



Aging and Cellular Therapy (in Lymphoma and Multiple Myeloma)

The ACT Now Study & Fit For CART

GEOFF SHOUSE, DO, PHD
MURALI JANAKIRAM, MD
ALEXEY DANILOV MD, PHD
ANDREW ARTZ, MD

CAR T Outcomes in Older Adults Demonstrate Excellent Response Rates but Significant Toxicity



Product	Disease	Ref	n	pts n(%)	ORR ≥65 vs <65 yrs n (%)		CR ≥65 vs <65 yrs n (%)		G≥3 CRS ≥65 vs <65 yrs n (%)		G≥3 NTX ≥65 vs <65 yrs n (%)		G≥3 Infxn ≥65 vs <65 yrs n (%)	
					≥65	<65	≥65	<65	≥65	<65	≥65	<65	≥65	<65
Axi-Cel	DLBCL	(1)	108	27 (25%)	22 (92%)	62 (81%)	18 (75%)	41 (53%)	2 (7%)	10 (12%)	12 (44%)	23 (28%)	5 (19%)	25 (31%)
Tisa-Cel	DLBCL	(2)	111	26 (23%)	13 (59%)	35 (49%)	NR	NR	NR	NR	NR	NR	NR	NR
Axi-Cel and Tisa-Cel	DLBCL	(3)	49	25 (51%)	NR	NR	51% overall and not different among groups		2 (8%)	3 (12%)	6 (25%)	4 (16%)	10 (42%)	15 (60%)
Axi-Cel and Tisa-Cel	DLBCL	(4)	804	330 (41%)	NR	NR	NR	NR	(all grades) 197 (59%)	(all grades) 302 (64%)	(all grades) 142 (43%)	(all grades) 171 (36%)	(sepsis) 11 (3%)	(sepsis) 5 (1%)
Liso-Cel	DLBCL	(5)	269	113 (42%)	82 (76%)	104 (70%)	65 (60%)	71 (48%)	NR	NR	NR	NR	NR	NR
Brexu-Cel	MCL	(6)	60	32 (53%)	30 (94%)	26 (93%)	NR	NR	NR	NR	NR	NR	NR	NR
Ide-Cel	MM	(7)	128	45 (35%)	32 (70%)	83 (90%)	NR	NR	NR	NR	NR	NR	NR	NR
Axi-Cel	Follicular	(8)	86	27 (31%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brexu-Cel	B-ALL	(9)	65	10 (15%)	NR	NR	8 (100%)	47 (71%)	NR	NR	NR	NR	NR	NR
Cilta-Cel	MM	(10)	97	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Cumulative Illness Rating Scale

