LENFOMADA TRANSPLANTASYON VERİLERİ- ASH 2021 GÜNCELLEMESİ

ELİF BİRTAŞ ATEŞOĞLU

KOÇ ÜNİVERSİTESİ HEMATOLOJİ BD

ILEG - 08 OCAK 2022

Haploidentical vs. Matched Unrelated Donor Transplants Using Post-Transplant Cyclophosphamide for Lymphomas: A Joint CIBMTR/EBMT Study

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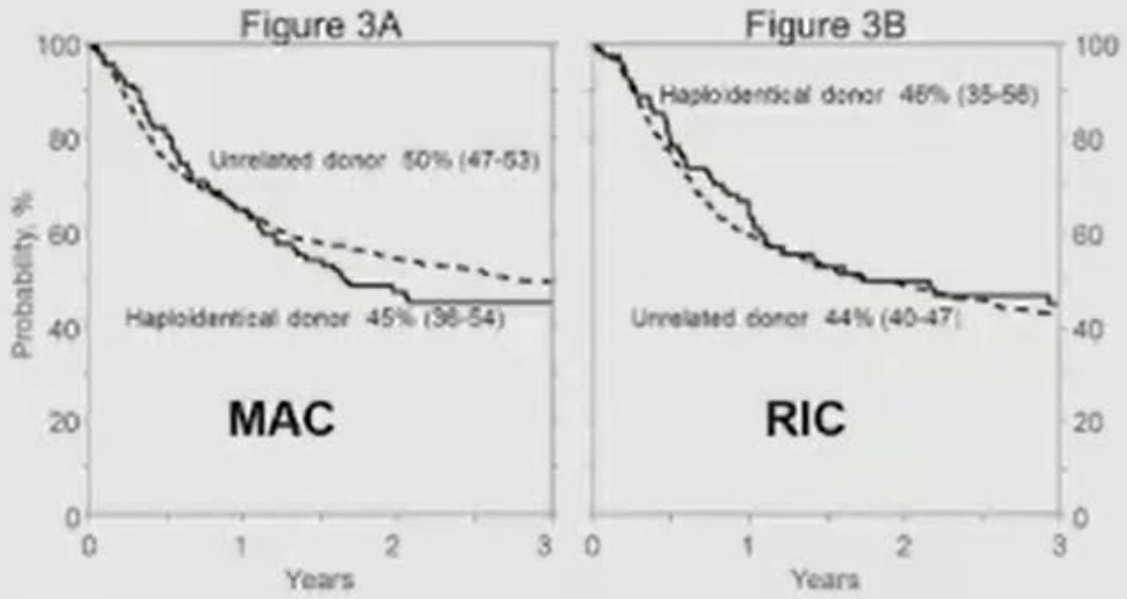
The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW).

