MSK Kids
Memorial Sloan Kettering

Durable Remission following "Off-the-Shelf" CAR T cells in Patients with Relapse/Refractory B-cell Malignancies

(NCT - 01430390)

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Disclosure Information

Kevin J. Curran, MD

I have the following financial relationships to disclose:

Research Support: Juno Therapeutics, Novartis

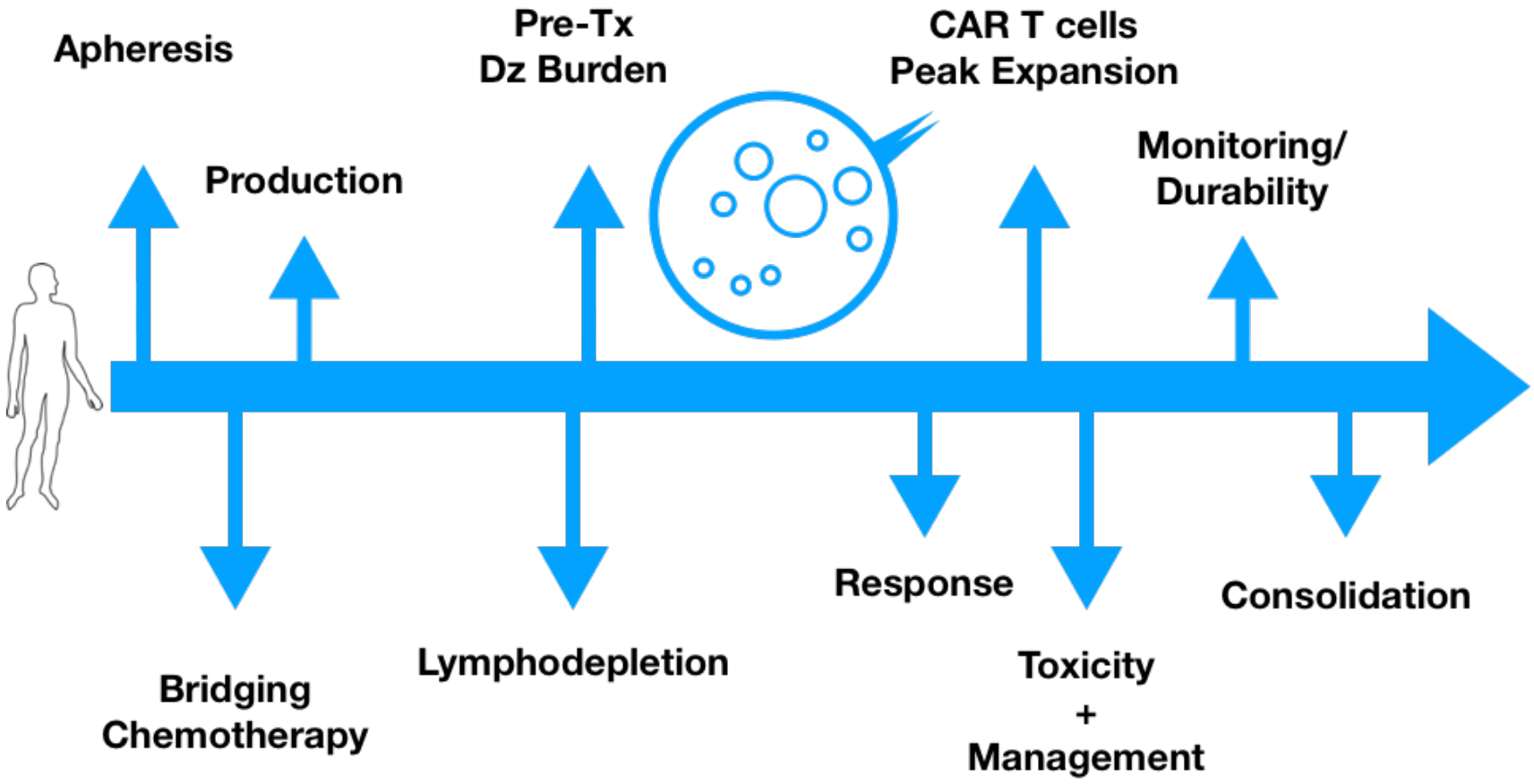
Consultant for: Novartis, Juno Therapeutics, Mesoblasts

I will discuss the following off label use and/or investigational use in my presentation:

CD19-specific CAR T cells

EBV-specific cytotoxic lymphocytes (EBV-CTLs)