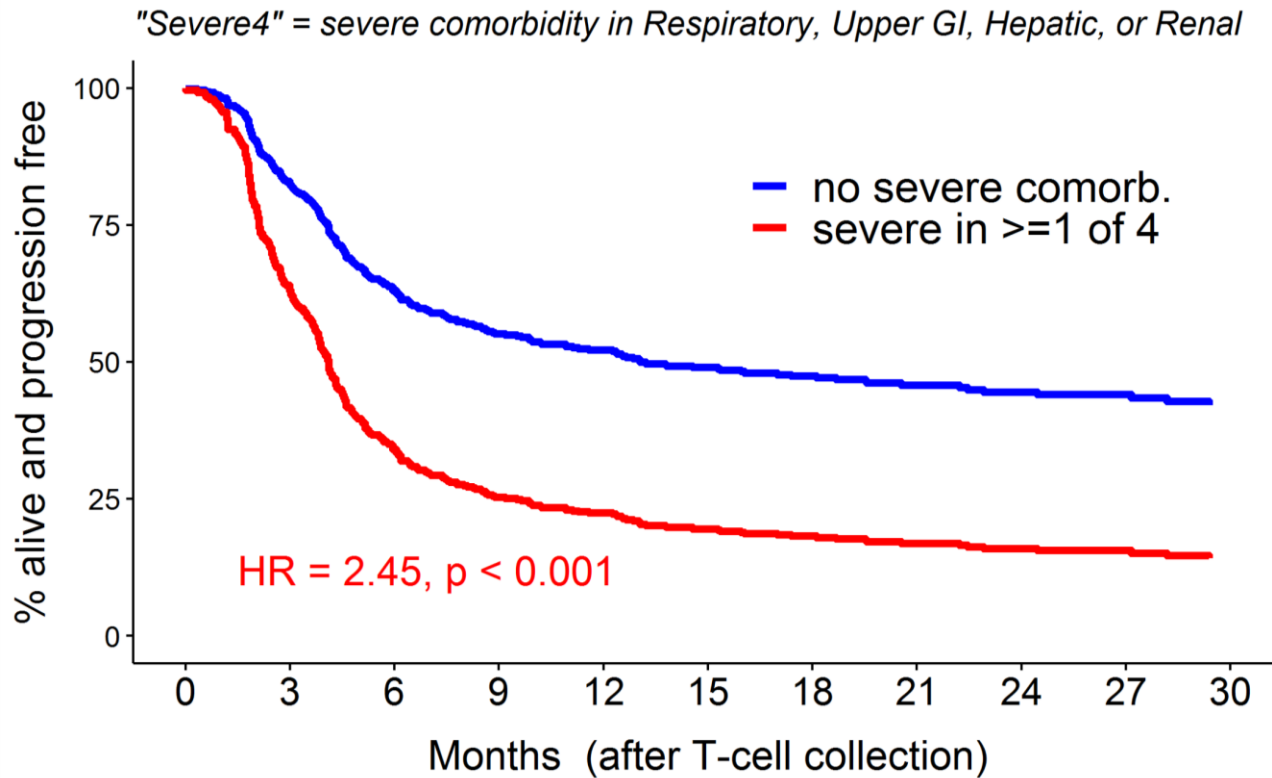
Organ System	Illness/Impairment Score
Cardiac	0-4
Hypertension	0-4
Vascular	0-4
Respiratory	0-4
Upper GI	0-4
Lower GI	0-4
Hepatic	0-4
Renal	0-4
Other GU	0-4
MSK	0-4
Neurological	0-4
Endocrine-Metabolic	0-4
Psychiatric/Behavioral	0-4
Total:	Sum of above scores

Impairment Score	
0	No problem
1	Current mild problem, does not interfere with normal activity, or past significant problem
2	Interferes with normal activity and/or requires first-line therapy
3	Severe problem and/or constant and significant disability and/or hard-to-control chronic problem
4	Extremely severe problem and/or treatment is urgent and/or severe functional impairment or organ failure

“Severe4” is highly correlated with PFS and OS

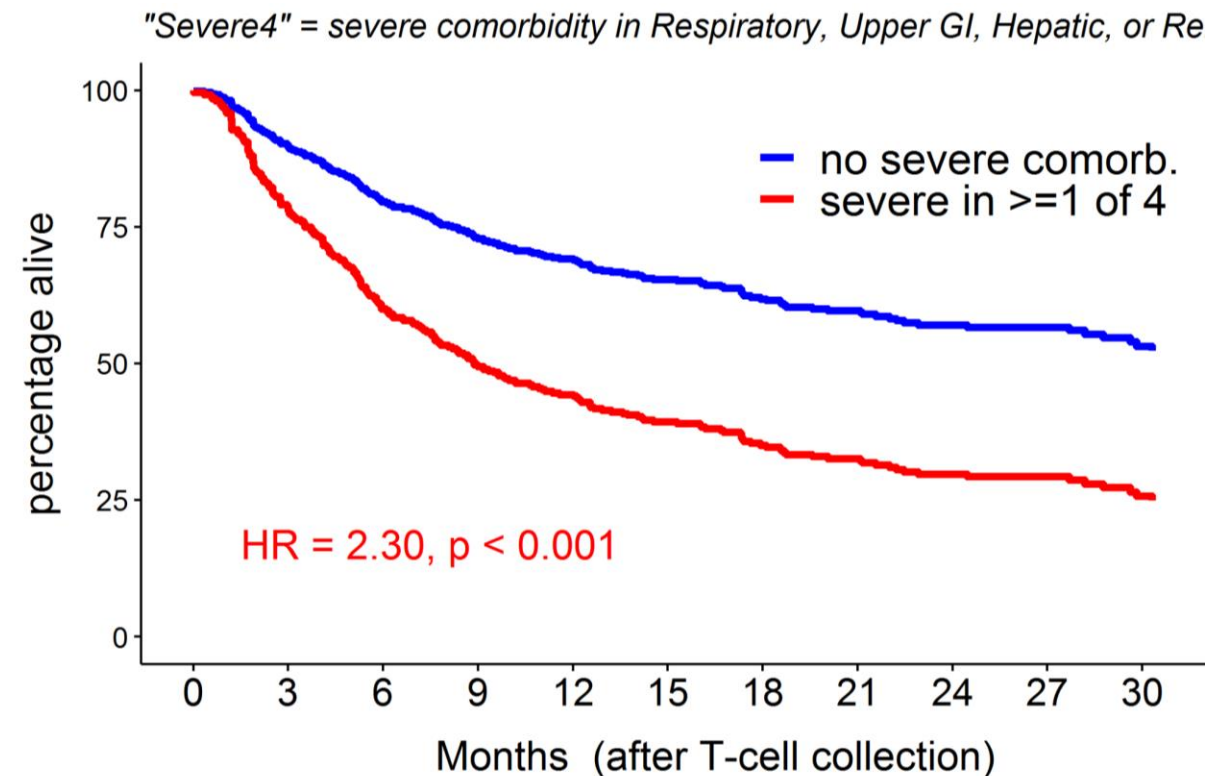
adjusting for ECOG, # of prior treatments, and molecular subtype (GCB vs. non)