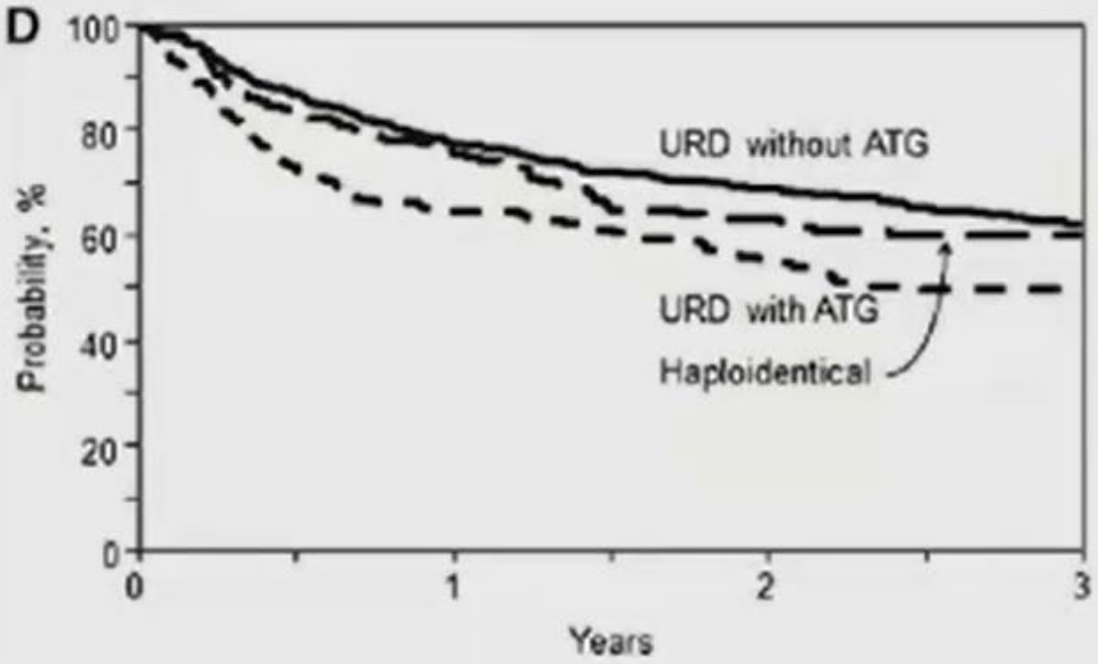
Study hypothesis

- Post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis strategy could neutralize differences between HLA haploidentical related donors and matched unrelated donors in allogeneic hematopoietic transplant outcomes for lymphomas.

HaploHCT With PTCy Has Same OS of MUD With Standard GVHD Prophylaxis



Acute myeloid leukemia,
Ciurea SO, Blood 2015



Lymphomas,
Kanate A, Blood 2016

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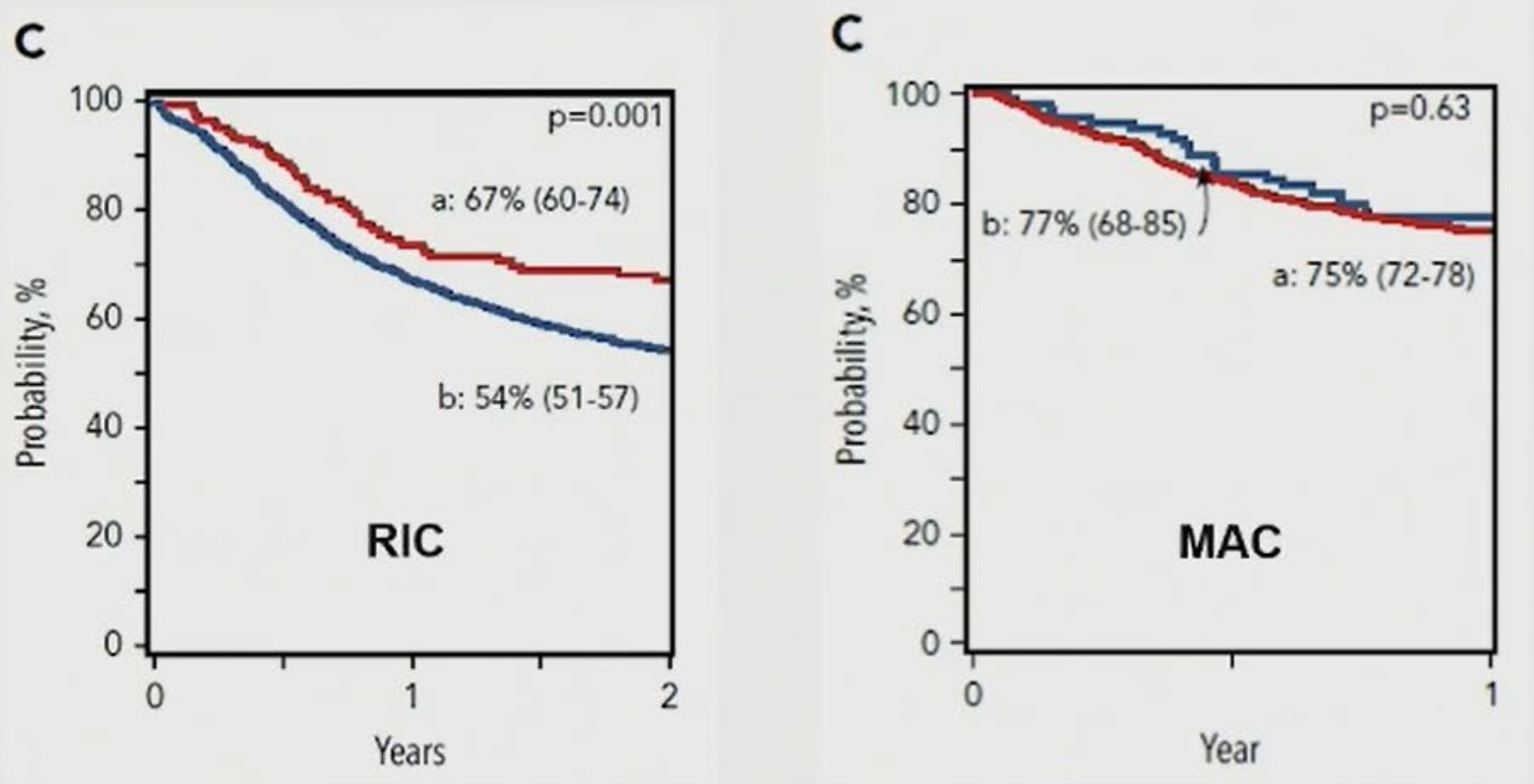
When Using PTCy and RIC, MUD Has Better Survival Than Haplo for Myeloid Malignancies



