Transplantation & Cellular Therapy: Are there changes to the Standards of Care? Reflections on ASH 2022

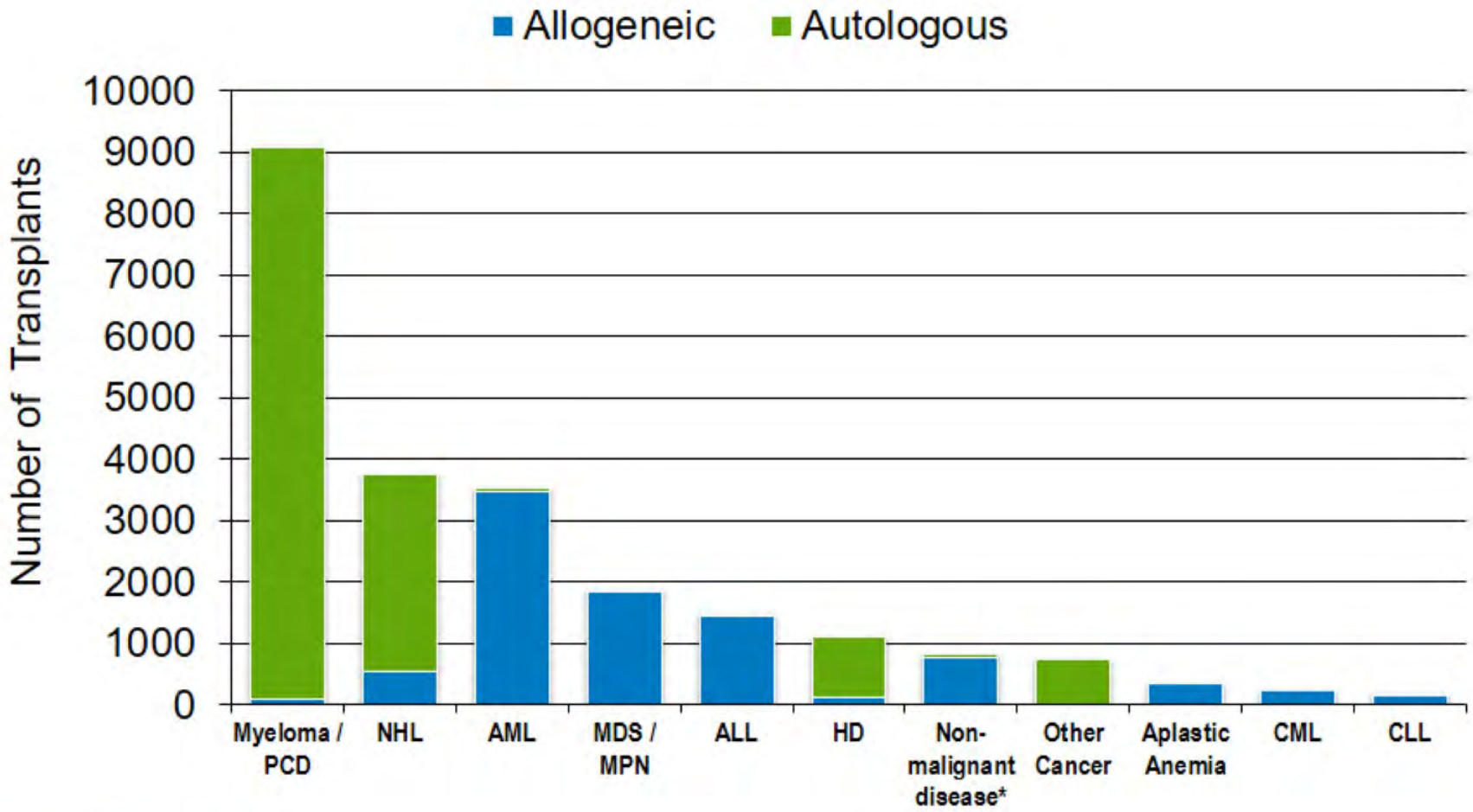
Richard Maziarz MD

January 20, 2023

Overview

- Introduction
- ASH highlights
  - Nonmalignant
  - HCT Lymphoma
  - HCT Myeloma
  - HCT GVHD
  - CAR-T

Indications for Hematopoietic Cell Transplant in the US, 2018



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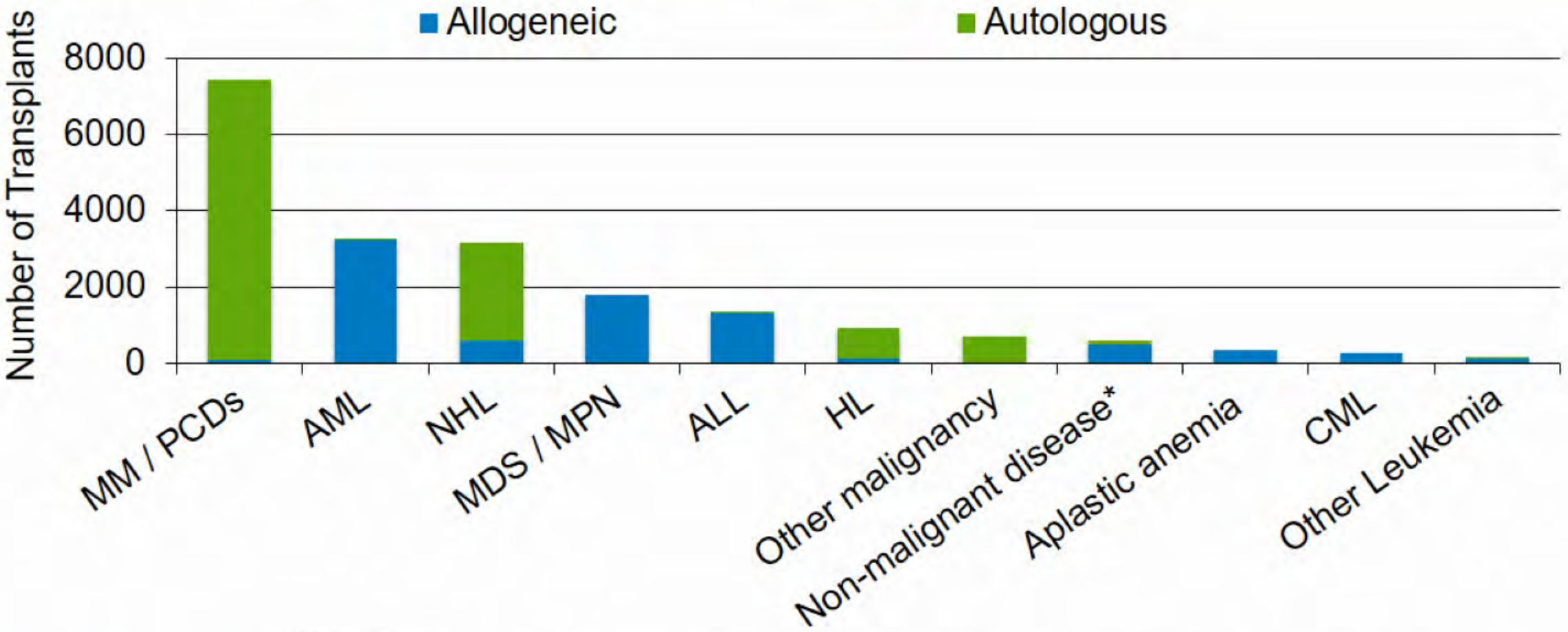
*excludes aplastic anemia.

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

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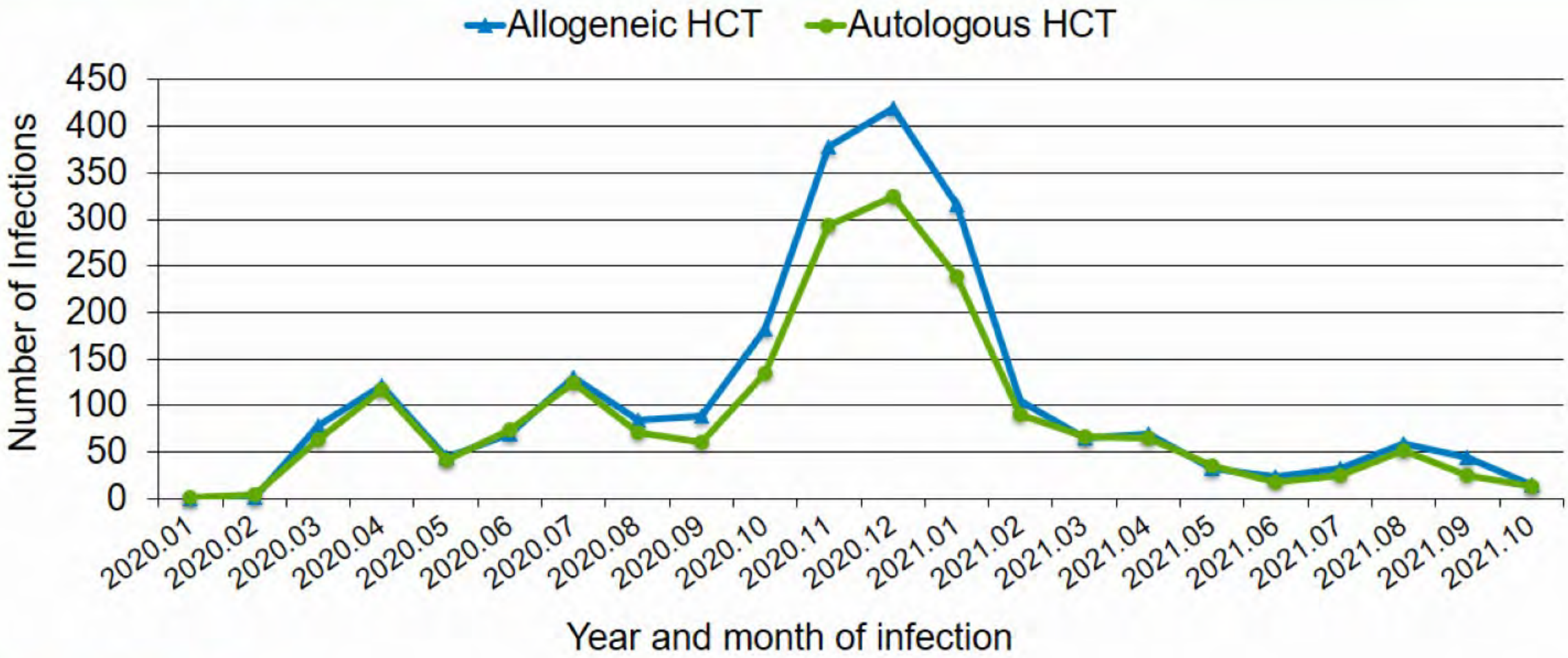
Number of COVID-19 Infections in HCT Recipients in the US Reported to CIBMTR by Transplant Type



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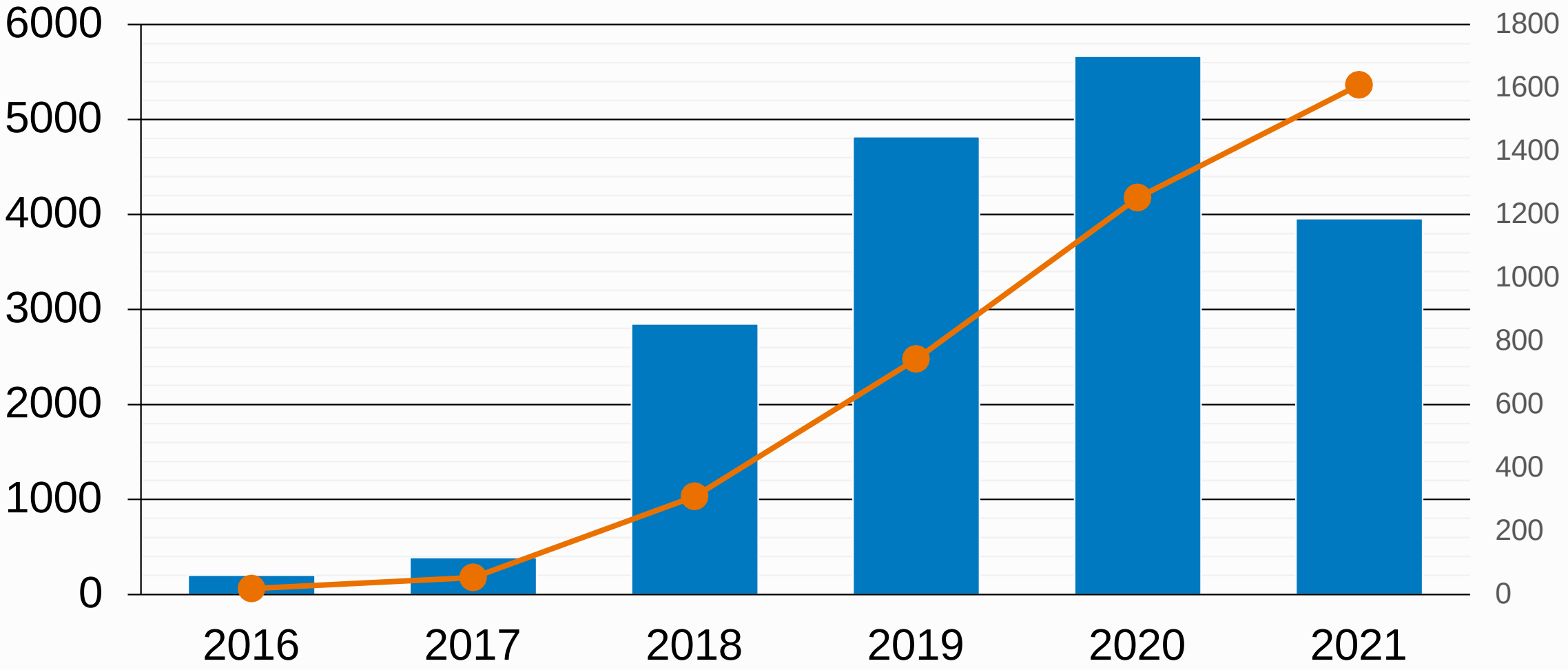
Data as of 12/01/2021; data may not complete for October due to data reporting lag

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

CELLULAR IMMUNOTHERAPY DATA RESOURCE



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Cumulative

Data Incomplete for 2020 & 2021

OHSU Adult HCT & CAR T activity

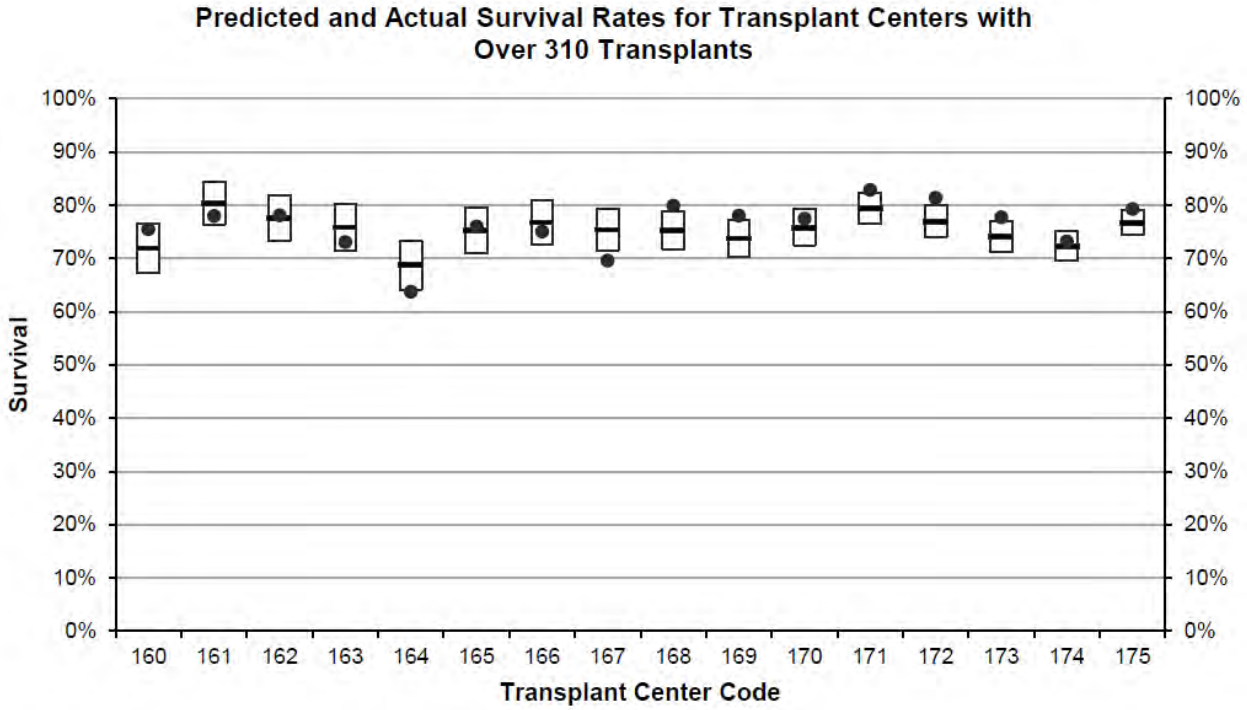
2018:	233	17
2019:	234	18
2020:	216	27
2021:	230	43
2022:	236	68
2023 (Jan):	20	7

2023 Annualized

240	*84 (Anticipate > 90)*

2022 Transplant Center Outcomes Report

Predicted and Actual Survival Rates for Transplant Centers with Over 310 Transplants



