A PHASE II TRIAL OF ANAKINRA FOR THE PREVENTION OF CAR-T CELL MEDIATED NEUROTOXICITY

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BACKGROUND

- In most cases, chimeric antigen receptor (CAR)-T cell therapy is limited to inpatient use due to risk of severe treatment-related toxicities
- The two primary toxicities observed with CAR-T therapy are cytokine release syndrome (CRS) and neurologic events (NE)
- These toxicities are associated with increased circulating inflammatory cytokines such as IL-6 and IL-1
- Targeting IL-6 with tocilizumab is effective for treating CRS but not NE
- Anakinra is an FDA-approved recombinant IL-1 receptor antagonist that competitively inhibits IL-1 receptor signaling and therefore blocks downstream production of inflammatory cytokines including IL-6

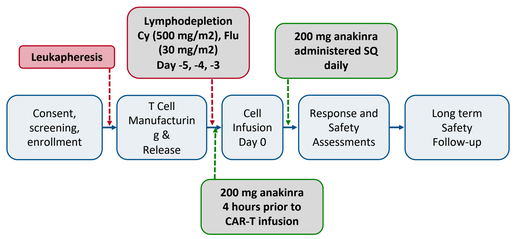
Hypothesis: Anakinra administered prophylactically will prevent severe CRS and NE in patients receiving axicabtagene ciloleucel (axi-cel).

- Here we report preliminary outcomes of this study

STUDY DESIGN

- This is a phase II single center, open-label study for patients ≥18years old with relapsed or refractory large B cell lymphoma.
- The original study was designed as 200 mg of subcutaneously administered anakinra starting 4 hours prior to axi-cel infusion and daily thereafter for a total of 7 days, with investigator discretion to extend to 14 days.
- CRS and NE were graded based on the Lee 2013 criteria and the CTCAE 4.03 criteria, respectively, to enable direct comparison to the pivotal ZUMA-1 cohorts.
- CAR-T cell expansion, serum cytokines, and circulating biomarkers of toxicity were measured at baseline, day 3, 7, 14, 21, and 28 post CAR-T cell infusion using a central platform for direct comparison to ZUMA-1.

Open label, single-arm, 2 sites (MGH and DFCI), N=11 to date



Key eligibility criteria

- Progressed after ≥2 lines of systemic therapy
- No CNS disease
- Not previously treated with CAR-T therapy or CD19 targeted therapy

Primary objectives

- Assess the impact of anakinra as preventative management of CAR-T related neurotoxicity

Secondary objectives

- Assess the impact of anakinra as preventative management of CAR-T related CRS
- To evaluate the efficacy of axi-cel in combination with preventative anakinra in terms of DOR, ORR, PFS, and OS

Clinical trial: NCT04150913

RESULTS

Table 1: Demographics and baseline characteristics of treated patients

	Anakinra ppx (n= 11)	ZUMA-1 Cohorts 1&2 (n=101)[1]	ZUMA-1 Cohort 4 (n=41)[2]	ZUMA-1 Cohort 6 (n=40)[3]
Age, median (range)	64.3 (42–79)	58.0 (23–76)	61.0 (19-77)	64.5 (37-85)
Gender Female Male	 6 (55%) 5 (45%)	 33 (33%) 68 (67%)	 13 (32%) 26 (68%)	 17 (43%) 23 (58%)
Histology type HGBCL tFL DLBCL, NOS PMBCL	 2 (18%) 5 (45%) 4 (36%) -	 - 16 (16%) 77 (76%) 8 (8%)	 3 (7%) 10 (24%) 26 (63%) 2 (55)	 7 (18%) 9 (23%) 24 (60%) -
DHL/THL	3/0	n/a	n/a	n/a
IPI pre-lymphodepletion, median (range)	3 (0–4)	2 (0-4)	2 (0-4)	2 (0-4)
Median prior lines of therapy	2 (2–4)	n/a	n/a	n/a
Prior auto SCT	1 (9%)	25 (25%)	14 (34%)	10 (25%)
Disease status Primary refractory Relapse refractory	 2 (18%) 9 (82%)	 3 (3%) 98 (98%)	 0 (0%) 41 (100%)	 2 (5%) 38 (95%)
Tumor burden Baseline LDH, median (range) Baseline SPD, median (range)	 390.0 (147–7565) 2156.9 1048–13,807)	 356 (116–7802) 3721 (171–23297)	 262 (145–4735) 2100 (204–24,758)	 236 (155–2042) 1183.5 (116–17,057)
Time to Follow-up, median (range)	6 months (0.75–12.5)	15.4 months	39.1 months	51.1 months