CAR T cell – Points of Interest



CD19-specific CAR T cell + B-ALL Response

	No. Pts Tx	CR/CRi (MRD%)	sCRS	sICANS	Allo-HSCT	Relapse
MSK – 1928z[1]	25	75% (89%)	16%	28%	83%	22%
Tisa – 19-BBz[2]	75	81% (100%)	≈47%	13%	13%	33%
CTL019 – 19BBz[3]	30	90% (85%)	27%	NR	11%	26%
PLAT2-19-BBz[4]	43	93% (100%)	23%	21%	26%	45%
NCI- 19-28z[5]	20	70% (60%)	29%	5%	50%	10%
Adult Patients Only						
MSK – 1928z[6]	53	83% (≈ 67%)	26%	43%	39%	57%
JCAR17-19BBz[7]	30	100% (97%)	23%	50%	43%	30%
MEDIAN		**83%**	**26%**	**24.5%.**	**39%**	**30%**

[1]Curran et. al *Blood* 2019; [2]Maude et. al. NEJM 2018; [3]Maude et. al. NEJM 2014; [4]Gardner et. al. Blood 2017; [5]Lee et. al. Lancet 2014; [6]Park et.al. NEJM 2018 [7]Turtle et. al. JCI 2016

CAR T cell – Room for Improvement

- Complex Manufacturing

- Production Failure
  - Absolute Failure
  - Out-of-Specification (OOS) Products

- Need for Bridging Therapy
  - Low Intensity vs High Intensity

- Toxicity
  - sCRS/sICANS

Off-the-Shelf CAR T cells

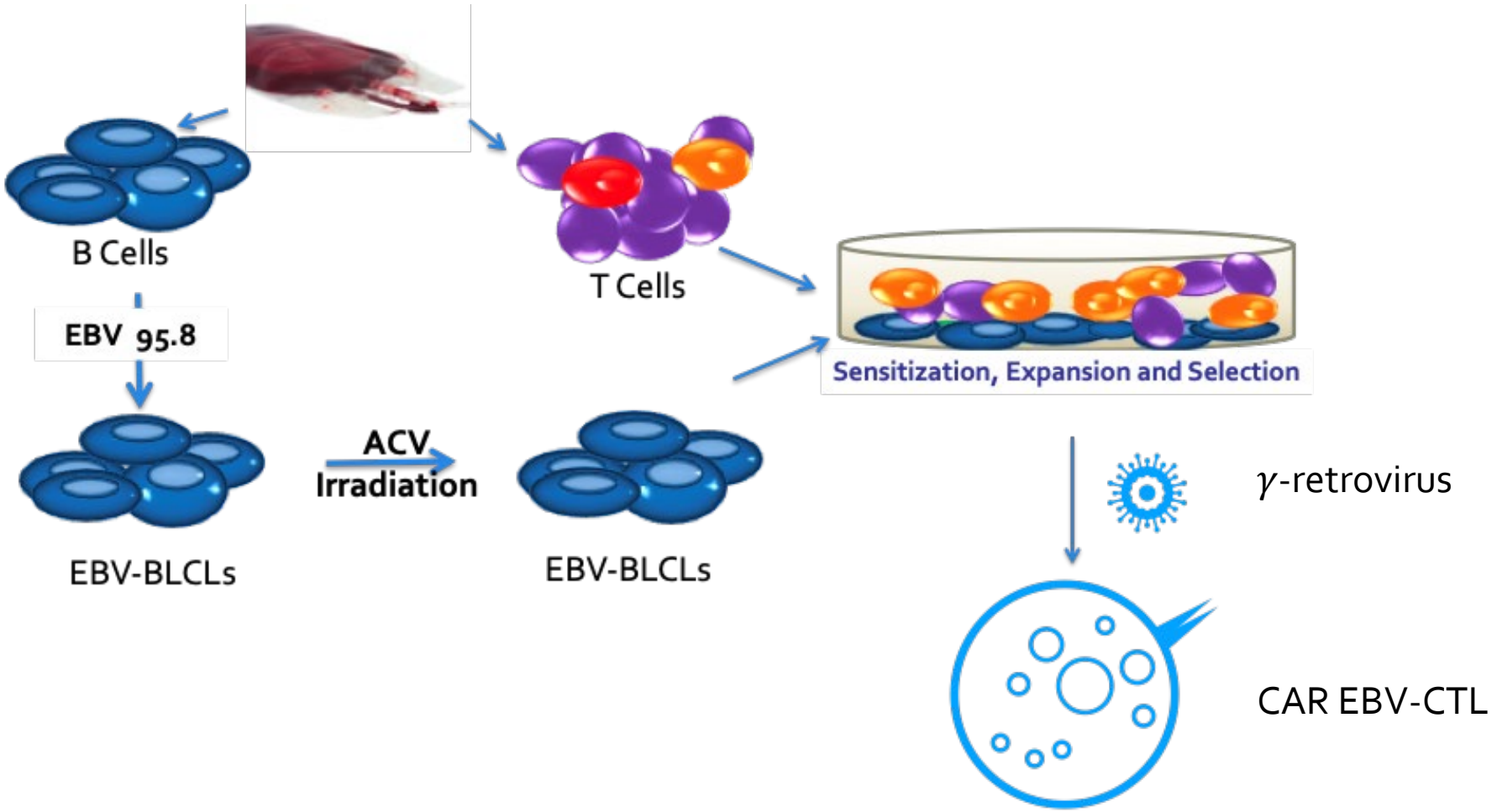
- Advantages
  - Logistics – no collection/production
  - Cost decreased - multiple patients
  - Quality of T cells – healthy donors