Myeloid diseases,
Gooptu M, Blood 2021

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Patient Population

Inclusions criteria

- Data Source-CIBMTR and EBMT Observational Database
- Patients with Hodgkin lymphoma or NHL (age ≥18 years)
- First allo-HCT between 2010-2019
- 8/8 allele-matched URDs (A-B-C-DRB1 HLA locus compatibility) or haploidentical donors
- BM or PB graft source
- MAC or RIC conditioning regimen
- PTCy only GVHD prophylaxis

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Baseline Characteristics

Variable	Haploidentical (n=1843)	MUD 8/8 (n=312)
Median age, years	46 (18-71)	53 (19-71)
Female gender (%)	665 (36)	95 (21)
KPS ≥ 90 (%)	1292 (70)	201 (69)
HCT-CI (%)		
0	681 (37)	91 (29)
1	145 (8)	29 (9)
2	230 (12)	37 (12)
3+	363 (20)	94 (30)
Disease type		
Follicular lymphoma	138 (7)	31 (10)
DLBCL	449 (24)	76 (24)
MCL	181 (10)	53 (17)
cHL	812 (44)	87 (28)
T-cell lymphoma	263 (14)	65 (21)

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Baseline Characteristics

Variable	Haploidentical (n=1843)	MUD 8/8 (n=312)
NHL chemo-sensitivity (%)	858 (83)	184 (82)
HL chemo-sensitivity (%)	668 (82)	71 (82)
Prior ASCT (%)	1105 (60)	168 (54)
Graft type (%)		
BM	748 (41)	28 (9)
PBSC	1095 (59)	284 (91)
Conditioning intensity RIC (%)	1425 (77)	230 (74)
GVHD prophylaxis (%)		
Cy + CNI (Csa/Tac) + MMF	1644 (89)	161 (52)
Cy + others	199 (11)	151 (48)
Donor age median (range)	37 (0-85)	28 (18-55)
Median follow-up survivors, months	33 (0-123)	21 (0-108)