[1]Neelapu SS et al, *The New England Journal of Medicine* 2017; [2]Topp et al, ASH 2019 #243; [3]Oluwole et al, TCT 2021 #70 .data are n (%) unless otherwise specified; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; IPI, international prognostic index; NOS, not otherwise specified; ppx, prophylaxis; SCT, stem cell transplantation; tFL, transformed follicular lymphoma; THL, triple-hit lymphoma

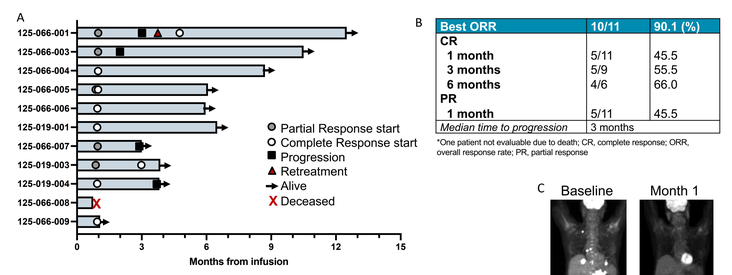
Table 2: Incidence, severity, and timing of CRS and Neurologic Events

CAR-T-Associated AEs	Anakinra (n=11)	ZUMA-1 Cohorts 1&2[1] (n=101) 24-month data	ZUMA-1 Cohort 4[2] (n=41) 12-month data	ZUMA-1 Cohort 6[3] (n=40) 12-month data
Max Grade CRS (Lee 2014[4]) Grade 1 Grade 2 Grade 3	 8 (73%) 2 (18%) 1 (9%)	 37 (37%) 46 (46%) 7 (7%)	 13 (32%) 24 (59%) 1 (2%)	 14 (35%) 18 (45%) 0 (0%)
Median Onset (day, range)	5 (1–8)	2 (1-12	2 (1–8)	5 (1-15)
Median Duration (days, range)	4 (1–10)	8 (2-58)	7 (2-16)	4 (1–11)
Max Grade Neurologic Events (CTCAE 4.03) Grade 1 Grade 2 Grade 3–4 Grade 5	 2 (18%) 1 (9%) 3 (27%) 1 (9%)	 21 (21%) 14 (14%) 29 (29%) 0	 14 (34%) 4 (10%) 7 (17%) 0	 10 (25%) 8 (18%) 5 (13%) 1 (3%)
Median Onset (day, range)	6 (5–12)	5 (1–17)	6 (1–93)	6 (2–162)
Median Duration (days, range)	6 (1–13)	15 (1-529)	8 (1-144)	19 (1-438)

[1]Neelapu SS et al, *The New England Journal of Medicine* 2017; [2]Topp et al, ASH 2019 #243; [3]Oluwole et al, TCT 2021 #70 [4]Lee et al *Blood* 2014; *combined grade 1 or 2 neurotoxicity for ZUMA-1 cohorts 1&2; data are n (%) unless otherwise specified; CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events

Table 3: Incidence and type of toxicity management

Toxicity Management	Anakinra (n=11)	ZUMA-1 Cohorts 1&2[1] (n=101)	ZUMA-1 Cohort 4[2] (n=41)	ZUMA-1 Cohort 6[3] (n=40)
Anakinra doses 7 days 14 days	 8 3	 - -	 - -	 - -
Patients given dexamethasone 1 dose 2 doses 3-4 doses ≥ 5 doses	**5 (45%)** 0 1 (9%) 0 4(36%)	**26 (26%)** 3 (12%) 1 (4%) 0 22 (85%)	**30 (73%)** 7 (23%) 7 (23%) 3 (10%) 13 (43%)	**40 (100%)** 1 (3%) 0 24 (60%) 15 (38%)
Mean* (mg) Median (mg) Range* (mg) *Dexamethasone	232 105 (20–712)	421 174 (0.2–3516)	168 30 (10–1071)	3523 40 (10–135733)
Patients given tocilizumab	4 (36%)	43 (43%)	31 (76%)	n/a
Siltuximab	1	n/a	n/a	n/a
Cytoxan	1	n/a	n/a	n/a



Best ORR	10/11	90.1 (%)
CR		
1 month	5/11	45.5
3 months	5/9	55.5
6 months	4/6	66.0
PR		
1 month	5/11	45.5
Median time to progression	3 months	

*One patient not evaluable due to death; CR, complete response; ORR, overall response rate; PR, partial response

Figure 1: (A) Timeline of responses per patient in the anakinra prophylaxis study. (B) Response rates for the whole cohort. (C) PET scan of one patient with high tumor burden at baseline, who had a complete response 1 month after axi-cel + anakinra prophylaxis with only grade 1 CRS and no NE.