- Challenges
  - GVHD
  - HLA compatibility/rejection

- Solution:

Donor EBV-CTLs + CAR = CAR EBV-CTL

CAR EBV-CTL Generation

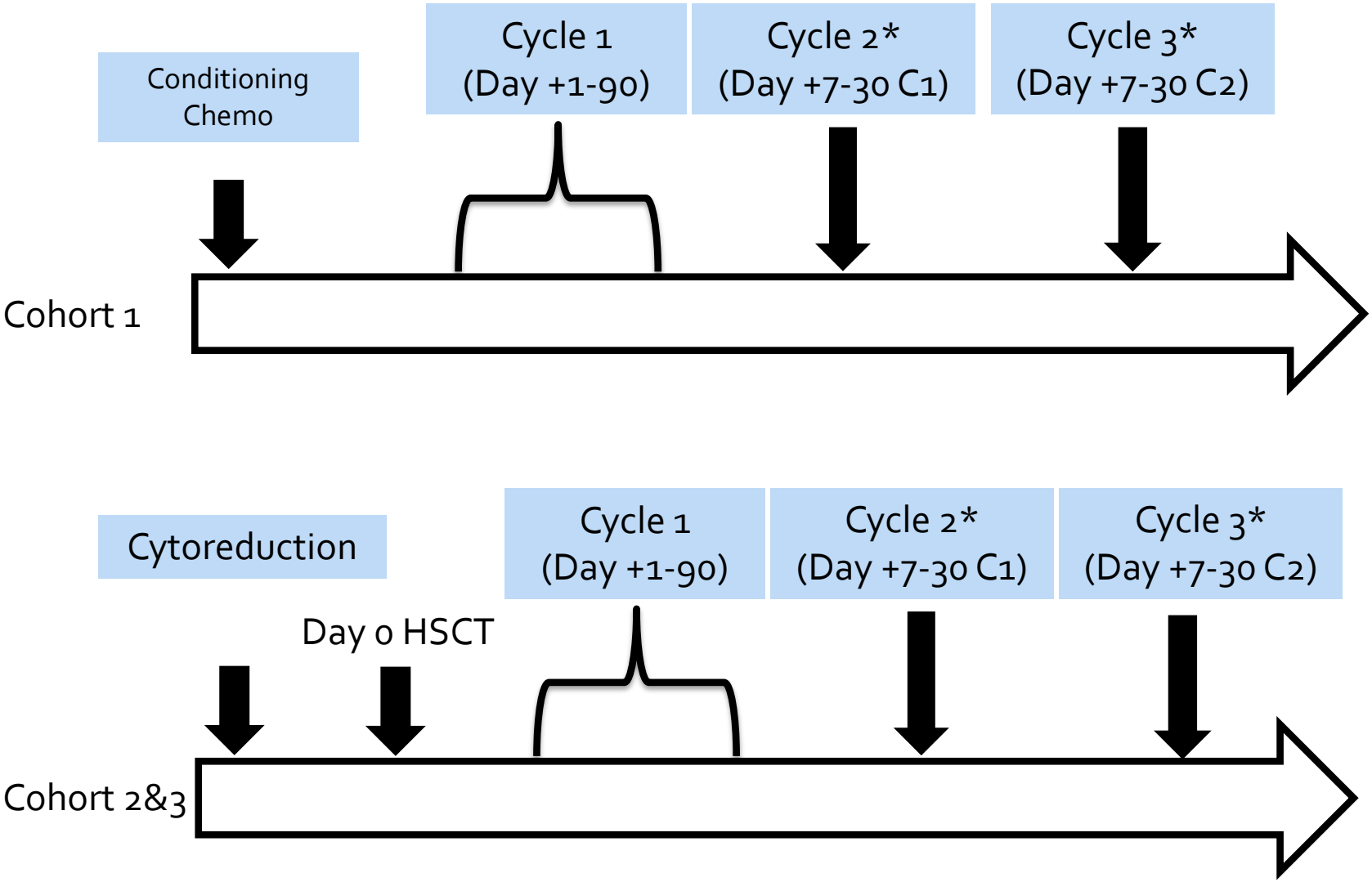


CAR EBV-CTL – Eligibility/Study Design NCT01430390

- Eligibility
  - Relapse/Refractory B-cell Malignancies
  - No Age restriction
  - HLA Compatible Line Available (Minimum 2/10 Match)