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

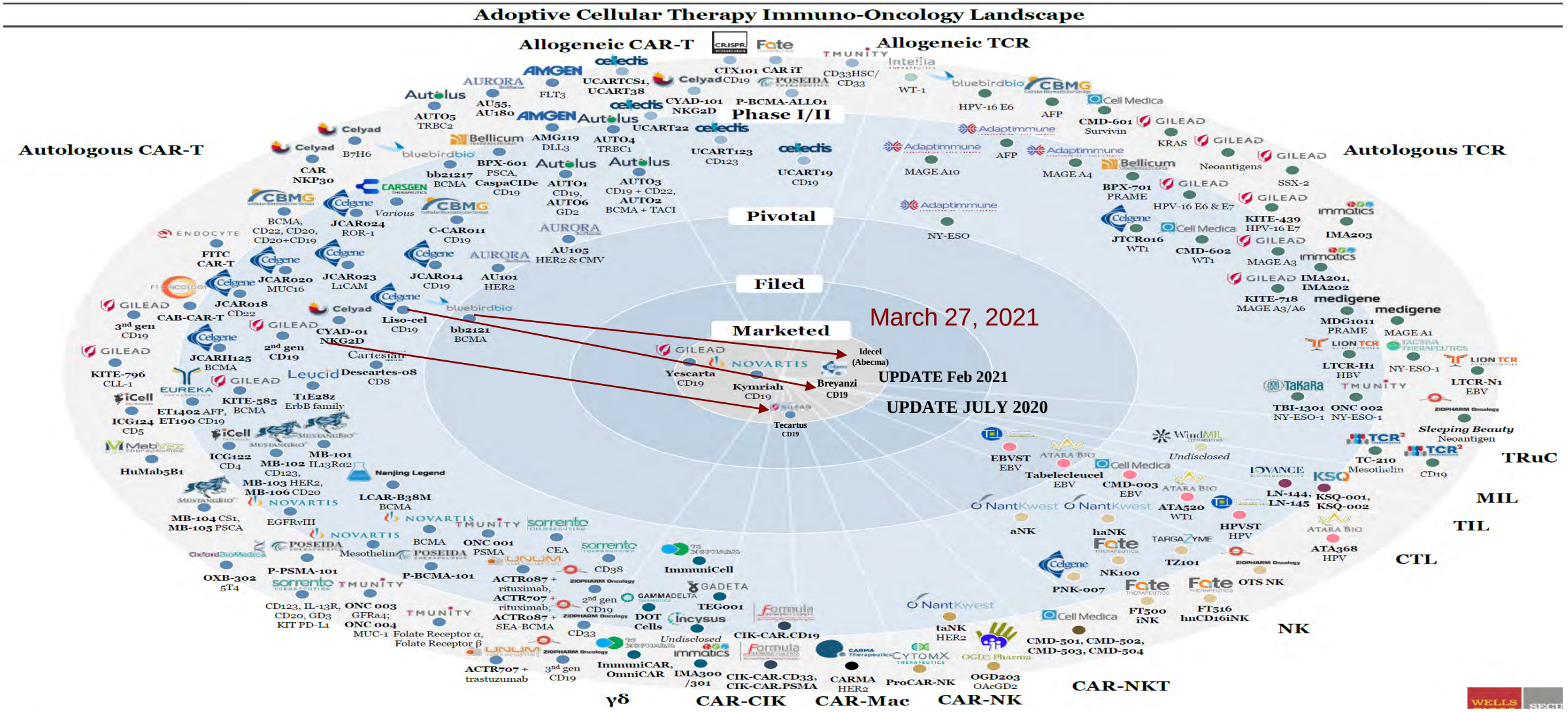
Solid line indicates predicted survival and box indicates 95% confidence interval. Dot indicates a center's actual survival; a dot below (above) the box indicates an under (over)-performing center relative to the network.

As a part of our federal contract to operate the Stem Cell Therapeutic Outcomes Database (SCTOD), the Center for International Blood & Marrow Transplant Research (CIBMTR) is required each year to perform a center-specific survival analysis providing one-year survival rates among U.S. centers. This report contains outcomes for transplants using both related and unrelated donors.

OHSU Pt: Relapsed, refractory DLBCL; no prior HCT

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

Cell Therapy Landscape: 2018-2021 View



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

Forecast (2021-2022 Pipeline)

Blood Disorders

- Hemophilia B (gene)
- Hemophilia A (gene)
- Transfusion dependent β-thalassemia (gene)

Cancer

- Follicular lymphoma (CAR-T expanded indications)
- Multiple myeloma (CAR-T)
- Bladder cancer (gene)
- Epstein-Barr virus-associated post-transplant lymphoproliferative disease (CTL)
- Cervical cancer (TIL)
- Metastatic melanoma (TIL)
- Marginal zone lymphoma (CAR-T expanded indications)
- Diffuse large B-cell lymphoma (CAR-T)
- Acute lymphoblastic leukemia (CAR-T)
- Synovial sarcoma (TCR T-Cell)

Ocular Disorders

- Choroideremia (gene)
- Leber hereditary optic neuropathy (gene)
- Wet & dry age-related macular degeneration (gene/cell)

Metabolic Disorders

- Cerebral adrenoleukodystrophy (gene)
- Mucopolysaccharidosis type III (gene)

Neurodegenerative

- Aromatic L-amino acid decarboxylase (AADC) deficiency (gene)
- Spinal muscular atrophy (expanded indications-gene)

Skin Disorders

- Recessive dystrophic epidermolysis bullosa (gene)
- Scleroderma (gene)

Inherited Immunodeficiencies

- Wiskott-Aldrich syndrome (gene)
- Leukocyte adhesion deficiency type I (gene)

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

Non-malignant diseases taking center stage

- Aplastic anemia
- Immune deficiency
- Hemoglobinapathies

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

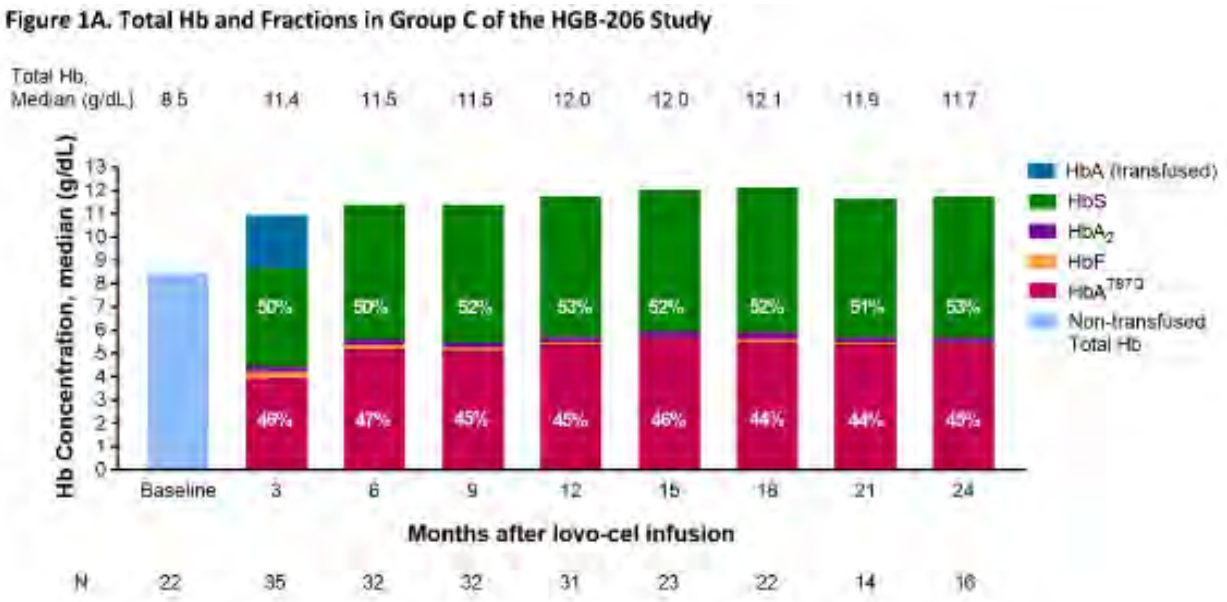
Zynteglo is a one-time gene therapy product administered single dose. Each dose of Zynteglo → customized treatment created using the pt's own bone marrow stem cells, genetically modified to produce functional beta-globin

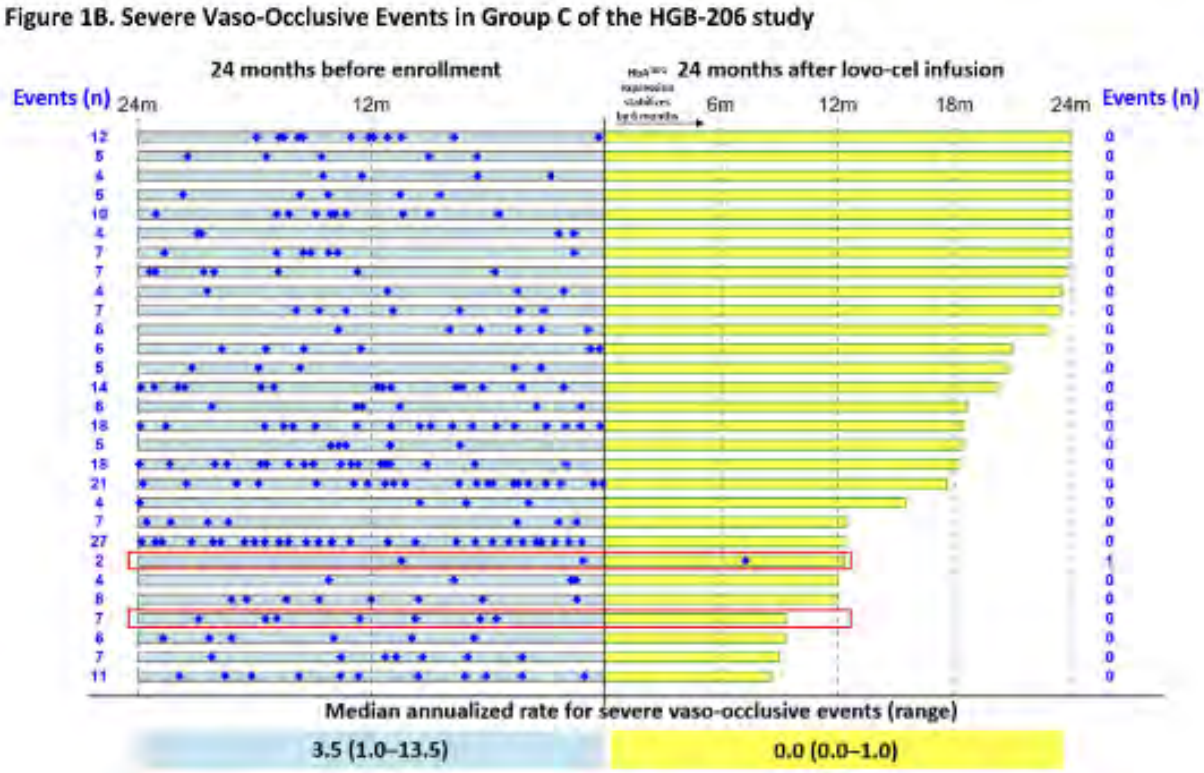
Zynteglo is cleared for transfusion-dependent beta thalassemia, but will come at a cost of $2.8 million per patient.

Gene Therapy is here to stay
Abst #11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al

- 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

Abst #11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al





Gene therapy for SS disease will also be costly.

Lymphoma advances

- Mantle cell
- Primary CNS lymphoma

Mantle cell lymphoma

- Accounts for approximately 4-6% of NHL
- Median age at diagnosis: 63-68 yrs
- Improvement in outcomes in past 10-20 yrs
  - 10-20 yrs ago, median *survival* was 2-3 yrs
  - now can expect 7-10 yr *first remission* in younger patients with low/intermediate risk disease by MIPI score

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Evolution of First-line Induction Therapy For Younger MCL Patients

- Regimens involving R-CHOP-like therapy combined with R-AraC, consolidation with auto-HCT
  - Nordic, R-CHOP/R-DHAP, CALGB 59909;
  - median PFS of 5 – 9 yrs.
- Several novel induction regimens under evaluation
  - Len/Rituximab; RBAC; Benda/Rituximab +/- Bortezomib (E1411); others
  - Some of these regimens produce high (>70-80%) rates of MRD-negativity
- **However, unclear whether auto-HCT confers survival benefit, especially after highly active modern induction regimens**

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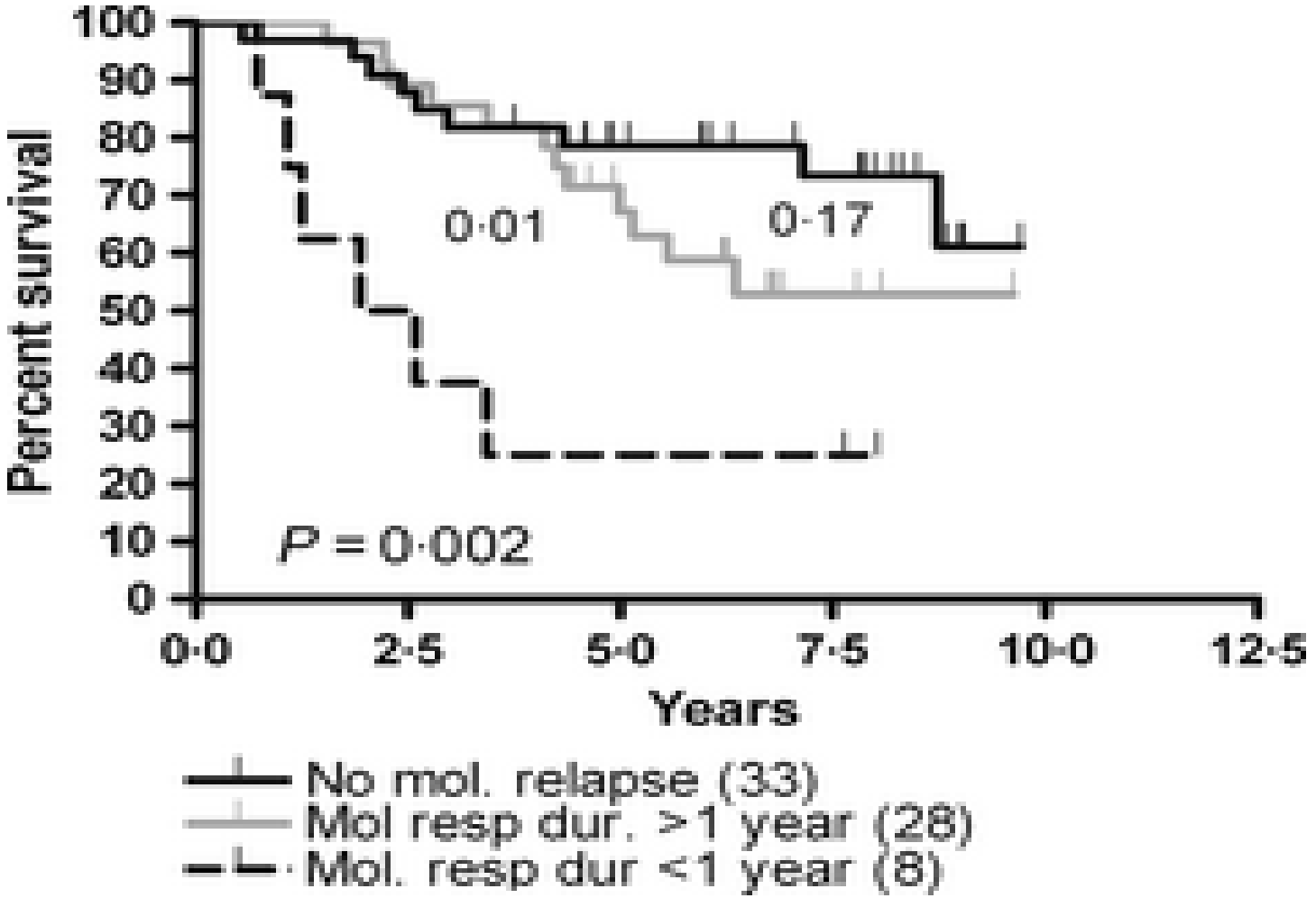
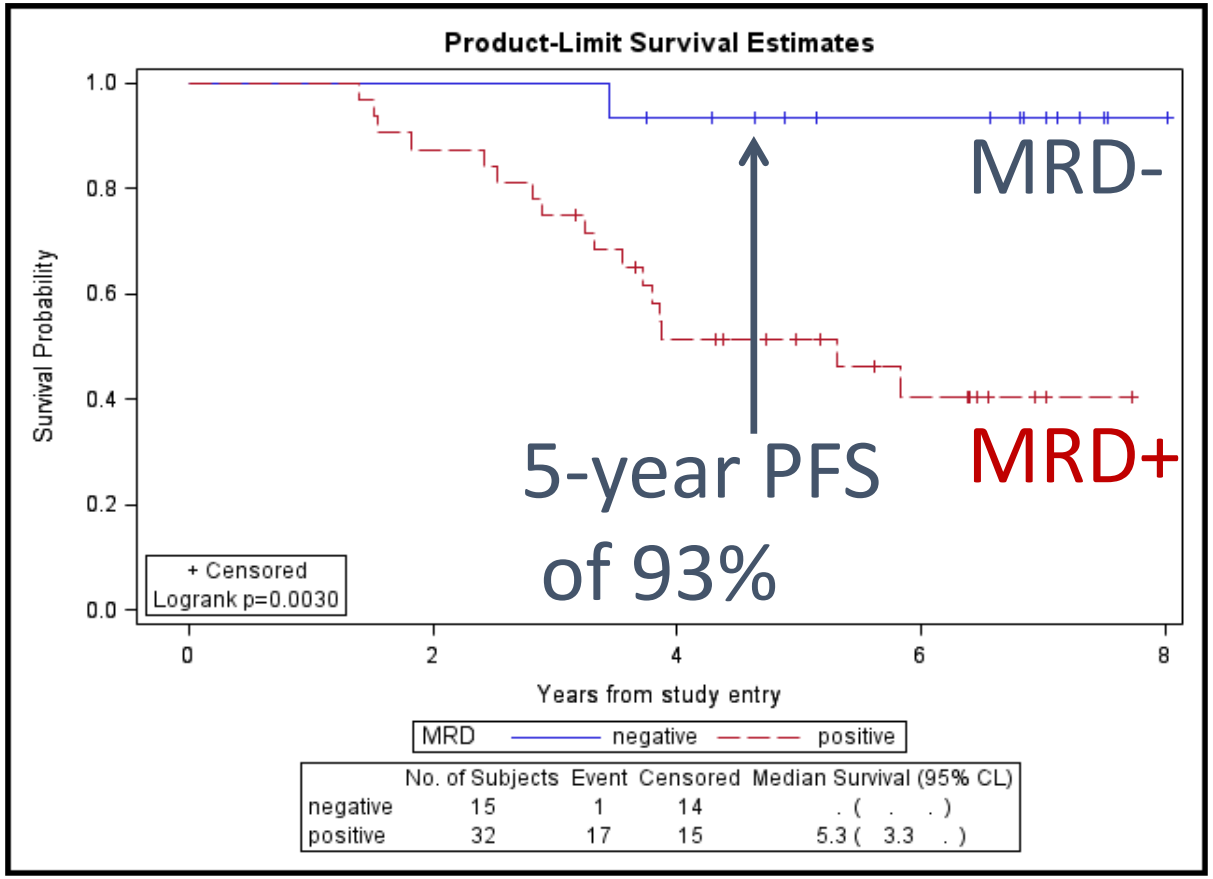
Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur



British Journal of Haematology
Volume 158, Issue 3, pages 355-362, 29 MAY 2012 DOI: 10.1111/j.1365-2141.2012.09174.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09174.x/full#bjh9174-fig-0004

Prognostic importance of MRD in MCL
CALGB 59909



N = 47 with MRD data (out of 151)

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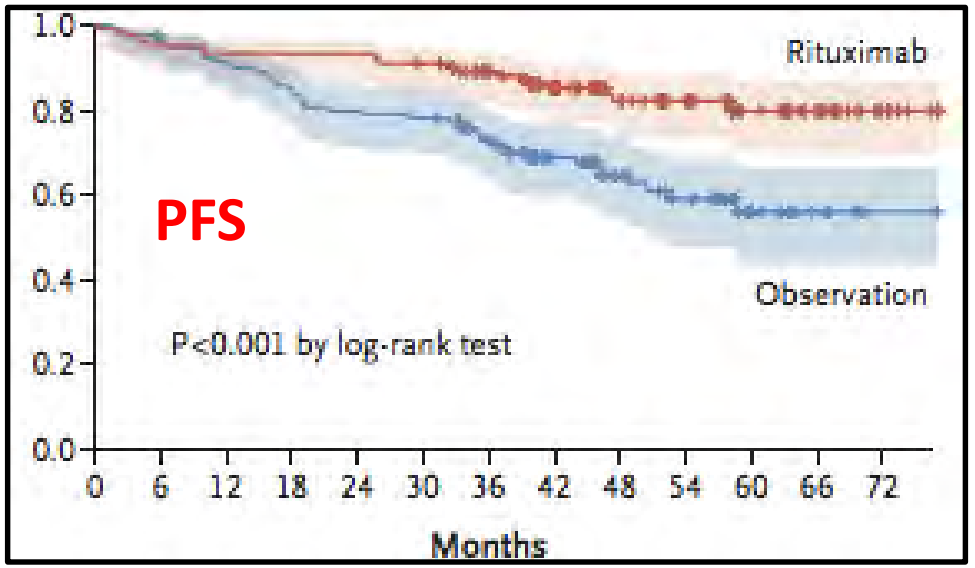
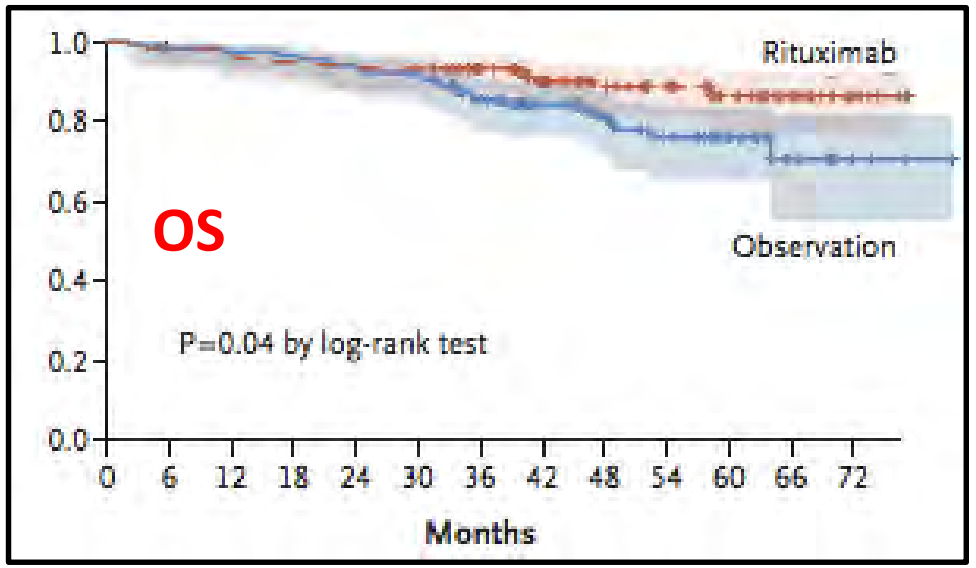
Kaplan et al, ASH 2015, #337

Maintenance rituximab after ASCT: LYMA





- N=299 enrolled
- 257 (86%) got AutoHCT
- 238 (80%) randomized
- Median f/u 52 mo after randomization

- 4 yr PFS 83% for maint rituximab arm (vs 64% for obsv)
- 4 yr OS
  - 89% (rituximab) vs 80% (obsv)
- Now SOC at most centers

LeGouill et al, NEJM 2017

Mantle cell lymphoma – role of autoHCT

- Despite improved PFS, unclear if intensive therapy actually *improves survival*
  - patient selection bias as to who gets intensive therapy
  - other improvements in care over time have occurred
  - Remains an area of controversy in the field with some respected lymphoma experts not recommending up front autoHCT
- Many MCL pts are at upper age limit for intensive therapy and therefore at high risk of toxicities
- **Ideal population to develop a "risk-adapted" approach**
  - Identify those most likely to benefit from intensive treatment and spare the others the risk/ toxicities

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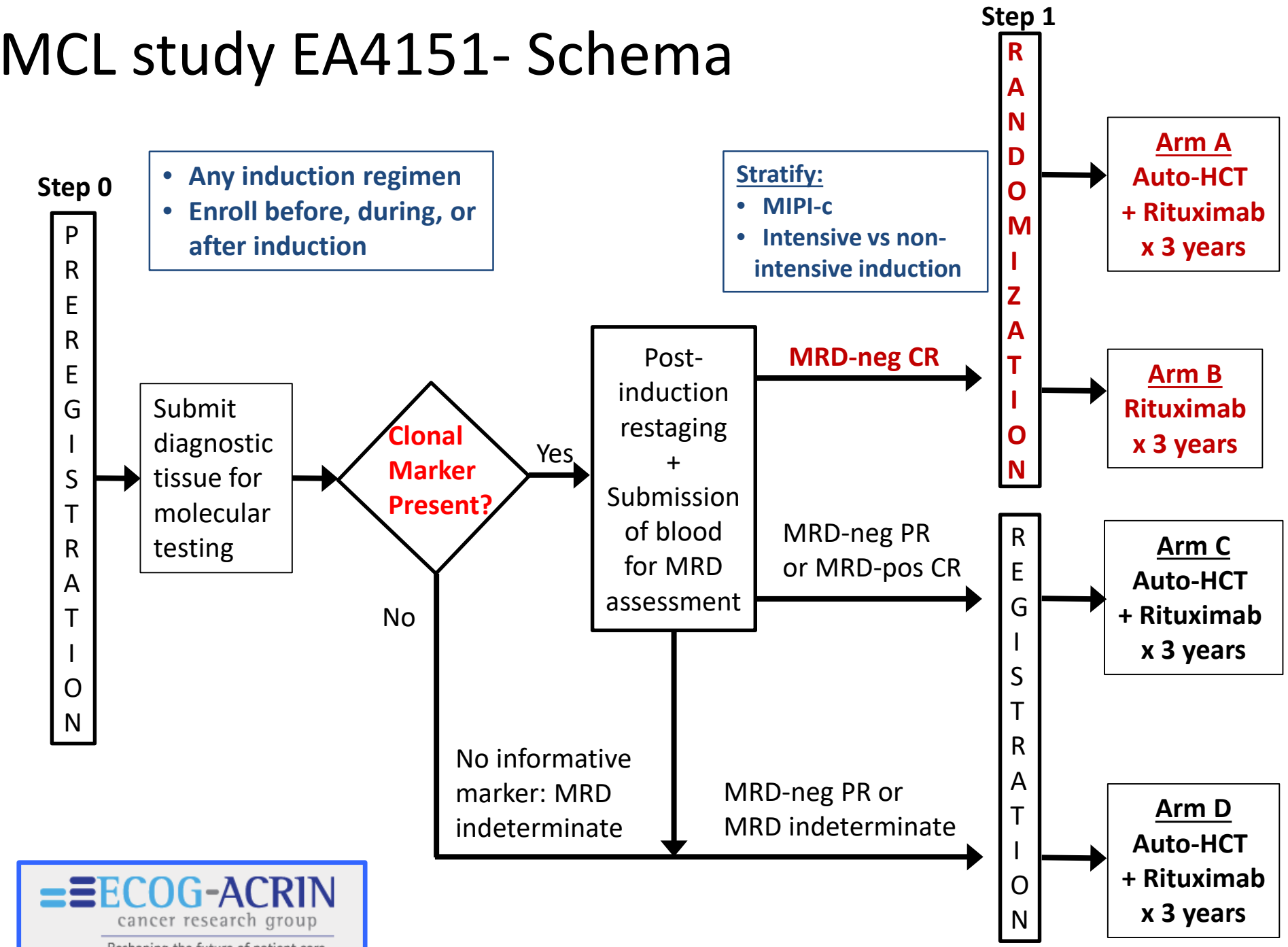
US MCL study EA4151- Schema



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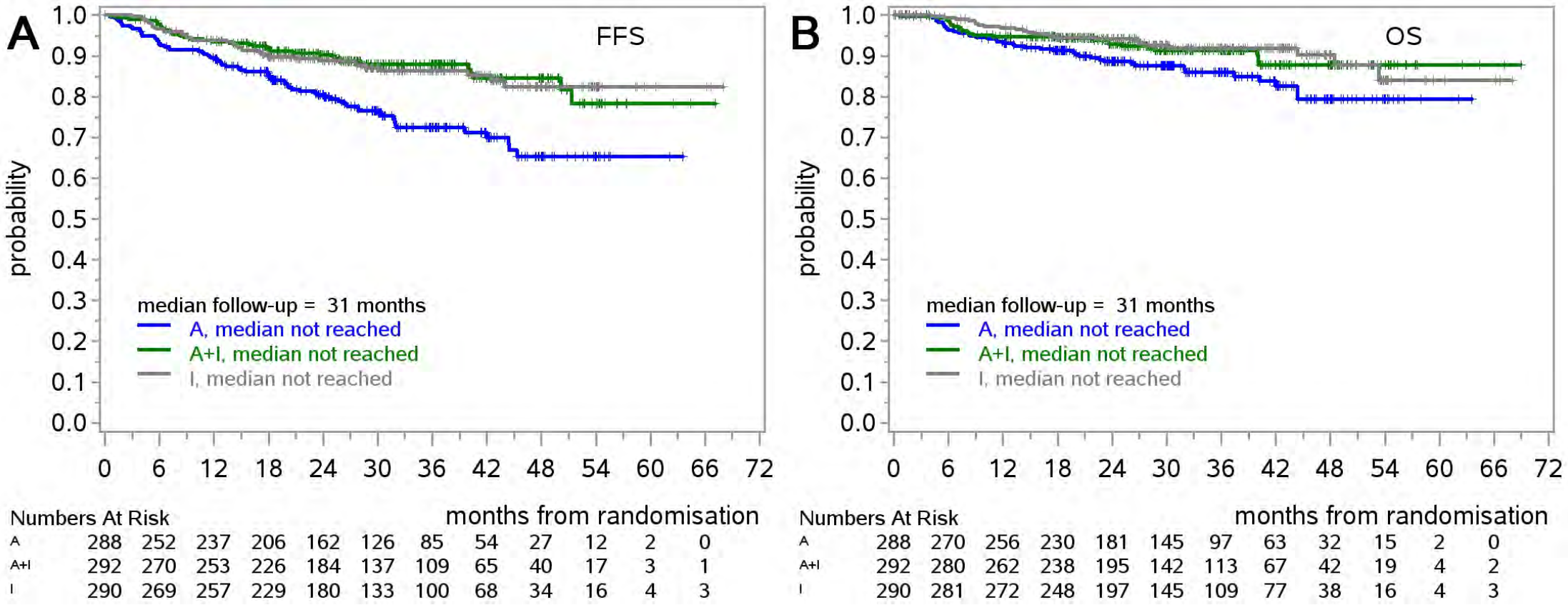
ASH Abstr #1: Efficacy & Safety of Ibrutinib Combined with Standard 1st-line Rx or Substitute for Autologous HCT in Younger Patients with Mantle Cell Lymphoma: Randomized Triangle Trial By the European MCL Network, Dreyling et al.

- Randomized, open-label, 3-arm TRIANGLE trial to evaluate addition of ibrutinib to SOC (arm A+I) in comparison to the previous SOC (arm A) and an ibrutinib containing treatment without ASCT (arm I)
- Untreated, advanced stage II-IV MCL, up to 65 years
- Study treatment: 3 cycles R-CHOP/R-DHAP without (arm A) or with ibrutinib added to R-CHOP and 2 years maintenance (arms A+I, I). ASCT planned for responding pts of arms A and A+I. Rit maintenance applied according to national guidelines in all responding patients irrespective of the trial arm [A (n=288), A+I (n=292), and I (n=290)]

ASH Abstr #1: **Efficacy & Safety of Ibrutinib Combined with Standard 1st-line Rx or Substitute for Autologous HCT in Younger Patients with Mantle Cell Lymphoma: Randomized Triangle Trial By the European MCL Network, Dreyling et al.**



Primary CNS lymphoma- ChemoimmuneRX vs HDC & autoHCT (MATRix trial,

Illerhaus et al, ASH LBA

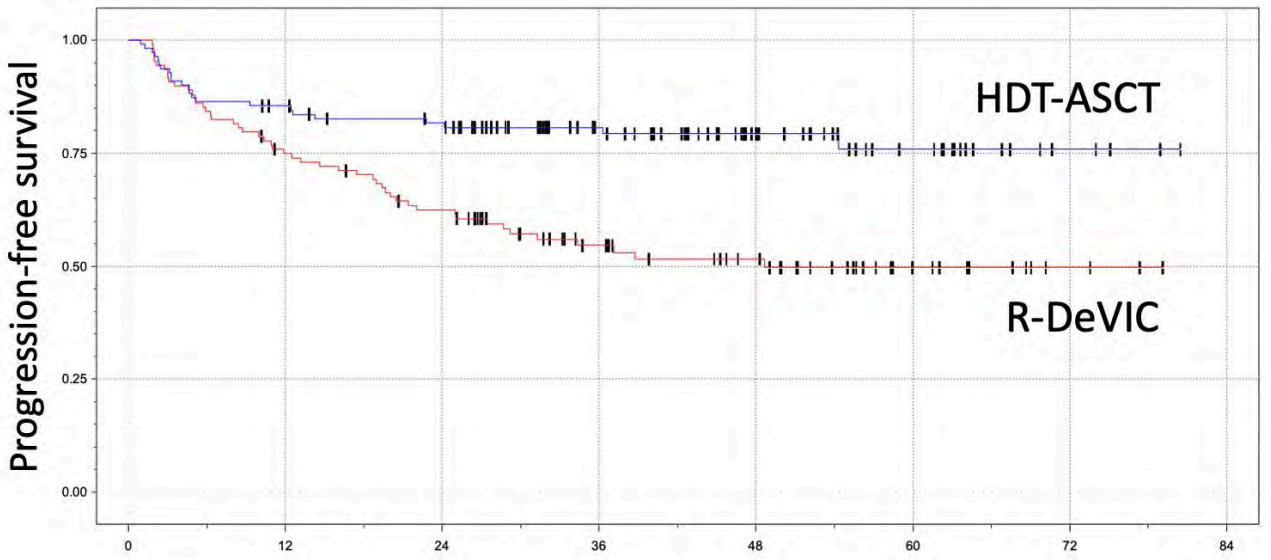
Open label, randomized, multicenter Ph III
Eligibility: new dx PCNSL, up to age 70, HIV-,

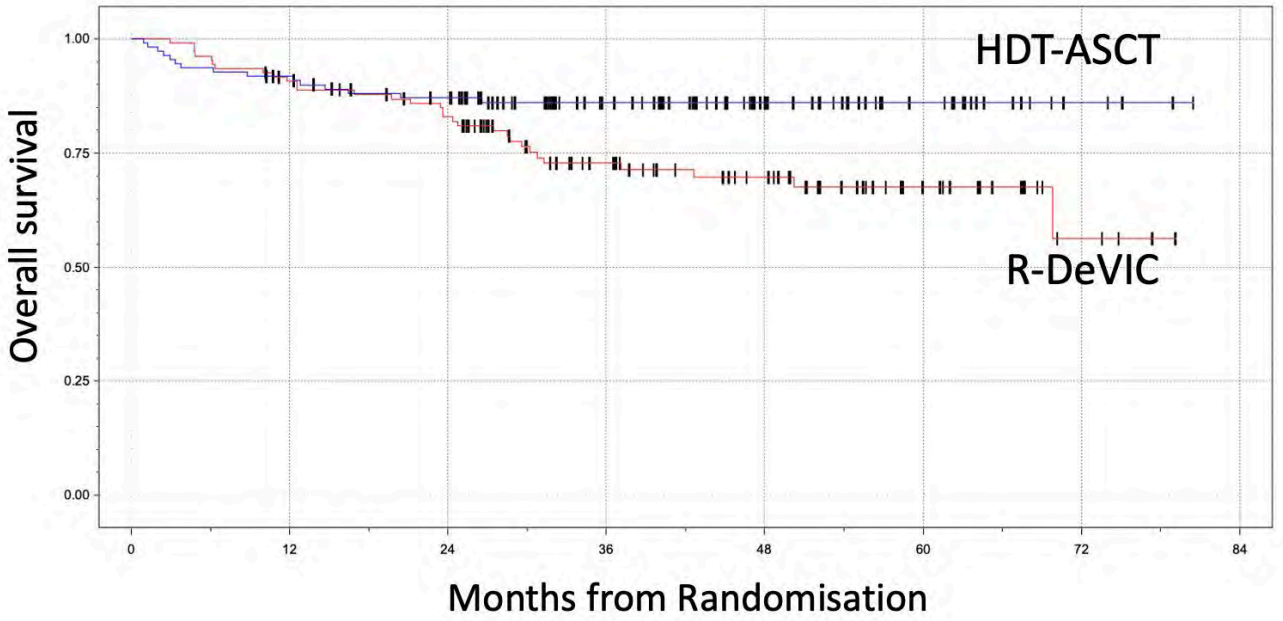
Induction: MATRix x 4. Pts with PR or better →
2 cycles R-DeVIC* vs BCNU/Thio + auto HCT

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

ASCO Plenary/ NEJM 2022

Does ASCT improve outcomes for New Dx MM patients receiving triplet induction (RVd) and lenalidomide maintenance until disease progression?

