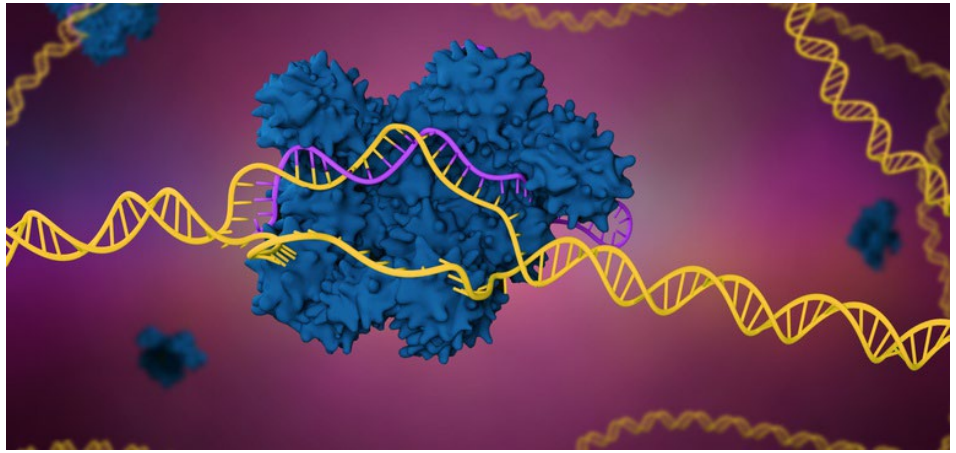
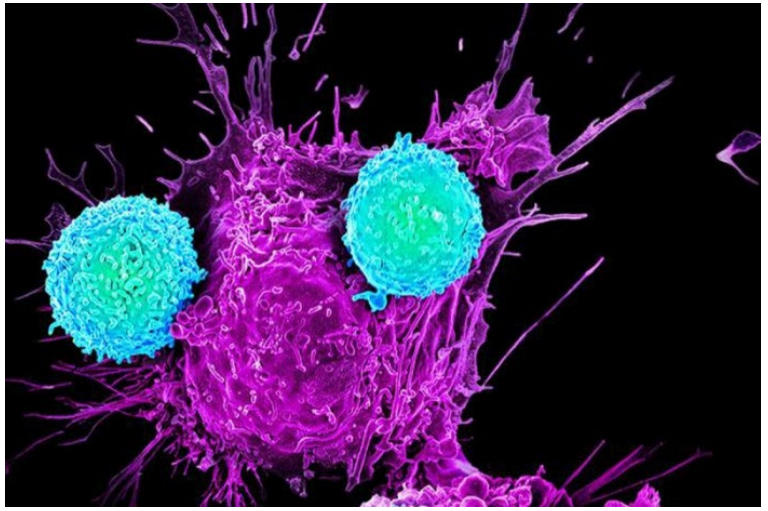
HCT & CAR T-Cell Therapy
The emerging field of
“Interventional Cellular Immunology”





Richard Maziarz MD

Director, Adult BMT & Immune Effector Cell Therapy Programs

March 3, 2023

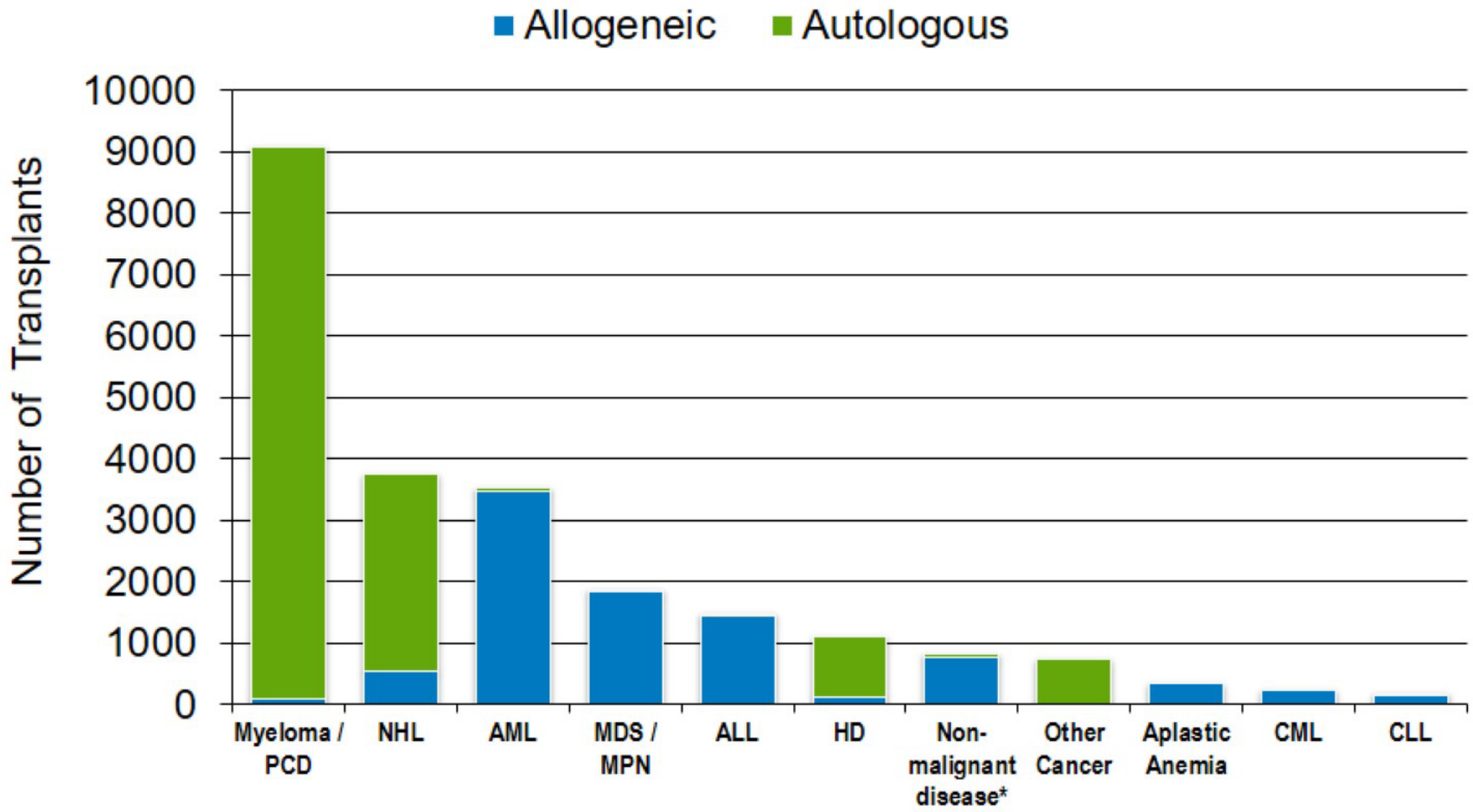
Disclosures

- Research Funding: Novartis, BMS, Allovir
- Consultancy: Novartis, Artiva Bio, Orca, Kite
- DSMB: Novartis, Vor Pharma, Athersys, Century Rx
- Patents & Royalties: Athersys, Springer Publishers

Overview

- Introduction
- Advances in Transplantation
- Advances in CAR T-cell therapy
- New frontiers: cell therapy for solid tumors & other indications

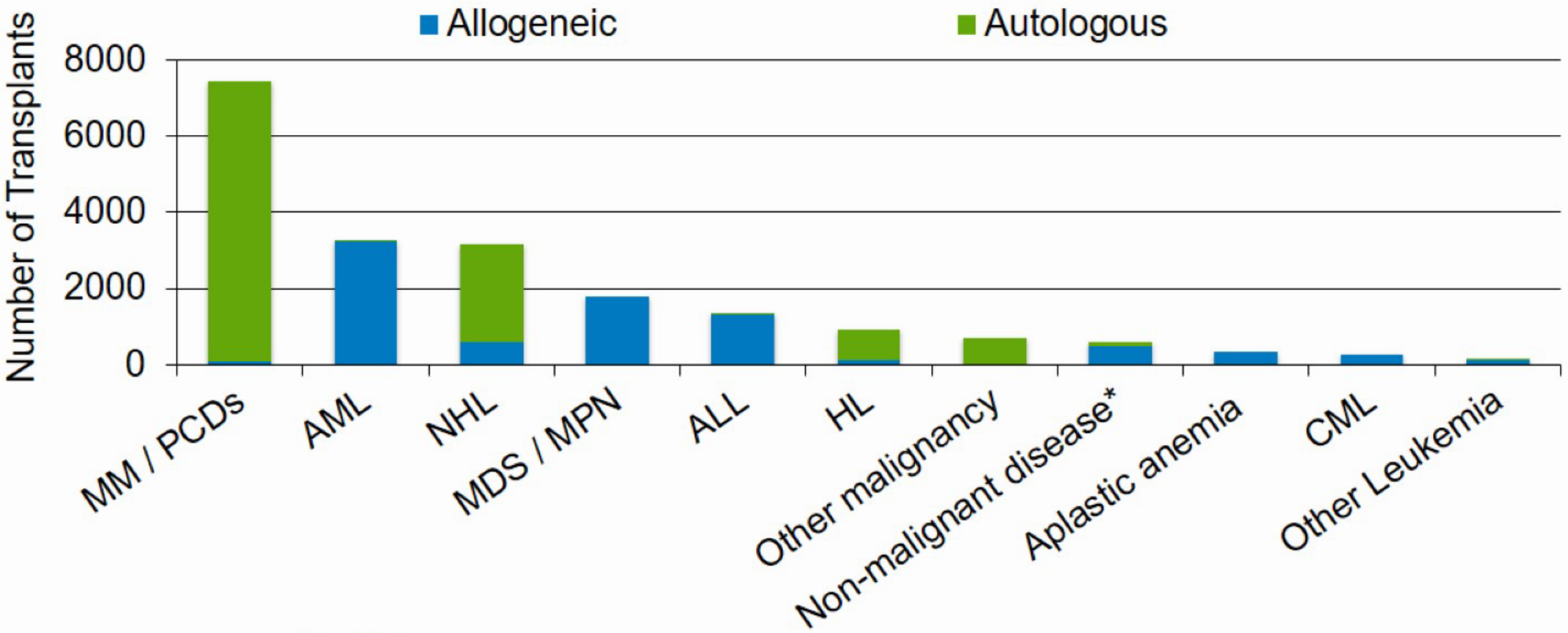
Indications for Hematopoietic Cell Transplant in the US, 2018



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

*excludes aplastic anemia.

Number of HCTs by Indications in the US, 2020

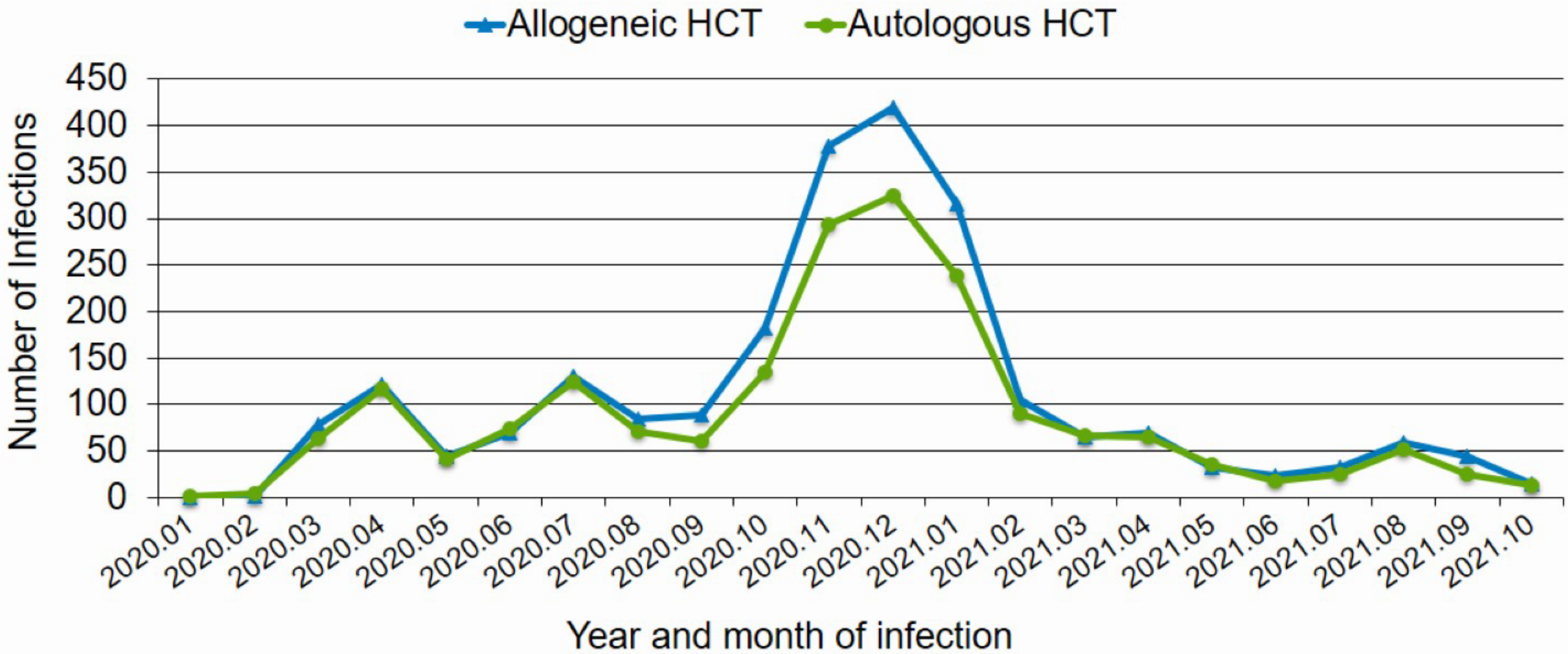


Abbreviations –
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
AML: Acute myelogenous leukemia;
NHL: Non-Hodgkin lymphoma;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
ALL: Acute lymphoblastic leukemia;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia

*excludes Aplastic anemia

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Number of COVID-19 Infections in HCT Recipients in the US Reported to CIBMTR by Transplant Type

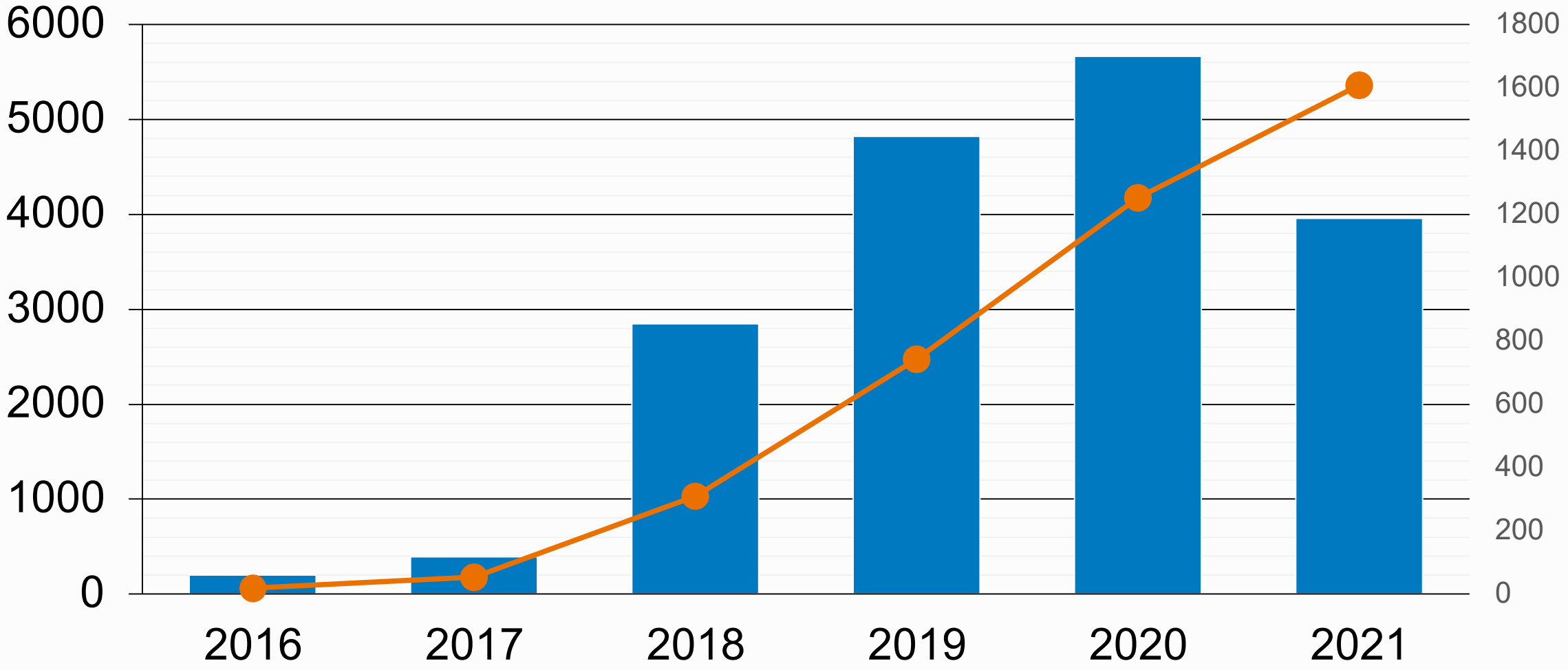


CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Data as of 12/01/2021; data may not complete for October due to data reporting lag

Number of CAR T cell infusions: 2016-2021 (5,364 patients and 5,625 infusions)

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

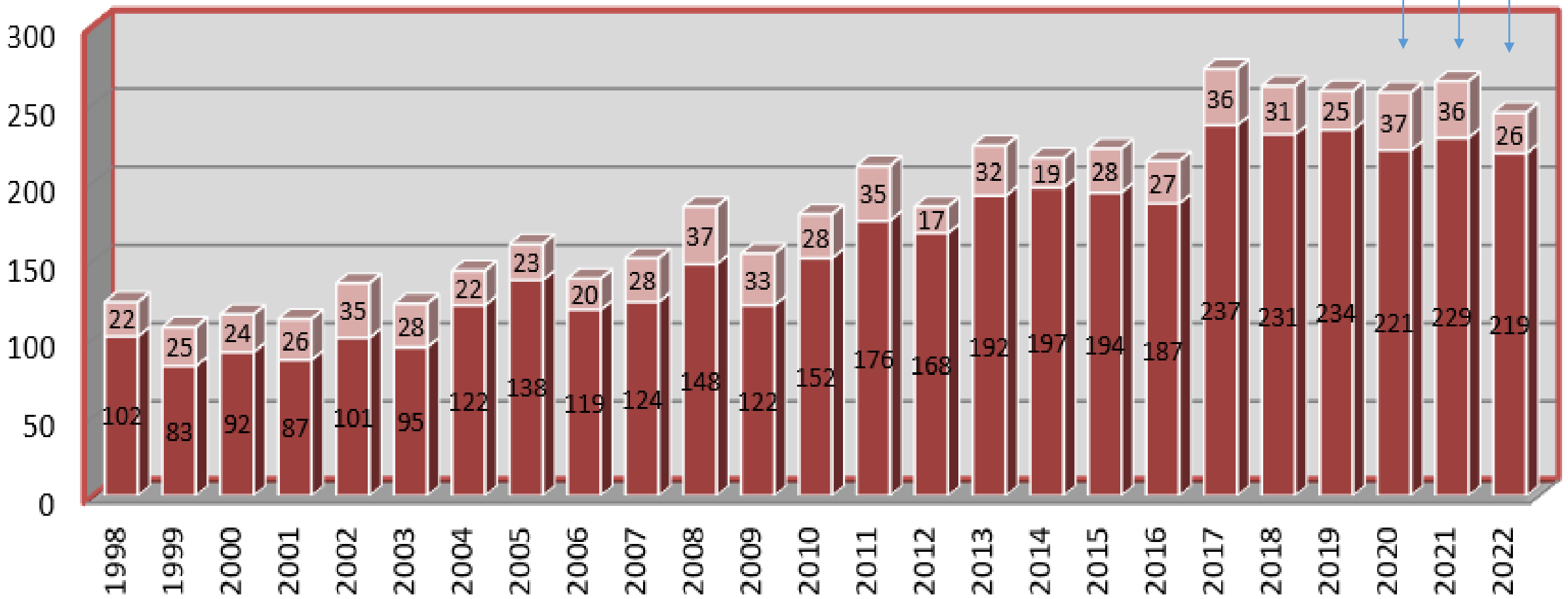


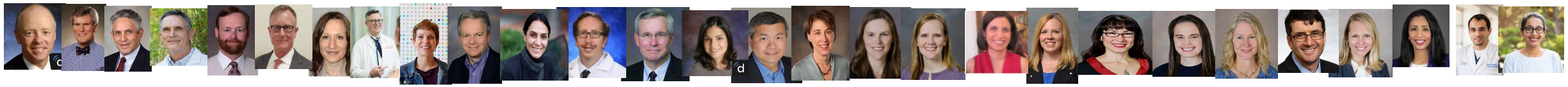
CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Cumulative

Data Incomplete for 2020 & 2021

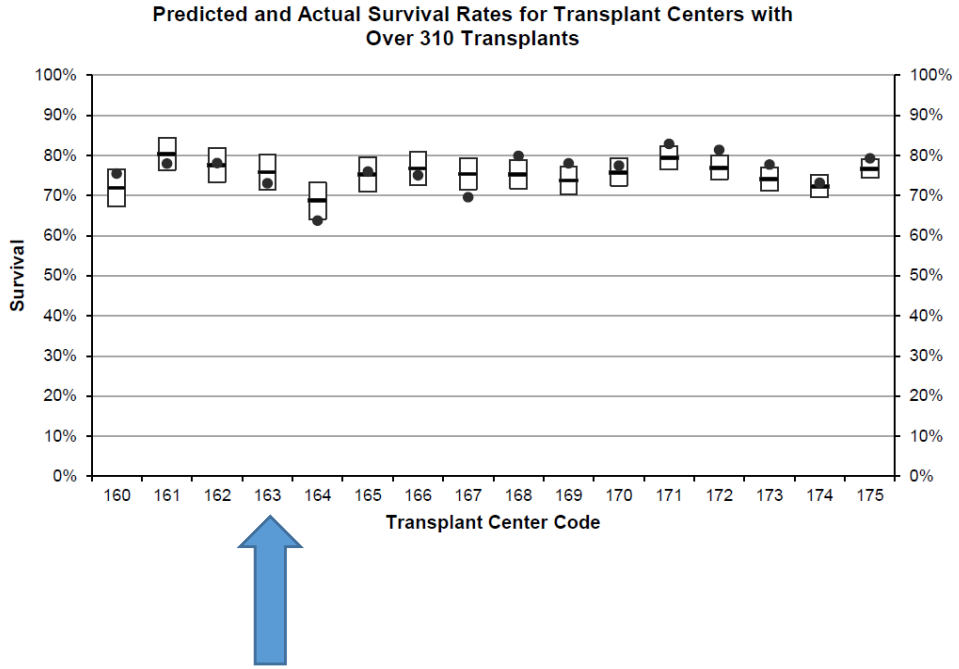
OHSU HCT Volumes





OHSU Adult HCT & CAR T activity

2018:	233	17
2019:	234	18
2020:	216	27
2021:	230	43
2022:	236	68
2023 Ann	*240*	*84 (prob > 90)*

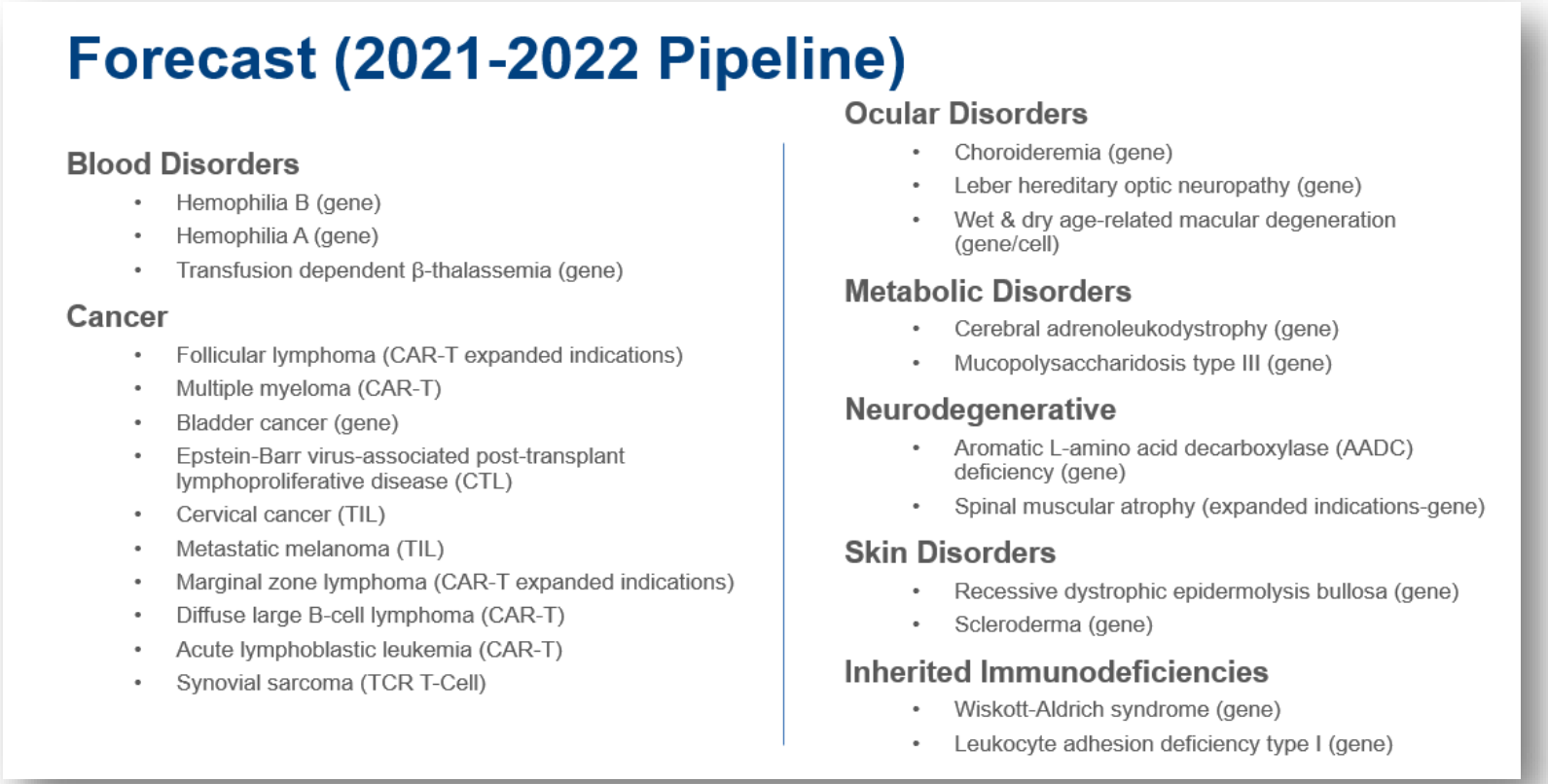


Transplant Center Code	Center Name
160	Froedtert & Medical College of Wisconsin
161	Baylor College of Medicine
162	The University of Michigan
163	University of Kansas
164	Barnes Jewish Hospital
165	Abramson Cancer Center University - Pennsylvania Medical Center
166	Oregon Health and Science University
167	Hackensack University Medical Center
168	Memorial Sloan Kettering Cancer Center - Adults
169	Moffitt Cancer Center
170	Stanford University Medical Center
171	The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
172	Fred Hutchinson Cancer Center
173	Dana-Farber Brigham Cancer Center
174	MD Anderson Cancer Center
175	City of Hope National Medical Center

Solid line indicates predicted survival and box indicates 95% confidence interval. Dot indicates a center's actual survival; a dot below (above) the box indicates an under (over)-performing center relative to the network.