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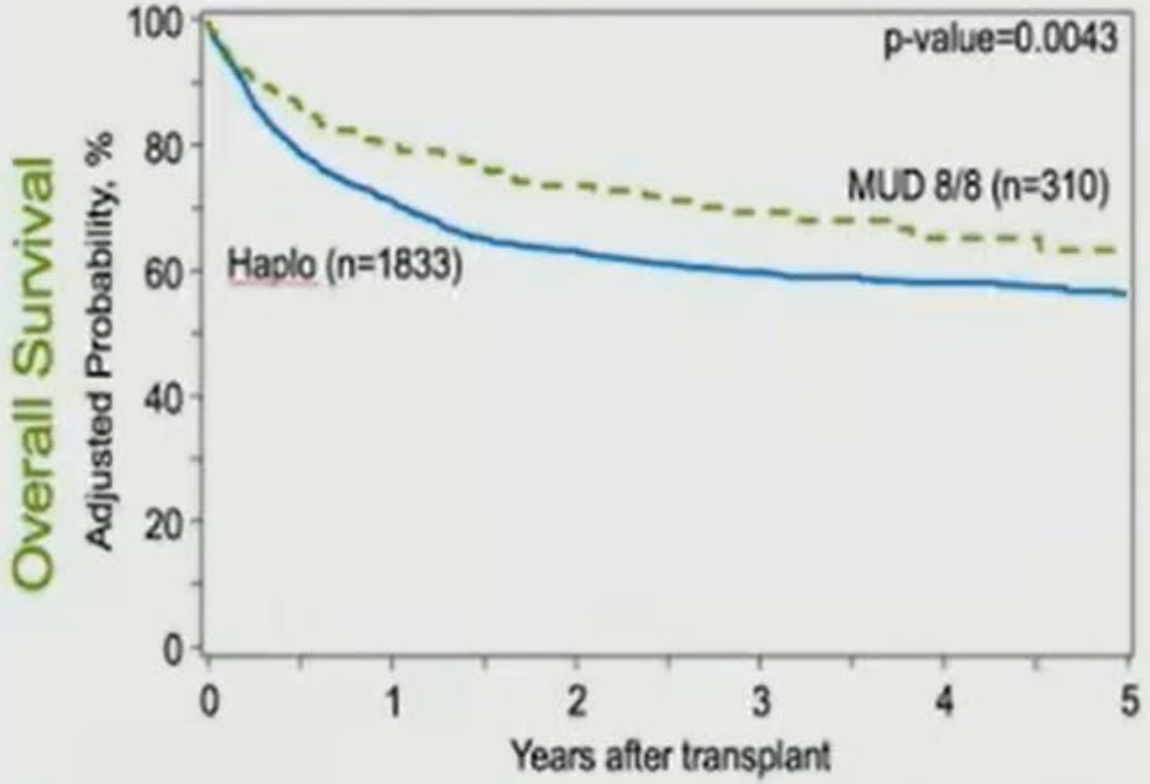