- ASCT with HD melphalan is a SOC for transplant-eligible NDMM patients [1,2]
- Optimal use of induction therapy, ASCT, maintenance in transplant-eligible NDMM patients continues to evolve
  - Triplet induction regimens are highly efficacious, with high response rates, high rates of MRD-negative responses, and prolonged clinical benefit [3–7]
  - Long-term maintenance therapy with lenalidomide also improves outcomes through prolonged disease control [8,9]
- In this context, how much does first-line ASCT enhance efficacy in NDMM, and can its use be delayed in selected patients? [10]

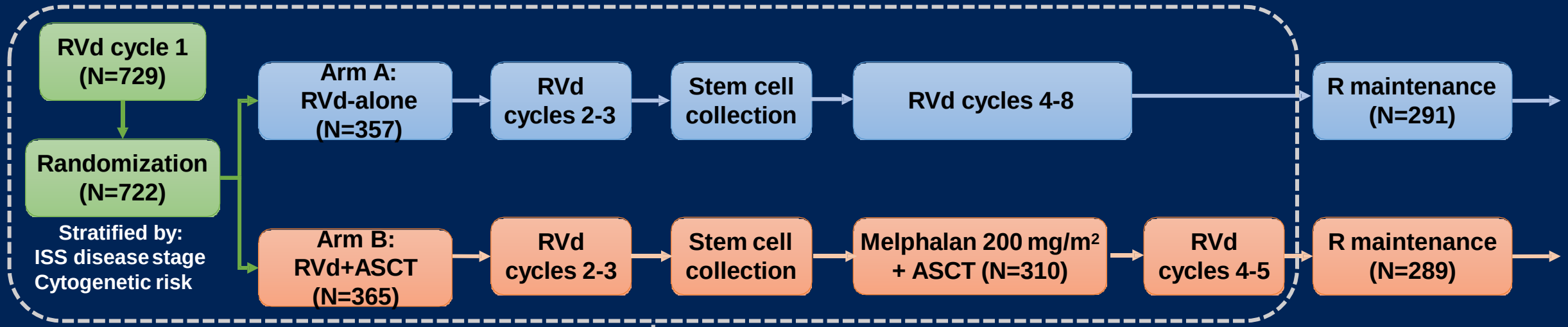
ASCT, autologous stem cell transplantation; HD, high-dose; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; RVd, lenalidomide, bortezomib, dexamethasone.

1. Callander NS, et al. J Natl Compr Canc Netw 2022;20:8–19. 2. Dimopoulos MA, et al. Ann Oncol 2021;32:309–22. 3. Richardson PG, et al. Blood 2010;116:679–86. 4. Kumar SK, et al. Lancet Oncol 2020;21:1317–30. 5. Attal M, et al. N Engl J Med 2017;376:1311–20. 6. Perrot A, et al. Blood 2020;136:39. 7. Durie BGM, et al. Lancet 2017;389(10068):519–27. 8. McCarthy PL, et al. J Clin Oncol 2017;35:3279–89. 9. McCarthy PL, et al. N Engl J Med 2012;366(19):1770–81. 10. Richardson PG, et al. Hematology Am Soc Hematol Educ Program. 2014;1:255–61

PRESENTED BY:
Paul G. Richardson, MD

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

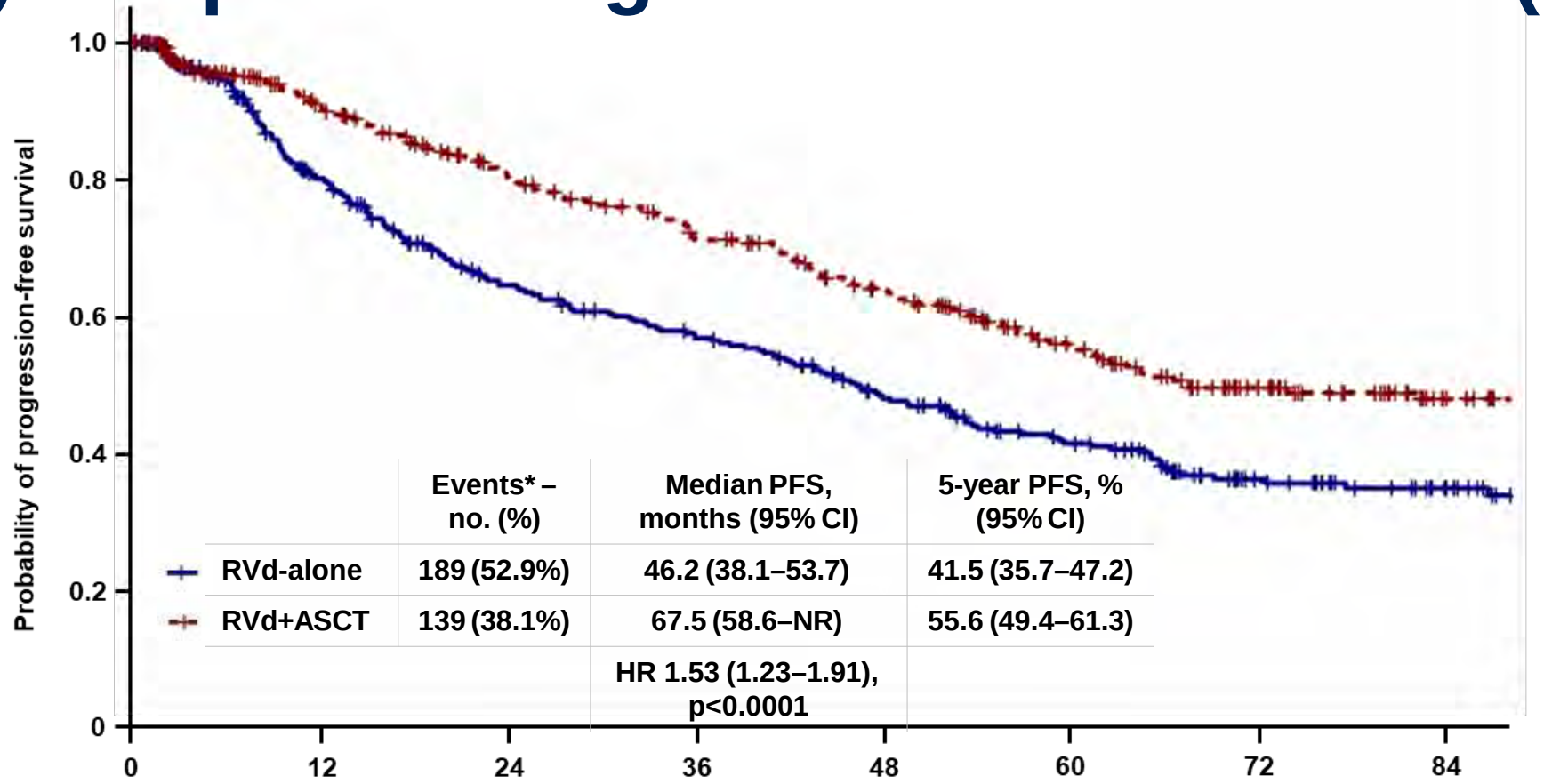
Lenalidomide maintenance
Months 1-3: 10 mg/day
Month 4 onwards: 15 mg/day

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

Primary endpoint: Progression-free survival (PFS)

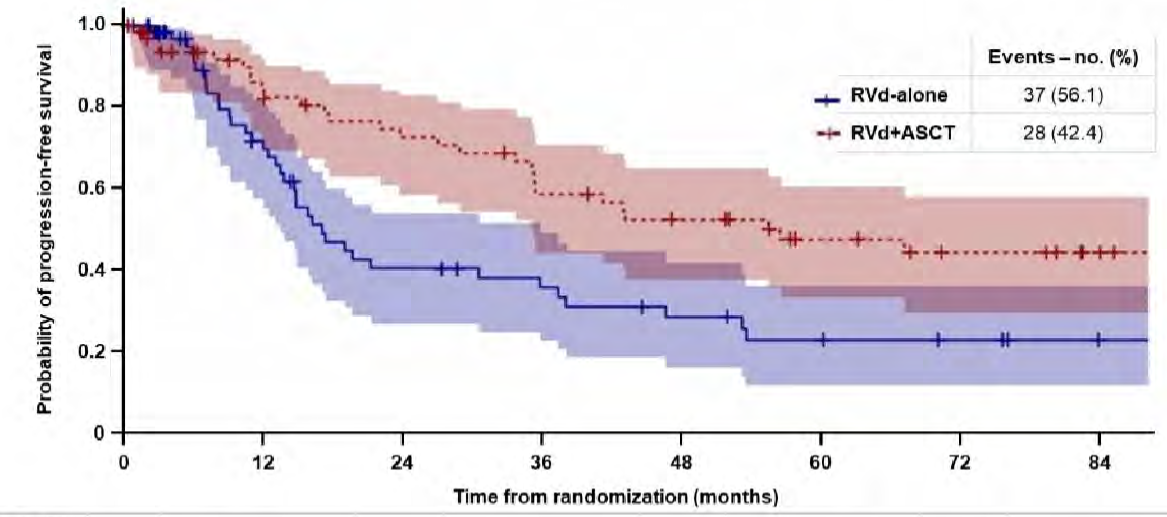


	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

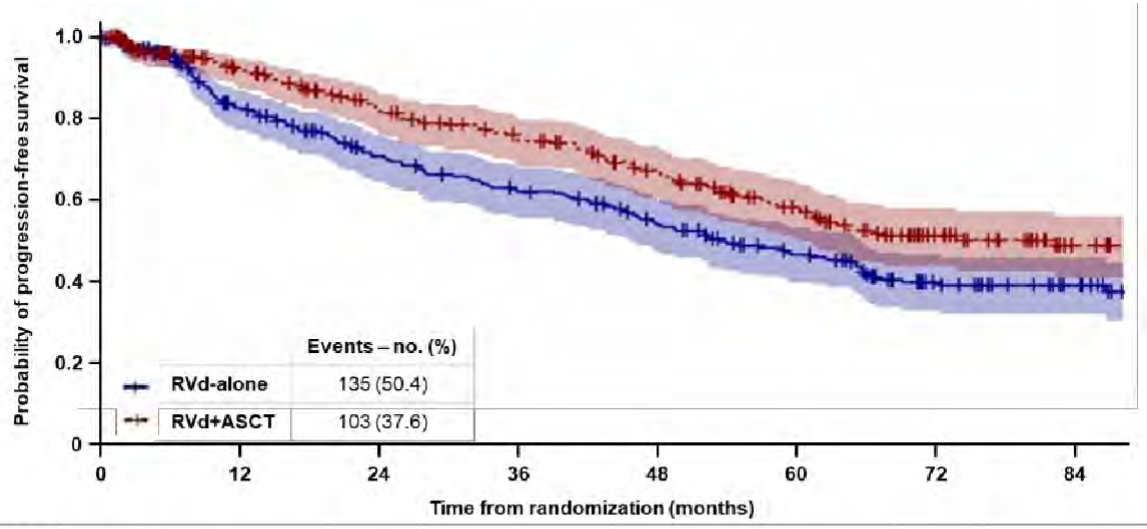
Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

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

PFS by stratification factor – cytogenetic risk



Patients at risk								
RVd-alone	66	36	19	16	11	8	6	3
RVd+ASCT	66	45	37	29	24	16	12	8



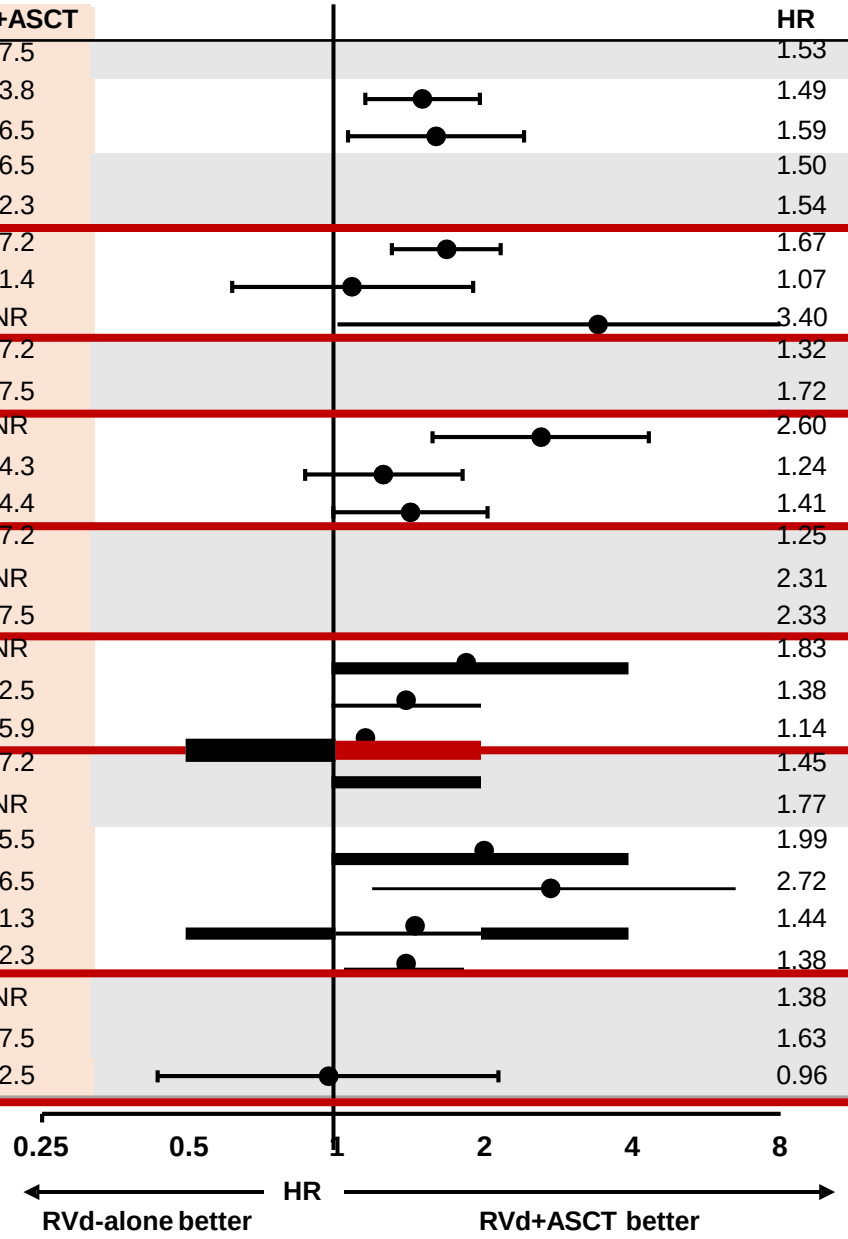
Patients at risk								
RVd-alone	268	197	156	134	109	83	50	34
RVd+ASCT	274	212	175	151	126	94	58	29

Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	

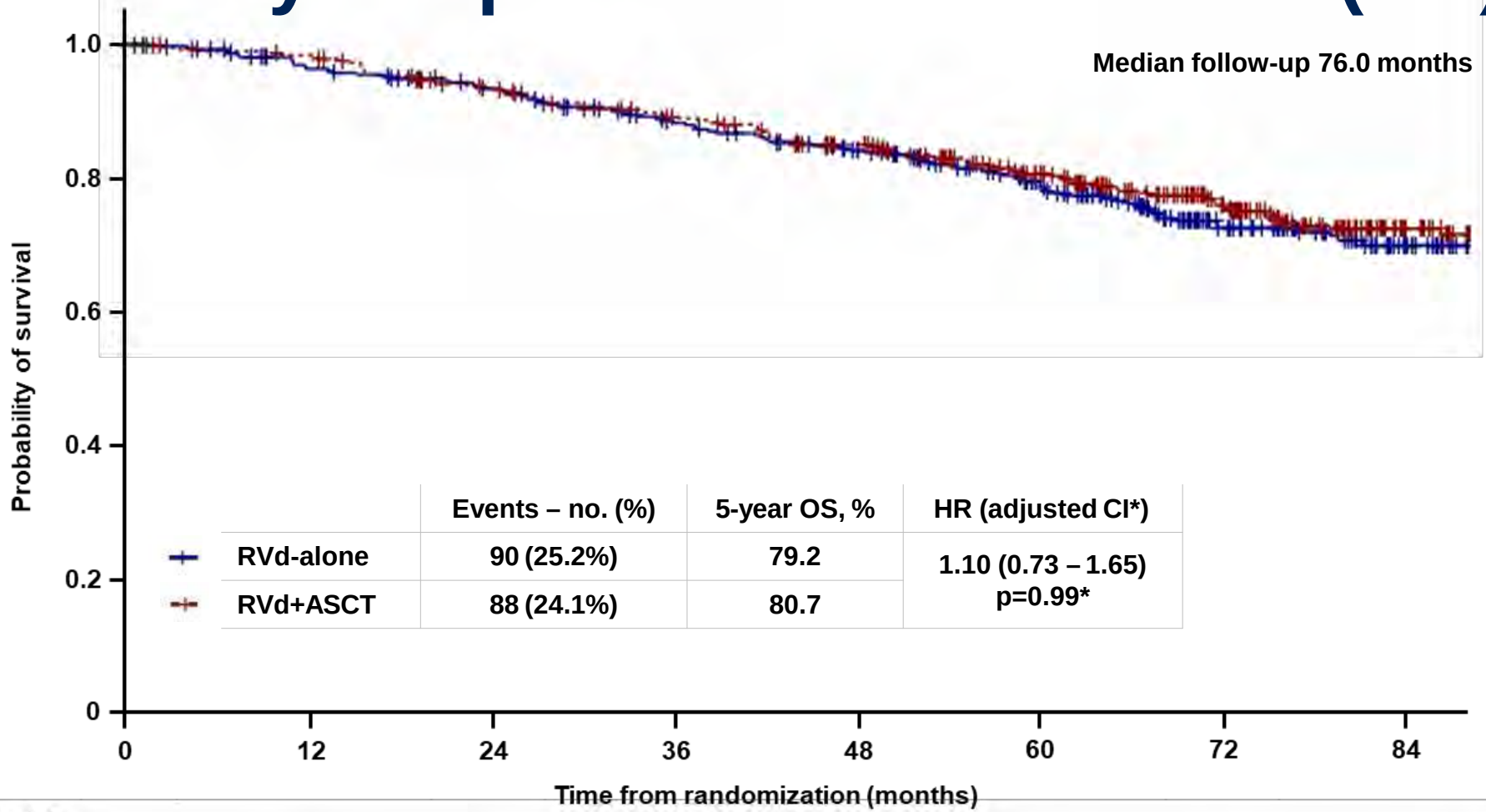
Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