Prediction: cell and gene landscape rapid growth

- Fewer than 10 cell and gene therapies currently approved and in use, but with another **10+ expected annually in 2021 and beyond**
- 1,000+ clinical trials for cell and gene therapies underway in the U.S. (asgct.careboxhealth.com)
- 24+ conditions on the near-term pipeline and constantly changing
- Number of manufacturers in cell and gene therapy market growing exponentially including big players
- Constantly shifting market; Not all cancer



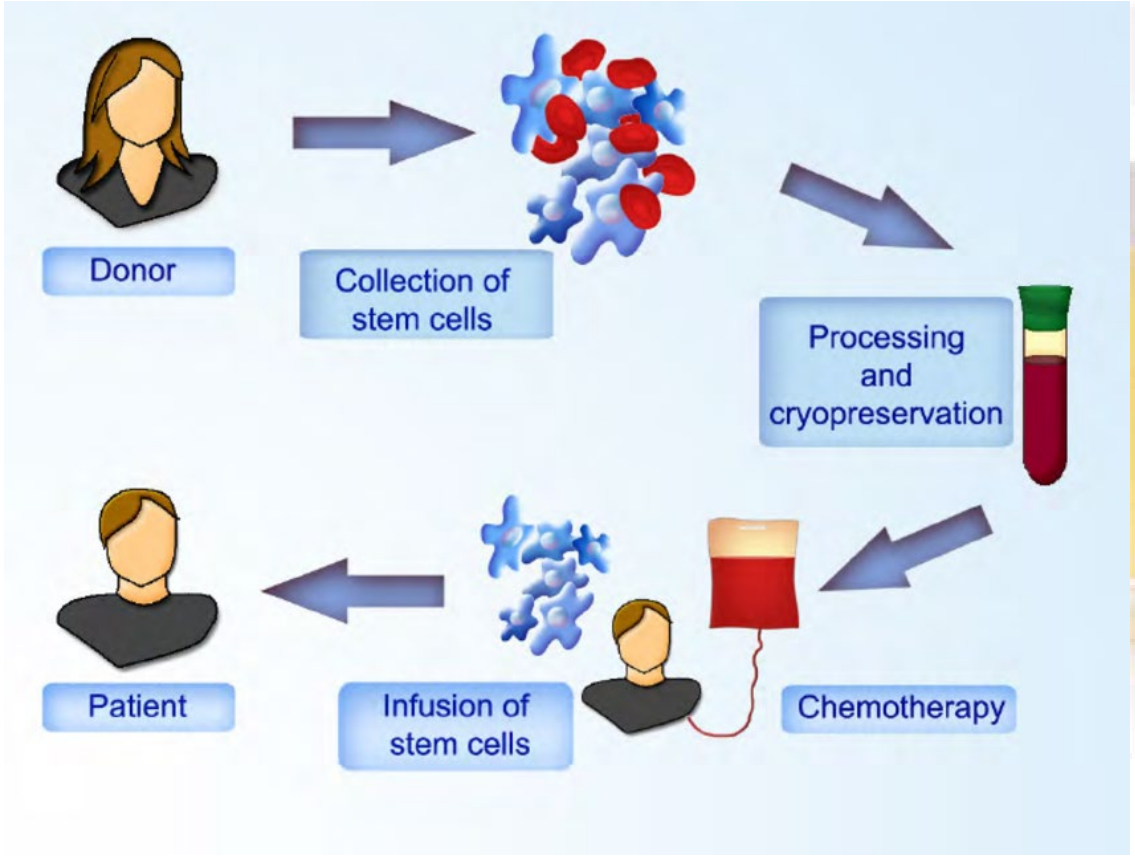
Translate this to the US Population

In 2022, US could see these annualized numbers of patients (or higher) in need of services:

Category	Patients / 50 Million Lives*
Organ Transplant	4,850
Bone Marrow Transplant	3,400
Leukemia / Lymphoma (CAR-T)	23,000
Spinal Muscular Atrophy (SMA)	120
Multiple Myeloma	3,300
Hemophilia A	4,000
Bladder Cancer	13,700
Total	52,370

*US population currently estimated at 333 million

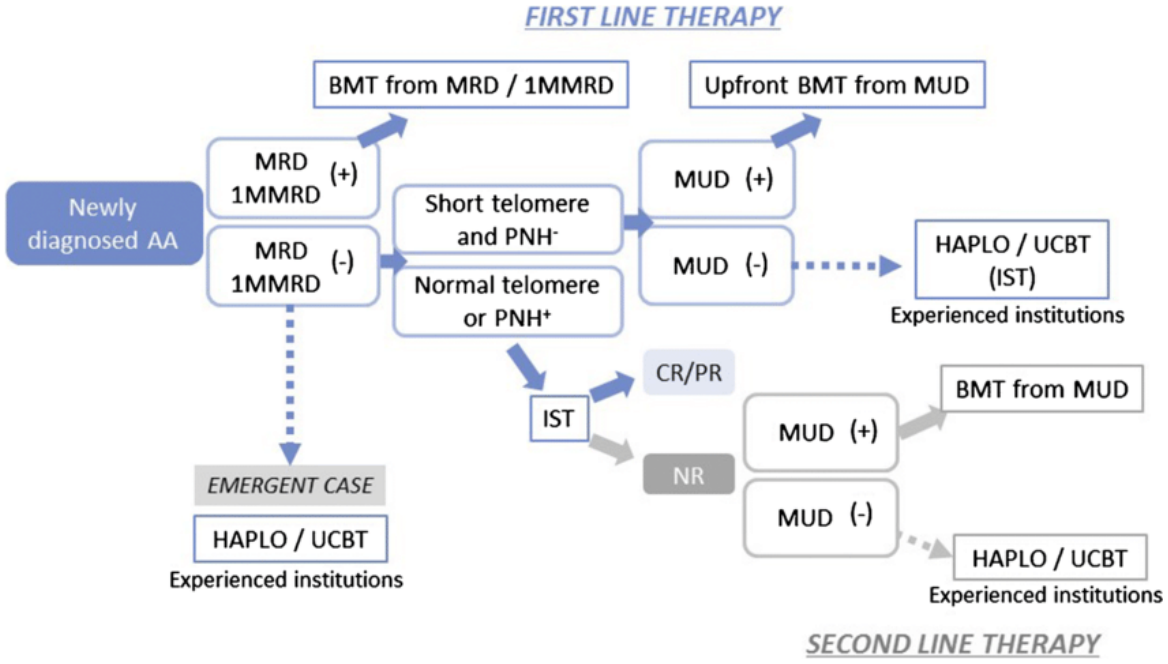
Hematopoietic Cell Transplantation

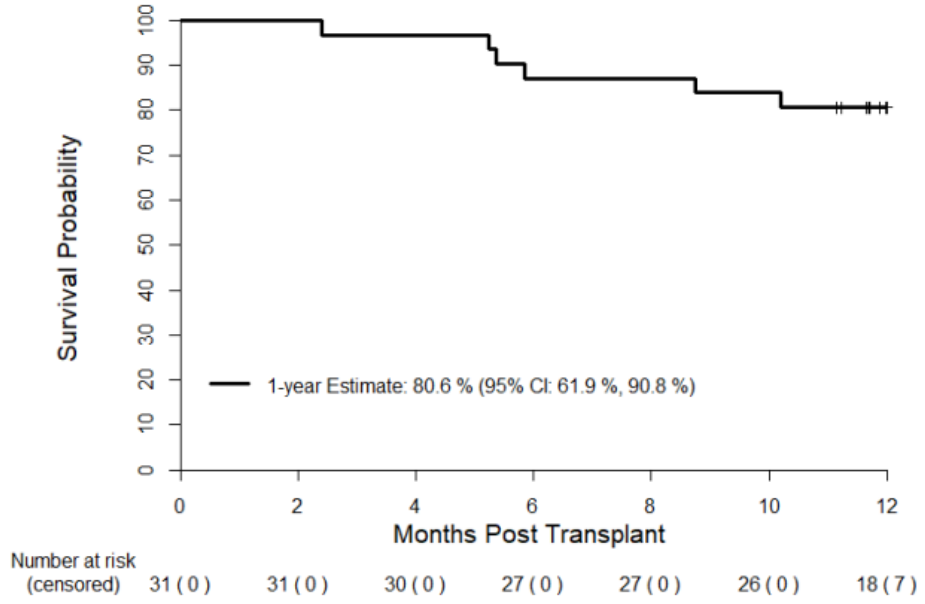


NOT either/or……but both Rx and Cells

Non-malignant diseases taking center stage

- Aplastic anemia- earlier application for children & older individual option
- Immune deficiency- Vexas
- Hemoglobinopathies

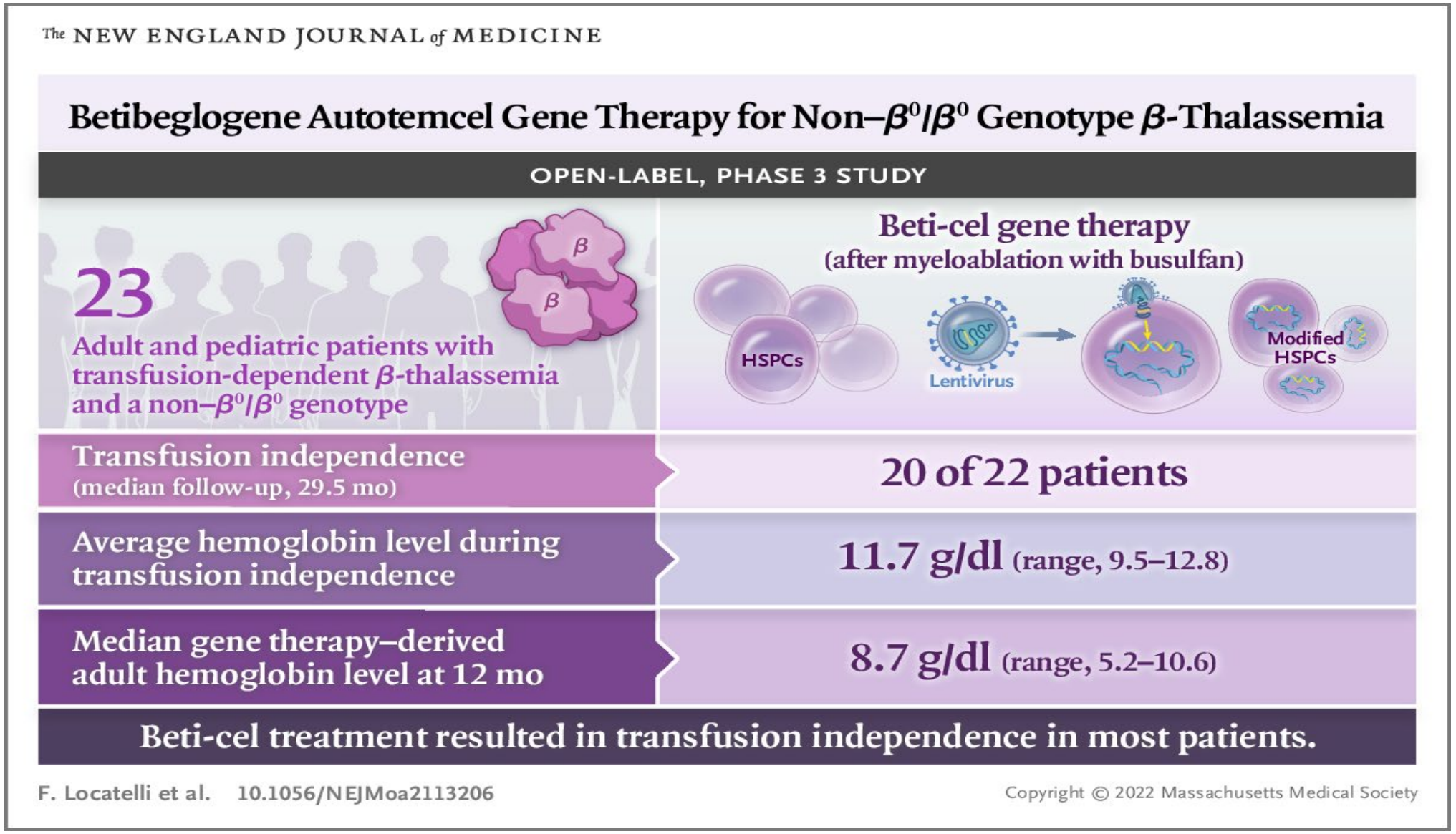




URD HCT as upfront pediatric therapy

DeZern, 2022: HaploID Allo HCT:eligible up to age 75

Autologous HCT and gene therapy



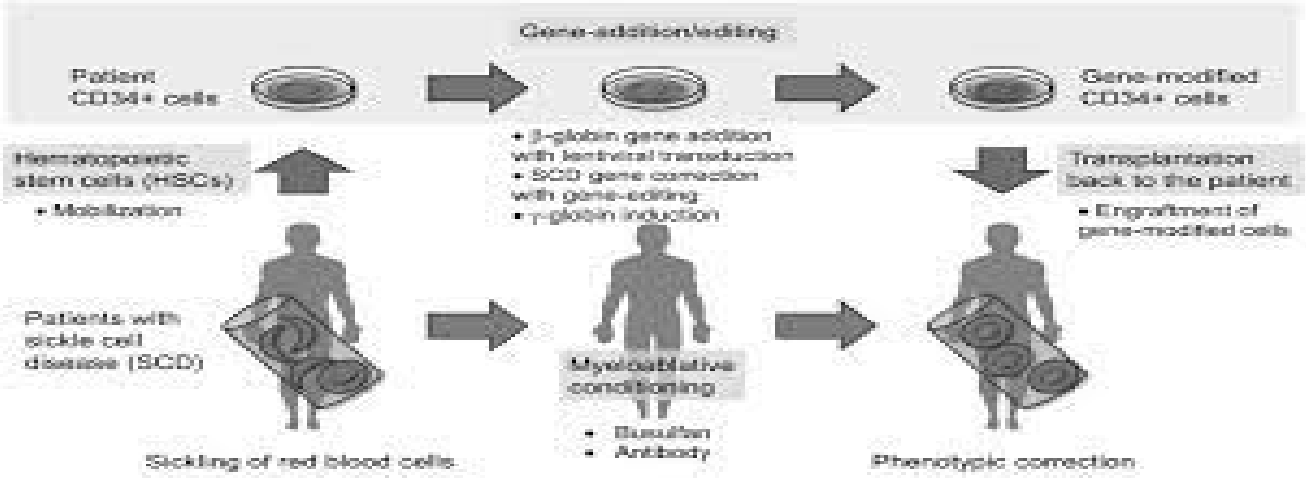
FDA Approves First Cell-Based Gene Therapy to Treat Adult and Pediatric Patients with Beta-thalassemia Who Require Regular Blood Transfusions: August 17, 2022

Zynteglo is a one-time gene therapy product administered single dose. Each dose of Zynteglo → customized treatment created using the pt's own bone marrow stem cells, genetically modified to produce functional beta-globin

Zynteglo is cleared for transfusion-dependent beta thalassemia, but will come with cost of $2.8 million per patient.

Gene Therapy is here to stay
Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease,
Walters et al, ASH, 2022

- Lovo-cel (bb1111; LentiGlobin for sickle cell disease [SCD]) gene therapy (GT) uses auto HCT of HSPC transduced with the BB305 lentiviral vector, coding for modified β-globin gene, →sickling hemoglobin (Hb), HbA^{T87Q}
- Eligiblity: SS pts, aged 12- 50, recurrent vaso-occlusive episodes
- Results- 35 pts highlighted (Gr C), med f/u 20.9 mos



Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al, ASH 2022

Figure 1A. Total Hb and Fractions in Group C of the HGB-206 Study

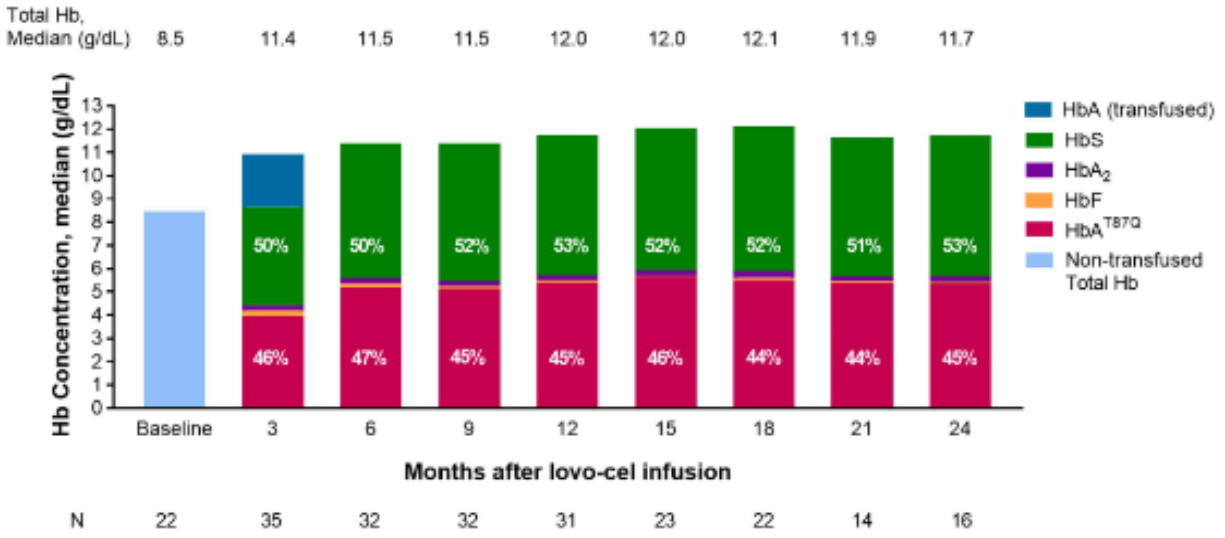
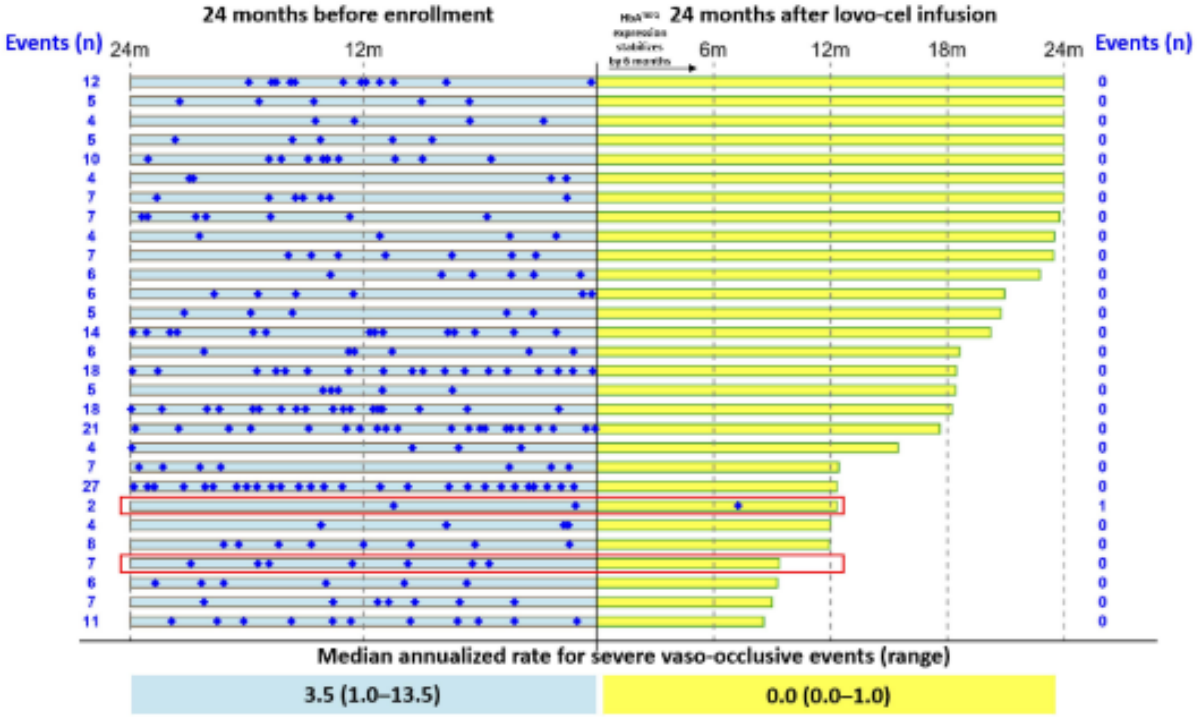


Figure 1B. Severe Vaso-Occlusive Events in Group C of the HGB-206 study



Gene therapy for SS disease will also be costly but
Will be balanced against lifetime burden of disease.