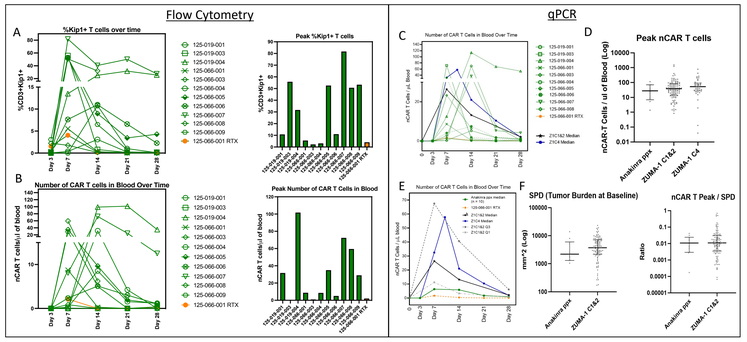


Figure 2: CAR T cell expansion and persistence. (A, B) CAR T cells were detected in patient blood by local flow cytometry staining for the CAR (Kip1+) or (C–F) qPCR (A) Percent of CAR T cells among CD3+ cells in individual patients' blood over time and peak CAR T cell percentage in the anakinra ppx cohort. (B) Number of CAR T cells in individual patients' blood over time and at peak based on absolute lymphocyte counts. (C–D) Number (n) of CAR T cells in individual patients (C) or the median (E) from the anakinra ppx cohort (green) compared to the median of the ZUMA-1 cohorts over time (C,E) and at peak levels (D). (F) Baseline tumor burden as measured by the sum of the products of diameters (SPD) compared to the peak number of CAR T cells per patient.

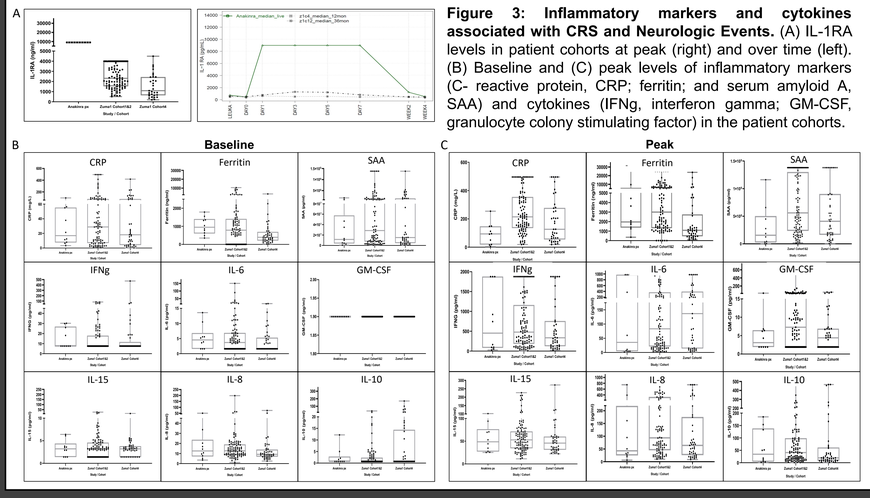


Figure 3: Inflammatory markers and cytokines associated with CRS and Neurologic Events. (A) IL-1RA levels in patient cohorts at peak (right) and over time (left). (B) Baseline and (C) peak levels of inflammatory markers (C- reactive protein, CRP; ferritin; and serum amyloid A, SAA) and cytokines (IFNg, interferon gamma; GM-CSF, granulocyte colony stimulating factor) in the patient cohorts.

CONCLUSIONS

- Daily dosing of anakinra is feasible and does not appear to impact response rate in patients with relapsed/refractory large B-cell lymphoma.
- Anakinra prophylaxis may delay CAR-T expansion but does not impact peak CAR-T expansion when normalized for tumor volume compared to ZUMA-1 cohort 1&2.
- Anakinra prophylaxis may decrease the rate of grade 2+ CRS (Lee 2014) and delay the median onset and duration of CRS compared to ZUMA-1 cohort 1&2.
- Prophylactic anakinra did not decrease the rates of NE compared to ZUMA-1 cohort 1&2 but may decrease total steroid utilization.
- Quantification of CAR T cell expansion by local flow cytometry were comparable to established quantitative central measurements by qPCR
- Daily dosing of anakinra results in on-target IL-RA effects and decreases the peak of a number of inflammatory markers, including CRP, ferritin, SAA, IL-6 , GM-CSF, and IL-18 compared to ZUMA-1 cohorts 1&2, but other serum analytes (such as IFNg, IL-15, IL-10) were not affected