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)



Key secondary endpoint: Overall survival (OS)



	Events – no. (%)	5-year OS, %	HR (adjusted CI*)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

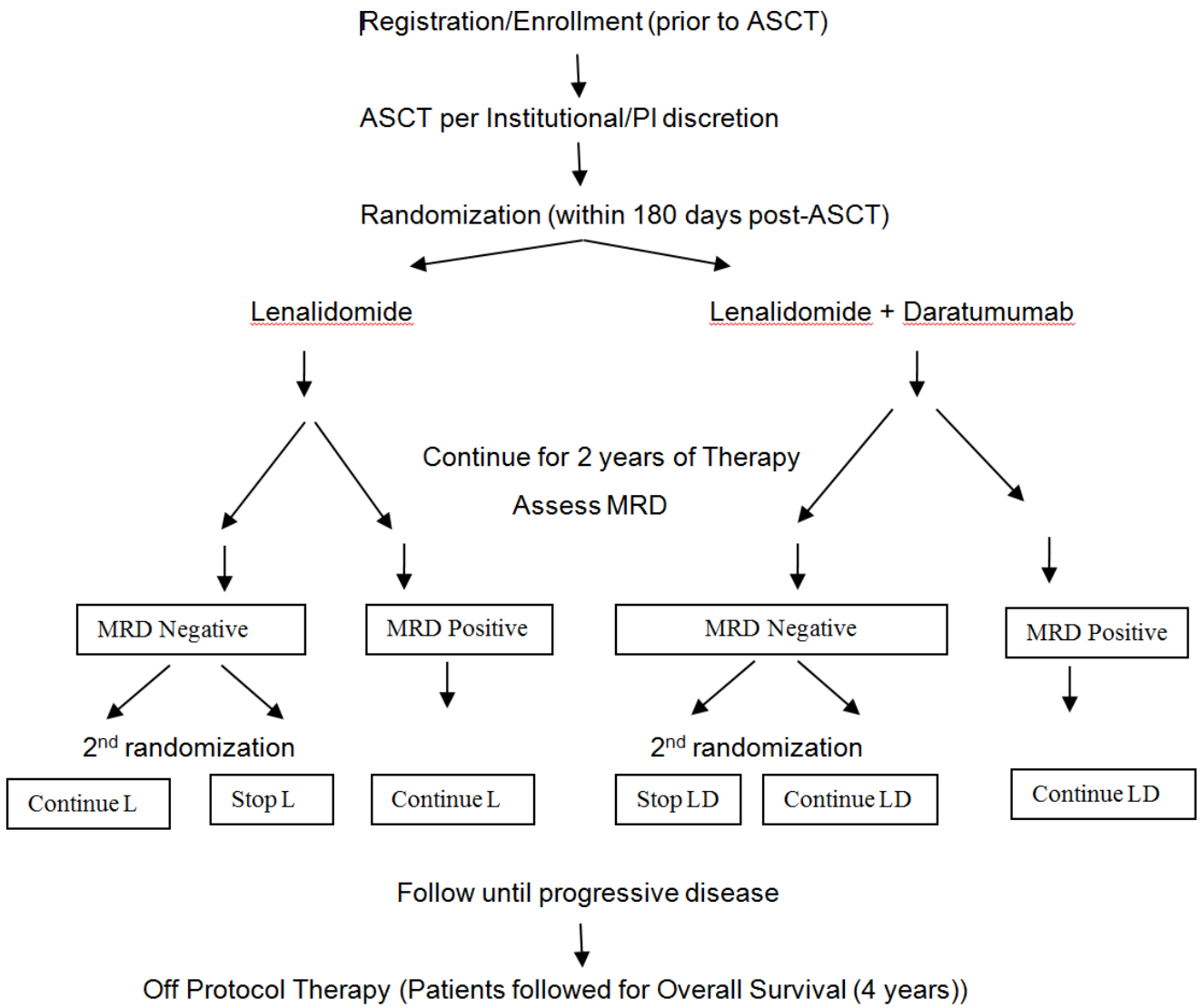
Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Data cutoff:12/10/21

What are we doing today?
US 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)



S1803: MM Maintenance Trial

Primary objective: To compare the overall survival (OS) between the two treatment arms

Major Secondary Objectives of First Randomization (LD vs. L):

To compare the best overall response rate (ORR), including partial remission (PR), very good partial remission (VGPR), and complete remission (CR, sCR) in the subset of patients not in PR at baseline (baseline is study entry pre HCT)

To compare progression free survival (PFS) between the study arms, and to report these findings once PFS data are mature and the study accrual has been completed.

To compare MRD-negativity on the two treatment arms at maintenance initiation, and at 24 months and 36 months post maintenance.

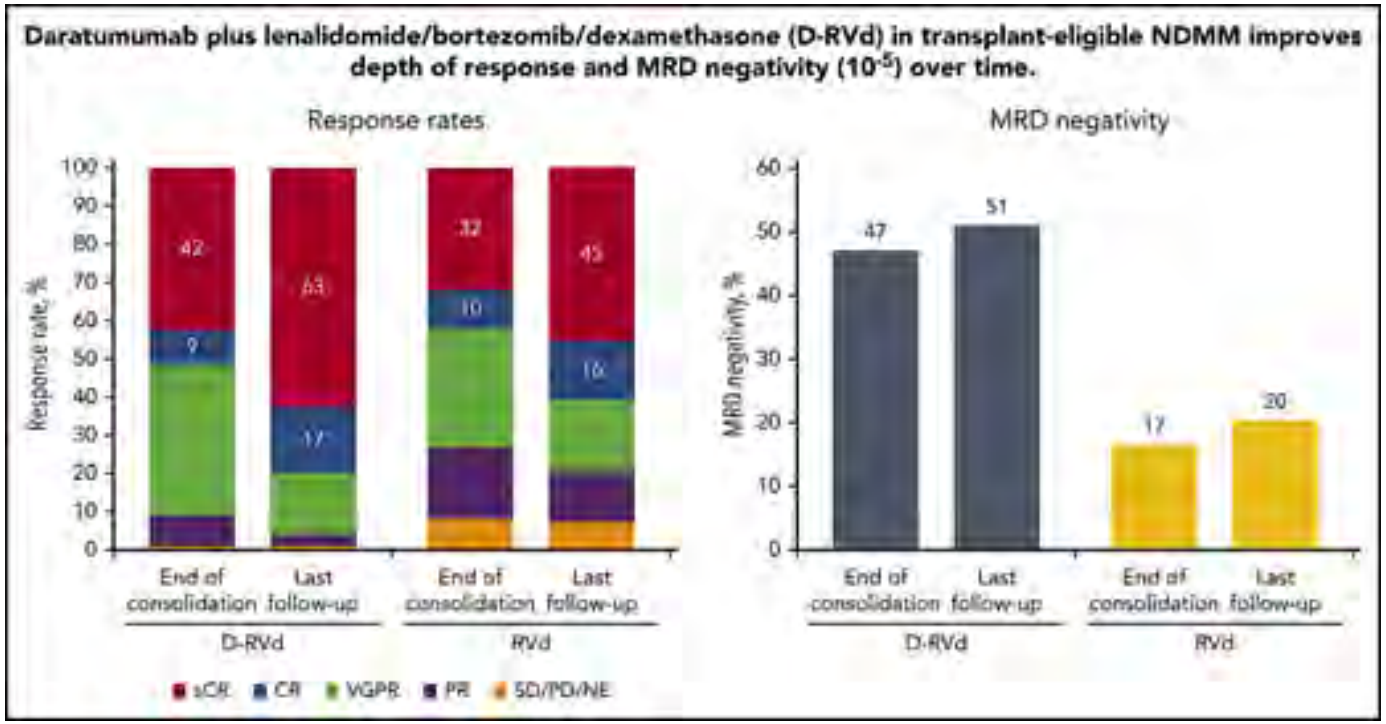
To compare toxicities and tolerability of long term therapy between the study arms.

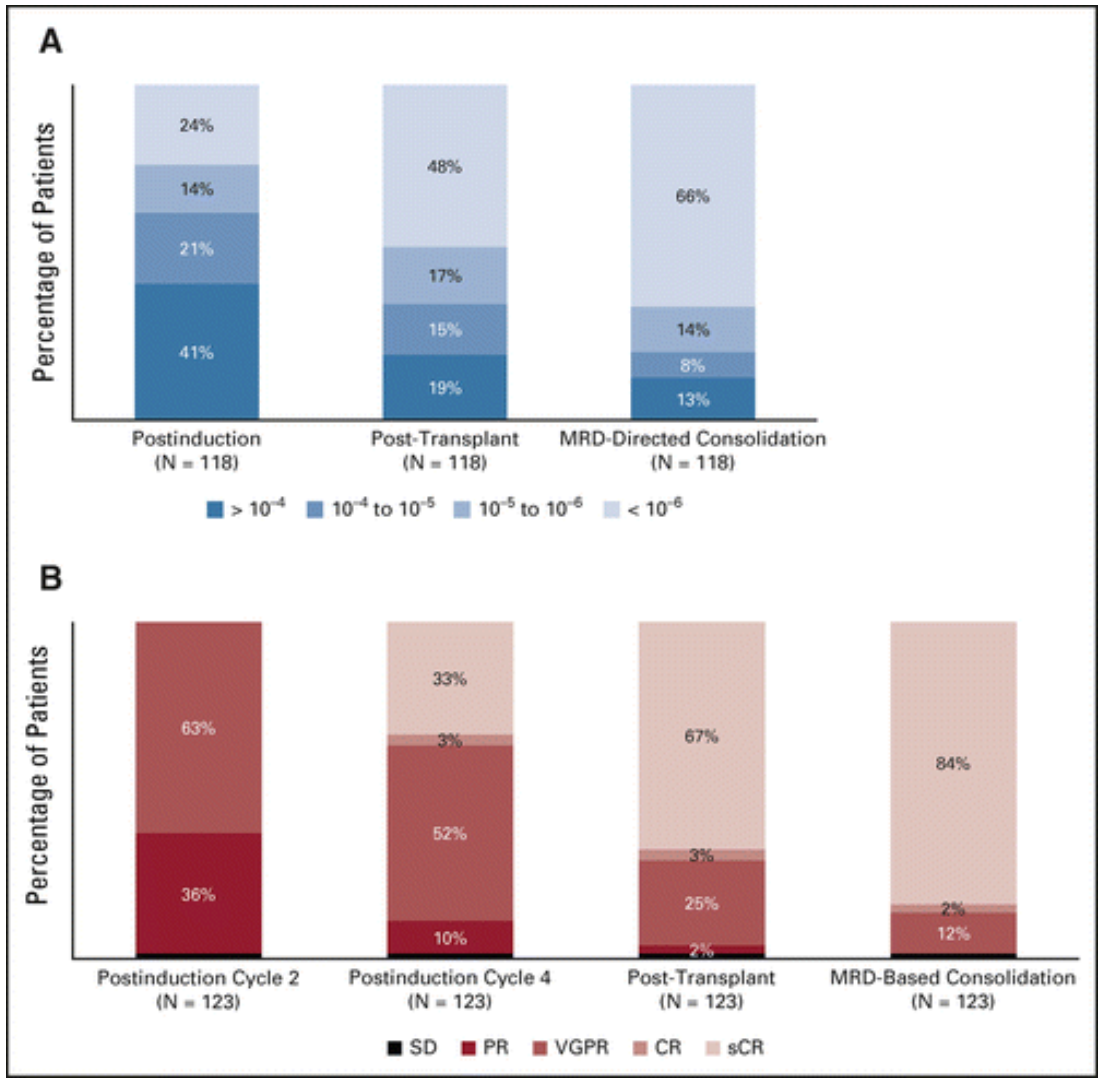
Primary Objectives of the Second Randomization:

- To compare progression free survival (PFS) between MRD negative patients randomized to indefinite L vs. discontinued L from the time of second randomization.
- To compare progression free survival (PFS) between MRD negative patients randomized to indefinite LD vs. discontinued LD from time of second randomization.

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%, respectively
  - BUT STRINGENT CRs are being seen





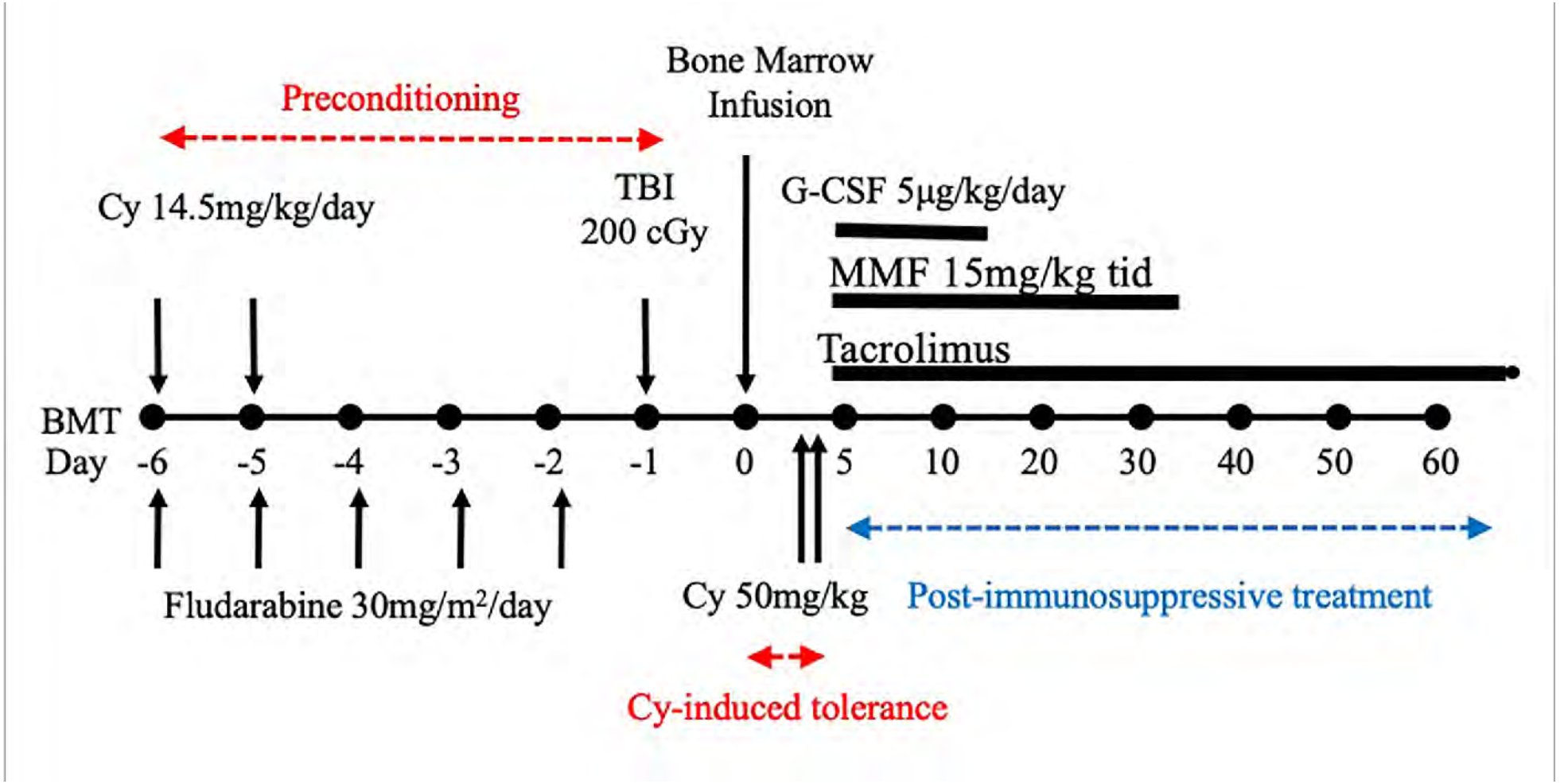
Thoughts: allo HCT

- Still the mainstay of activity
- Major advances in the past half decade
- New grading scales- Minnesota/Ann Arbor aGVHD; NCI cGVHD
- FDA approvals for acute & chronic GVHD
  - Prophylaxis: Abatacept
  - Treatment: MSC, ruxolitinib in aGVHD; ibrutinib, ruxolitinib, belumosodil in cGVHD

GVHD:

- Many trials, limited success in new GVHD prophylaxis strategies over the past 3 decades
- Calcineurin inhibitor and MTX remained 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
- Phase III trial needed