Primary CNS lymphoma:

ChemoimmuneRX vs Hi Dose Chemo & autoHCT (MATRix trial,

Illerhaus et al, ASH LBA

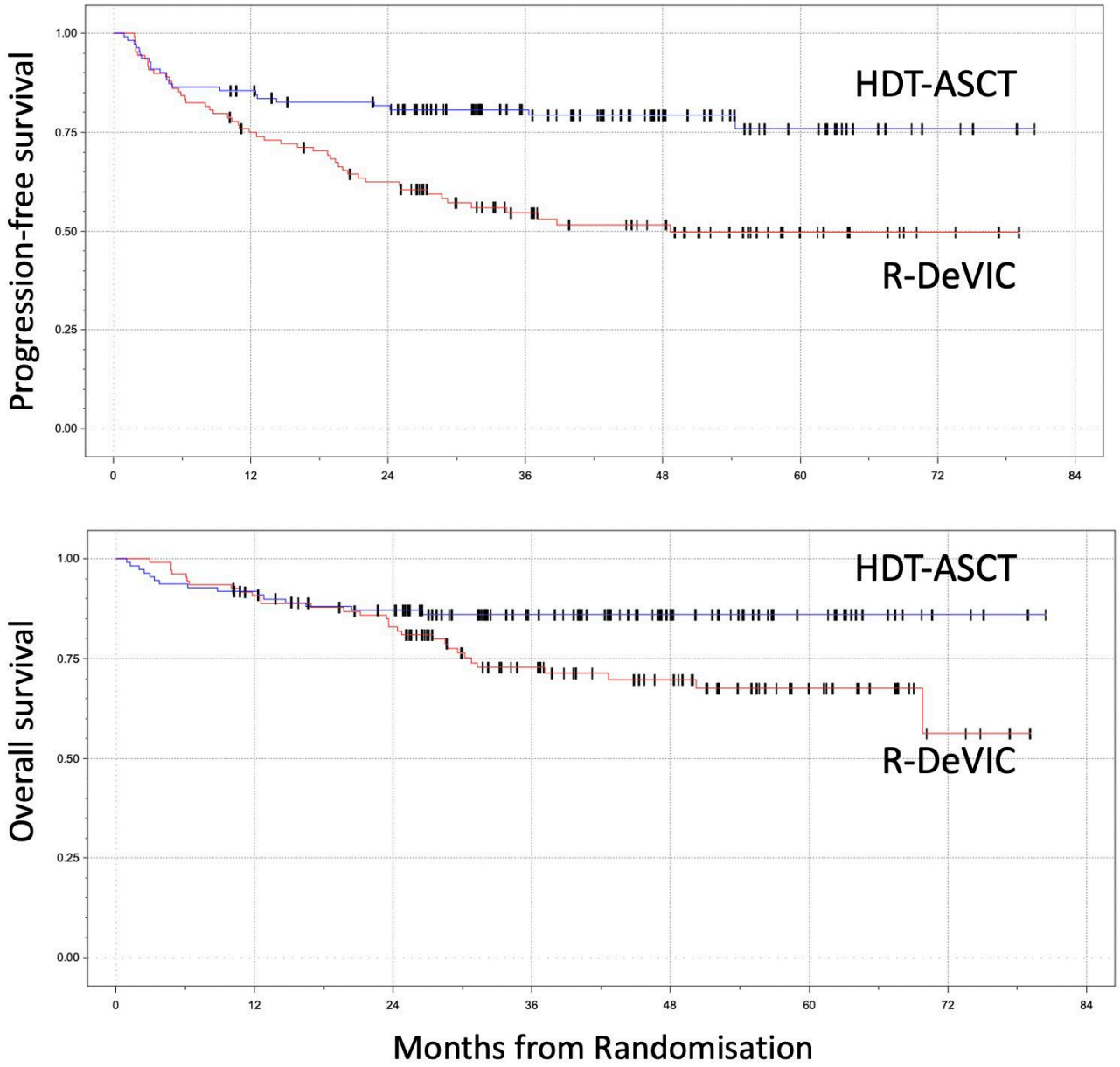
Open label, randomized, multicenter Ph III
Eligibility: new dx PCNSL, up to age 70, HIV-,

Induction: MATRix x 4. Pts with PR or better →
2 cycles R-DeVIC* vs BCNU/Thio + auto HCT

368 registered: 260 completed induction (75%),
229 randomized

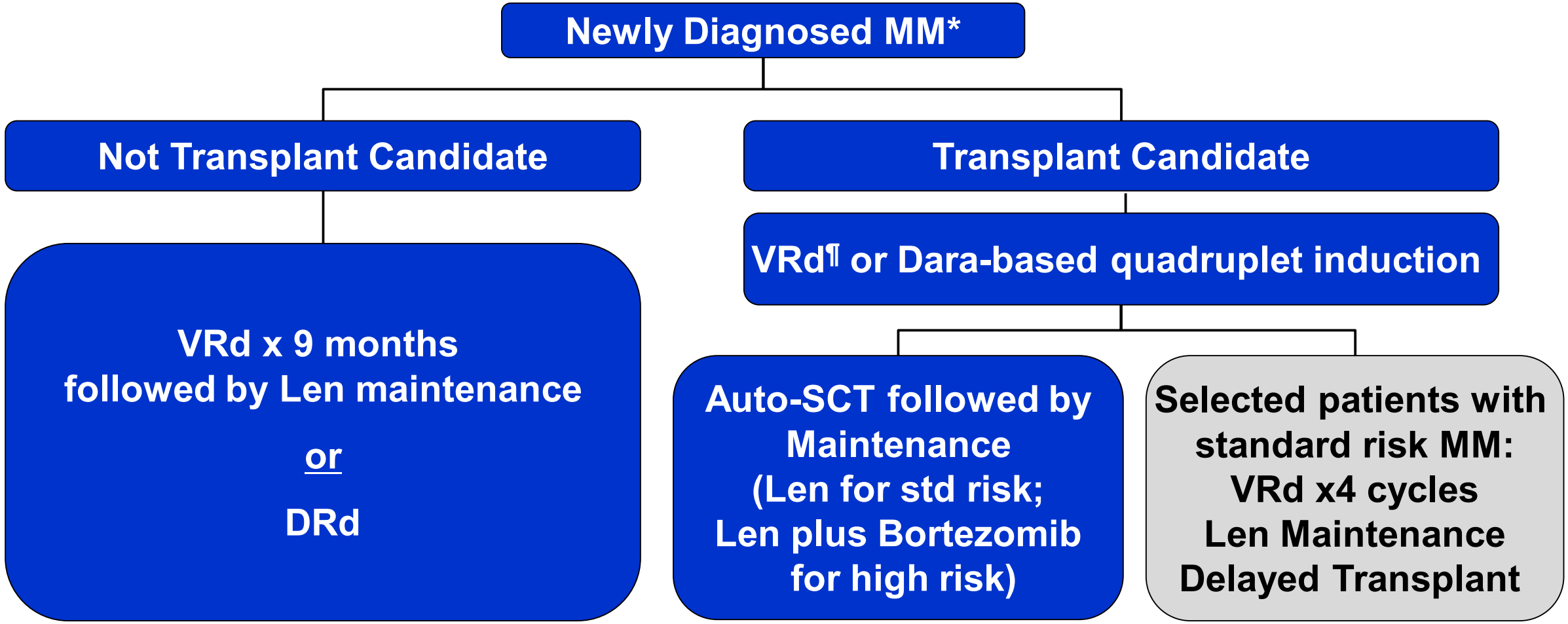
After induction→ 27% CR, 52% PR
After consolidation→ R-DEVIC 65%, HCT 68% CR

PFS at 3 yrs: 53% vs 79 % (p= .0003)
OS at 3 yrs: 71% vs 86% (p = .01) HR = .42
Neurocognitive assessment- No difference in arms



*R-DeVIC regimen (375 mg/m^2 Rit day 0; dexamethasone 40 mg/d days 1 to 3; etoposide 100 mg/m^2/d days 1 to 3; ifosfamide 1500 mg/m^2/d days 1 to 3; carboplatin 300 mg/m^2 day 1)

Myeloma: Frontline Treatment



*Based on CALGB 100104, S0777, IFM-2009, CTN 0702, HOVON, MAIA, CASSIOPEIA

¶ VTd/VCd if VRd not available

Rajkumar SV © 2020
P. Moreau

Phase 3 DETERMINATION trial (NCT01208662; DFCI 10-106/BMT CTN 1304): Background

- RVd highly efficacious in phase 2 studies: ORR 93–100%; ≥VGPR 61–67% [1,23]
- DETERMINATION originally a parallel study to phase 3 IFM 2009 trial- lenalidomide maintenance for 1 year [4]
  - CALGB-100104 demonstrated benefit of lenalidomide maintenance to disease progression (median TTP 46 mos) [5]
  - DETERMINATION protocol: lenalidomide maintenance until disease progression in both arms
- IFM 2009 demonstrated significantly superior PFS with ASCT-based approach [4,6]

CALGB, Cancer and Leukemia Group B; CR, complete response; IFM, Intergroupe Francophone du Myelome; ORR, overall response rate; TTP, time to progression; VGPR, very good partial response

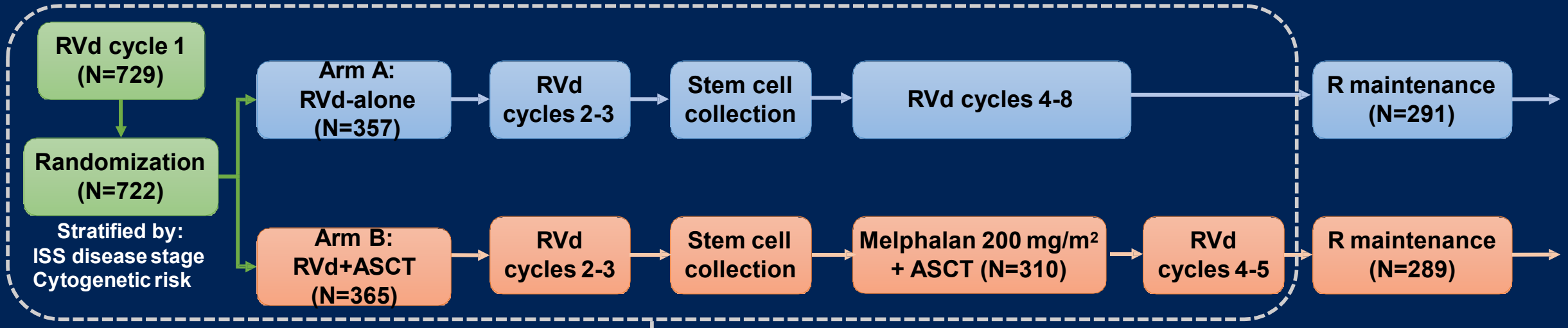
1. Richardson PG, et al. Blood 2010;116(5):679–86. 2. Kumar S, et al. Blood 2012;119(19):4375–82. 3. Roussel M, et al. J Clin Oncol 2014;32(25):2712–7. 4. Attal M, et al. N Engl J Med 2017;376:1311-20. 5. McCarthy PL, et al. N Engl J Med 2012;366(19):1770–81. 6. Perrot A, et al. Blood 2020;136:39.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy



Each RVd cycle (21 days):
R 25 mg/day PO, days 1-14
V 1.3 mg/m² IV/SC, days 1, 4, 8, 11
Dex 20/10 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12

Induction ± ASCT + consolidation treatment duration = ~6 months

Lenalidomide maintenance
Months 1-3: 10 mg/day
Month 4 onwards: 15 mg/day

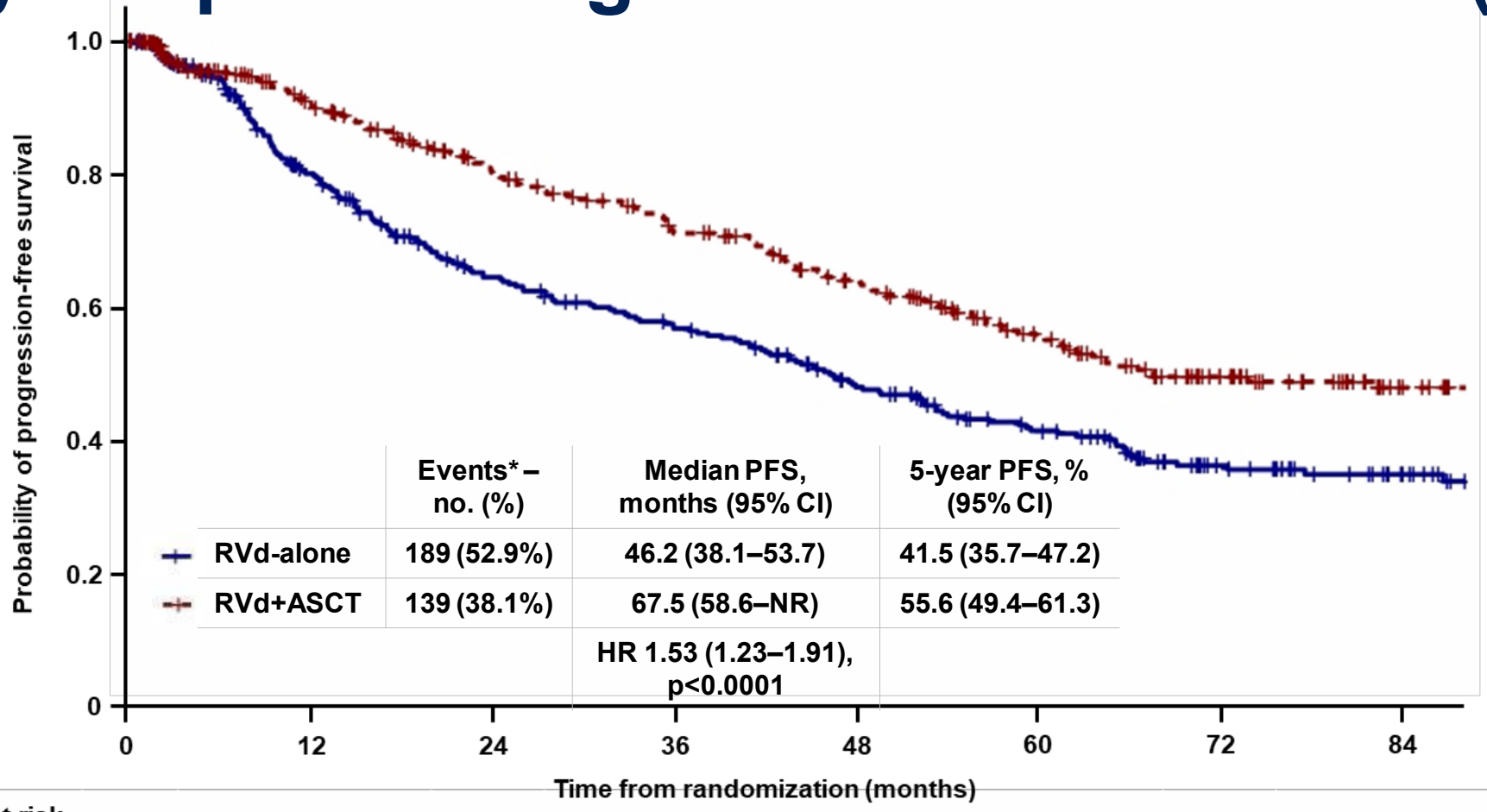
Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Primary endpoint: Progression-free survival (PFS)



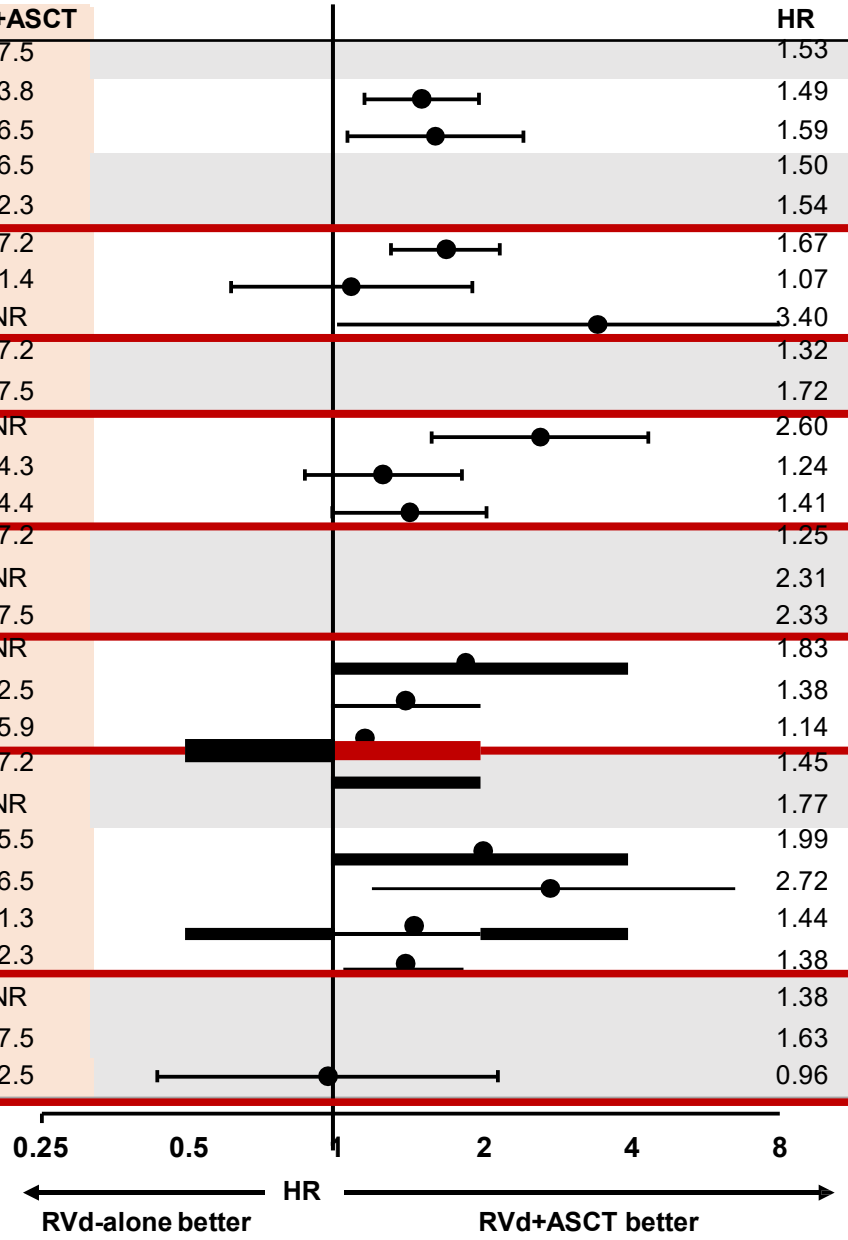
Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

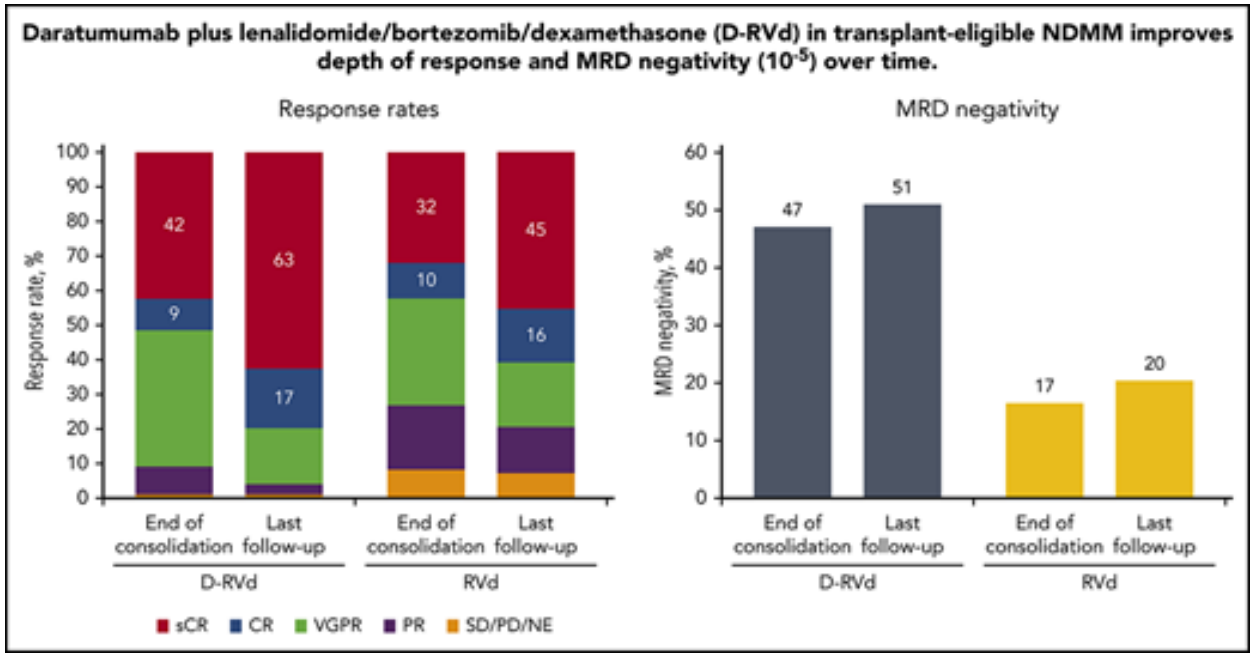
PFS by subgroup

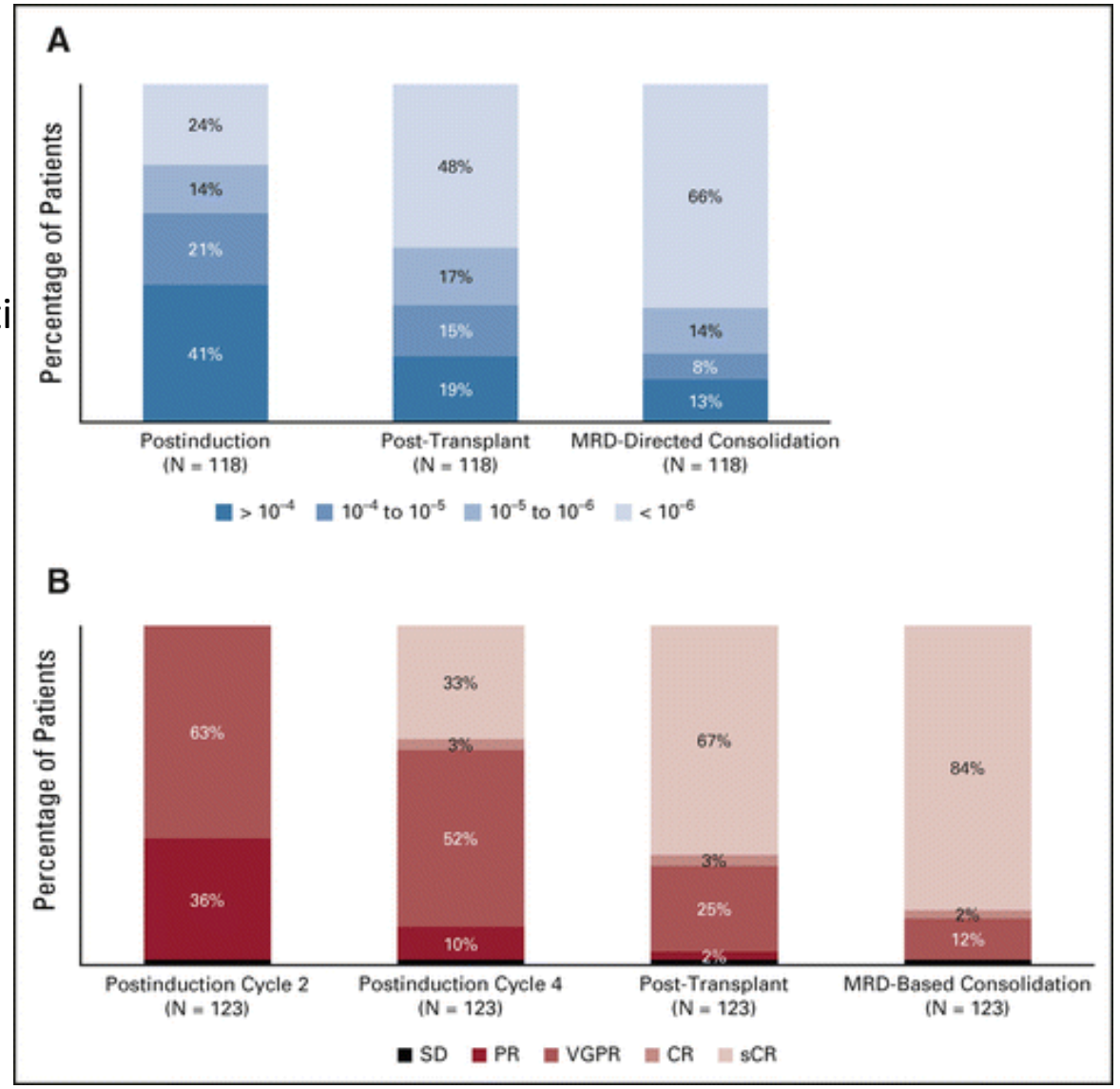
Subgroup		Events / patients		Median, months		HR	(95% CI)
		RVd-alone	RVd+ASCT	RVd-alone	RVd+ASCT		
All	**ITT analysis**	189/357	139/365	46.2	67.5	1.53	(1.23–1.91)
Age	<60 years	122/235	100/263	46.2	73.8	1.49	(1.14–1.95)
	≥60 years	67/122	39/102	46.5	66.5	1.59	(1.05–2.40)
Sex	Male	107/202	81/215	47.4	66.5	1.50	(1.11–2.02)
	Female	82/155	58/150	45.3	82.3	1.54	(1.09–2.17)
Race	White/Caucasian	150/268	104/272	44.3	67.2	1.67	(1.29–2.15)
	Black/African American	24/66	24/66	NR	61.4	1.07	(0.61–1.89)
	Other	12/17	5/21	38.1	NR	3.40	(1.00–11.5)
ECOG	0	76/153	64/164	56.7	67.2	1.32	(0.94–1.86)
	1–2	113/204	75/200	37.5	67.5	1.72	(1.28–2.32)
BMI	<25	49/80	25/81	33.6	NR	2.60	(1.56–4.31)
	25 to <30	71/141	53/127	52.3	64.3	1.24	(0.86–1.80)
	≥30	69/136	61/157	45.8	64.4	1.41	(0.98–2.02)
MM	IgG	108/220	80/200	53.3	67.2	1.25	(0.93–1.67)
	IgA	43/72	33/95	46.5	NR	2.31	(1.43–3.74)
	Light chain	21/34	16/41	23.3	57.5	2.33	(1.14–4.74)
ISS	I	89/178	62/184	52.0	NR	1.83	(1.32–2.54)
	II	69/130	56/134	46.2	62.5	1.38	(0.96–1.96)
	III	31/49	21/47	40.3	35.9	1.14	(0.64–2.01)
LDH	Not elevated (<225 U/L)	132/260	106/270	47.7	67.2	1.45	(1.12–1.88)
	Elevated (≥225 U/L)	56/96	31/92	41.1	NR	1.77	(1.09–2.88)
FISH	High risk	37/66	28/66	17.1	55.5	1.99	(1.21–3.26)
	t(4;14)	18/32	11/28	19.8	56.5	2.72	(1.19–6.24)
	Del(17p)	22/38	18/34	16.3	41.3	1.44	(0.76–2.73)
	Standard risk	135/268	103/274	53.2	82.3	1.38	(1.07–1.79)
R-ISS	I	45/103	39/105	59.1	NR	1.38	(0.90–2.12)
	II	109/202	78/211	40.9	67.5	1.63	(1.22–2.19)
	III	17/28	11/21	22.2	32.5	0.96	(0.43–2.13)