PFS outcome



K-M medians: **13.0** vs **4.1** months

OS outcome



K-M medians: **NR** vs **7.8** months

Background: Function and Endurance at Baseline - COH Commercial CAR-T Patients (NHL)



n = 78	6MWT ≥ 500 ft (n = 61)	6MWT < 500 ft (n = 17)	p
LOS > 20D	13% (n = 8)	47% (n = 8)	0.02
AGE > 64 years	31% (n = 19)	89% (n = 8)	0.69
CRS	85% (n = 52)	94% (n = 16)	0.81
ICANS	41% (n = 25)	76% (n = 13)	0.08
ORR	98% (n = 41)	78% (n = 28)	0.06
30D OS	98% (n = 60)	82% (n = 14)	0.07
100D OS	96% (n = 59)	65% (n = 11)	0.002

Pilot Grant Funding: CARG – Cancer and Aging Research Grant



- **Title:** Fit for CAR T: Quantifying the impact of baseline functional impairments on chimeric antigen receptor T cell therapy (CAR T) toxicity and functional recovery in older adults with diffuse large B-cell lymphoma (DLBCL).

- **Specific Aims:**
 - **Aim 1:** To quantify the impact of baseline functional impairment as determined by the short physical performance battery (SPPB) on CAR T-mediated toxicities including cytokine release syndrome (CRS) and neurotoxicity through day 30 among older adults treated with CD19 CAR T-cell therapy for relapsed and/or refractory (r/r) DLBCL.

 - **Aim 2:** To characterize the influence of baseline functional impairment as determined by the SPPB on functional recovery by day 30 after CD19 CAR T-cell therapy in older adults with r/r DLBCL.

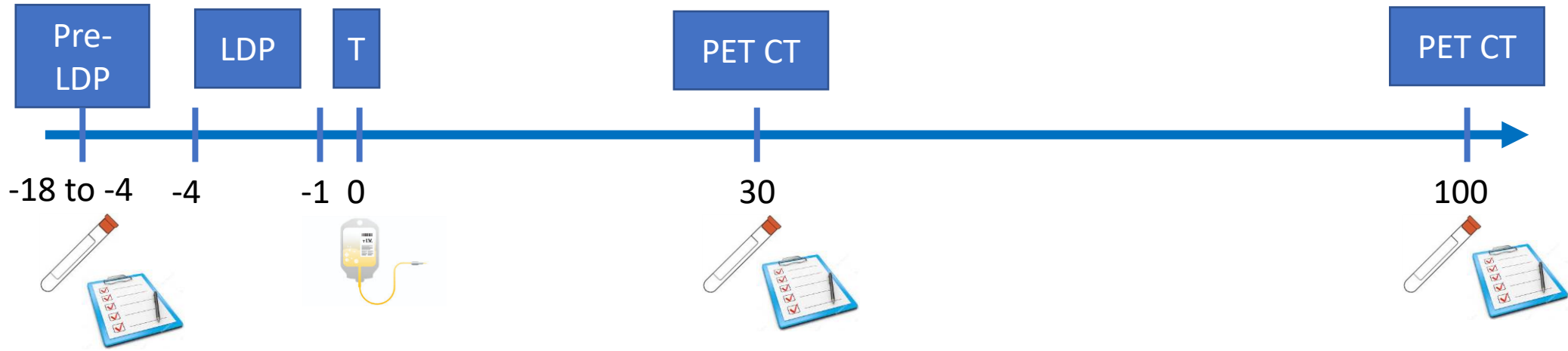
- ***Overall Hypothesis:*** Patients with baseline functional impairment will have higher rates of CAR T-mediated toxicities, and delayed functional recovery by day 30 after CD19 CAR T-cell therapy for r/r DLBCL.