GVHD prophylaxis with post-HCT CTX



cGVHD/Relapse-free Survival

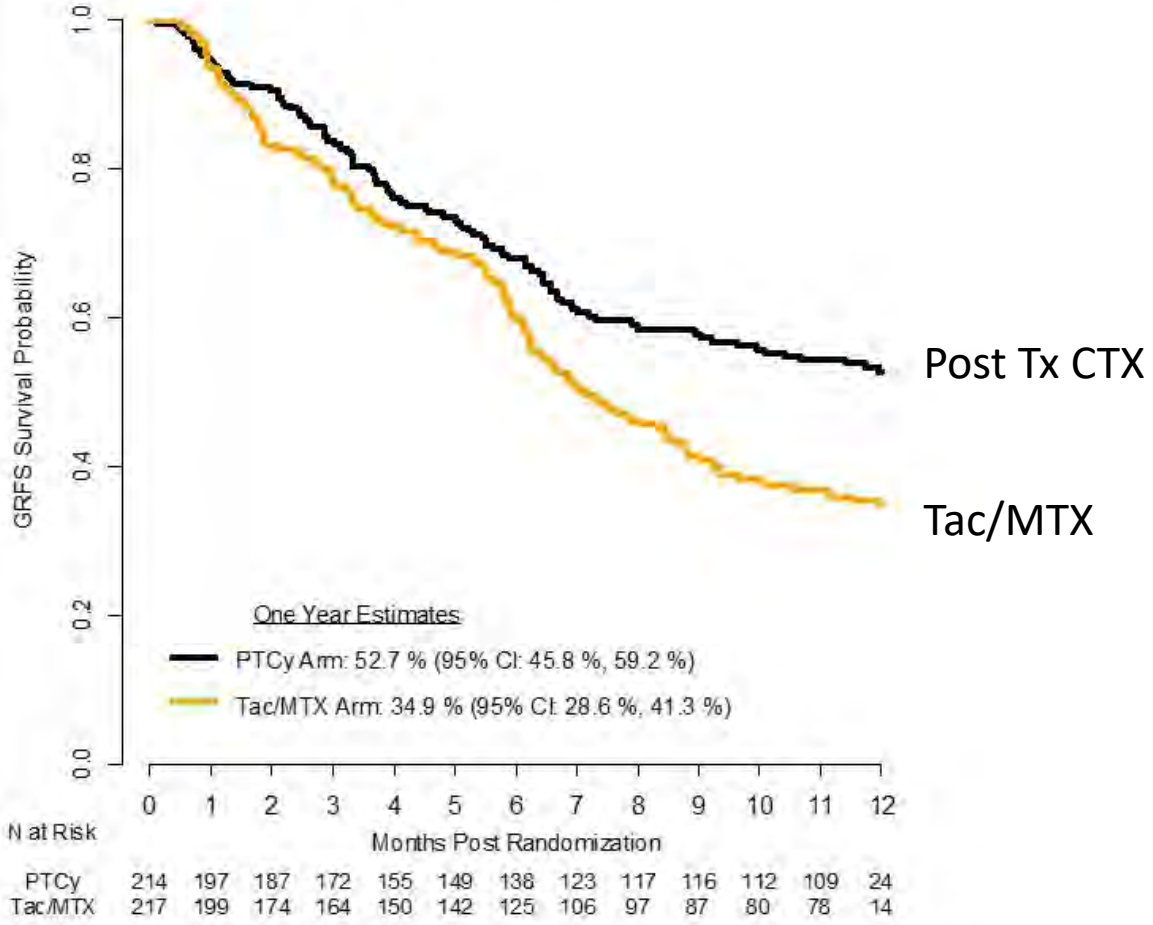
- Good approximation to the endpoint of interest **current GVHD (or IS)/relapse-free survival at 1 year.**
- Time to event composite endpoint:
  - Event = cGVHD, relapse or death
- Assumptions
  - aGVHD would have resolved by 1 year (either resulting in death, withdrawal of IS or progression to cGVHD)
  - Patients who developed cGVHD are still on IS at 1 year

GVHD prophylaxis for RIC, Holtan, ASH LBA

A. Patient Characteristics

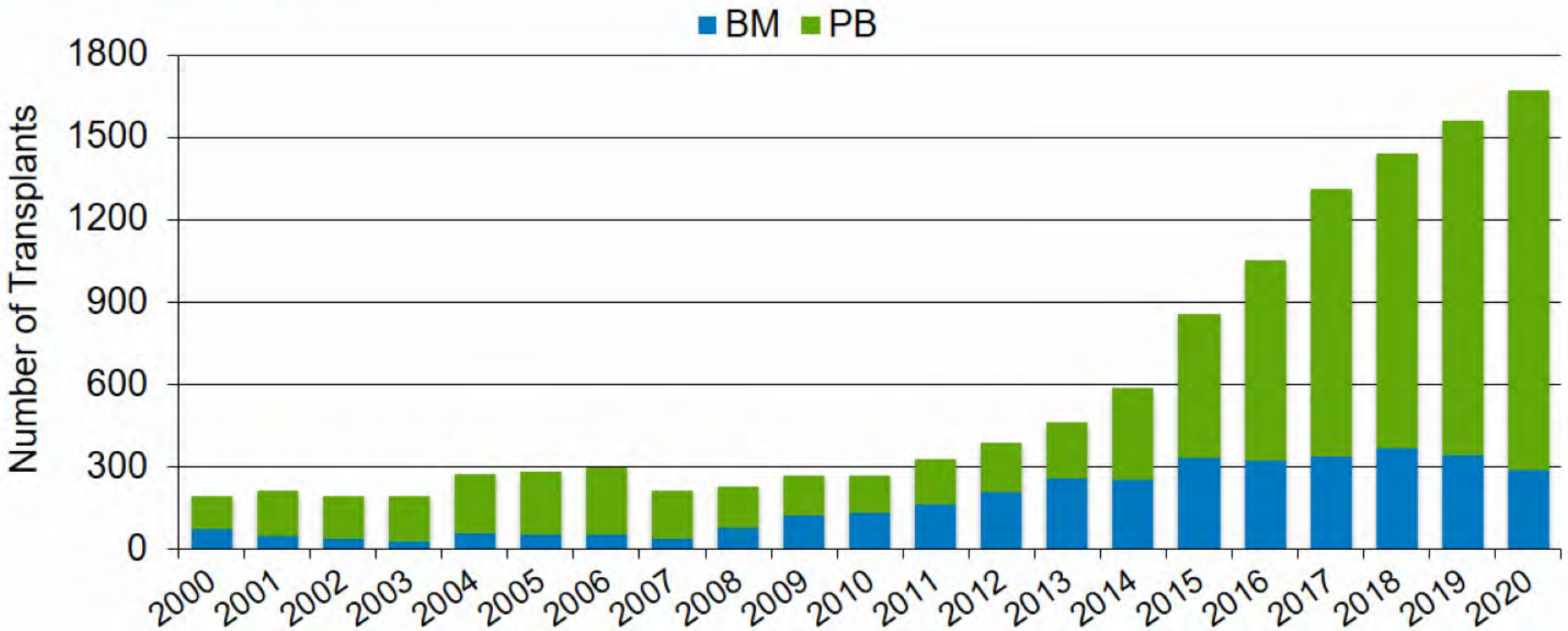
	Treatment Arm		
	PTCy/Tac/MMF	Tac/MTX	All
	(N=214)	(N=217)	(N=431)
Demographic Variable	N (%)	N (%)	N (%)
Gender			
Male	134 (62.6%)	126 (58.1%)	260 (60.3%)
Female	80 (37.4%)	91 (41.9%)	171 (39.7%)
Age (years)			
Mean (SD)	64.2 (8.5)	64.5 (8.9)	64.3 (8.7)
Median (Range)	66.1 (20.7, 78.6)	66.3 (26.3, 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.

Number of Haploidentical Donor# HCTs in the US in Recipients Aged ≥18 Years by Graft Source



CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

#includes all mismatched related donors; Abbreviations - BM: Bone marrow; PB: Peripheral blood

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

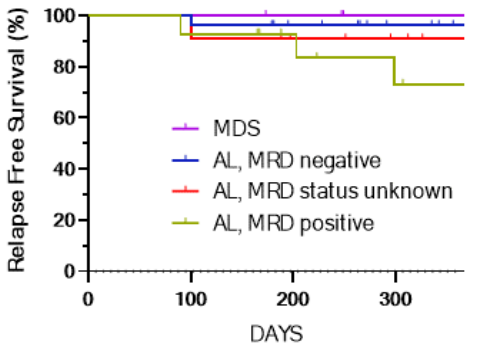
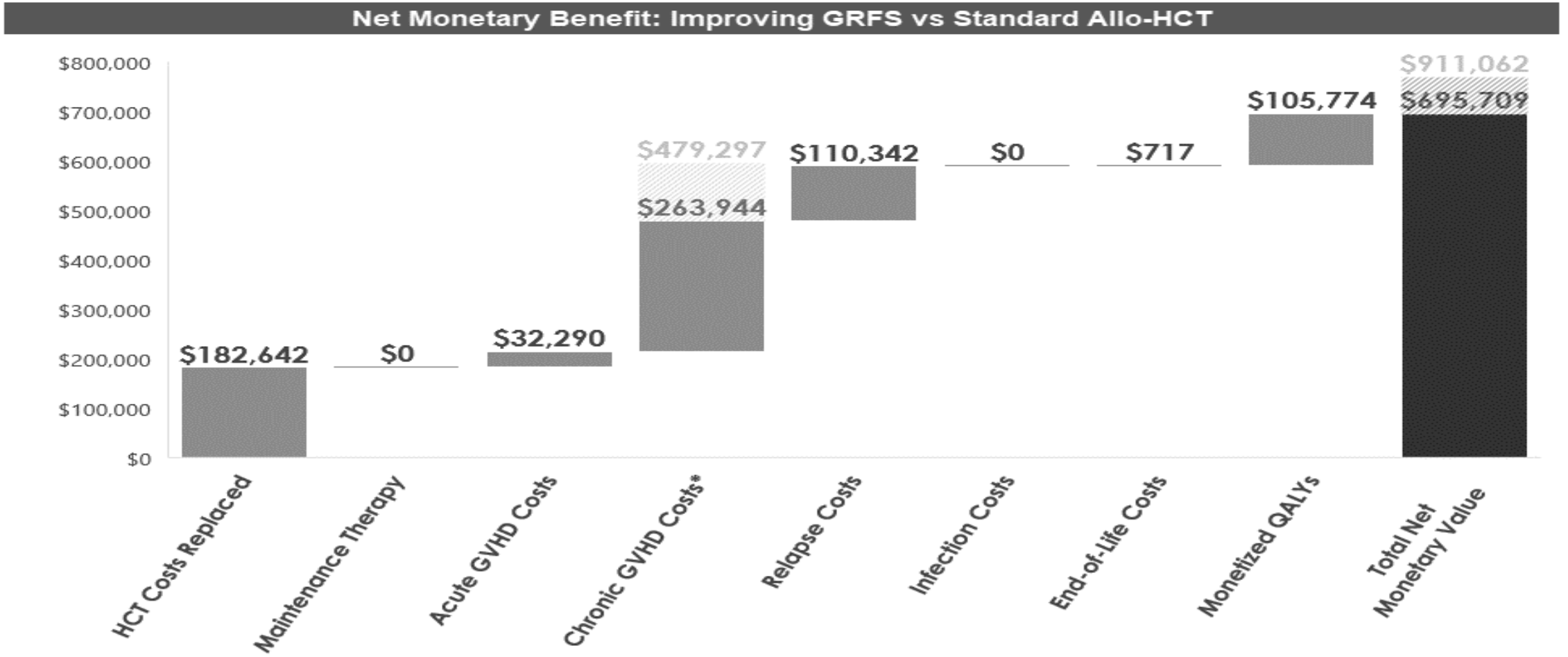


Figure 1. Relapse-free survival in patients who received BFT conditioning followed by Orca-T. AL = acute leukemia.

Abstr. # 4865

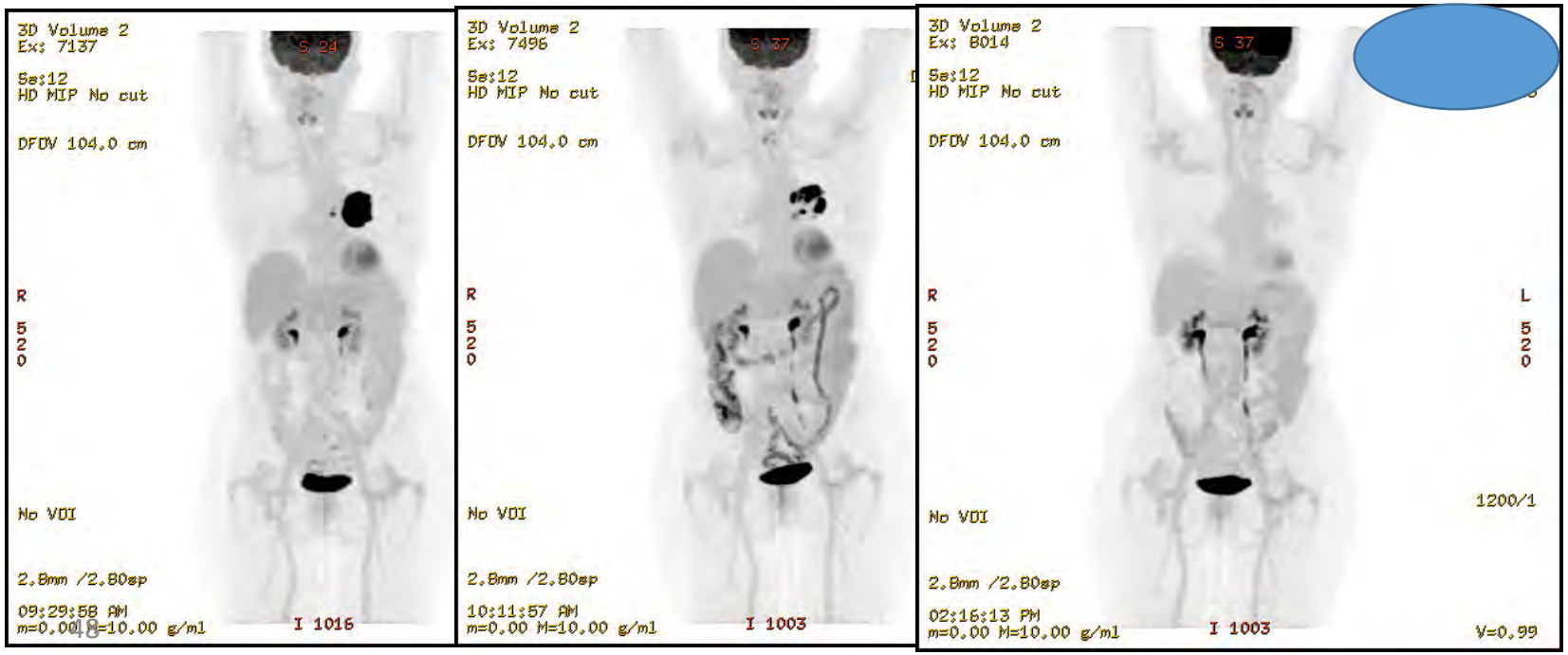
Estimating the Lifetime Medical Cost Burden of an Allogeneic Hematopoietic Cell Transplantation Patient and the Value of Addressing the Unmet Need, Maziarz et al



*Scenario 2 resulted in $479,297 of additional value due to chronic GVHD (versus $263,944 in Scenario 1) offsets for a total net monetary value of $911,062.
Scenario 1 modeled as doubled improvement in GRFS (69% GRFS in year 1 as opposed to 34%) with 15% of chronic GVHD patients remaining on treatment after two years.
Scenario 2 modeled as doubled improvement in GRFS (69% GRFS in year 1 as opposed to 34%) with 39% of chronic GVHD patients remaining on treatment after two years.