    - Initial Design: Dose escalation (EBV-CTL/kg)
    - Final Design: fixed dose ($3x10^6$ EBV-CTL/kg) + multiple doses

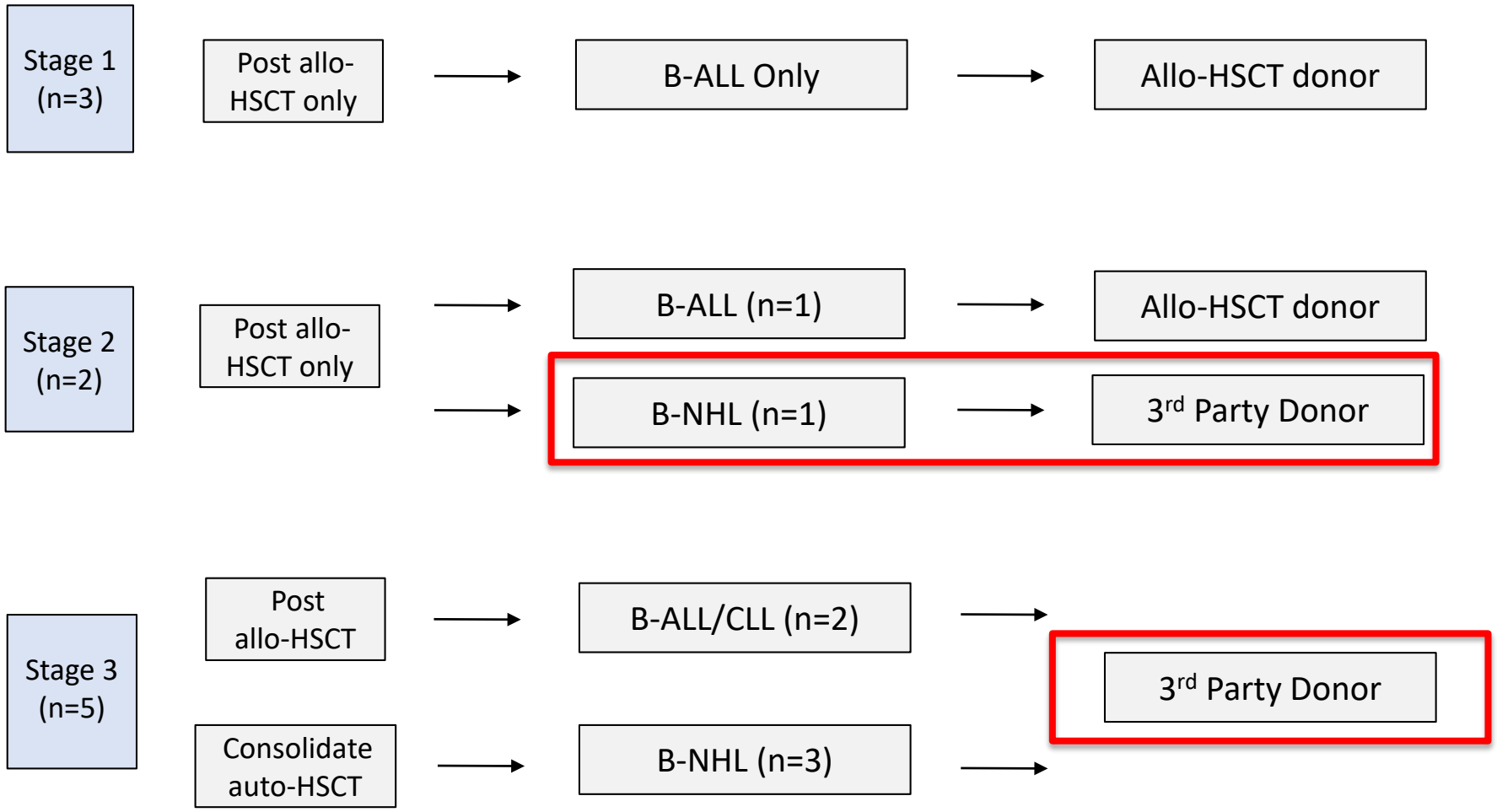
- Cohorts
  - Cohort 1 - R/R B-cell malignancy following allo-HSCT
  - Cohort 2 - R/R B-cell malignancy eligible for auto-HSCT
    - CAR-EBV consolidation
  - Cohort 3 - R/R B-cell malignancy eligible for allo-HSCT
    - CAR-EBV consolidation