Myeloma: SOC remains→ AutoHCT early after induction therapy

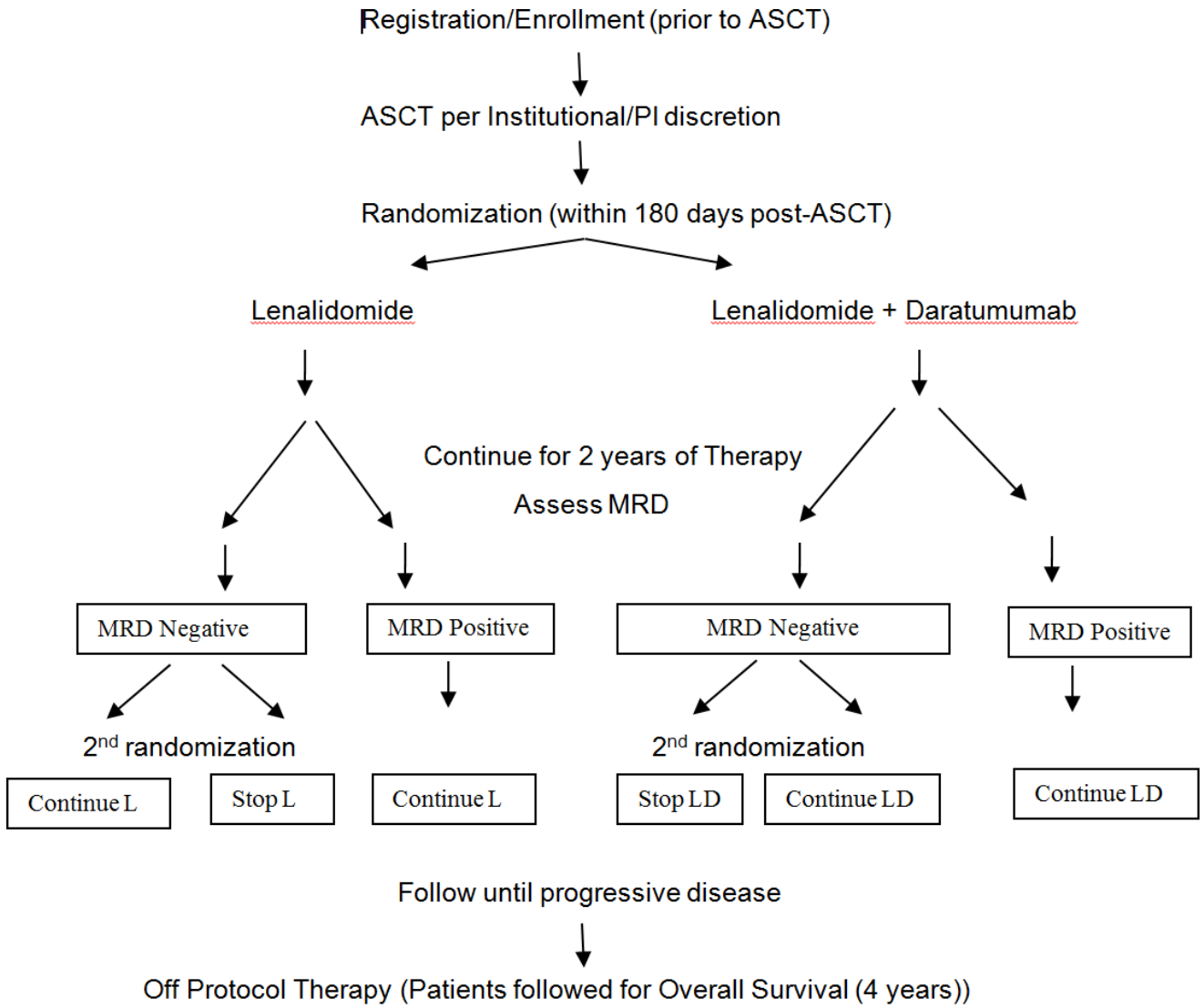
- What's next? Advanced auto HCT trials
- Master trial – Dara+KRD → MRD driven RX
- Griffin trial – Ph II VRD vs Dara + VRD → HCT→ DR maint
  - 36-month PFS & OS rates were 78.1% and 93.8%, respecti
  - BUT STRINGENT CRs are being seen





SWOG / BMT CTN Myeloma Trial

S1803:
Phase III Study of Daratumumab (NSC- 791647) + Lenalidomide (LD) or Lenalidomide (L) as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) Using Minimal Residual Disease to Direct Therapy Duration (DRAMMATIC Study)



What about allogeneic HCT? GVHD: a new horizon?

- Prophylaxis
- New diagnosis
- Steroid refractory
- Chronic GVHD- steroid dependent/ refractory

GVHD:

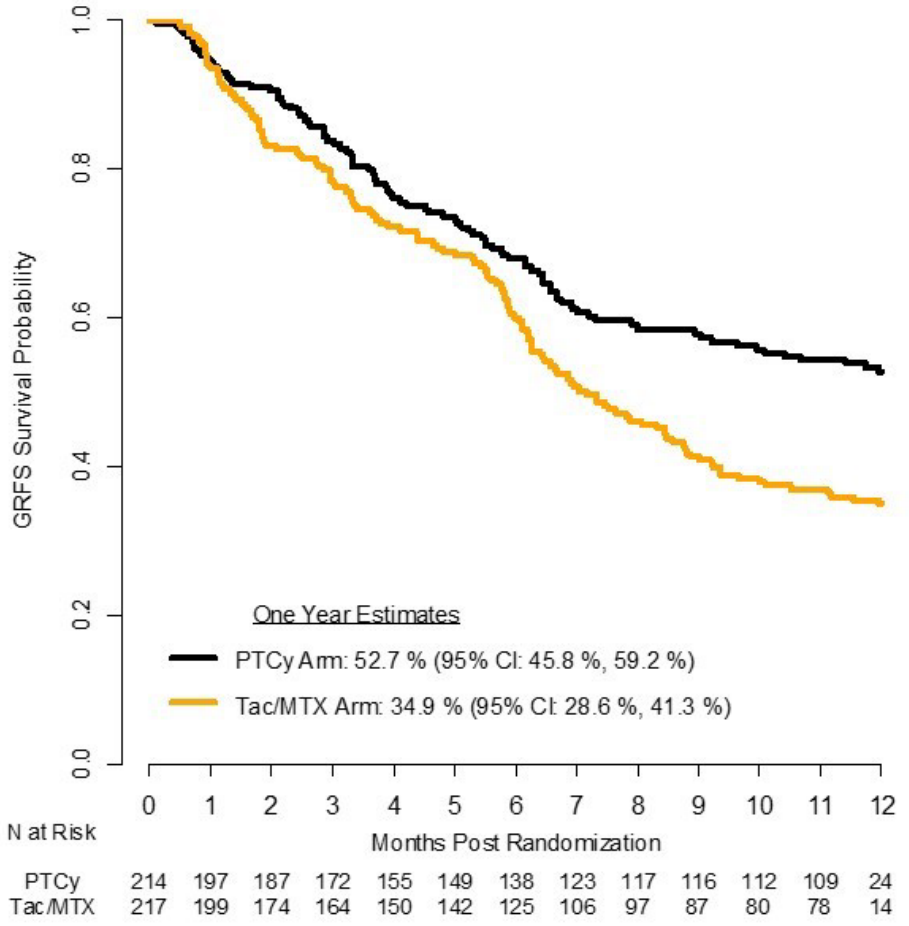
- Many trials, limited success in new GVHD prophylaxis strategies over the past 3 decades
- Calcineurin inhibitor and MTX remain standard
- Other regimens equivalent outcomes- different toxicity profiles
- Previous 4 arm randomized phase II national trial- BMT CTN 1202: contemporary Tac/MTX vs Tac/MTX/Marivaroc vs Tac/MTX/Bortezomib vs Tac/MMF/ post HCT CTX
- Results: Tac/MMF/post HCT CTX appeared superior to marivaroc or bortezomib arms
- New Phase III trial

GVHD prophylaxis for RIC, Holtan, ASH LBA

A. Patient Characteristics

	Treatment Arm		
	PTCy/Tac/MMF	Tac/MTX	All
	(N=214)	(N=217)	(N=431)
Demographic Variable	N (%)	N (%)	N (%)
Gender			
Male	134 (62.6%)	126 (58.1%)	260 (60.3%)
Female	80 (37.4%)	91 (41.9%)	171 (39.7%)
Age (years)			
Mean (SD)	64.2 (8.5)	64.5 (8.9)	64.3 (8.7)
Median (Range)	66.1 (20.7, 78.6)	66.3 (26.3, 77.4)	66.3 (20.7, 78.6)
Karnofsky / Lansky Performance Score			
At least 90	106 (49.5%)	108 (49.8%)	214 (49.7%)
Less Than 90	108 (50.5%)	109 (50.2%)	217 (50.3%)
Primary Disease			
Acute lymphoblastic leukemia (ALL)	12 (5.6%)	27 (12.4%)	39 (9.0%)
Acute myelogenous leukemia (AML)	107 (50.0%)	100 (46.1%)	207 (48.0%)
Biphenotypic leukemia	1 (0.5%)	1 (0.5%)	2 (0.5%)
Chronic myelogenous leukemia (CML)	6 (2.8%)	5 (2.3%)	11 (2.6%)
Myelodysplastic syndrome (MDS)	63 (29.4%)	65 (30.0%)	128 (29.7%)
Lymphoma (all subtypes)	23 (10.7%)	17 (7.8%)	40 (9.2%)
Disease Risk Index			
Low	19 (8.9%)	21 (9.7%)	40 (9.3%)
Intermediate	125 (58.4%)	125 (57.6%)	250 (58.0%)
High / Very High	70 (32.7%)	71 (32.7%)	141 (32.7%)
Hematopoietic Cell Transplant - Comorbidity Index			
<4	164 (76.6%)	154 (71.0%)	318 (73.8%)
4+	40 (18.7%)	55 (25.3%)	95 (22.0%)
Missing/Unknown	10 (4.7%)	8 (3.7%)	18 (4.2%)
Donor Type and HLA Matching			
Related donor 6/6	60 (28.0%)	68 (31.3%)	128 (29.7%)
Unrelated donor 7/8	7 (3.3%)	8 (3.7%)	15 (3.5%)
Unrelated donor 8/8	147 (68.7%)	141 (65.0%)	288 (66.8%)
Conditioning Regimen			
Fludarabine/Busulfan	56 (26.2%)	61 (28.1%)	117 (27.1%)
Fludarabine/Melphalan	122 (57.0%)	123 (56.7%)	245 (56.8%)
Fludarabine +/- Cyclophosphamide +/- TBI	30 (14.0%)	29 (13.4%)	59 (13.7%)
Missing/Unknown	6 (2.8%)	4 (1.8%)	10 (2.3%)
Planned Post-Transplant Maintenance Therapy			
No	159 (74.3%)	170 (78.3%)	329 (76.3%)
Yes	55 (25.7%)	47 (21.7%)	102 (23.7%)

B. Probability of GVHD-free, Relapse-free Survival



At one yr, no difference in relapse rates, degree of chimerism, graft failure rates or OS.

ASH # 265- Resurrecting Graft Engineered Donor Allografts- Will Orca-T® emerge? Oliai et al

Orca-T is a high-precision, immunotherapy allograft; Day 0 → CD34+ stem cells & Tregs; Day 2→ Tcon
Then Single agent GVHD proph with Tac or Siro
Total treated: n =180
127 subjects > 180 days f/u

Results: Case match contemporary control with CIBMTR cases from 2016-2018; Tac/ MTX only

Early engraftment – D13 neutrophils; D16 platelets
Low severe (Gr III) infections 11%

GRFS @ 18 months 69%
OS @ 18 months 86%

Table 1.

Parameter	*CIBMTR Control*	***Orca-T***
n	375	**127**
Median follow-up in months (range)	31 (4-50)	**13 (1-69)**
Relapse-free survival @ 12 months (95% CI)	62% (55-69)	**81% (74-88)**
Relapse-free survival @ 12 months (95% CI) – BFT conditioning	n/a	**90% (81-99)**
Relapse-free survival @ 12 months (95% CI) – MRD+ acute leukemia	48% (39-58)	**68% (48-88)**
Relapse-free survival @ 12 months (95% CI) – MRD neg acute leukemia	66% (61-72)	**90% (82-98)**
Grade ≥ 3 aGVHD through Day +180* (95% CI)	16% (2-19)	**5% (1-9)**
Moderate to Severe cGVHD through Day +365 (95% CI)**	38% (33-44)	**6% (0-12)**
Non-relapse mortality @ 1 year (95% CI)	10% (7-13)	**5% (1-9)**
GVHD and Relapse-Free Survival at 1 year (95% CI)	34% (30-39)	**76% (68-84)**
Overall survival at 1 year (95% CI)	68% (63-73)	**91% (84-96)**

*MAGIC Grading Criteria, **NIH Consensus Grading

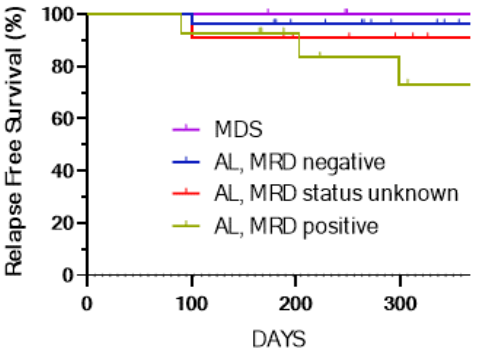
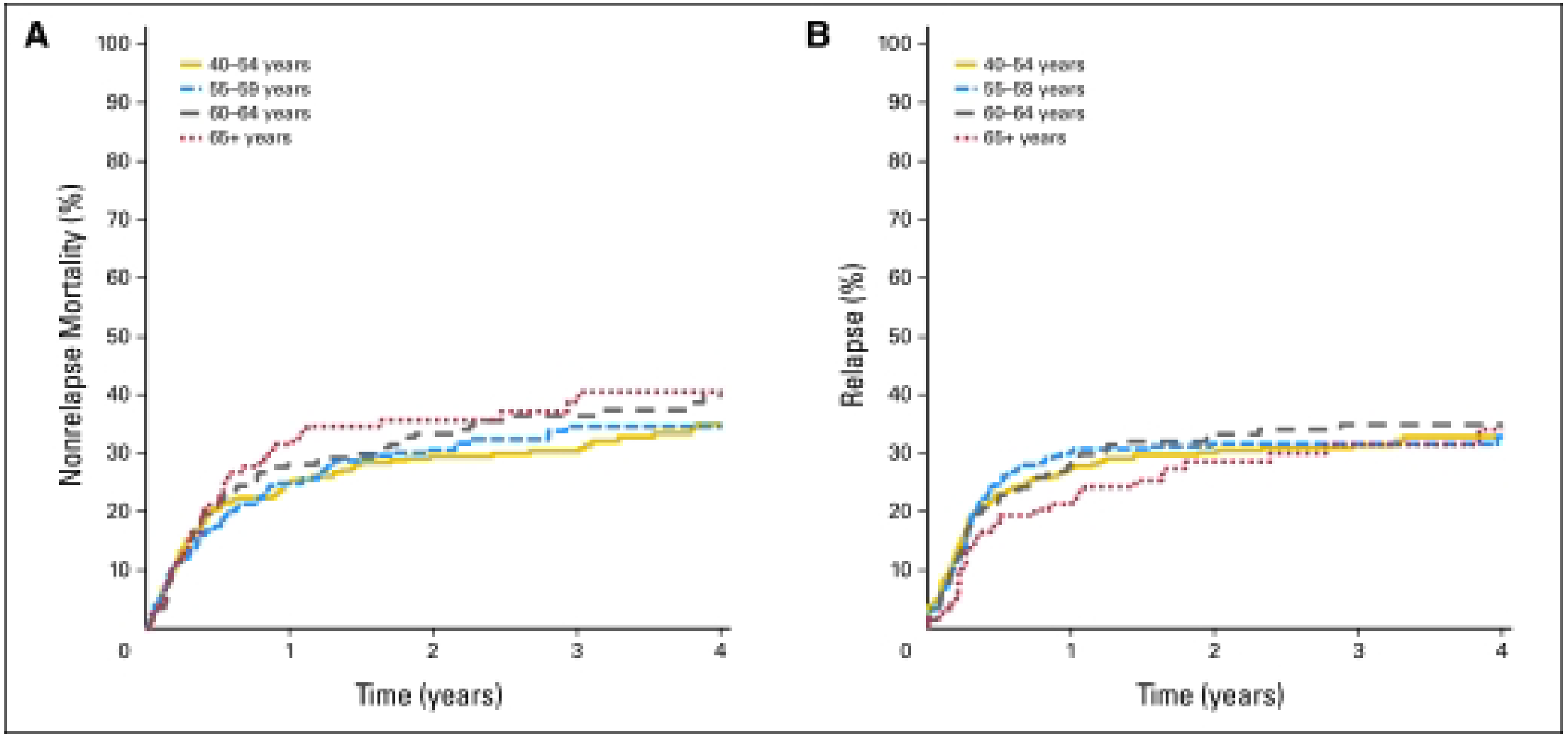
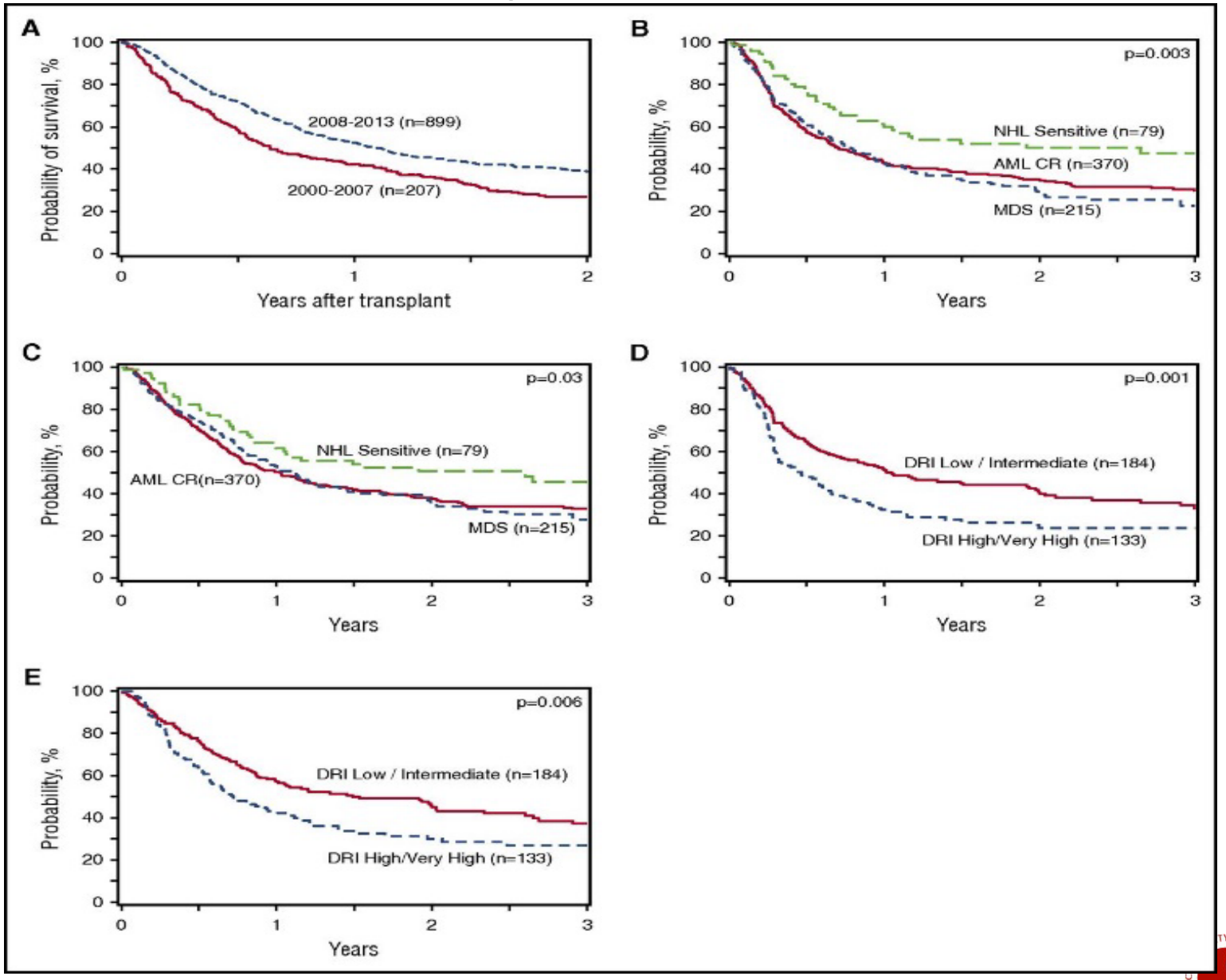


Figure 1. Relapse-free survival in patients who received BFT conditioning followed by Orca-T. AL = acute leukemia.