OHSU PT: Relapsed, Refractory DLBCL- post auto HCT

Baseline Day 30 Day 90



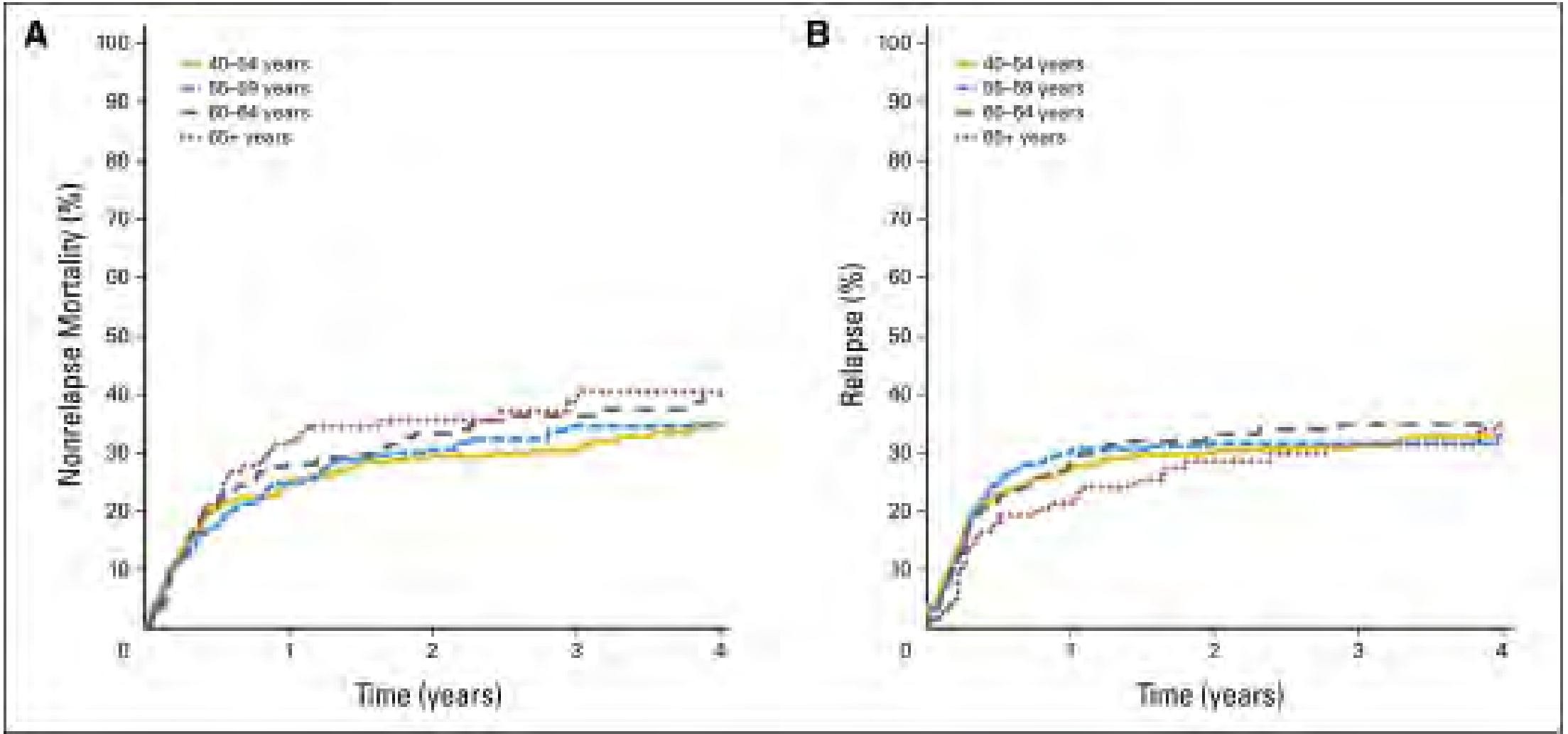
Approved CAR- T Products & Indications

- 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

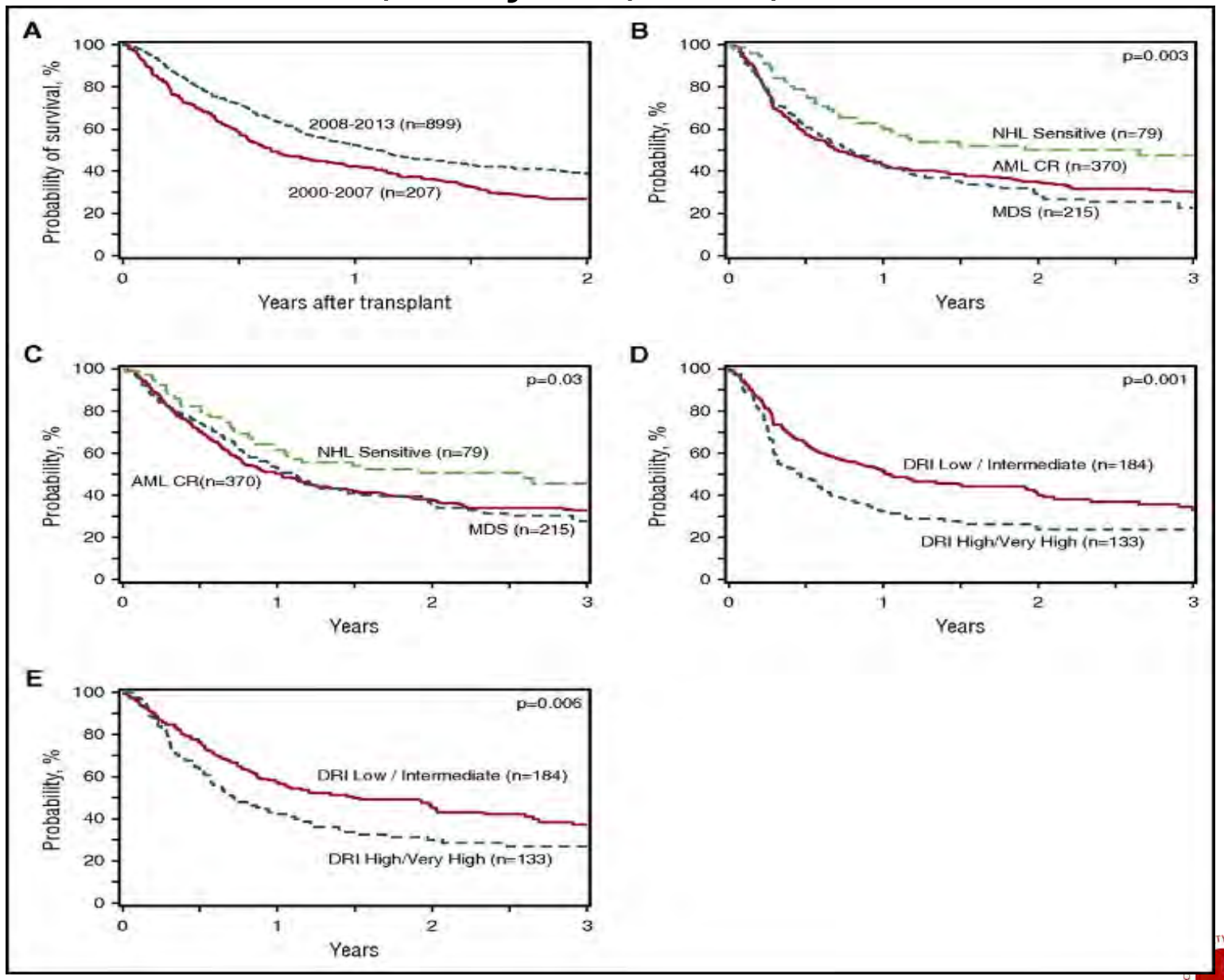
→ Anticipated 2023- TIL for Advanced Melanoma- Lifileucil

CAR- T cell therapy: who & when

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

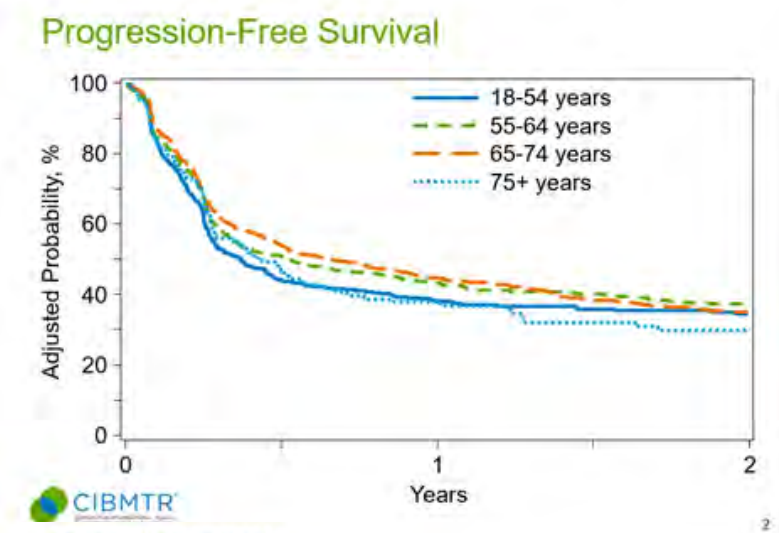


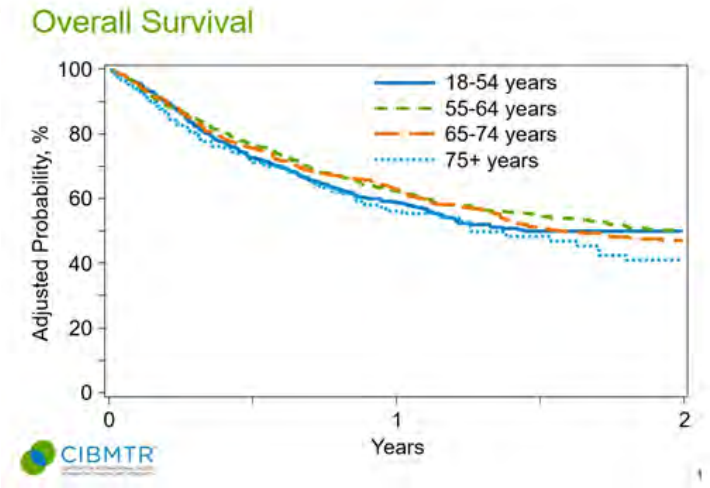
Who?

Abstr # 2024: CAR T outcomes and age, Mirza et al

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

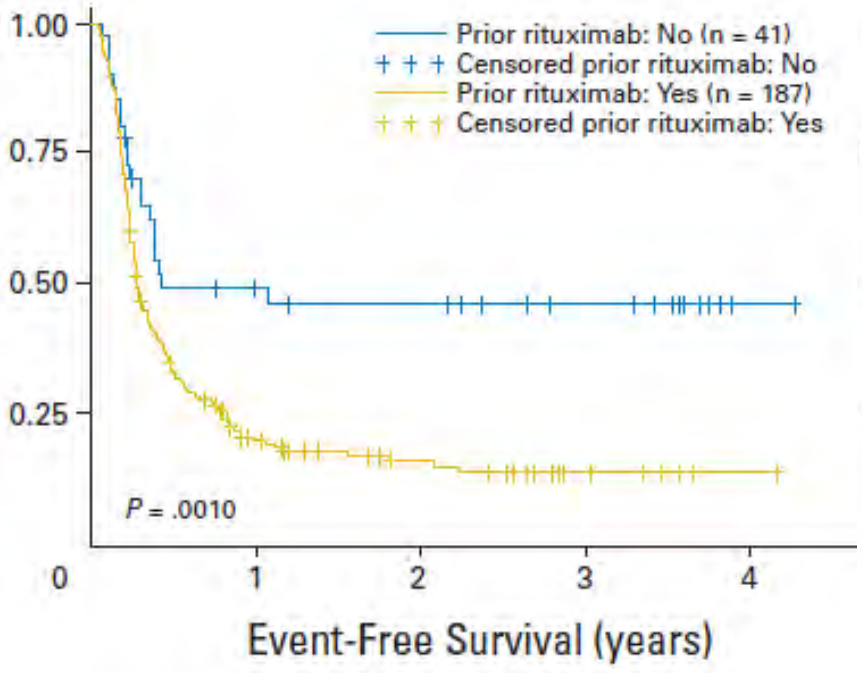
4. CRS					0.3933
18-54 years	469	1.000			-
55-64 years	599	0.821	0.606	1.113	0.2039
65-74 years	642	1.031	0.762	1.396	0.8424
75+ years	201	0.914	0.611	1.368	0.6629
5. ICANS					<0001
18-54 years	469	1.000			-
55-64 years	599	1.306	1.008	1.693	0.0436
65-74 years	642	2.061	1.588	2.675	<.0001
75+ years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

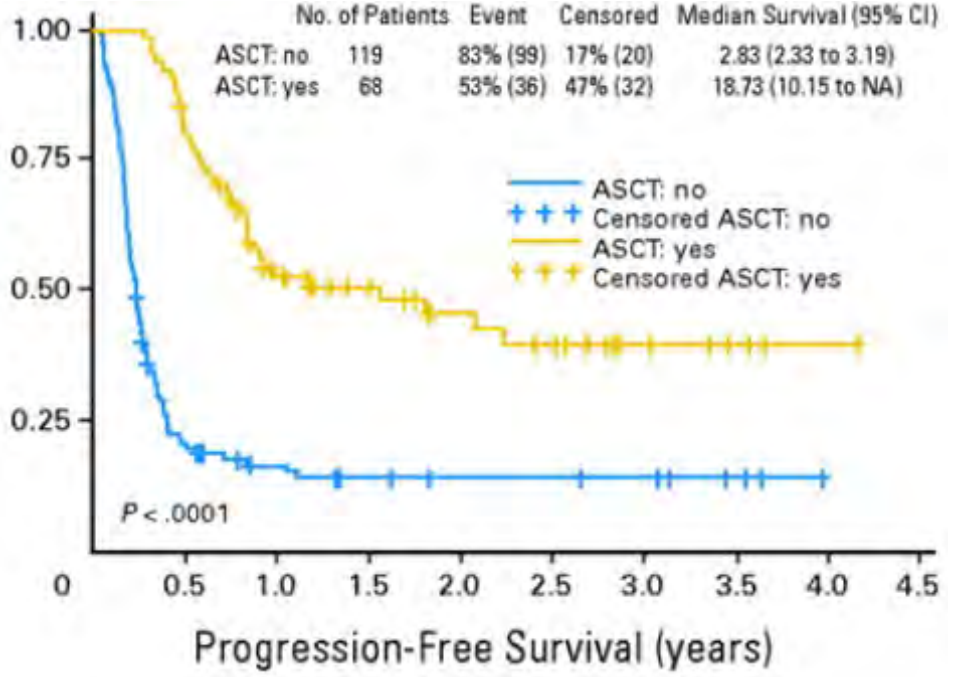




When-Paradigm shift?
CAR T for first relapse DLBCL w/in 12 months of 1^{o} therapy

CORAL trial data



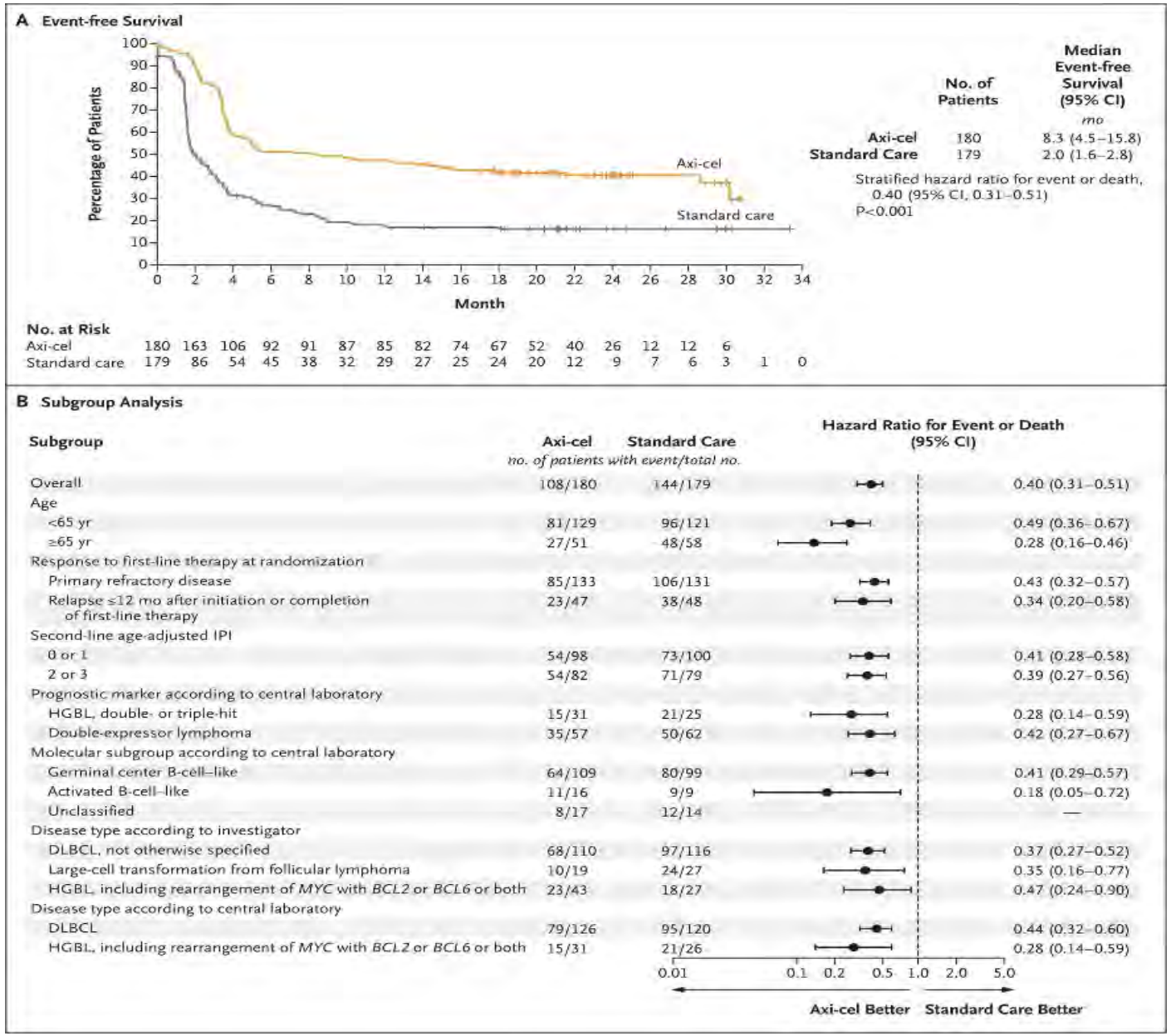


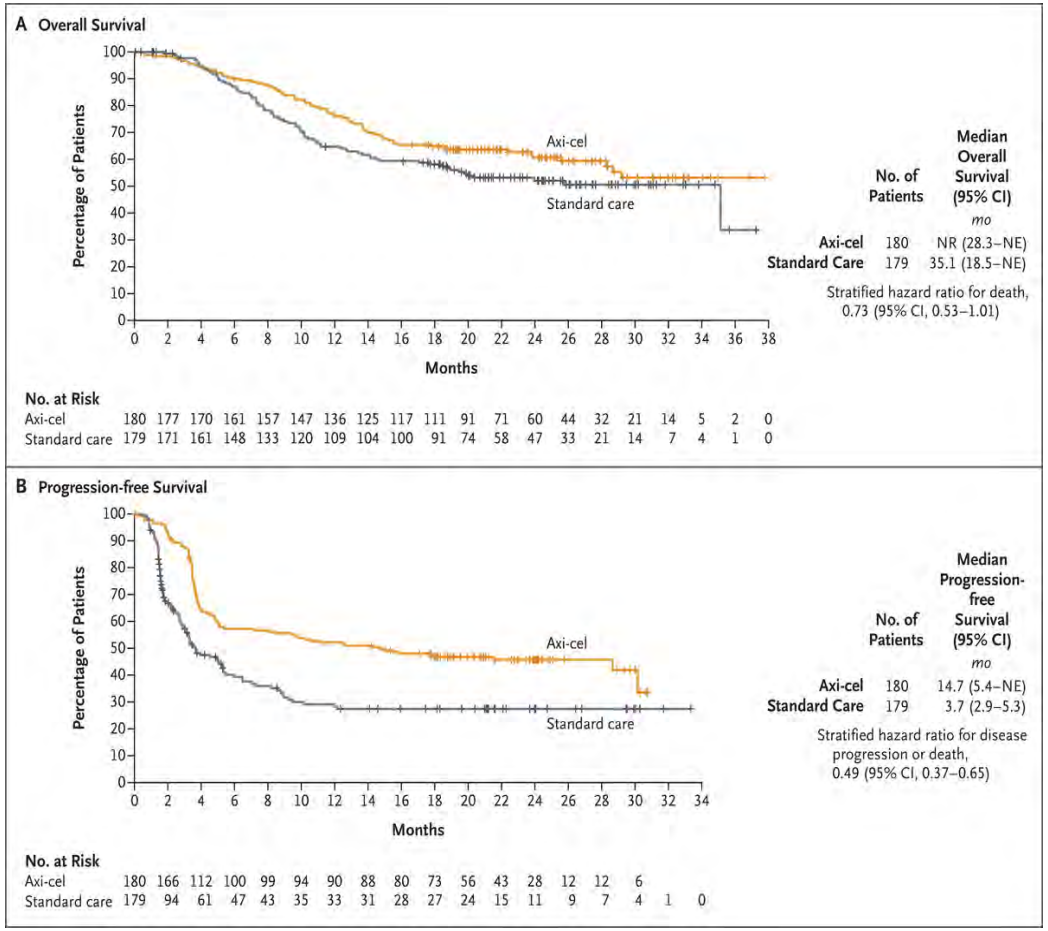
60% of early relapse do not respond to 1st salvage

- 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

ASH #655: Liso-cel vs SOC for second line rx for R/R DLBCL: Transform study, update,

Abramson et al.