Trial Schema



*recommend interval is 14 days between cycles

Trial Stages



Overall Trial Characteristics

Characteristic	
Age	14.7 (1.3-70.5)
Disease	
B-ALL	5 (50%)
NHL	4 (40%)
CLL	1 (10%)
Cohort	
One: Relapse post HSCT	7 (70%)
Two: With auto-HSCT	3 (30%)
Patient EBV seropositive	8 (80%)
Allo-HSCT donor	4 (40%)
3rd Party	6 (60%)
HLA Matching	
10/10	3 (30%) } Allo-HSCT donors
6/10	2 (20%) } Allo-HSCT donors
5/10	1 (10%) } 3rd Party
4/10	2 (20%) } 3rd Party
2/10	2 (20%) } 3rd Party

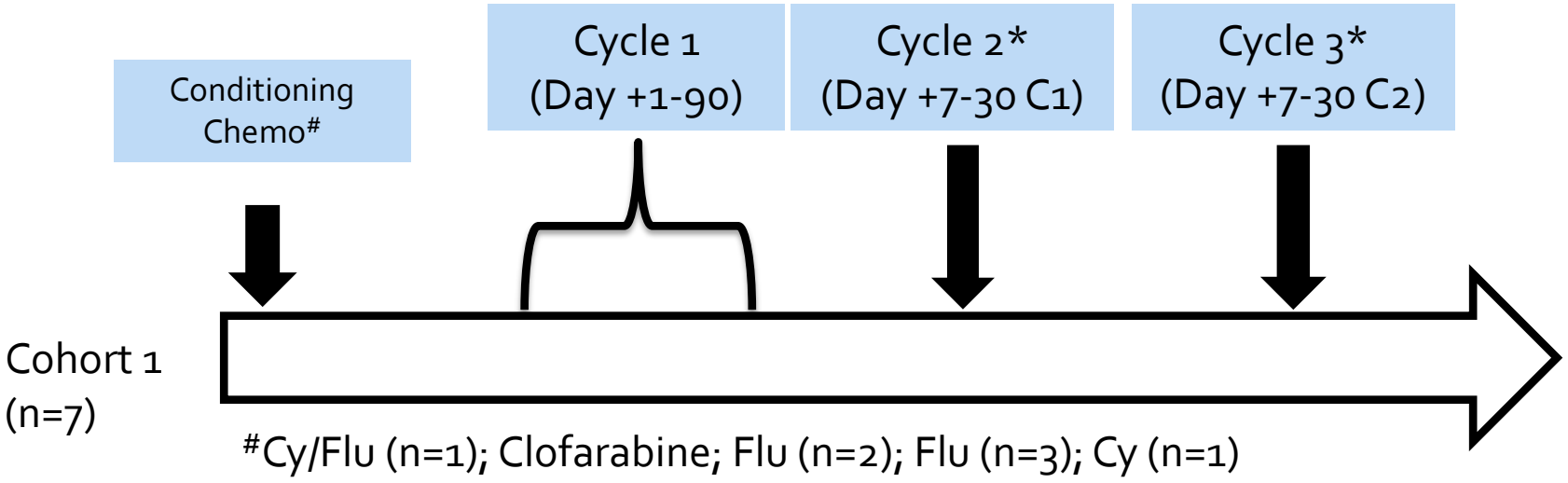
Overall Trial Characteristics

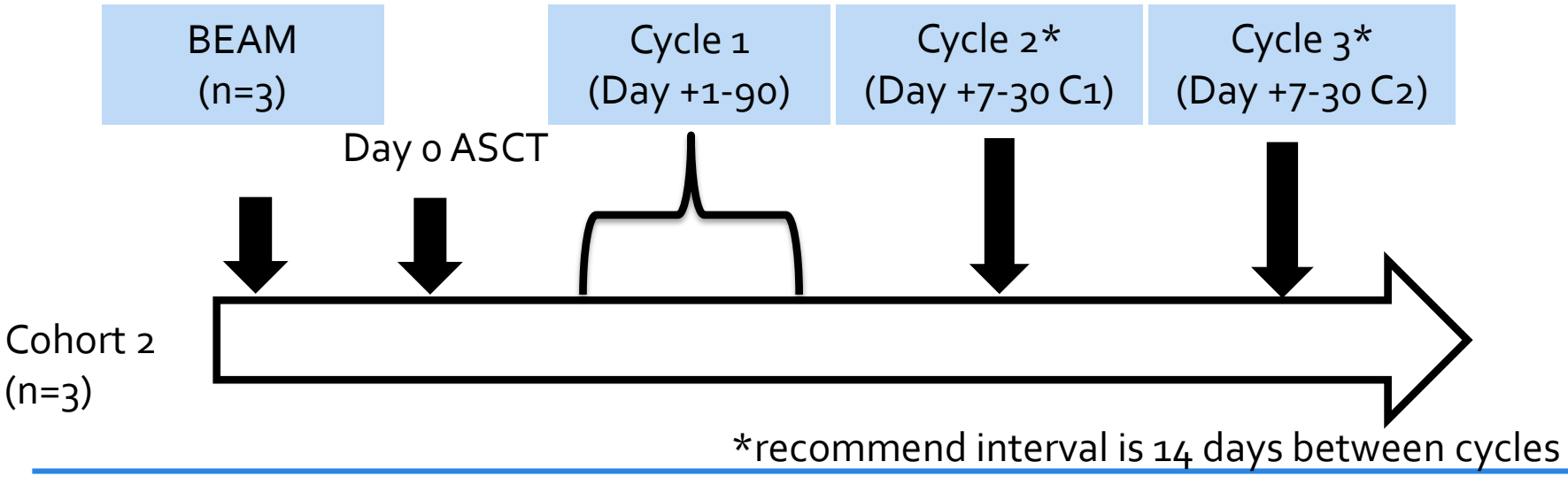
Characteristic	
Median (range) T cell dose infused	$2.2x10^6$ (0.6 – 7.5 $x10^6$)
Median (range) CAR T cell dose	$0.4x10^6$ (0.05 – 1.2 $x10^6$)
Median (range) CAR T cell transduction	20.5% (7.4-41%)