Age & Outcome of HCT for Older Patients With AML in CR1 or MDS, McClune et al, JCO 2010



Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States, Muffly et al, Blood, 2017



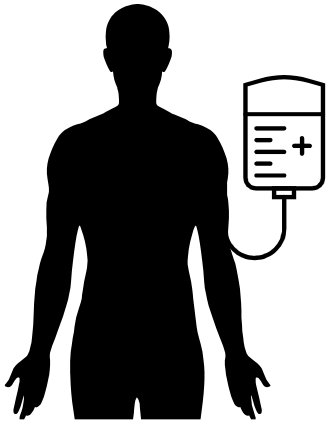
Copyright © 2023 American Society of Hematology

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

CAR T-Cell Therapy: Underlying Principles

Leukapheresis

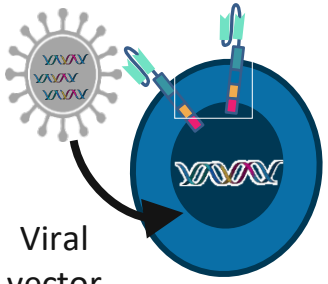
Collect patient's white blood cells

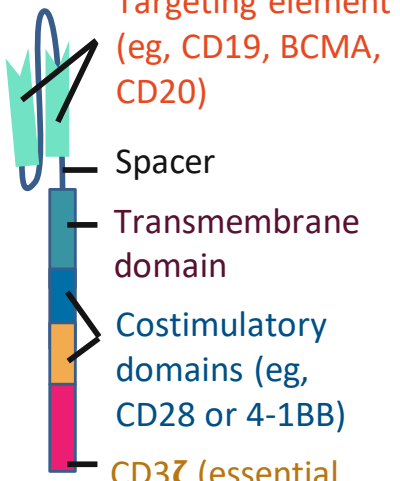


Manufacturing

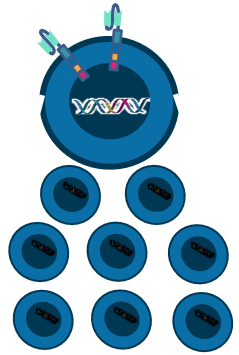
Isolate and activate T-cells

Engineer T-cells with CAR gene





Expand CAR T-cells

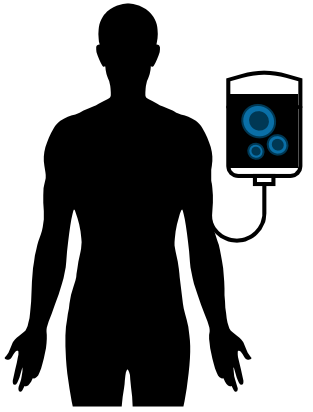


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Infusion

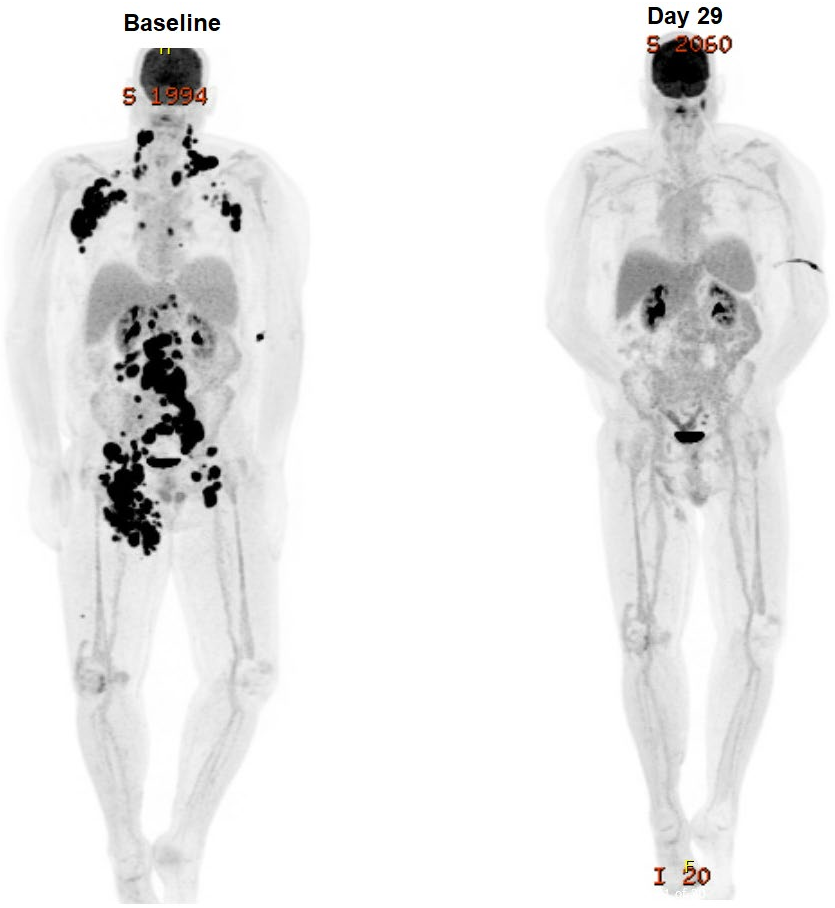
Infuse same patient with CAR T-cells



Activity

Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

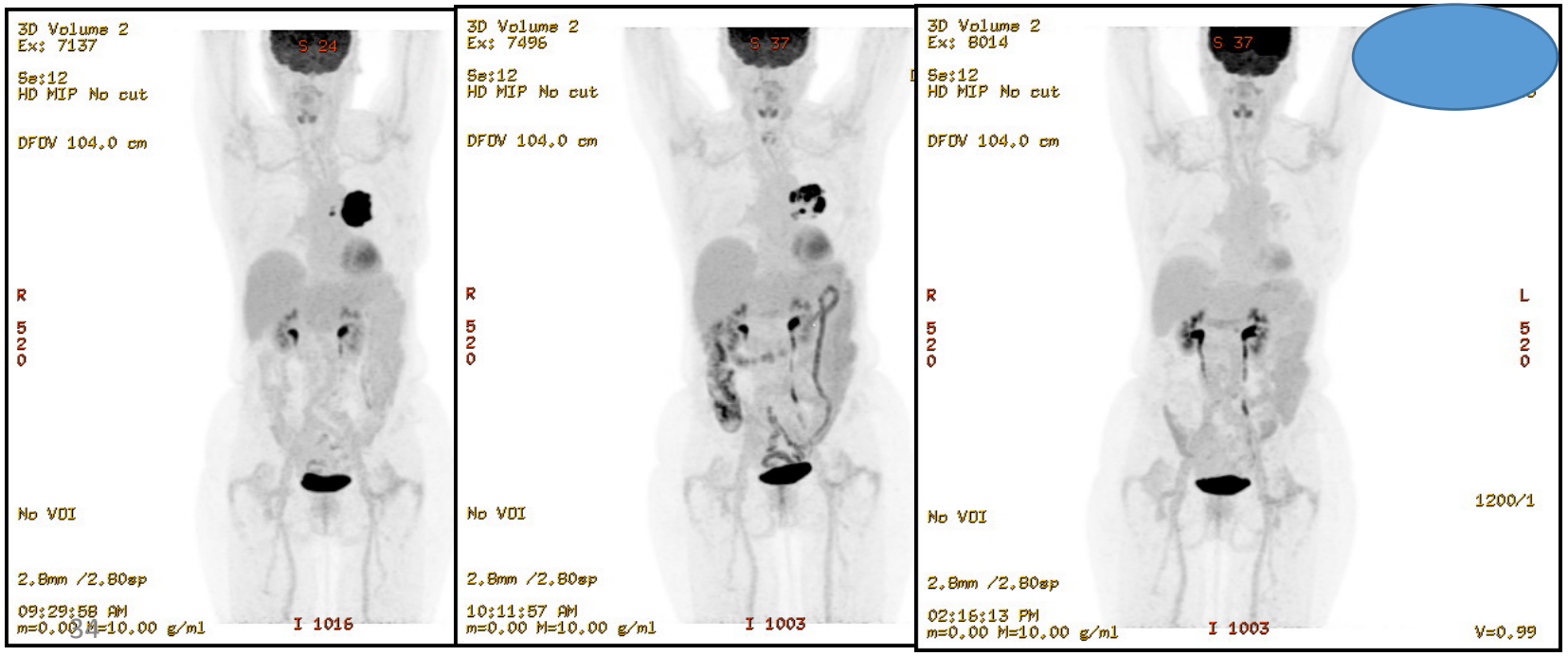
CAR T-cell Therapy



Maximal Survival estimates of R/R DLBCL: Scholar trial: <7% CR, 15% OS at 2 yrs, Crump et al, Blood, 2017

OHSU PT: Relapsed, Refractory DLBCL- post auto HCT

Baseline Day 30 Day 90



Approved CAR- T Products & Indications

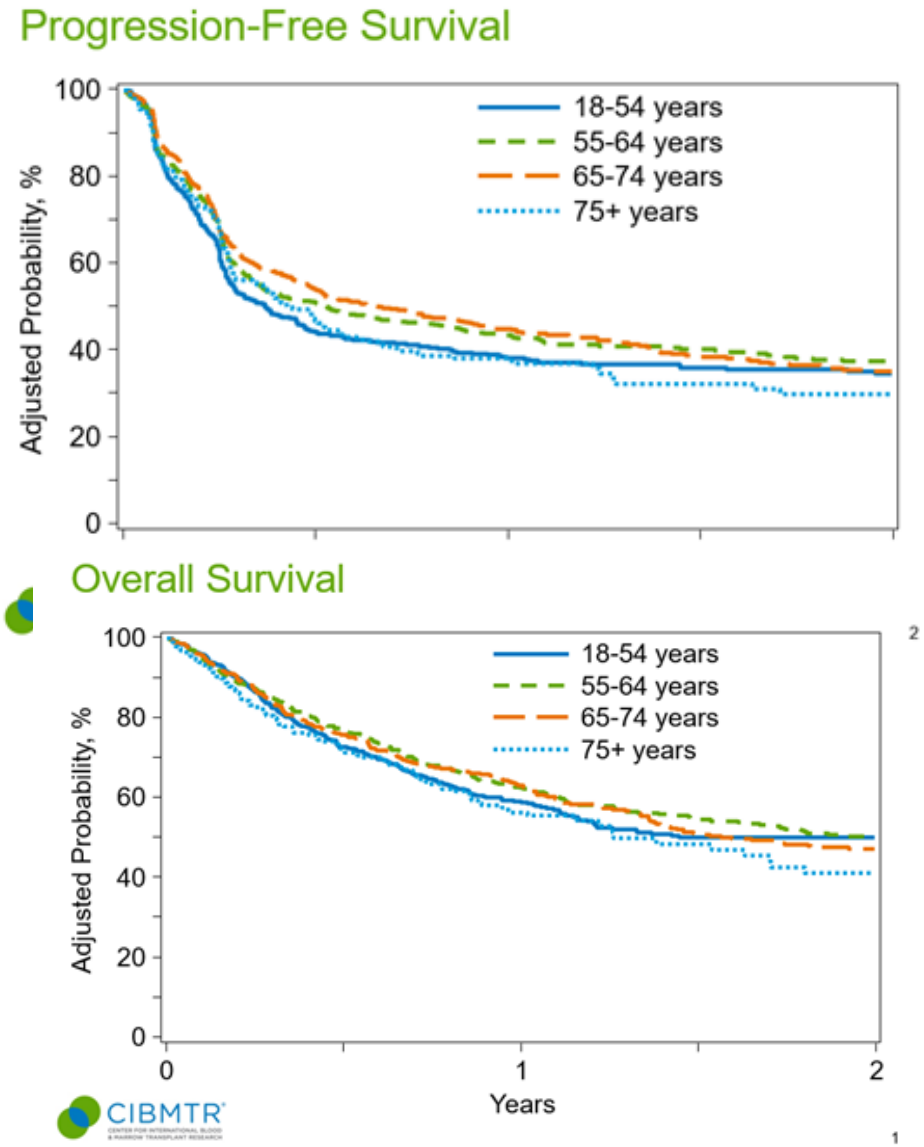
- R/R DLBCL- 3rd line- Tisagenlecleucel, Axicabtagene, Lisocabtagene
- **R/R DLBCL- 2nd line- Axicabtagene**
- R/R Follicular Lymphoma- 3rd line Axicabtagene
- Mantle cell lymphoma- Brexucabtagene
- Pediatric/young adult ALL- > 2nd line- Tisagenlecleucel
- Adult ALL- Brexucabtagene
- Myeloma- Beyond 4th line- Idecabtagene, Ciltacabtagene
- **R/R – 2nd line- Lisocabtagene**
- R/R Follicular Lymphoma- Tisagenlecleucel

→ Anticipated 2023- TIL for Advanced Melanoma- Lifileucil

Who can be eligible- DLBCL?
CAR T outcomes and age, Mirza et al, ASH 2022

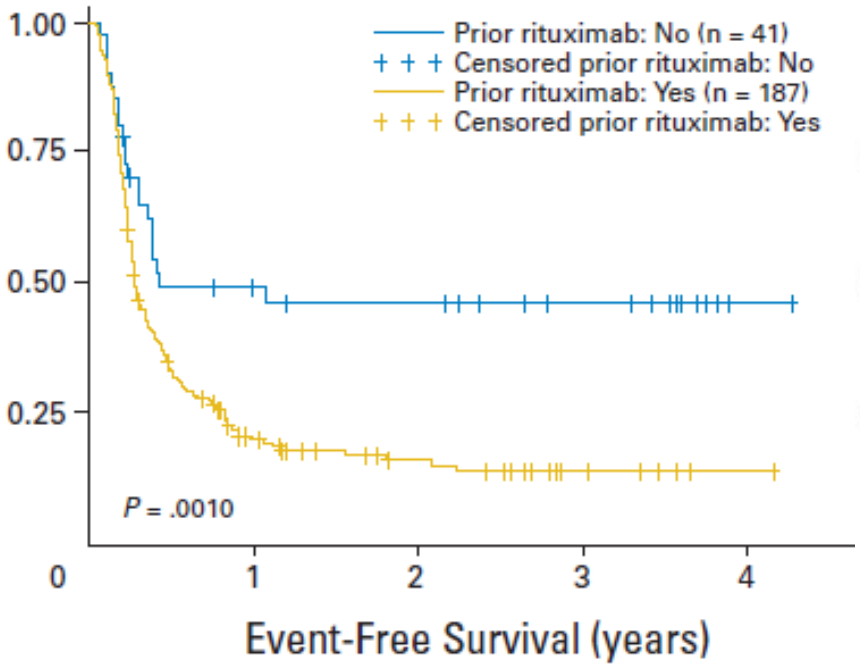
CIBMTR analysis
Retrospective
Real World
N = 1916 adults
Axicabtagene- 1438; Tisagenlecleucel- 481
Median age – 63 (range: **18-91**)

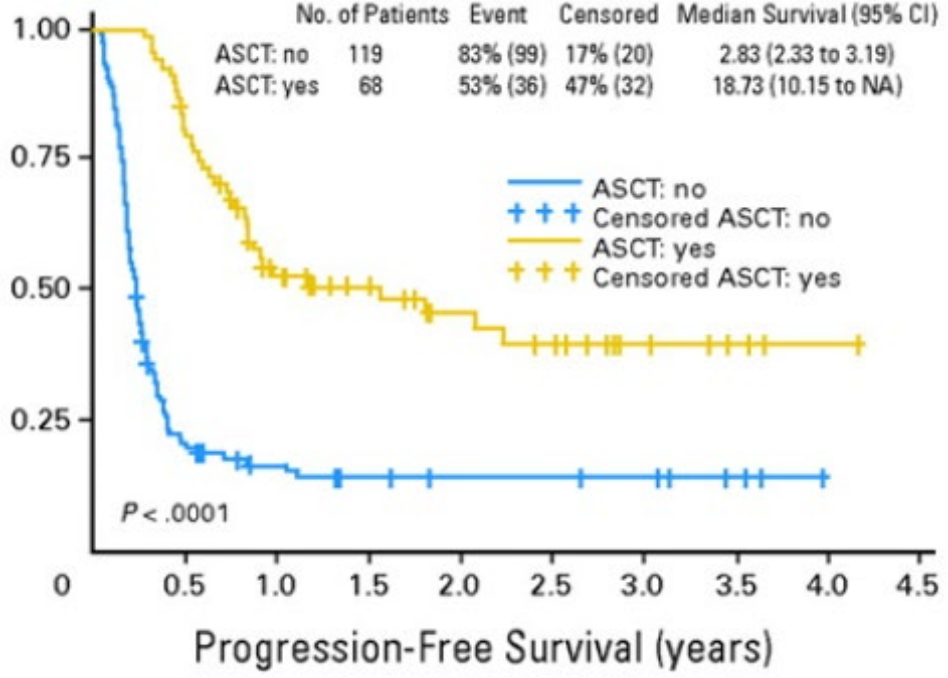
4. CRS					0.3933
18-54 years	469	1.000			-
55-64 years	599	0.821	0.606	1.113	0.2039
65-74 years	642	1.031	0.762	1.396	0.8424
75+ years	201	0.914	0.611	1.368	0.6629
5. ICANS					<.0001
18-54 years	469	1.000			-
55-64 years	599	1.306	1.008	1.693	0.0436
65-74 years	642	2.061	1.588	2.675	<.0001
75+ years	201	2.560	1.766	3.711	<.0001



When-Paradigm shift for DLBCL?
CAR T for first relapse DLBCL w/in 12 months of 1^{o} therapy

CORAL trial data



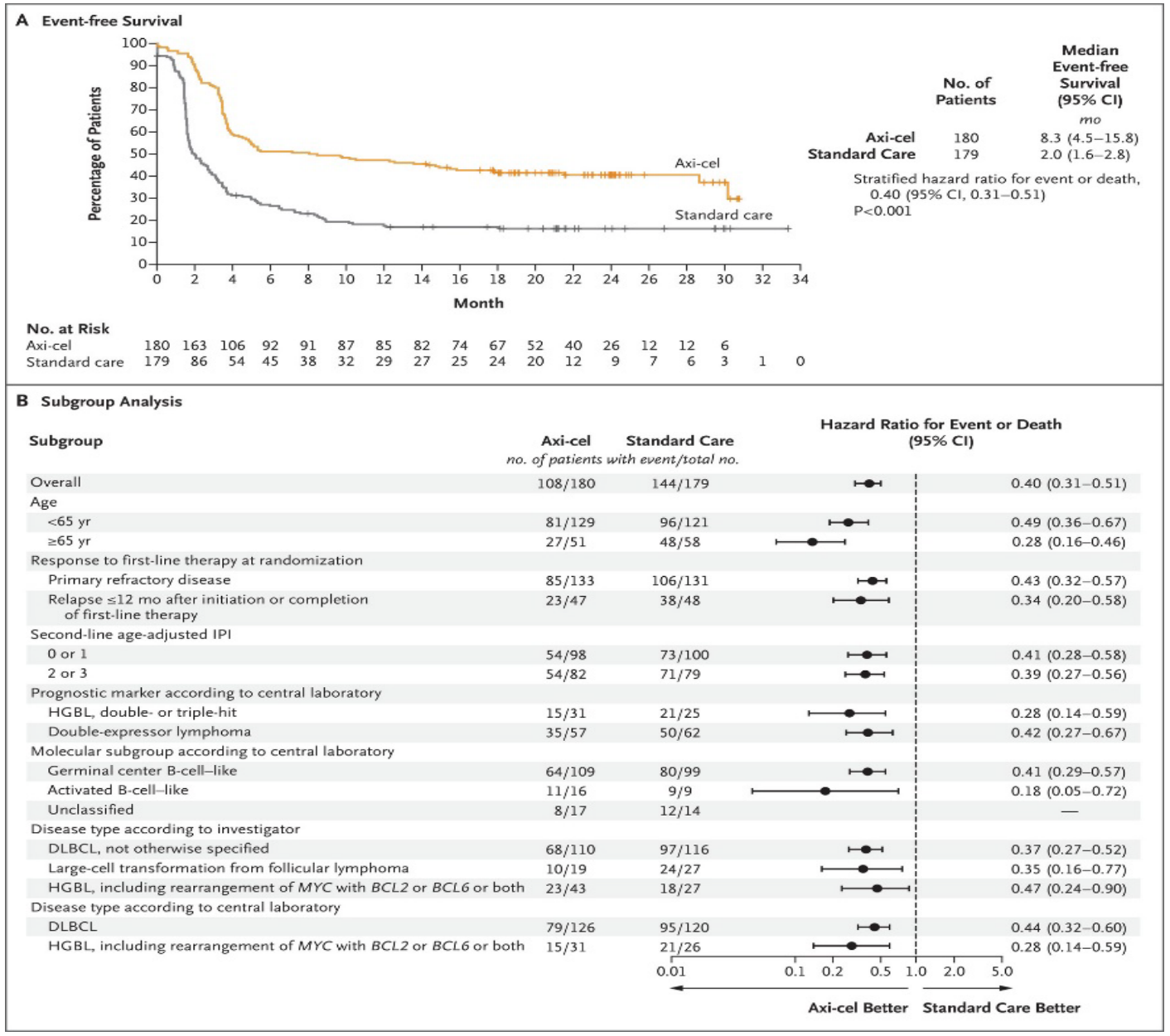


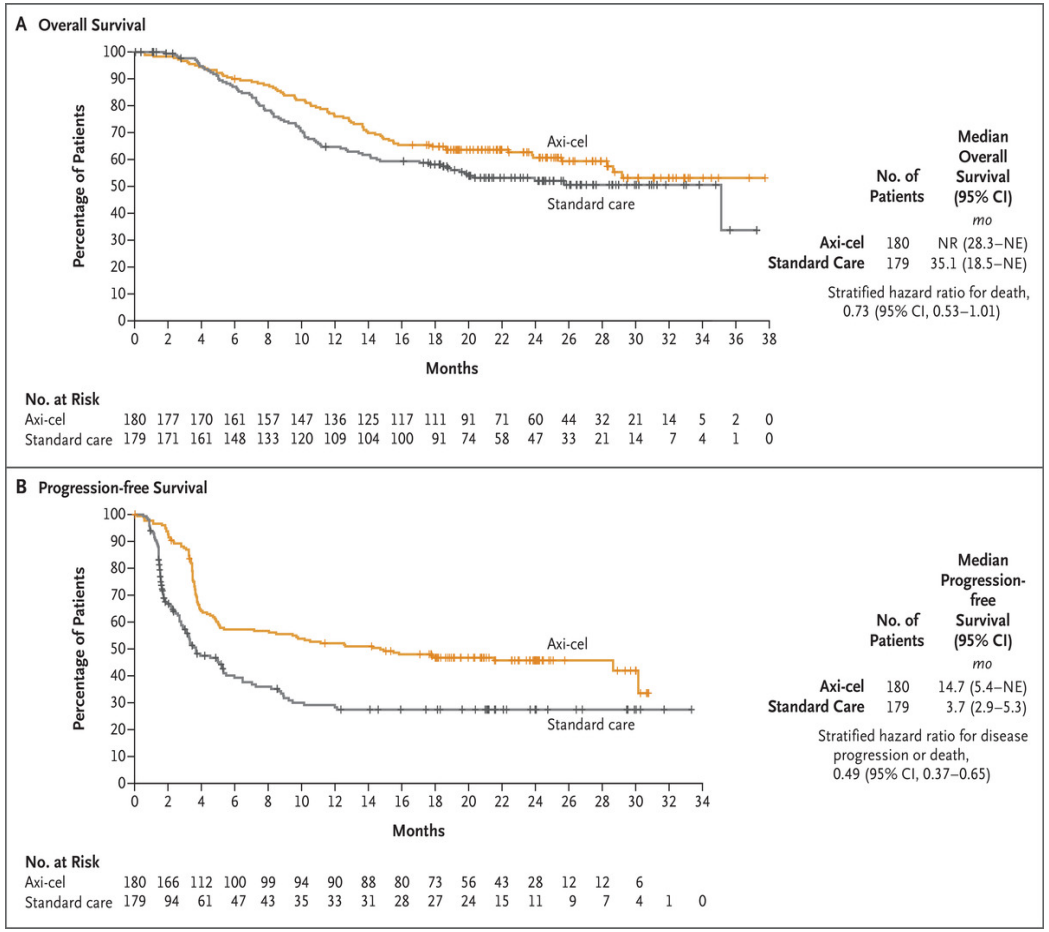
60% of early relapse do not respond to 1st salvage

- If respond & proceed to autoSCT, then 3 yr EFS = 39%

Gisselbrecht, JCO, 2010

Axicabtagene ciloleucel vs chemo/auto HCT for first & **early** relapse of DLBCL





Locke et al, NEJM, 2022

Liso-cel vs SOC for second line rx for R/R DLBCL: Transform study, update,

Abramson et al, ASH, 2022

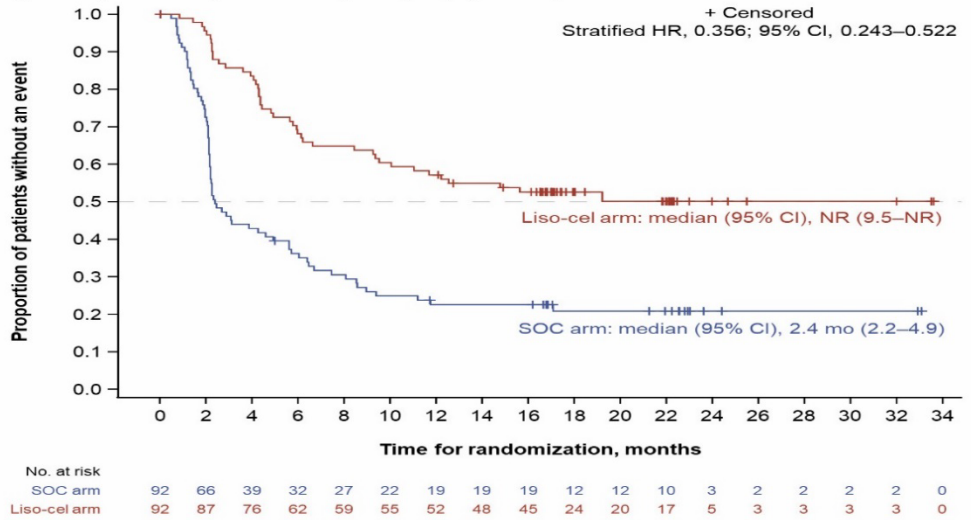
N = 184 randomized; 92 / arm
CAR T arm- bridging/ CAR T
SOC- chemo x 3 → autoHCT

CR: 74 vs 43%-- CAR T vs SOC
PFS: Not reached @ 12.6 mos vs 6.2 mos

91 pts on SOC arm, 67% X-over to Liso-cel

Conclusion: with med f/u 17.5 months, Stat signif increase in EFS, CR and PFS.