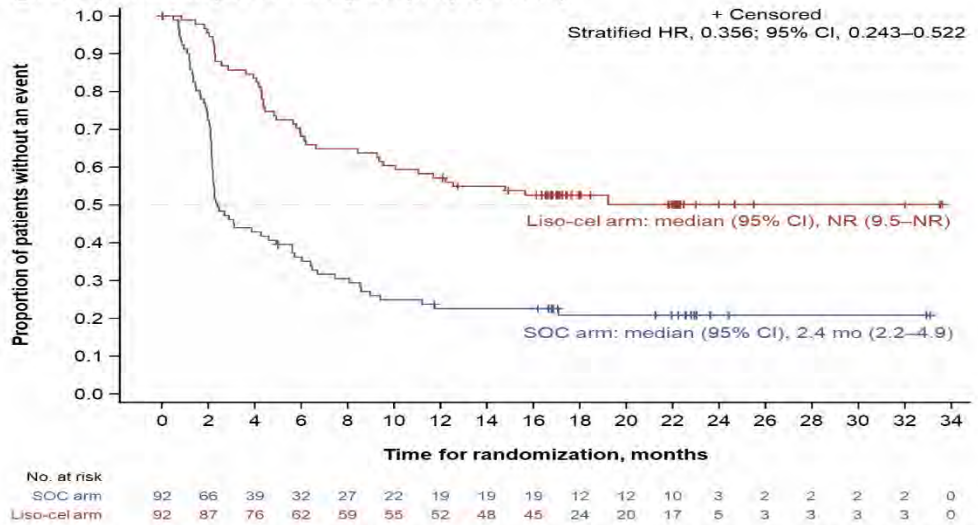
N = 184 randomized; 92 / arm
CAR T arm- bridging/ CAR T
SOC- chemo x 3 → autoHCT

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

Of 91 pts on SOC arm, 67% cross over to Lisocel

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

Salvage therapy can impact CAR T outcomes:
Iacoboni et al, ASH #658

Retrospective, multicenter study
Commercial CAR T products
N=370

Bendamustine treated N= 74
Characteristics: older, higher ECOG score

Results: Benda cohort → lower & delayed CART expansion
Lower central & effector Tmem
CR rates: recent benda vs late benda→ 45 vs 67%
PFS rates: recent benda vs late benda→ 1.5 vs 7.1 mos

Figure 1.- CAR T-cell composition at peak expansion after infusion according to previous bendamustine exposure.

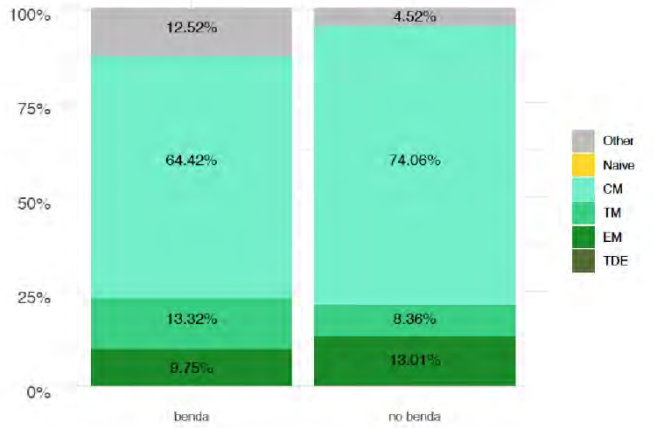


Figure 2.- Best response achieved after CAR T-cell therapy depending on the use and timing of previous bendamustine.

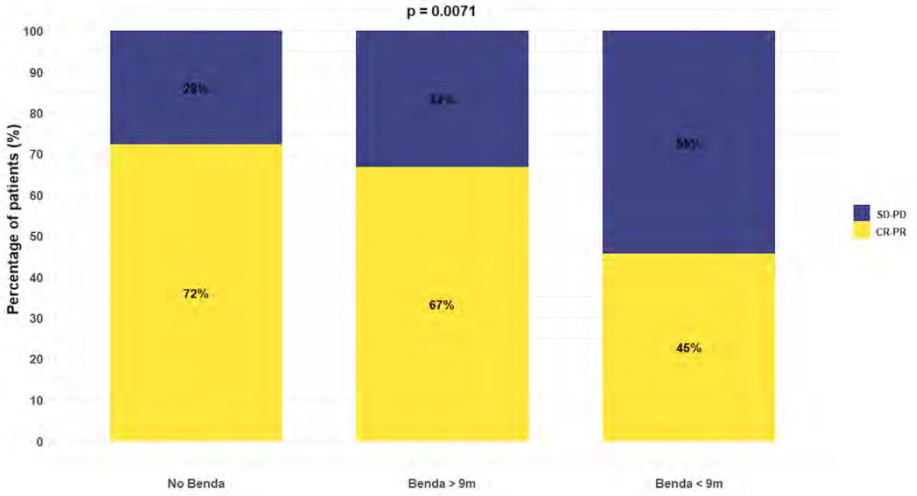
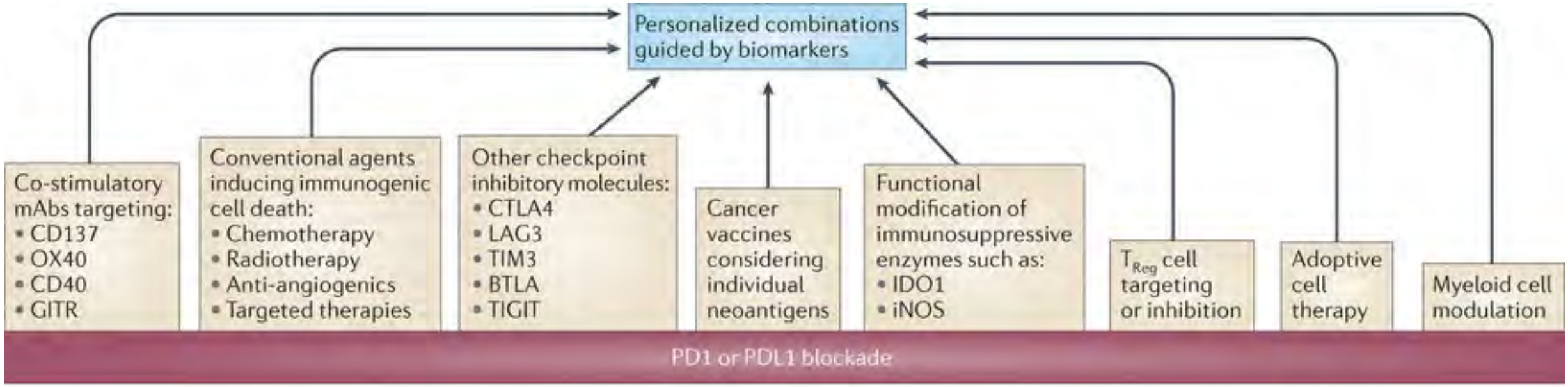


Figure abbreviations: CM central memory, TM transitional memory, EM, effector memory, TDE terminal effector, CR complete response, PR partial response, SD stable disease, PD progressive disease

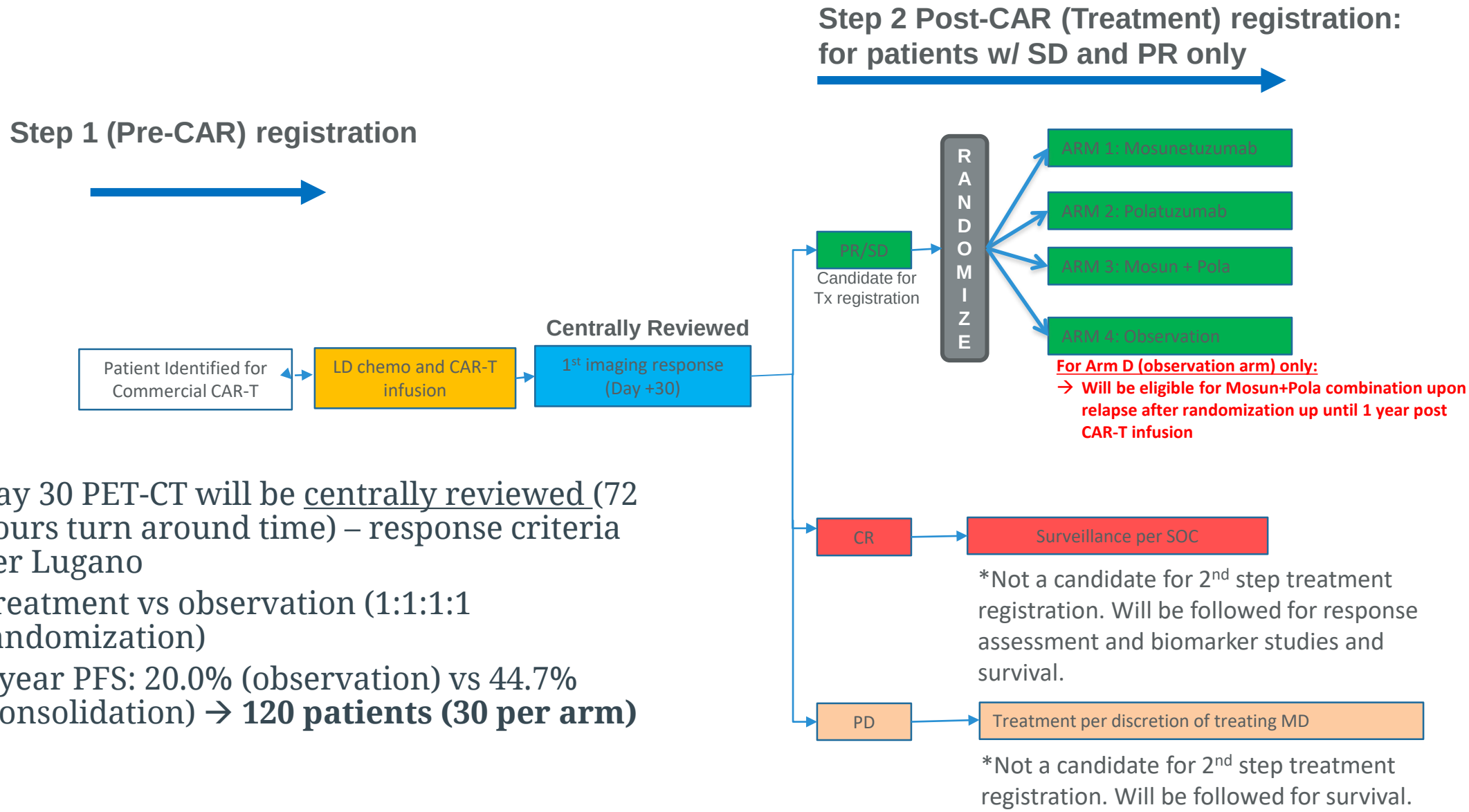
How to improve on outcomes? Potential trial candidates



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)**

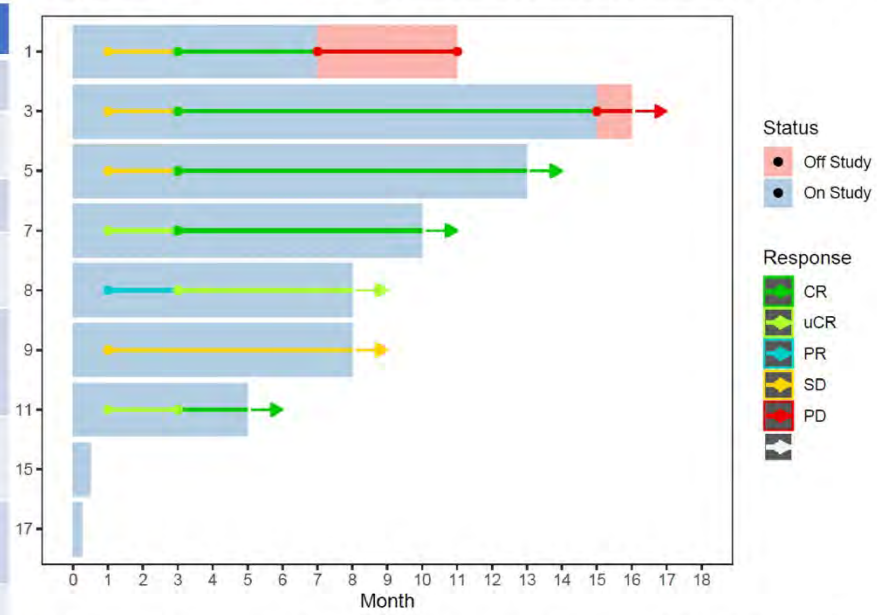
Other CAR T futures: New advances Primary CNS lymphoma

Axicabtagene ciloleucel
Pilot study
N = 9
6/9 1o PCNSL
Mostly parenchymal
Prior therapies (1-6)
ORR- 86%
Evaluable at 3 months- all in CR

Table 1. Patient Characteristics

Characteristic		N (%)
Gender		
	Male Female	4 (44) 5 (56)
Age (years)	Median (Range)	60 (33-74)
Primary v Secondary CNSL	Primary Secondary	6 (67) 3 (33)
Cell of Origin	GCB Non-GCB Unknown	1 (11) 5 (56) 3 (33)
DHL/THL	Yes No Unknown	0 (0) 6 (67) 3 (33)
Double Expresor	Yes No Unknown	3 (33) 4 (44) 2 (22)
Tumor Location	Parenchymal only Leptomeningeal only Both Ocular CSF cytology positive	8 (89) 0 (0) 1 (11) 1 (11) 2 (22)
Number or prior systemic therapies	Median (Range)	2 (1-6)
Disease status to last line of therapy	Relapsed Refractory	4 (44) 5 (56)
Time from CNSL diagnosis to enrollment	Days (range)	281 (121-8666)
Time from last therapy to enrollment	Days (range)	57 (16-392)

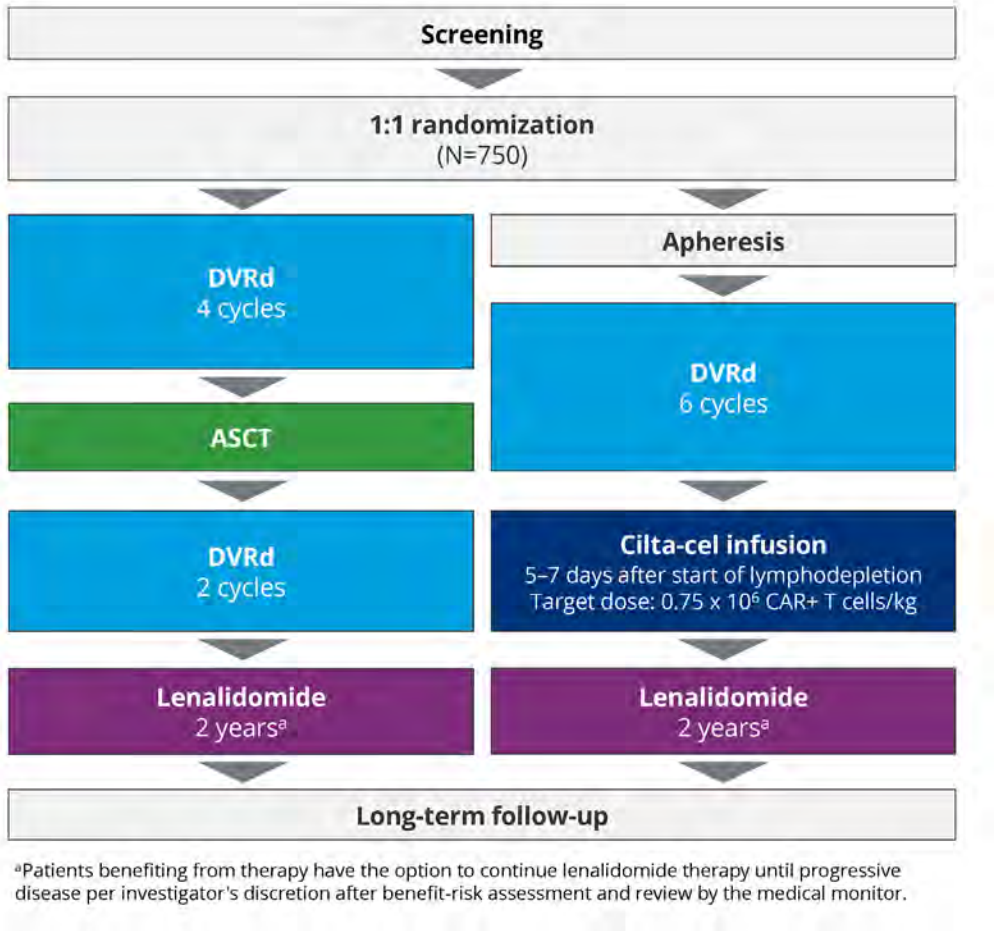
Figure 1. Swimmer Plot of Response to Axi-cel Over Time



CR: complete response; uCR: unconfirmed complete response; PR: partial response; SD: stable disease (SD); PD: progressive disease

Abstr: 2023

DVRd Followed By Ciltacabtagene Autoleucel Versus DVRd Followed By ASCT in Patients with Newly Diagnosed Multiple Myeloma Who Are Transplant Eligible: A Randomized Phase 3 Study (*EM*agine/CARTITUDE-6)



Novel trial→ future studies that may change the standard of care

1:1 randomization

1º endpoints:

- PFS
- Sustained MRD neg state ≥ 12 mos

Key 2º endpoints:

- ORR
- CR rate
- OS
- AEs
- QOL

Thanks for listening!

Memorial Day weekend, 2022- Commissioning of the USS Oregon