No. Patients Receiving >1 infusion Cohort 1 Cohort 2 B-ALL NHL CLL AlloHSCT Donor 3rd Party Donor	6 (median 2; range 1-3) 67% (4/6) 66% (2/3) 60% (3/5) 75% (3/4) 100% (1/1) 50% (2/4) 67% (4/6)

Cohort 1, 2, 3rd Party

Characteristic	Cohort 1 (n=7)	Cohort 2 (n=3)	3rd Party (n=6)
Age	12.8 (1.3 - 67.9)	21.9 (17.5 – 70.5)	19.7 (1.3 - 70.5)
Disease B-ALL NHL CLL	 5 (71%) 1 (14%) 1 (14%)	 0 (0%) 3 (100%) 0 (0%)	 1 (17%) 1 (17%) 4 (67%)
Cohort One: Relapse post HSCT Two: With auto-HSCT	 7 (100%) 0 (0%)	 0 (0%) 3 (100%)	 3 (50%) 3 (50%)
T cell dose	$0.9x10^6$ ($0.6 – 7.5 x10^6$)	$2.7x10^6$ ($2.4 – 3.22 x10^6$)	$2.9x10^6$ ($0.6 – 7.5 x10^6$)
CAR T cell dose	$0.25x10^6$ ($0.05 – 1.2 x10^6$)	$0.6x10^6$ ($0.4 – 1.2 x10^6$)	$0.7x10^6$ ($0.05 – 1.2 x10^6$)
Patient EBV seropositive	100% (7/7)	33% (1/3)	67% (4/6)
HLA Matching 10/10 6/10 5/10 4/10 2/10	 3 (43%) 1 (14%) 0 (0%) 2 (28%) 1 (14%)	 0 (0%) 1 (33%) 1 (13%) 0 (0%) 1 (33%)	 0 (0%) 1 (17%) 1 (17%) 2 (34%) 2 (34%)