Figure. Kaplan-Meier plot of EFS by IRC (ITT population)



EFS was defined as the time from randomization to death from any cause, progressive disease, failure to achieve complete or partial response by 9 weeks after randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurred first. Stratified by response to first-line therapy (relapsed vs refractory) and secondary age-adjusted International Prognostic Index (0–1 vs 2–3).
CI, confidence interval; EFS, event-free survival; IRC, independent review committee; ITT, intent to treat; HR, hazard ratio; liso-cel, lisocabtagene maraleucel; NR, not reached; SOC, standard of care.

Table. Primary analysis: IRC-assessed efficacy per Lugano 2014 criteria (ITT population)

Parameter	Liso-cel arm (n = 92)	SOC arm (n = 92)
Primary endpoint		
EFS, n with event	44	71
Median (95% CI), mo	NR (9.5–NR)	2.4 (2.2–4.9)
HR (95% CI)	0.356 (0.243–0.522)	
EFS rate at 12 mo, % (95% CI)	57.1 (47.0–67.3)	22.5 (13.9–31.2)
EFS rate at 18 mo, % (95% CI)	52.6 (42.3–62.9)	20.8 (12.2–29.5)
Secondary endpoints[a]		
ORR, n (%) [95% CI]	80 (87.0) [78.3–93.1]	45 (48.9) [38.3–59.6]
CR rate, n (%) [95% CI]	68 (73.9) [63.7–82.5]	40 (43.5) [33.2–54.2]
	$P < 0.0001$[b]	
Duration of CR, n with event	21	21
Median (95% CI), mo	NR (NR–NR)	9.3 (5.1–NR)
Duration of CR at 12 mo, % (95% CI)	72.6 (61.8–83.4)	47.6 (31.6–63.6)
Duration of CR at 18 mo, % (95% CI)	65.2 (52.3–78.0)	43.3 (26.6–59.9)
PFS, n with event	37	52
Median (95% CI), mo	NR (12.6–NR)	6.2 (4.3–8.6)
HR (95% CI)	0.400 (0.261–0.615; $P < 0.0001$[c]	
PFS rate at 12 mo, % (95% CI)	63.1 (53.0–73.3)	31.2 (20.2–42.3)
PFS rate at 18 mo, % (95% CI)	58.2 (47.7–68.7)	28.8 (17.7–40.0)
OS, n with event	28	38
Median (95% CI), mo	NR (29.5–NR)	29.9 (17.9–NR)
HR (95% CI)	0.724 (0.443–1.183); $P = 0.0987$[c]	
OS rate at 12 mo, % (95% CI)	83.4 (75.7–91.1)	72.0 (62.7–81.3)
OS rate at 18 mo, % (95% CI)	73.1 (63.9–82.3)	60.6 (50.2–71.1)

[a]The significance threshold to reject the null hypothesis for key secondary endpoints was ≤ 0.021; [b]Stratified 1-sided *P* value based on Cochran-Mantel-Haenszel test; [c]One-sided *P* value based on a stratified Cox proportional hazards model.
CI, confidence interval; CR, complete response; EFS, event-free survival; HR, hazard ratio; IRC, independent review committee; ITT, intent to treat; liso-cel, lisocabtagene maraleucel; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

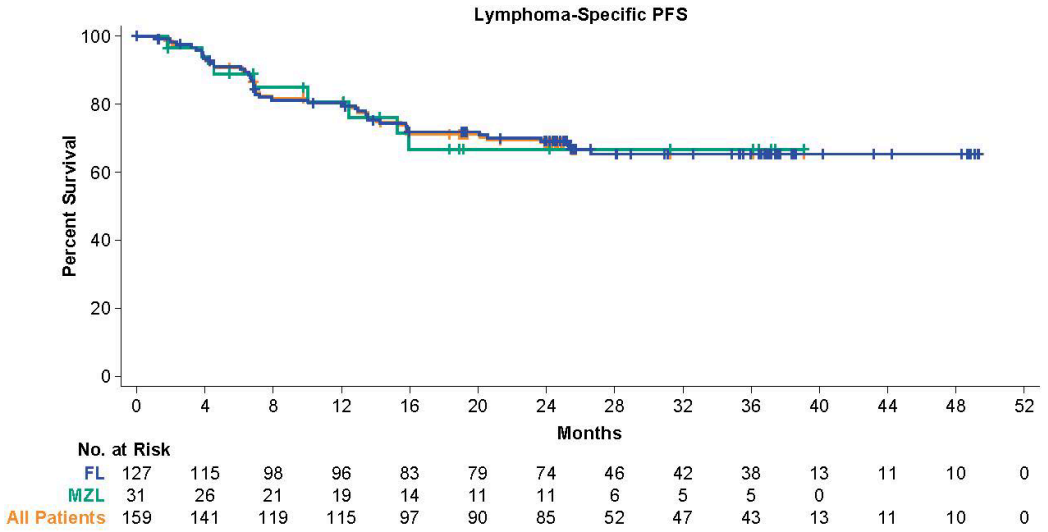
Second line CAR T for R/R DLBCL is new SOC

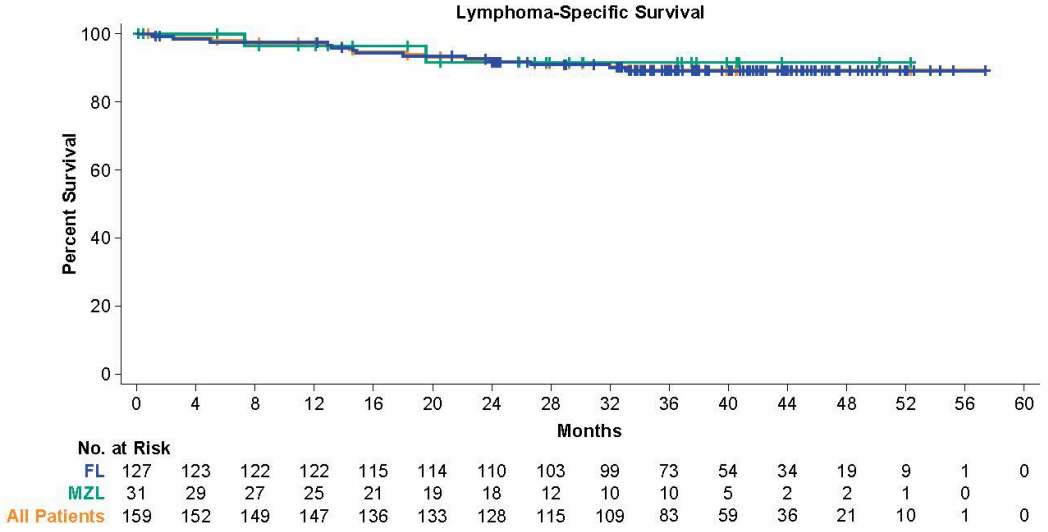
- Clinical Considerations:
  - In randomized trials→ CAR T is superior to chemo/auto HCT. Was not compared to auto HCT. If one treats with chemo intervention→ PR or better, auto HCT still can be beneficial
  - Only applies to pts who relapse within 12 mos of completing R-CHOP or equivalent
  - Axicabtagene and Lisocabtagene met endpoints. Tisagenlecleucel in a similar, but significantly different designed trial, did not.
  - Different products have subtle differences in FDA label guiding choice
  - Apheresis before chemotherapy salvage may be ideal. Early referral is beneficial to all

Other CAR T futures: Followup studies
Zuma-5: Follicular Lymphoma

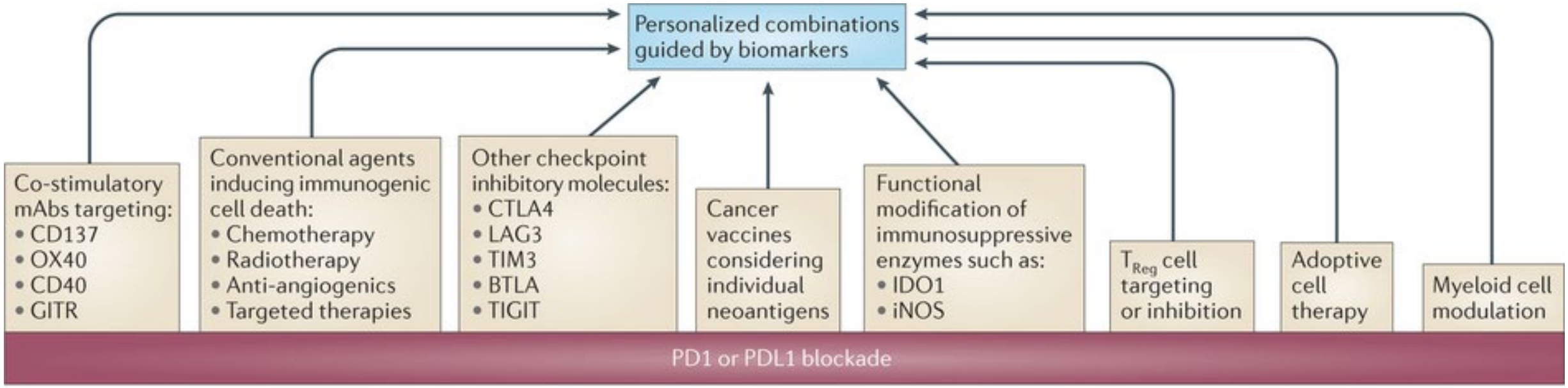
Axicabtagene ciloleucel
Phase II study
N = 159
3 yr followup with Med F/u 40.5 mos

Med PFS- 40.2 mos
3 yr OS – 75%





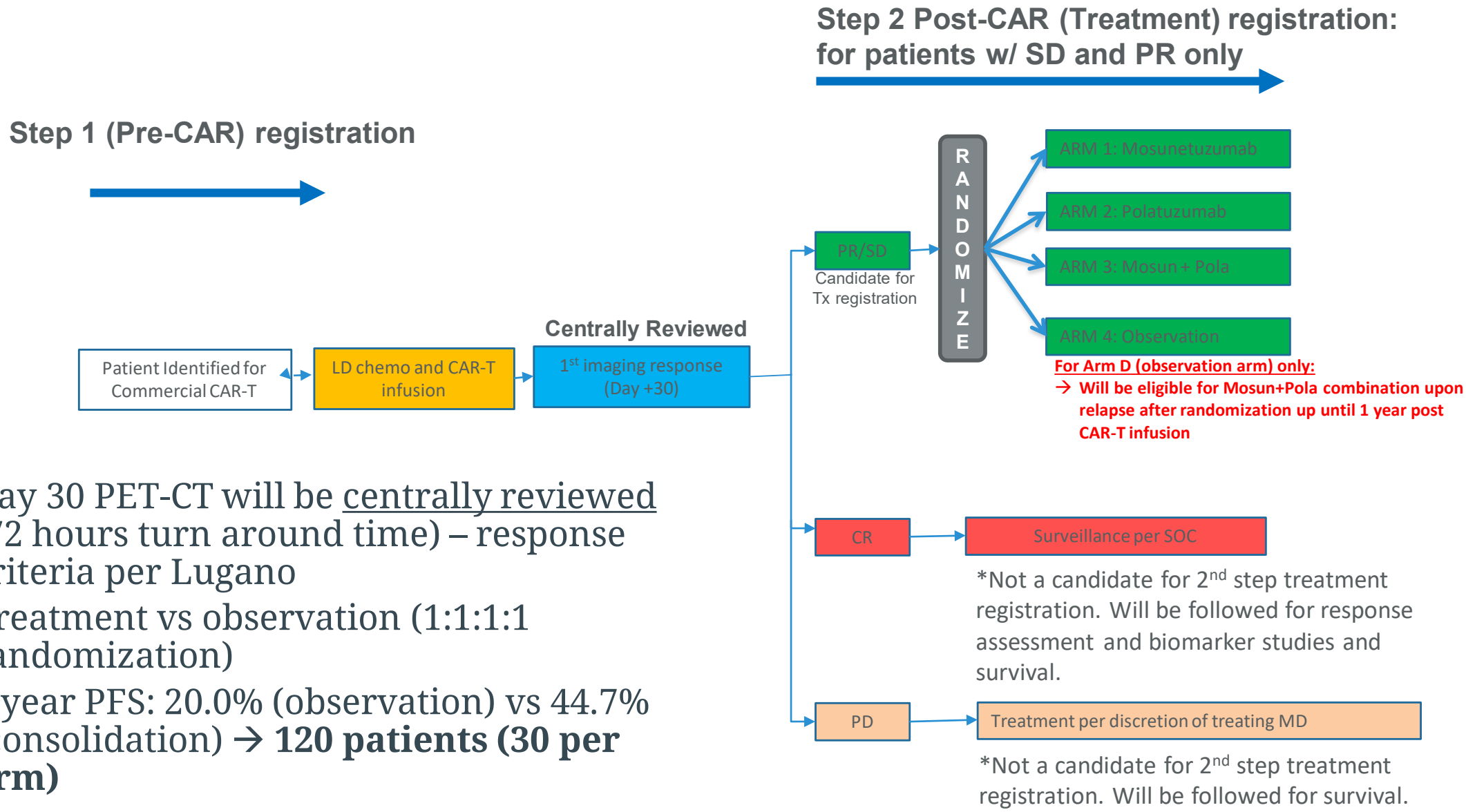
How to improve on outcomes? Potential trial candidates



There is an internal message: WORK IS NOT DONE

CAR T still does not cure all!!!!!

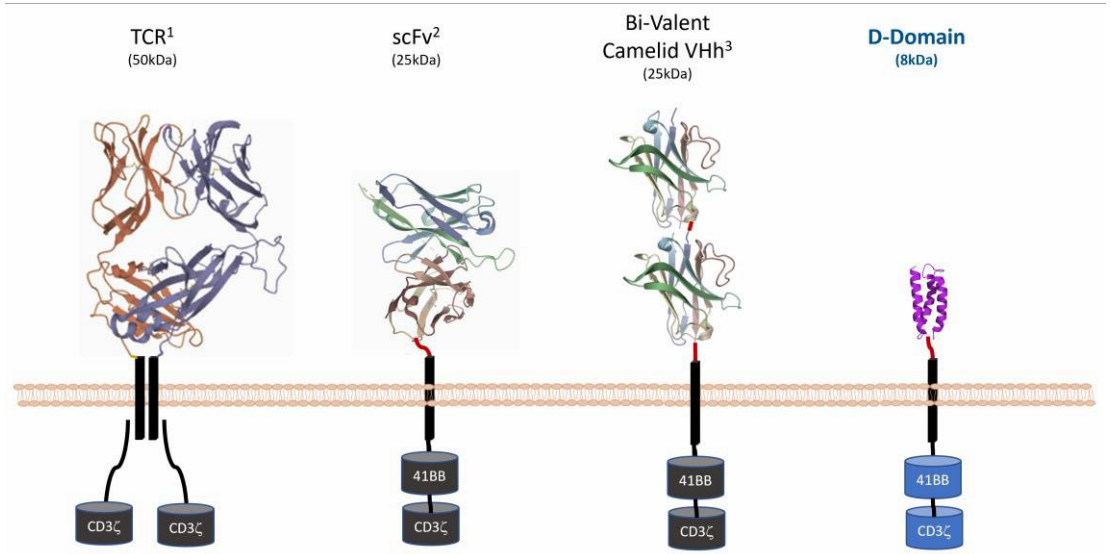
SWOG 2114: A Randomized Phase II trial of Consolidation Therapy following CD19 CAR T-cell Treatment for Relapsed/Refractory Large B-cell Lymphoma or Grade IIIB Follicular Lymphoma



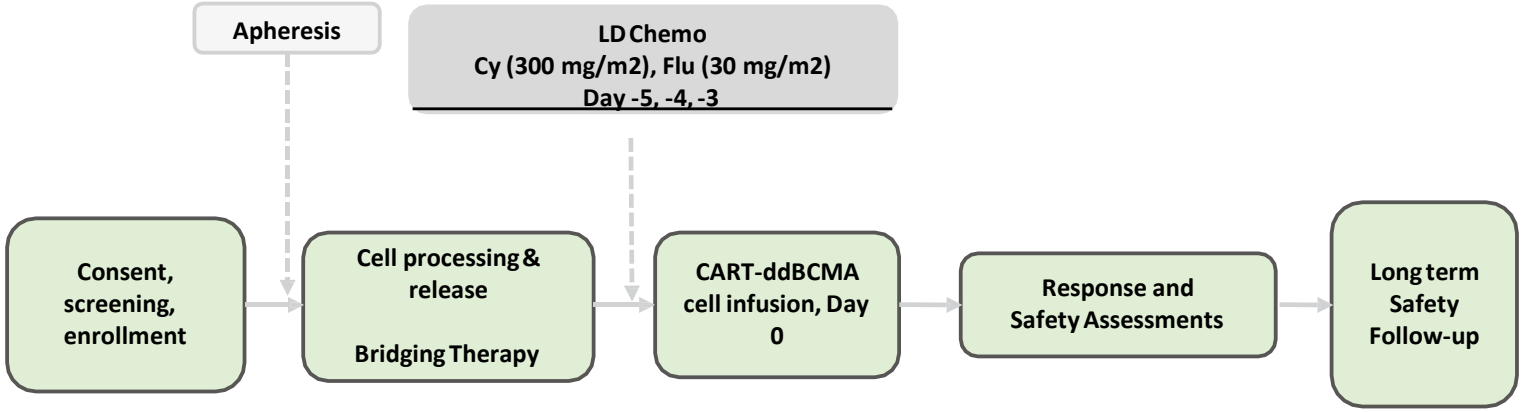
- Day 30 PET-CT will be centrally reviewed (72 hours turn around time) – response criteria per Lugano
- Treatment vs observation (1:1:1:1 randomization)
- 1 year PFS: 20.0% (observation) vs 44.7% (consolidation) → **120 patients (30 per arm)**

Multiple Myeloma: another CAR T Target Disease

- CART-ddBCMA is an autologous CAR-T containing a novel computationally designed synthetic protein[1,2] binding domain (non-scFv) engineered to reduce the risk of immunogenicity and is highly stable
- Phase 1 first-in-human trial is in progress, enrolling patients with relapsed or refractory myeloma
  - Prior IMiD, PI, and CD38-targeted therapy
  - Received ≥3 prior therapies or triple refractory
  - 2 Dose Levels evaluated, 6 subjects in each dose escalation cohort.
    - DL1 = 100 x 10^6 CAR+ cells; DL2 = 300 x 10^6 CAR+ cells
  - Expansion cohort is enrolled at DL1



[1] Chan, KF. et al. 2018., Nat Commun 9:1026–1026
[2] Bjerragaard-Anderson, K., et al 2018. Sci. Rep., 8:10836–10836.
[3] https://commons.wikimedia.org/wiki/File:1I3V_(Lama_VHH_domain

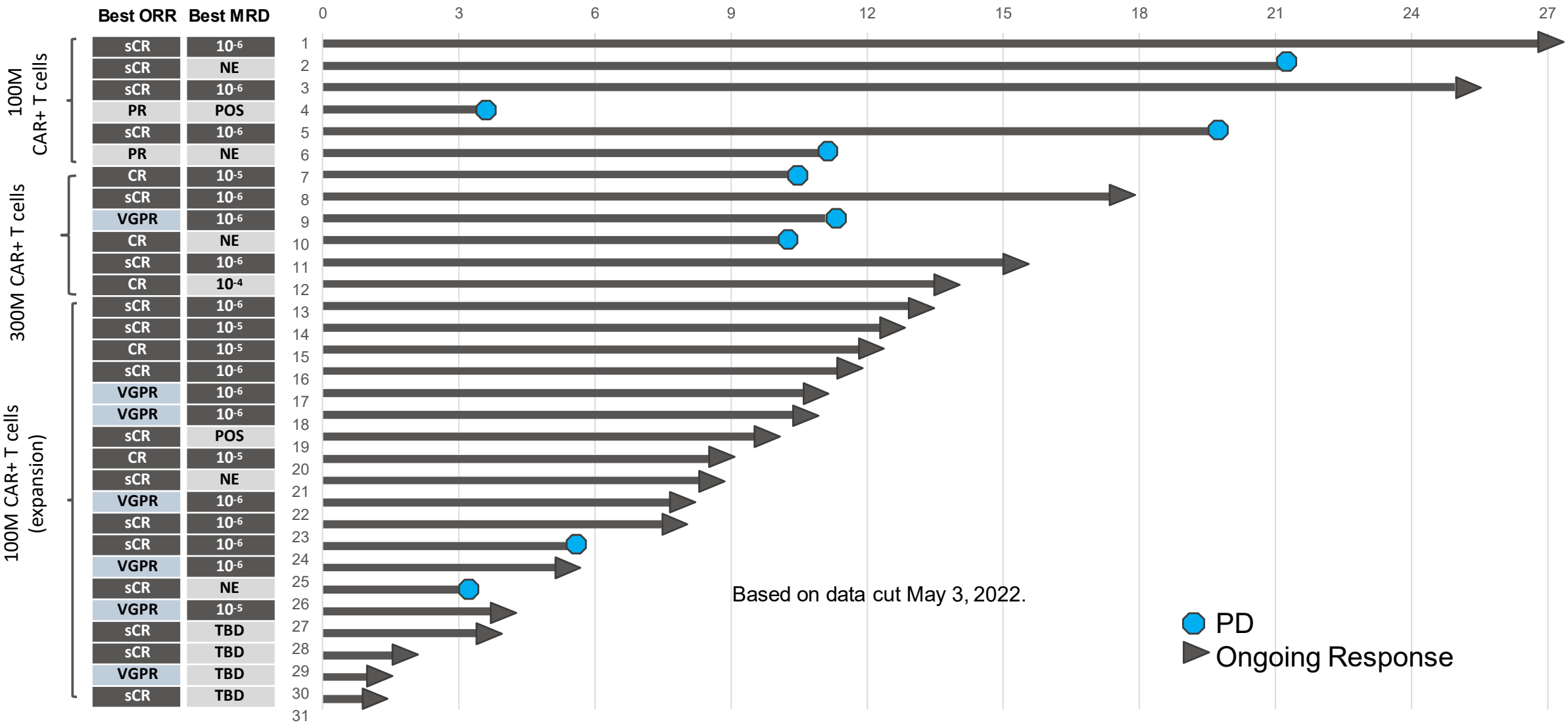


[1]Rotte, et al. "BCMA targeting CAR T cells using a novel D-domain binder for multiple myeloma: clinical development update." *Immuno-Oncology Insights 2022; 3(1), 13–24*

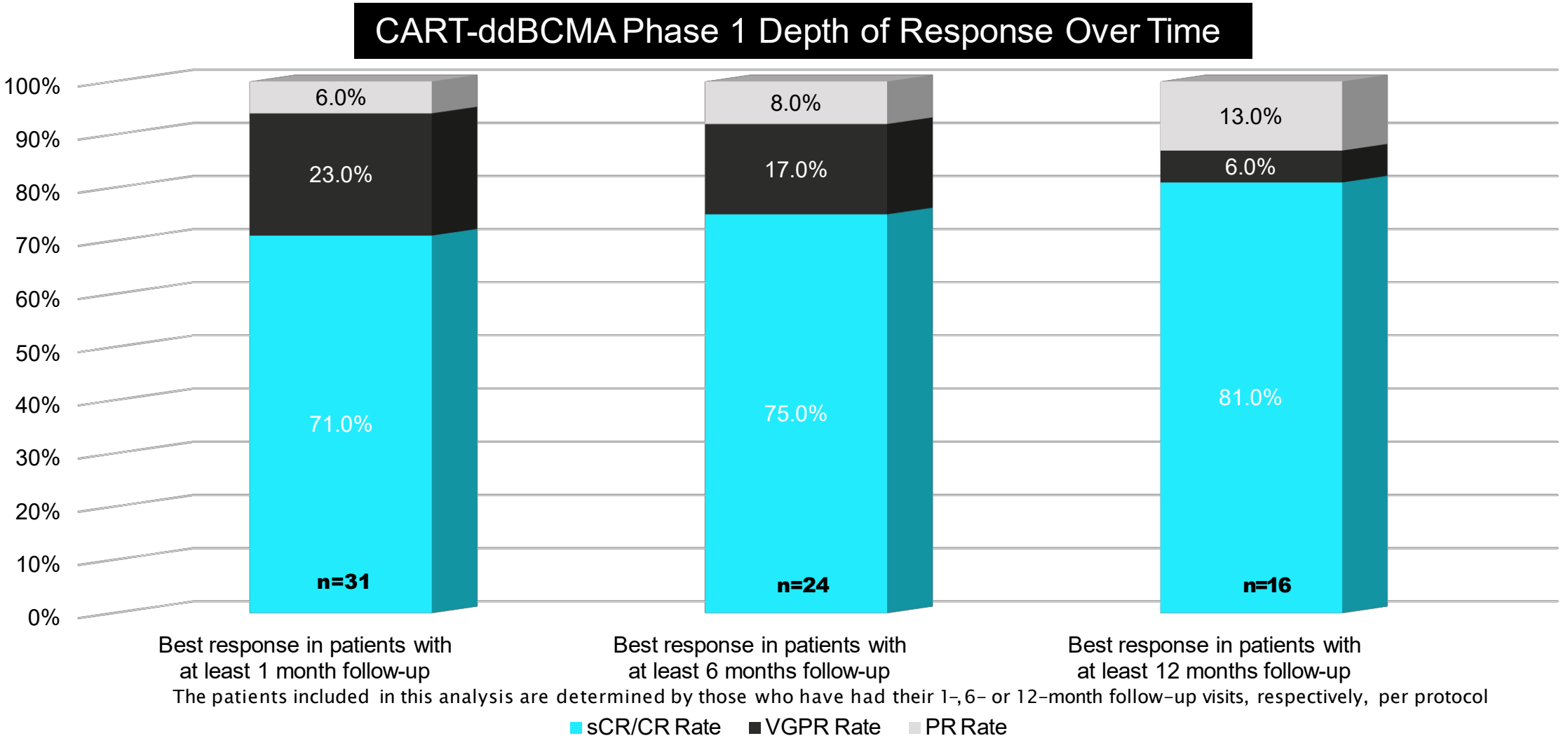
[2]Frigault et al. "Phase 1 Study of CART-ddBCMA for the treatment of subjects with relapsed and refractory Multiple Myeloma." Blood Advances 2022; bloodadvances.2022007210. doi: https://doi.org/10.1182/bloodadvances.2022007210.