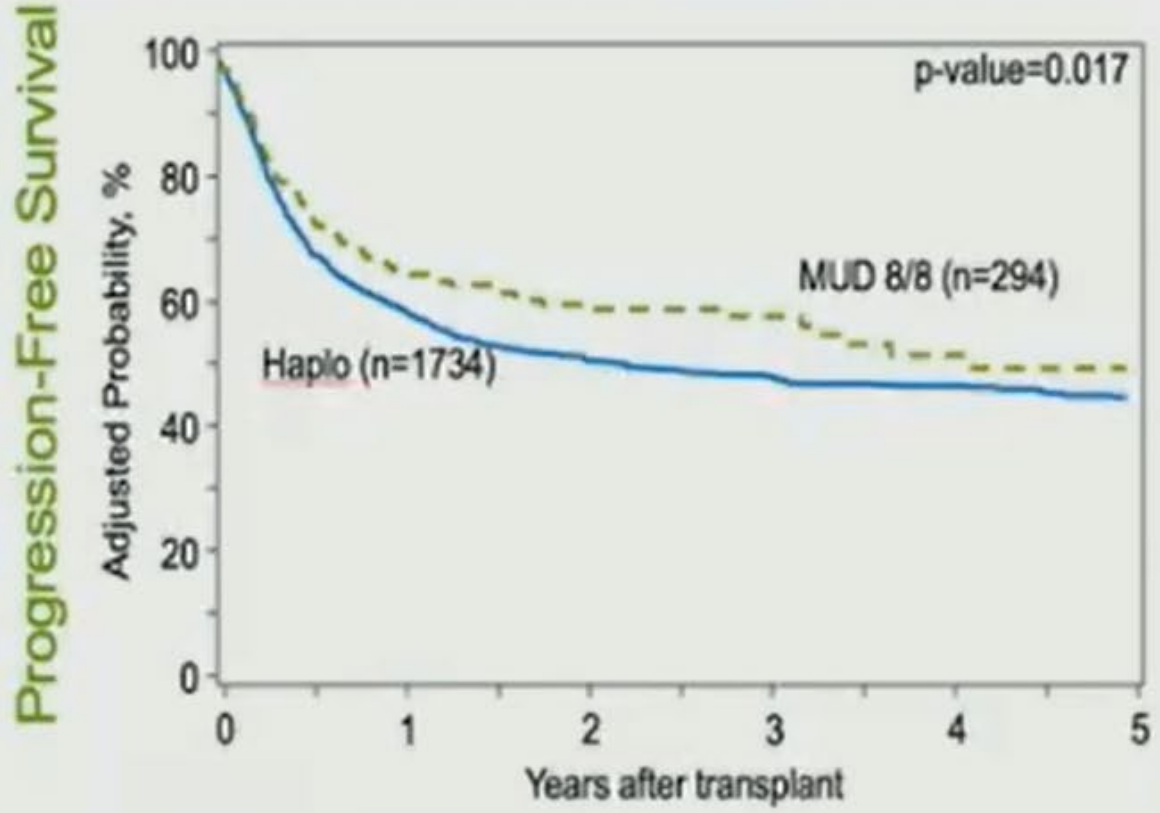

	1-year (95% CI)		2-years (95% CI)	
	Haplo	MUD 8/8	Haplo	MUD 8/8
PFS	61 (58-63)	68 (63-74)	52 (50-55)	63 (57-69)
OS	72 (70-74)	80 (75-85)	63 (61-66)	73 (67-79)

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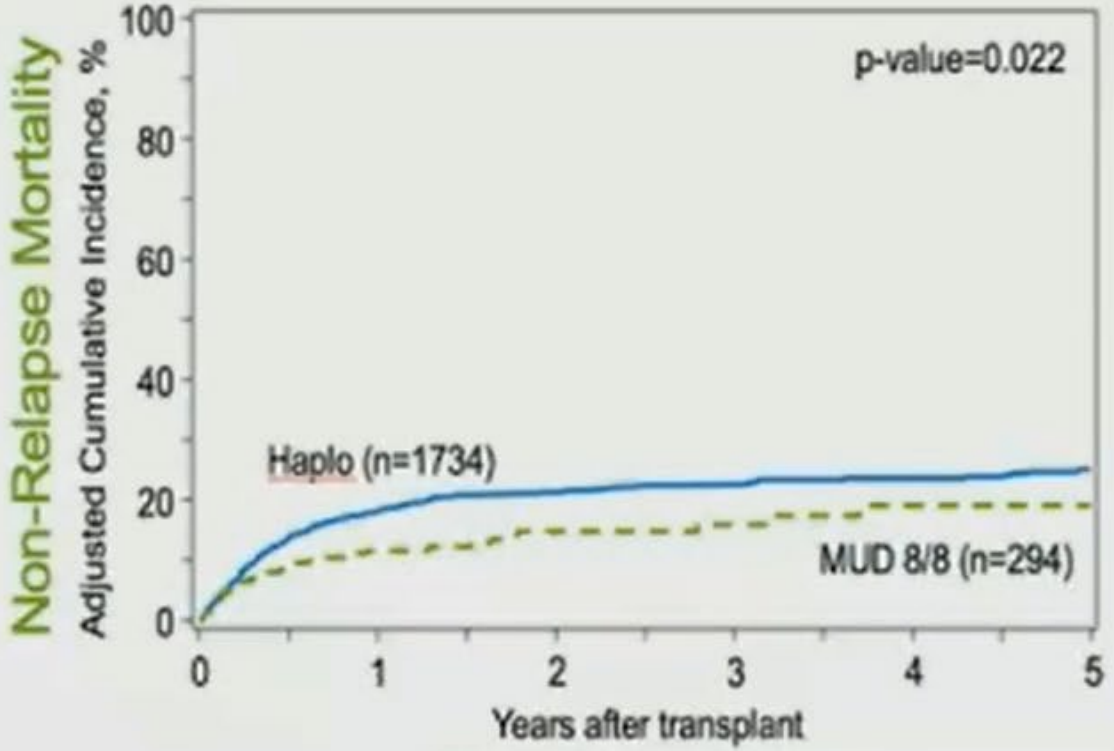