Objectives ACT Now Study



- Primary Objective: Determine the trajectory of functional recovery in patients ≥ 60 years of age undergoing CAR T therapy for multiple myeloma (MM) or B-cell non-Hodgkin lymphoma (B-NHL) prior to lymphodepletion until day +30 after CAR T infusion
 - *We hypothesize that there will be objective measures of functional decline with delayed recovery after CAR T therapy*
- To quantify the impact of baseline frailty and aging-related functional impairments on CAR T-related toxicity
- Interrogate the relationship between the kinetics of immune cell subsets (T cell, NK cell, B cell) and markers of T cell activation, exhaustion and senescence, CAR T efficacy, and frailty in older adults

Schema



Aging Domain	Test
Function	SPPB, phenotypic frailty, OARS, IADL, MOS-PH
Cognition	MoCA,
SOC data	CRS, neurotoxicity, ICU, relapse, OS
QoL	PROMIS global health
PB blood	Cryopreserve plasma and cells
CAR T Product	T cell subsets/polyfunctionality index

SPPB: Short physical performance battery
 Frailty: 5 component frailty index. Weight loss, grip strength, 4 meter walk, exhaustion, activity
 IADL: instrumental activities of daily living
 MOS-PH Medical outcomes study physical health survey
 MOCA: Montreal Orientation Memory concentration

Sample Size



- **Primary Endpoint:** Change from baseline to day +30 of the Short Physical Performance Battery (0-12)
 - Change score of 1 – 1.5 is considered substantial
- Assume 43 subjects enrolled per arm (B-NHL and MM) with 10% not proceeding to CAR T, leaves 39
- 80% power for a change score of 1.25 between the two time points at a two sided alpha of 0.05

Correlative Studies



- Evaluate quality of life using the PROMIS Global Health Scale at baseline (before lymphodepletion), and days +30 and +100 after CAR T cell infusion.
- Measure immunologic parameters, including T cell exhaustion, senescence and CD8 T cell cytotoxic function among older myeloma/ B-NHL patients undergoing commercial CAR T therapy.
- Correlate the immunological profile with functional assessment in older patients undergoing CAR T therapy
- Correlate the immunological profile obtained at baseline (before lymphodepletion) with the heterogeneity of the CAR T cell infusion product
- Evaluate the ability of the treating physician and the patient to predict how likely the patient is to functionally recover by SPPB by day +30 after CAR T infusion, using a single question survey and the LIKERT scale



Rising Tide Hematology Project

GERIATRIC ASSESSMENT (GA) GUIDED INTERVENTION TO ACCELERATE FUNCTIONAL RECOVERY AFTER CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY FOR LYMPHOMA AND MYELOMA IN PATIENTS 60+ YEARS THROUGH THE CANCER AND AGING RESEARCH GROUP (CARG) CONSORTIUM

A. ARTZ¹, A. ROSKO², H. KLEPIN³

Barriers



- Buy-in from cellular therapy

Current Status



- Protocol is finalized
- Informed consent form is nearly completed
 - Adding in appendix of surveys
- IRB submission to follow shortly
- Next steps:
 - Consenting patients, collecting data, collecting and processing samples

Updates on Funding



- CARinG Pilot Grant



- Generous endowment from



Questions?

