provided by Second City Science LLC and funded by Allogene Therapeutics, Inc.