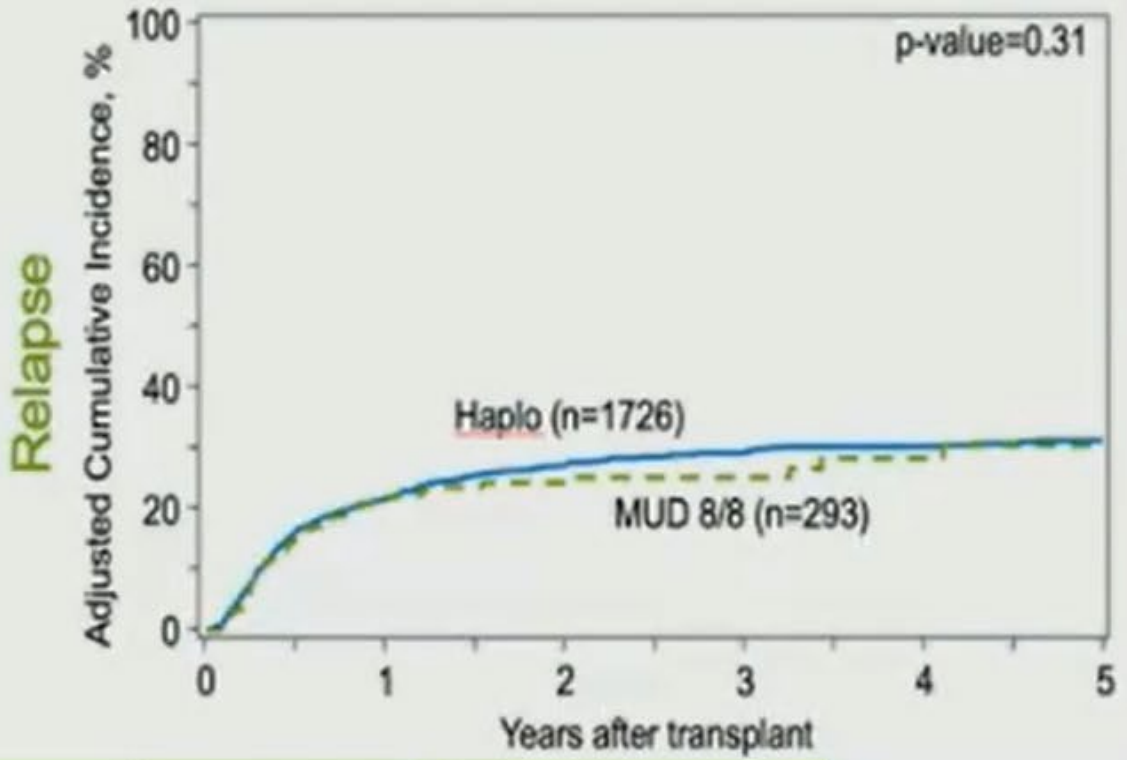

	1-year (95% CI)		2-years (95% CI)	
	Haplo	MUD 8/8	Haplo	MUD 8/8
NRM	18 (16-20)	11 (8-16)	21 (19-23)	14 (10-19)
Relapse	22 (20-24)	20 (16-25)	27 (25-29)	22 (17-28)

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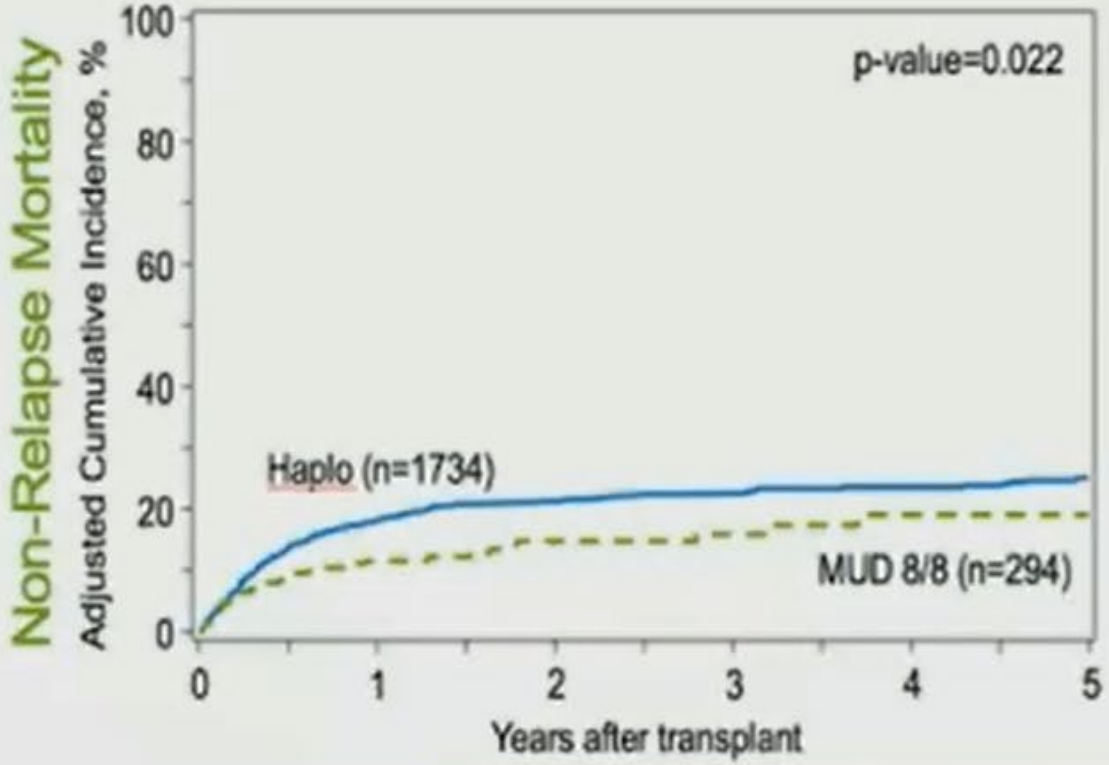