CONFIDENTIAL

CART-DDBCMA: 100% ORR AND DURABLE RESPONSES



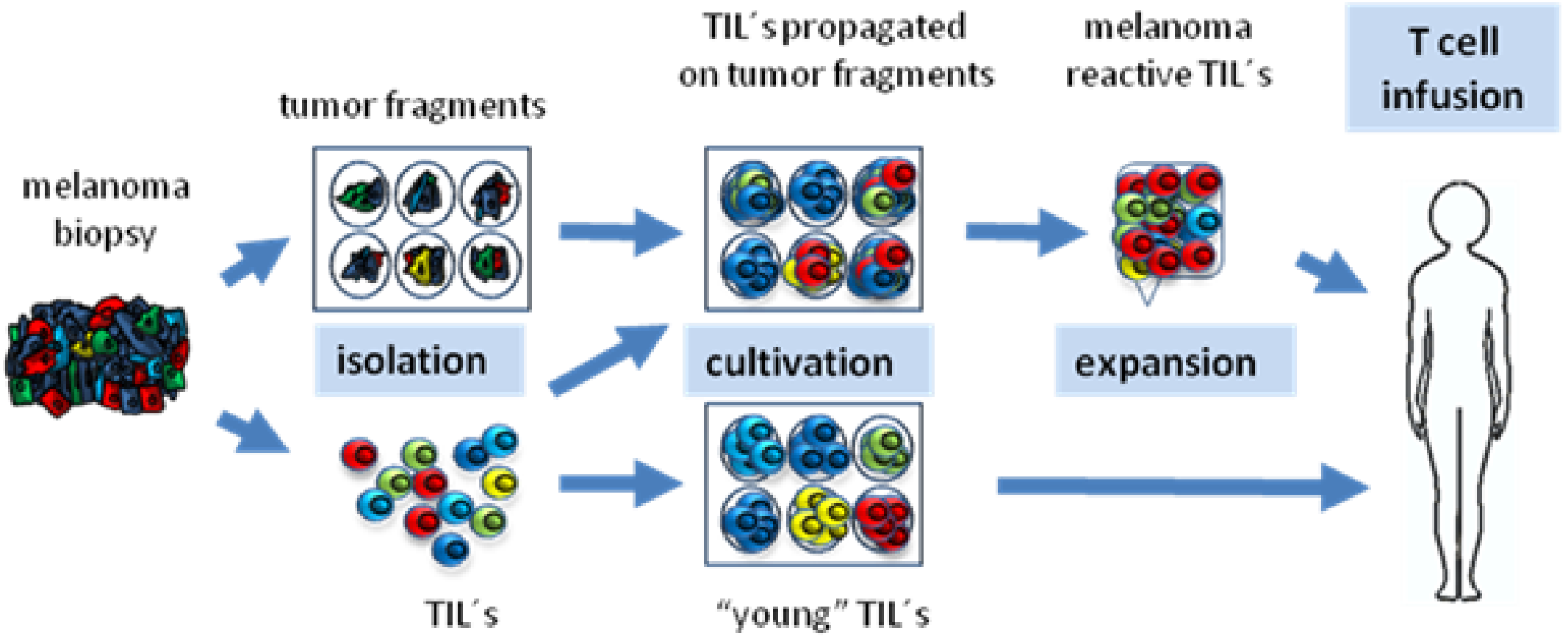
PROPORTION OF PATIENTS WITH SCR/CR INCREASED OVER TIME



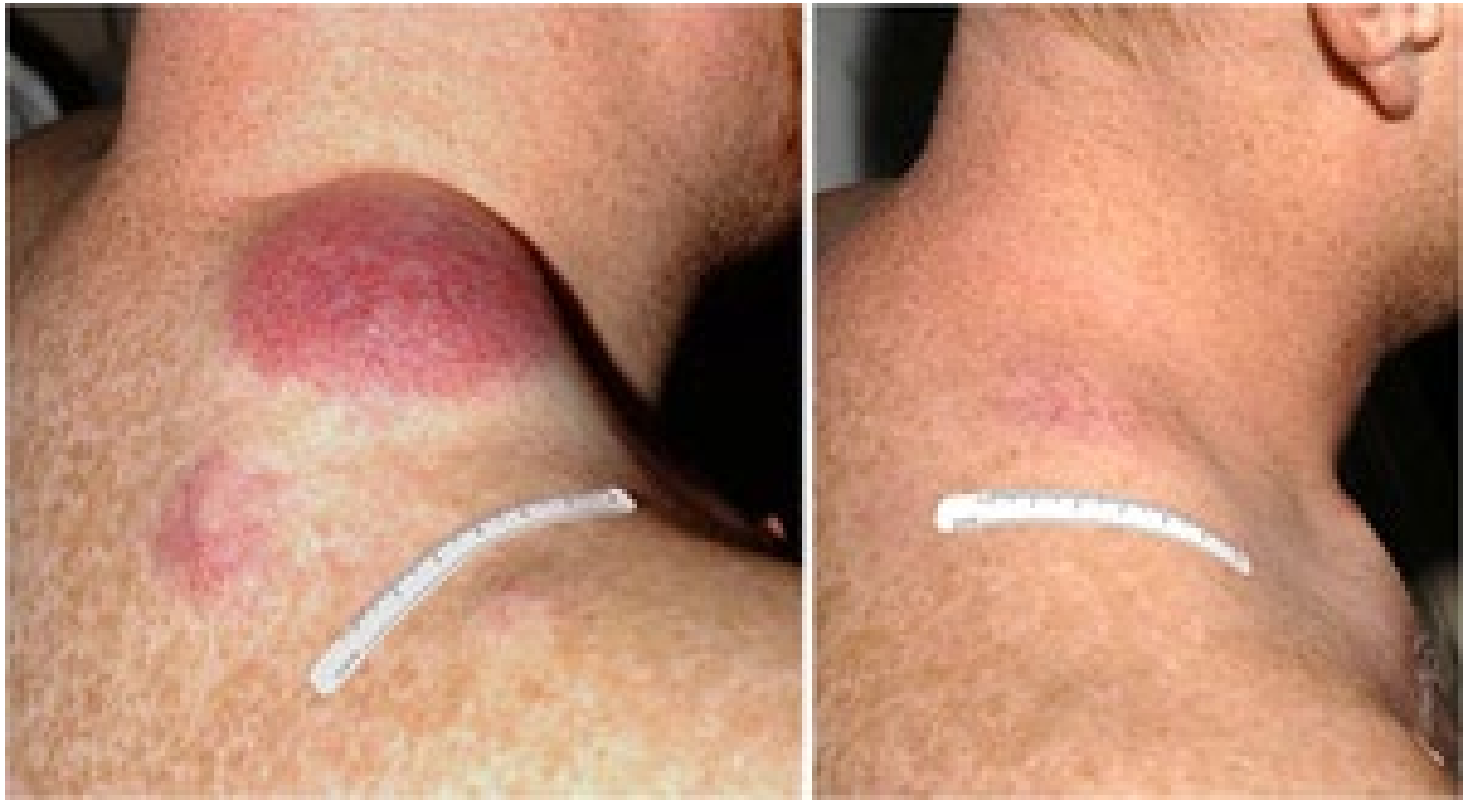
Solid Tumors:
the next evolution for Cell Therapy

- Multiple cell populations being used
- CAR T-cell
- TIL
- NK cells
- Macrophage/monocyte
- Natural Killer cell

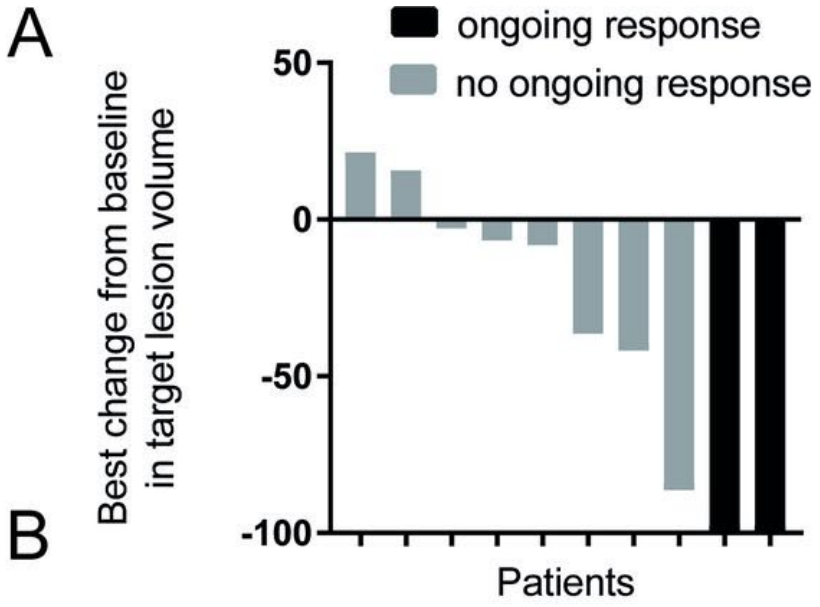
Generation of TIL (tumor infiltrating lymphocytes)

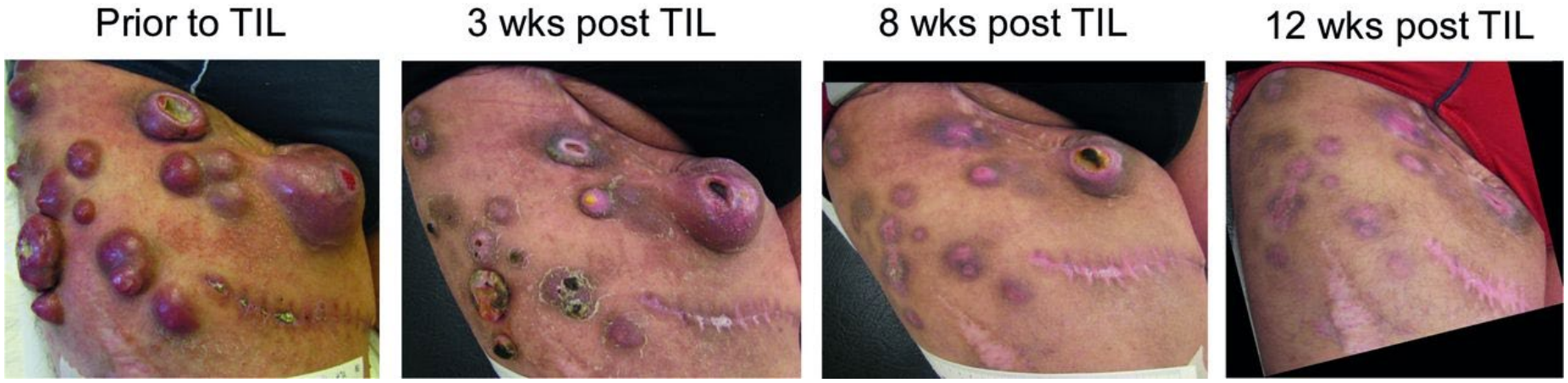


TIL Responsive Melanoma

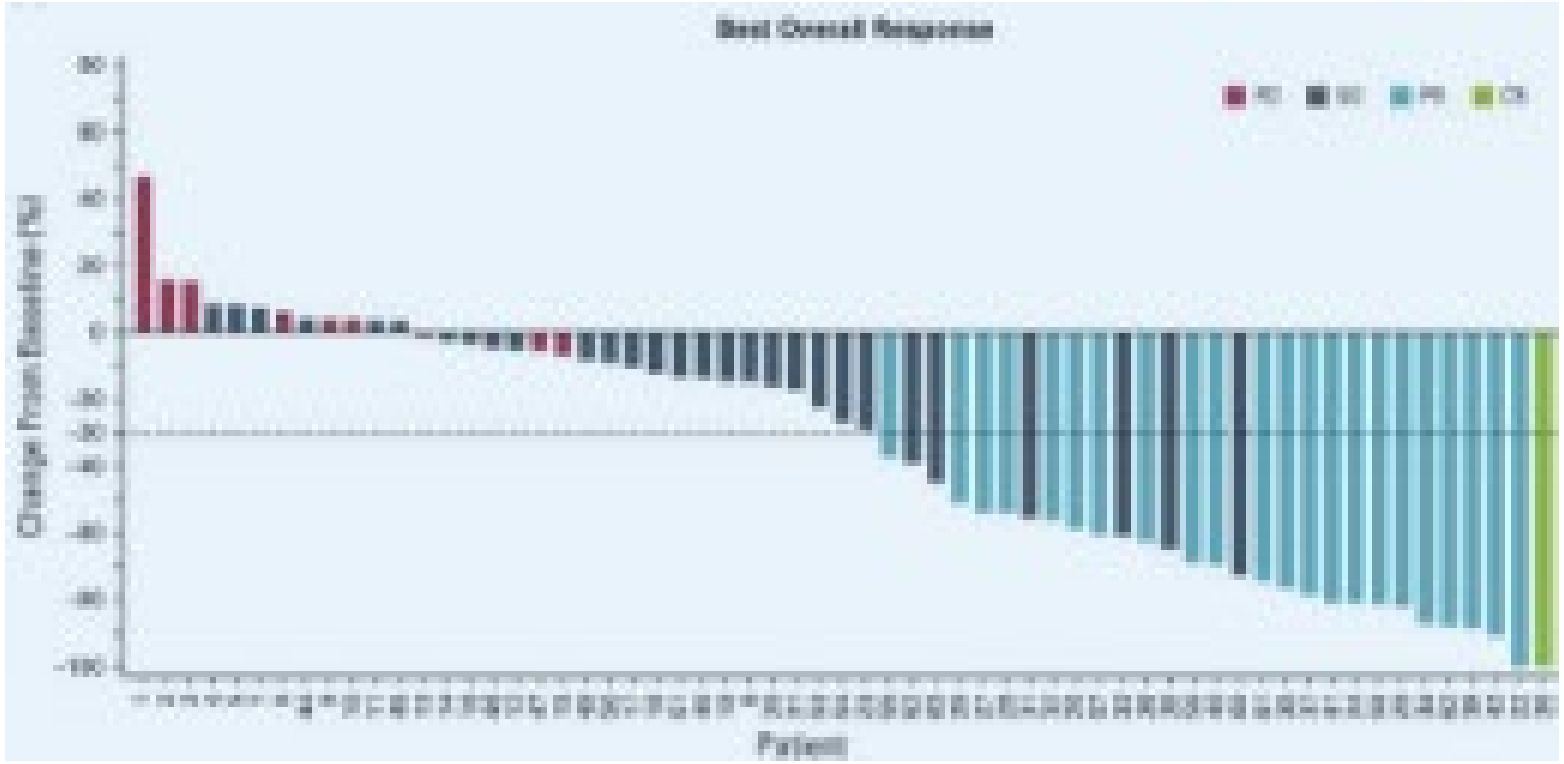


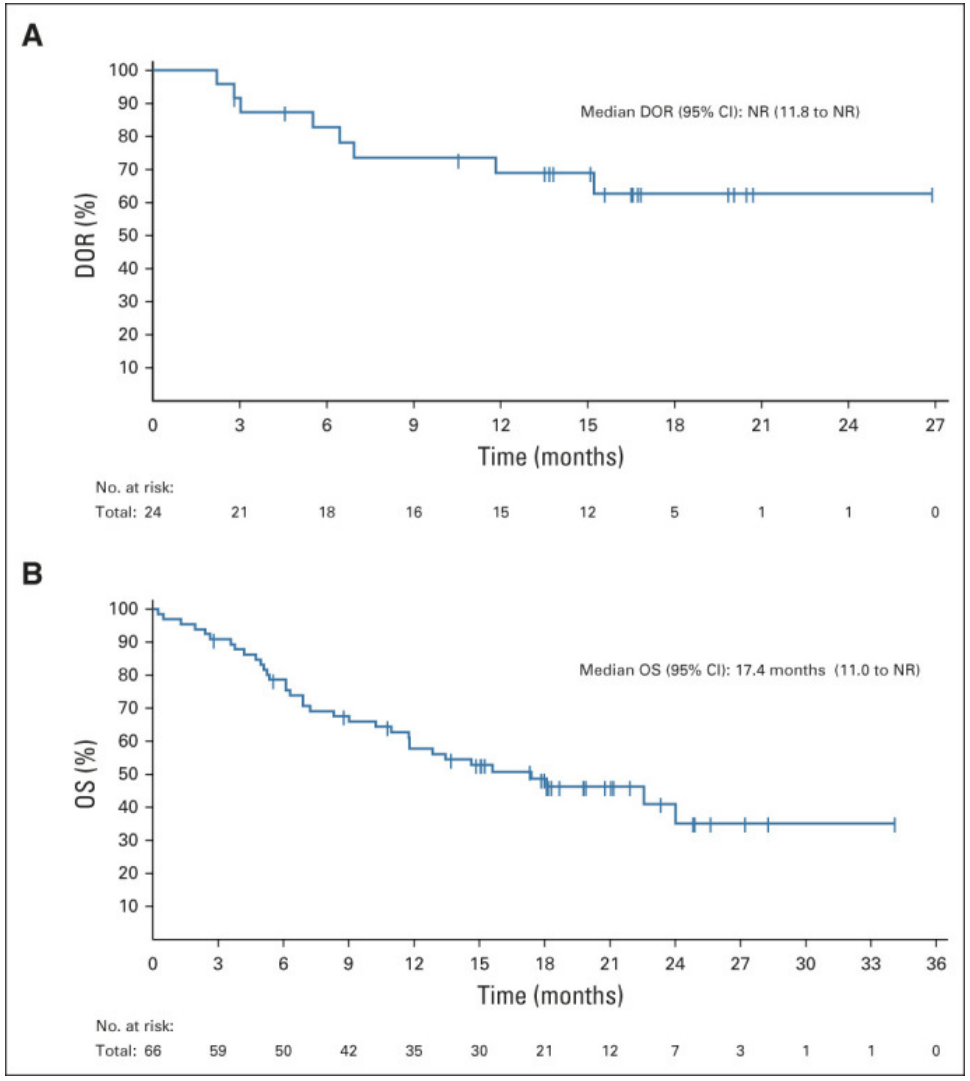
Tumor Infiltrating Lymphocytes, ven den Berg, JITC, 2020





Lifileucel, Sarnaik et al, JCO, 2021





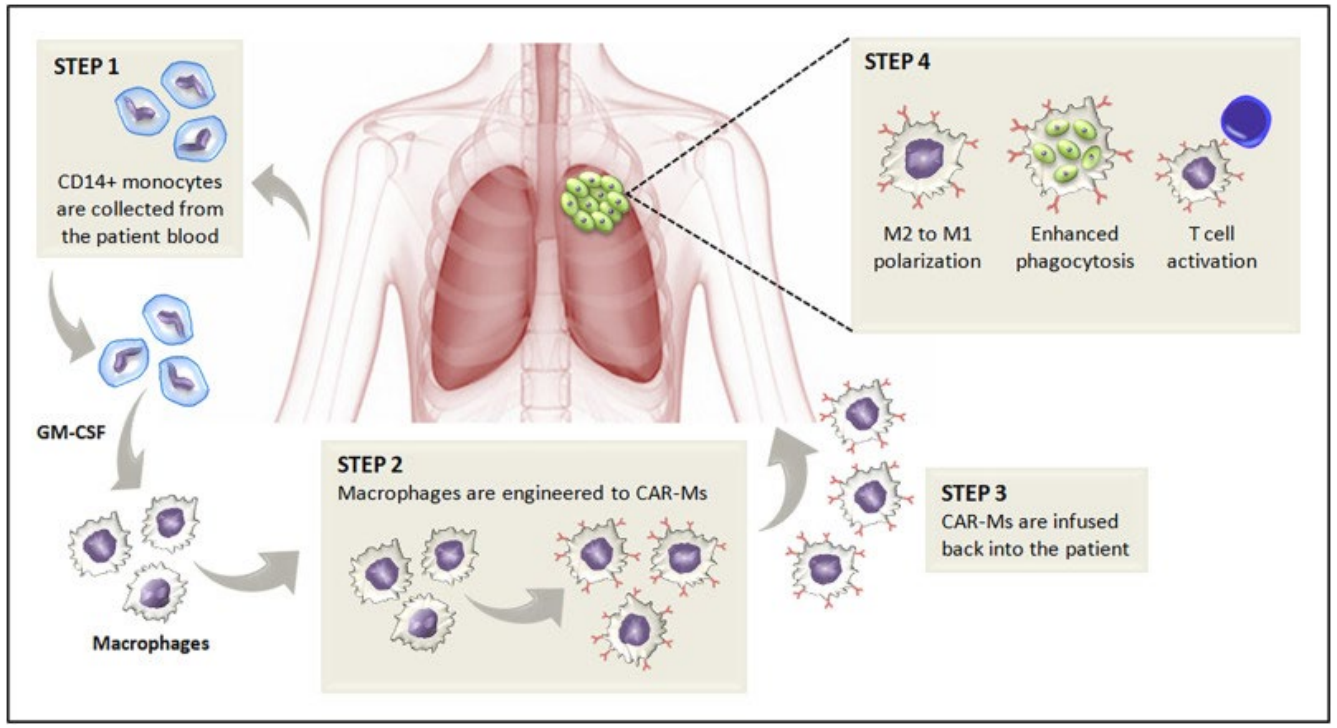
Phase II, open label, prior checkpoint inhibitor, BRAF treated patients

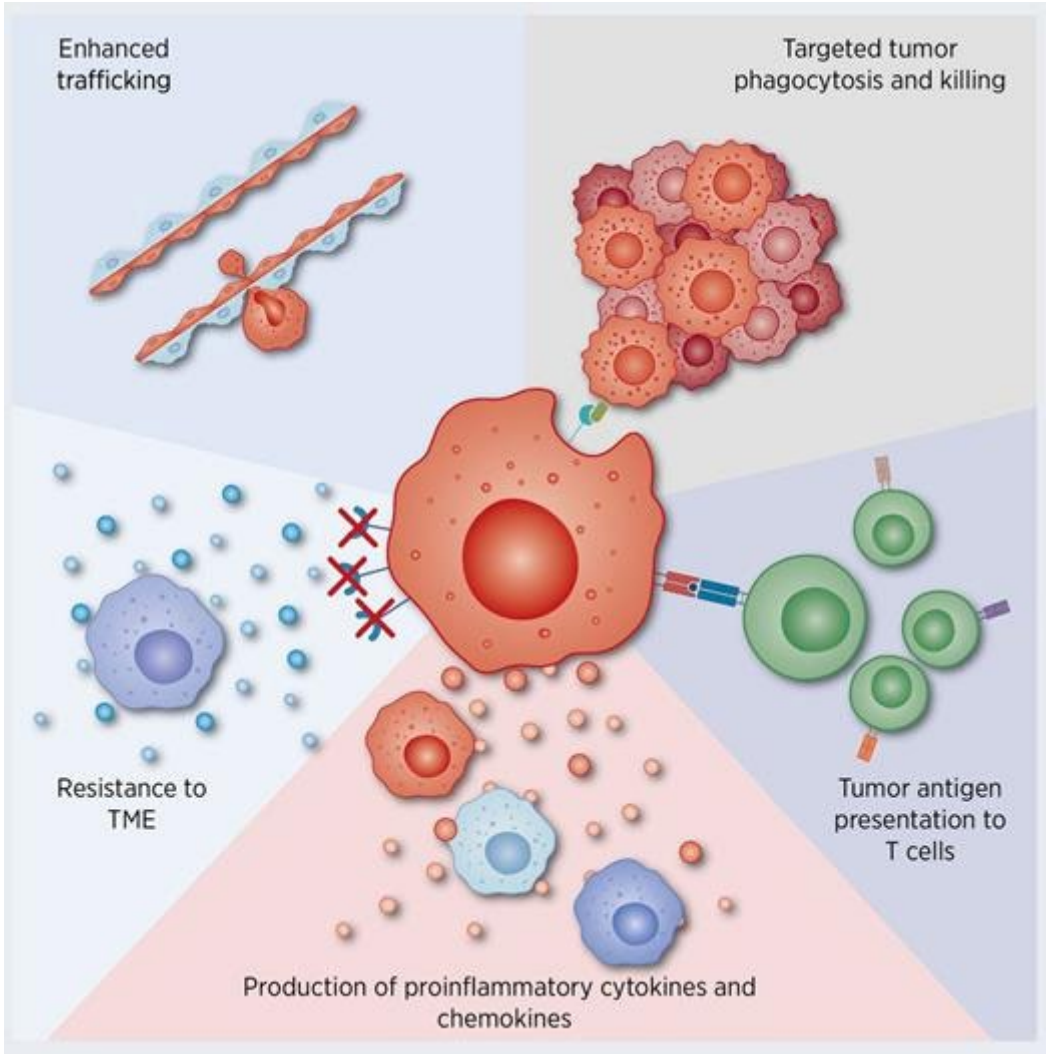
66 enrolled

Med DOR not reached with Median 18.7 months

UNDER FDA REVIEW FOR BLA APPROVAL CONSIDERATION

Macrophage- CAR products





CARISMA Therapeutics: Phase I, 6 center clinical trial for Her2/Neu overexpressed malignancies.