Trial Schema - Conditioning Chemotherapy





*recommend interval is 14 days between cycles

Cohort 1, 2, 3rd Party

Characteristic	Cohort 1 (n=7)	Cohort 2 (n=3)	3rd Party (n=6)
Toxicity	Skin GVHD (Gr 1) (n=1)	Skin GVHD (Gr 1) (n=1)	Skin GVHD (Gr 1) (n=1)
	CRS Grade 1 (n=1)	Pneumonitis/Hypoxia (n=1)	Pneumonitis/Hypoxia (n=1)
			CRS Grade 1 (n=1)
Response*	57% (4/7)	100% (3/3)	83% (5/6)
Response by Disease B-ALL NHL CLL	 40% (2/5) 100% (1/1) 100% (1/1)	 0 (0%) 100% (3/3) 0 (0%)	 0% (0/1) 100% (4/4) 100% (1/1)

No sCRS or sICANS

Response*
B-ALL/CLL – Day 28 BMA
NHL – 3m PET/CT

Pre-Treatment Disease Burden/Response

- B-ALL
  - BMA prior to pre-conditioning chemotherapy/CAR EBV-CTLs
  - 4/5 patients with +morphologic disease
    - 1 patient with NED (extramedullary disease)
  - 2 patients with Day 28 (CR/MRD-neg)
    - 1 relapse
    - 1 remains alive and well

Pre-Treatment Disease Burden/Response

- NHL
  - PET/CT prior to AutoHSCT (n=3)
    - Deauville 4 (n=3)

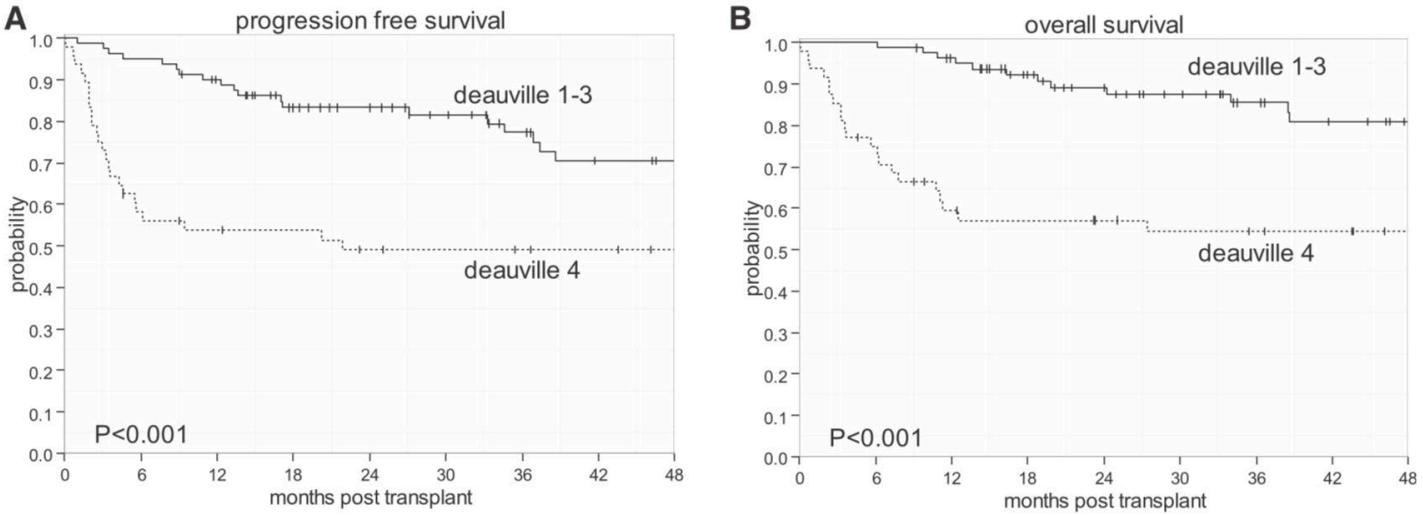
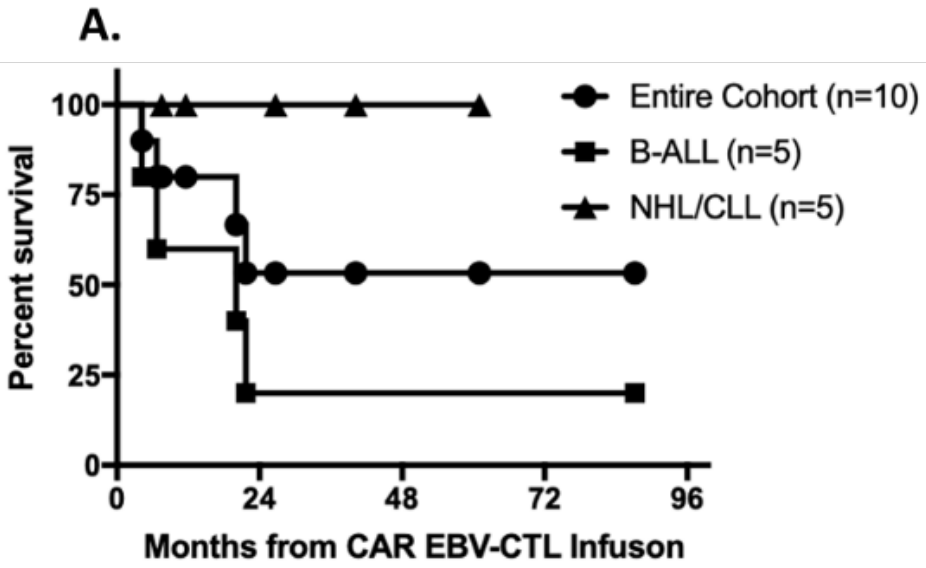


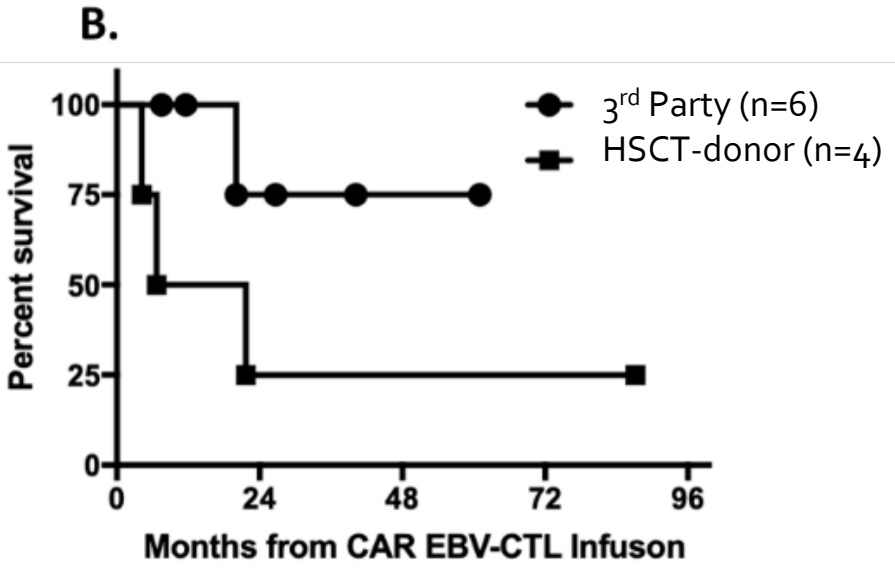
Figure 1. Kaplan-Meier survival estimates based on Deauville responses to ST. (A) PFS. (B) OS.

  - One patient (relapse Burkitt 18 days post Allo-HSCT)
    - Clofarabine x 5 days - PET/CT - NED
    - Fludarabine + 3rd Party CAR EBV-CTL

Sauter et. al. Blood 2015

Overall Survival





NHL median follow up: 33.9m (13-80.1m)
3rd Party median follow up: 26.9m (13-80.1m)

Conclusions/Study Limitations

Conclusions

- Favorable Toxicity Profile (no sCRS/sICANS)
- 3rd Party/Off-the-Shelf CAR EBV-CTL
  - Safe
  - Feasible
- Overall Survival in NHL patients (n=4) favorable

Limitations

- Conditioning Chemotherapy (Cohort 1) – not standardized
- Pre-Treatment Disease Assessment (Cohort 2) – no PET/CT prior to CAR Therapy
- Small sample size

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