Targets : GI, Ovarian, Breast

ENVOY-001 (SQZ-AAC-HPV-101): A Phase 1, Multicenter, Open-Label Study of SQZ-AAC-HPV as Monotherapy and in Combination with Immune Checkpoint Inhibitors in HLA-A*02+ Patients with HPV16+ Recurrent, Locally Advanced or Metastatic Solid Tumors. (Trial in Progress)

Victoria Villaflor, Rajwanth Veluswamy, Elena Garralda, Richard Maziarz, Emese Zsiros, Anthony Shields, Mariano Ponz-Sarvise, Martijn Lolkema, Mehdi Brahmi, Julia Jennings, Nathan Miselis, Lindsay Moore, Katarina Blagovic, Rui-Ru Ji, Scott Loughhead, Ricardo Zwirtes, Sandip Patel

City of Hope, Duarte, CA, Mount Sinai, New York, NY, Vall d'Hebron Institut d'Oncologia, Barcelona, Spain, Oregon Health & Science University, Portland, OR, Roswell Park, Buffalo, NY, Karmanos Cancer Institute, Detroit, MI, Centro de Investigación Médica Aplicada, Navarra, Spain, Erasmus Medical Center, Rotterdam, Netherlands, Centre Léon Bérard, Lyon, France, SQZ Biotechnologies, Watertown, MA, UC San Diego Health, La Jolla, CA

AACR, 2022
RBC as Immune cell Stimulators;
Target: any HPV16+ CA
Eligibility: HLA-A2.01+ status

Dose escalation

Background

- In clinical cancer immunotherapy, therapeutic vaccines have been identified as a promising approach to increase the number of tumor-specific T cells to drive tumor regression. Effective antigen presentation on MHC-I has been a barrier to generating effective therapeutic cancer vaccines. We use a microfluidics-based approach to squeeze (Cell Squeeze® technology) antigens and adjuvant into red blood cells (RBC) to stimulate antigen-specific activation of endogenous T cells against a tumor. (**Figure 1**).
- The Cell Squeeze® approach allows delivery of antigen and adjuvant directly to cytosol of RBCs creating antigen activating cells (AACs). The resultant SQZ-AACs express greater extracellular phosphatidylserine, in effect aging the RBC. SQZ-AACs leverage the natural destruction of aged RBC (**Figure 2**).
- SQZ-AACs are phagocytosed by professional antigen presenting cells (APCs) which will in turn activate CD8+ T cells (**Figure 3**).
- SQZ-AACs enter the immunogenic response downstream of other therapeutic vaccines close to the TCR-MHC-I Handshake, primarily in the spleen and liver (**Figure 3**).
- SQZ-AAC-HPV is an innovative, investigational autologous therapeutic HPV-16 cancer vaccine squeezed with synthetic long peptides (SLPs) containing MHC-I restricted epitopes from HPV16 E6 and E7 antigens and adjuvant polyinosinic-polycytidylic acid (poly I:C). Importantly, SQZ-AAC-HPV is neither genetically modified nor immune effector cells.
- Treatment with AACs squeezed with antigen demonstrate antigen specific CD8+ T cell activation (**Figure 4**).
- In the murine TC-1 tumor model, tumor regression correlated with an influx of HPV16-specific CD8+ TILs (**Figure 5**).

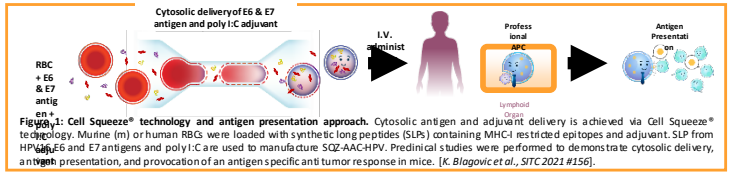


Figure 1: Cell Squeeze® technology and antigen presentation approach. Cytosolic antigen and adjuvant delivery is achieved via Cell Squeeze® technology. Murine (m) or human RBCs were loaded with synthetic long peptides (SLPs) containing MHC-I restricted epitopes and adjuvant. SLP from HPV16 E6 and E7 antigens and poly I:C are used to manufacture SQZ-AAC-HPV. Preclinical studies were performed to demonstrate cytosolic delivery, antigen presentation, and provocation of an antigen specific anti tumor response in mice. [*K. Blagovic et al., SITC 2021 #156*].

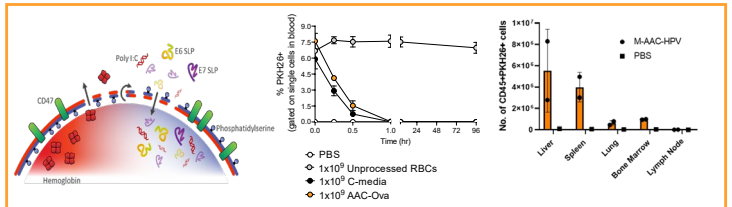


Figure 2: LEFT: RBCs appeared as aged as a result of the Cell Squeeze® process. As a result of the Cell Squeeze® technology, there is an increase in phosphatidylserine on the surface of the AAC relative to the starting RBC, aging the cells. These AACs are leverage the body's natural destruction of aged RBCs to present Cell Squeeze® cargo in lymphoid organs. **CENTER: Squeezed cells are rapidly cleared.** In murine models, RBCs were labeled with membrane dye PKH26 and squeezed with poly I:C adjuvant and ovalbumin (AAC-Ova) or squeezed with media alone (C-media). Carriers are rapidly cleared from circulation compared to labeled, unprocessed RBCs. **RIGHT: Primarily Taken up in Liver and Spleen.** Shown is the percentage of PKH26+ macrophages (Kupffer cells in the liver and RPM in the spleen), DCs and B cells in spleen and liver collected 1-2 hours after the intravenous administration of PKH26-labeled MAAC-HPV or PBS control.

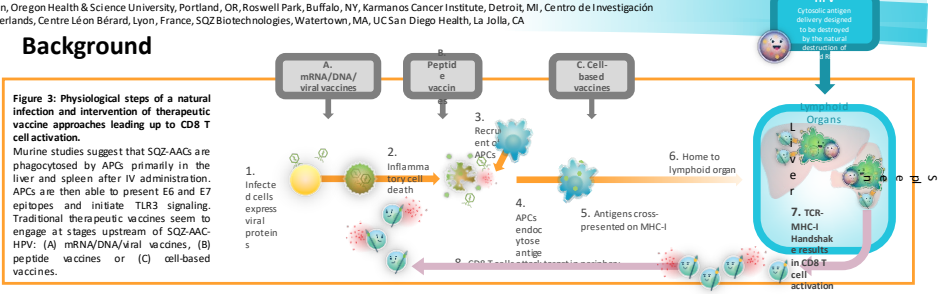


Figure 3: Physiological steps of a natural infection and intervention of therapeutic vaccine approaches leading up to CD8 T cell activation.
Murine studies suggest that SQZ-AACs are phagocytosed by APCs primarily in the liver and spleen after IV administration. APCs are then able to present E6 and E7 epitopes and initiate TLR3 signaling. Traditional therapeutic vaccines seem to engage at stages upstream of SQZ-AAC-HPV: (A) mRNA/DNA/viral vaccines, (B) peptide vaccines or (C) cell-based vaccines.

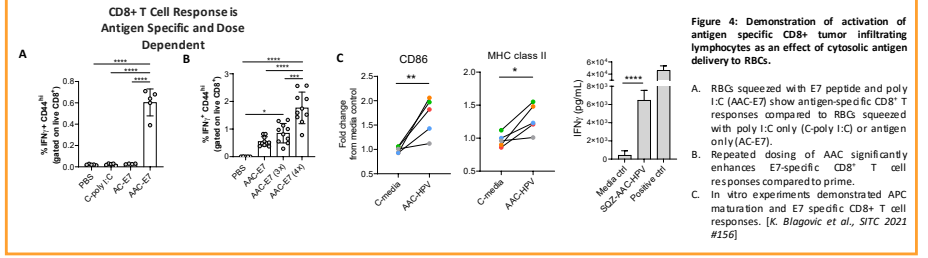


Figure 4: Demonstration of activation of antigen specific CD8+ tumor infiltrating lymphocytes as an effect of cytosolic antigen delivery to RBCs.

A. RBCs squeezed with E7 peptide and poly I:C (AAC-E7) show antigen-specific CD8+ T responses compared to RBCs squeezed with poly I:C only (C-poly I:C) or antigen only (AC-E7).
B. Repeated dosing of AAC significantly enhances E7-specific CD8+ T cell responses compared to prime.
C. In vitro experiments demonstrated APC maturation and E7 specific CD8+ T cell responses. [*K. Blagovic et al., SITC 2021 #156*]

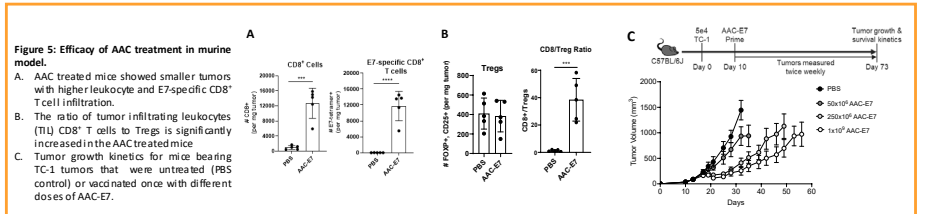


Figure 5: Efficacy of AAC treatment in murine model.

A. AAC treated mice showed smaller tumors with higher leukocyte and E7-specific CD8+ T cell infiltration.
B. The ratio of tumor infiltrating leukocytes (TIL) CD8+ T cells to Tregs is significantly increased in the AAC treated mice
C. Tumor growth kinetics for mice bearing TC-1 tumors that were untreated (PBS control) or vaccinated once with different doses of AAC-E7.

Methods

Study Design

- ENVOY-001 (SQZ-AAC-HPV-101; NCT04892043) is open for enrollment to HLA A*02+ patients with HPV16+ recurrent, locally advanced or metastatic solid tumors and includes a Monotherapy Dose Escalation Phase and a Combination Safety Phase with immune checkpoint inhibitors (**Figure 6**).
- Eligible diseases are all HPV-16 driven cancers (including anal, cervical, head and neck, penile, vaginal, and vulvar).
- Patients will receive SQZ-AAC-HPV Q3W for up to 1 year or until available autologous drug product is exhausted.
- Eligible patients will undergo a **single whole blood collection** at the study site. (**Figure 7**).
- Treatment **does not require a preconditioning regimen** e.g. immuno- or myeloablative regimen.
- Dose limiting toxicity (DLT) period is 28 days for monotherapy and 42 days for the combination phase.
- Patients must have a lesion that can be biopsied at Screening and on study.

Study Assessments

- Safety and tolerability to identify the monotherapy Recommended Phase 2 Dose (RP2D) and RP2D in combination with immune checkpoint inhibitors
- Preliminary evidence of antitumor activity of SQZ-AAC-HPV monotherapy and in combination with immune checkpoint inhibitors will be evaluated per RECIST 1.1
- Immunogenic evaluations
  - The pharmacodynamic evaluations focus on measurement and characterization of CD8+ T cells within the tumor and circulation. Mechanisms of resistance in the tumor microenvironment are also assessed
  - Antigen-specific reactivity of circulating CD8+ T cells using methods including, but not limited to, Elispot
  - Cytokine responses
- Other Pharmacodynamic Evaluations: Circulating cell-free HPV16 DNA levels in plasma

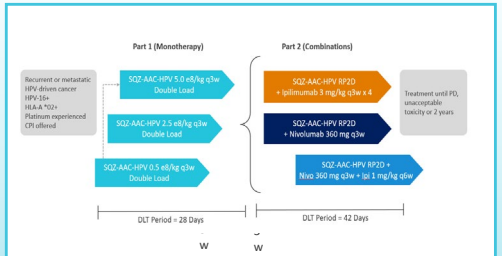


Figure 6: ENVOY-001 (SQZ-AAC-HPV-101) Study Protocol. A monotherapy dose is tested with at least 2 different cell dose levels to identify the optimal dose. Additional higher or lower dose cohorts may be opened.

Combination Safety Phase cohorts:
- SQZ-AAC-HPV RP2D plus ipilimumab*
- SQZ-AAC-HPV RP2D plus nivolumab
- SQZ-AAC-HPV RP2D plus nivolumab and ipilimumab**

*Maximum of 4 doses of ipilimumab. SQZ-AAC-HPV dosing may continue after ipilimumab treatment is complete.
**Contingent on the safety of respective doublets: SQZ-AAC-HPV plus nivolumab and ipilimumab

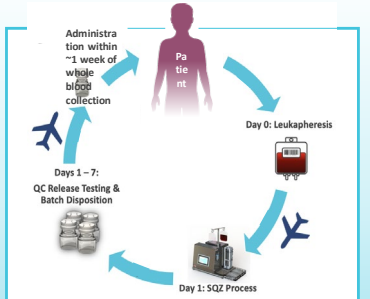
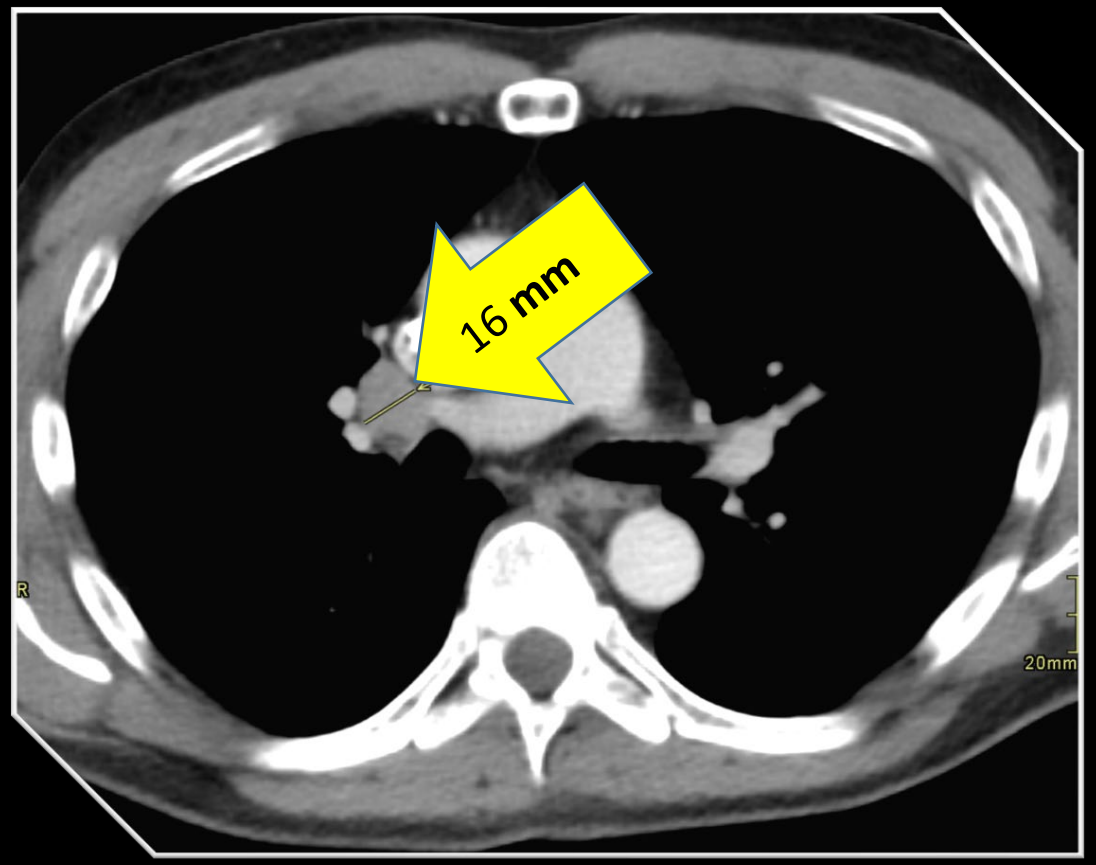


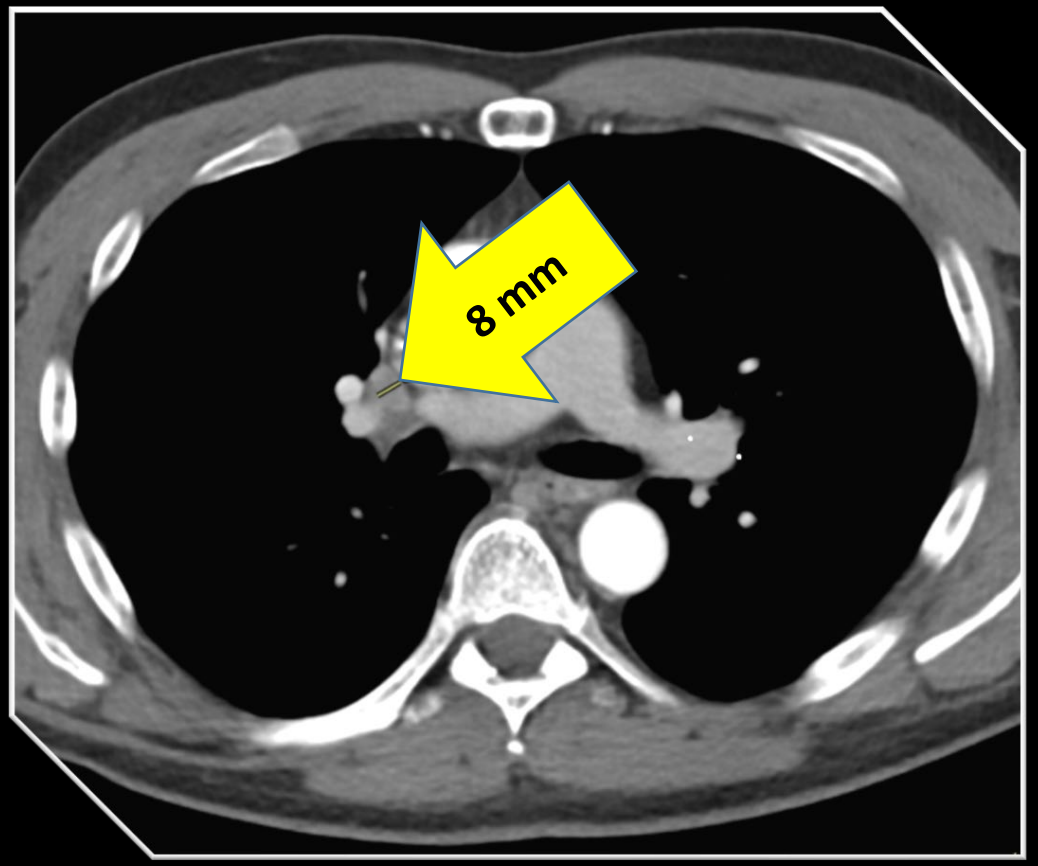
Figure 7: Vein to Vein Process for a Patient. In our Phase 1 GMP compliant manufacturing process, patient cells are processed in less than 24 hours to generate cryopreserved drug product.

The vein-to-vein time for the 1st administration is approximately one week. Patients do not require a conditioning regimen before the 1st administration.

10 2022



2 2023



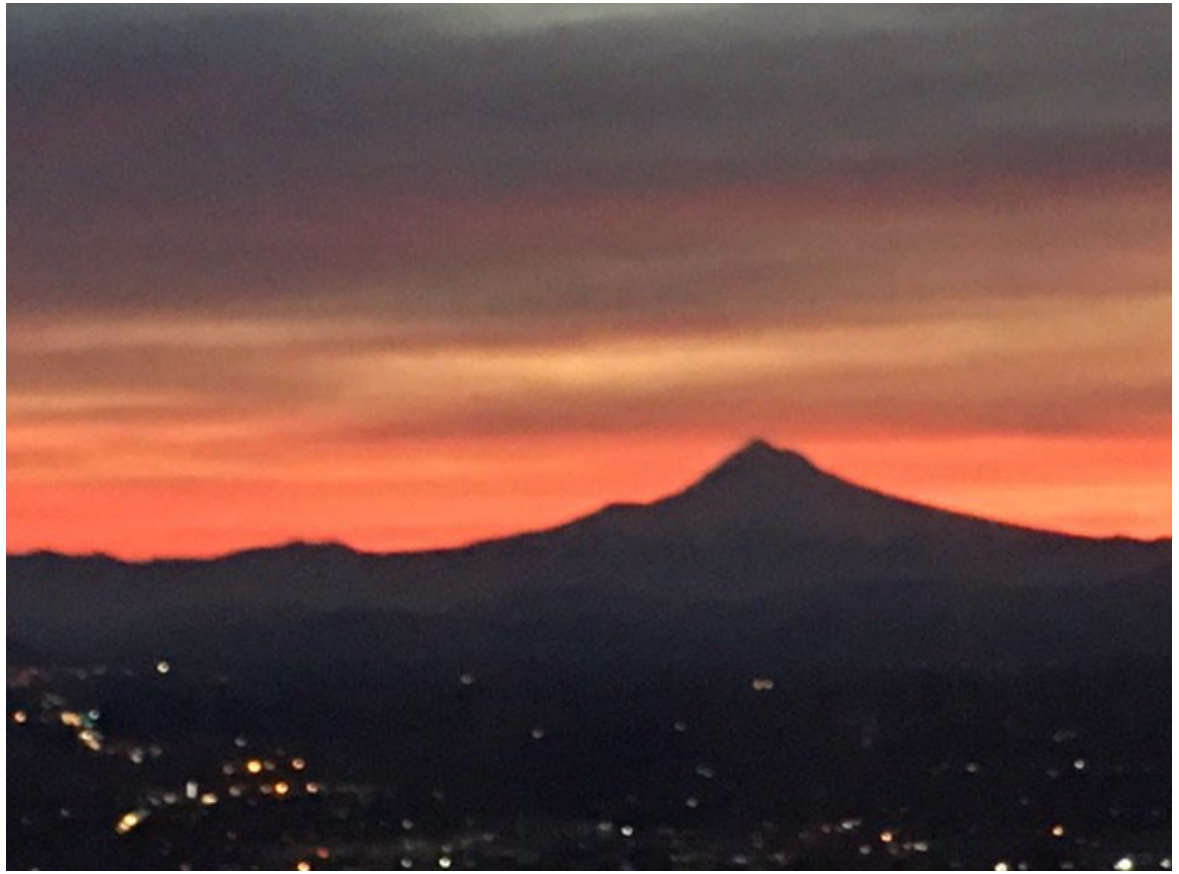
Chest CT showing decrease in right hilar lymph node over time

OHSU Solid Cancer Clinical Trials

- Autologous ROR1 targeting CAR T-cells for advanced solid tumor malignancies
- HLA restricted, NY ESO peptide specific autologous T cells for Synovial Cell Sarcoma
- HLA restricted, NY ESO peptide specific autologous T cells for advanced Ca
- Autologous TIL for R/R NSCLC
- Autologous TIL for advanced malignancies: melanoma, CRC, NSCLC
- Her2/Neu Macrophage CAR for overexpressed HER2/Neu malignancies
- HPV peptide loaded RBC + poly IC as systemic tumor vaccine for HPV+ malignancies
- Autologous Claudin-1 CAR T-cells for Upper GI and Pancreatic ca

- Future studies under consideration: HCC and SCLC

Immune Effector Cell Therapy: the work continues & the work evolves



Thanks to all patients, to the OHSU/KCI clinical & research staff & teams, and to all practice partners across the region