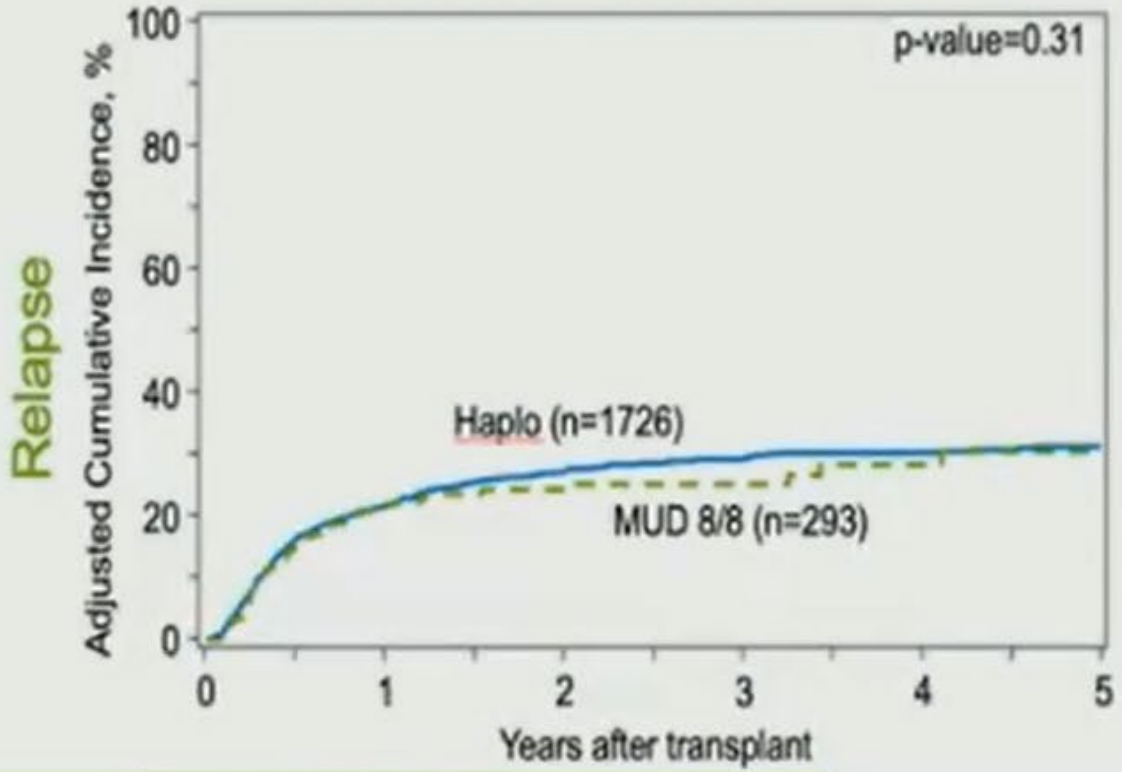

	1-year (95% CI)		2-years (95% CI)	
	Haplo	MUD 8/8	Haplo	MUD 8/8
NRM	18 (16-20)	11 (8-16)	21 (19-23)	14 (10-19)
Relapse	22 (20-24)	20 (16-25)	27 (25-29)	22 (17-28)

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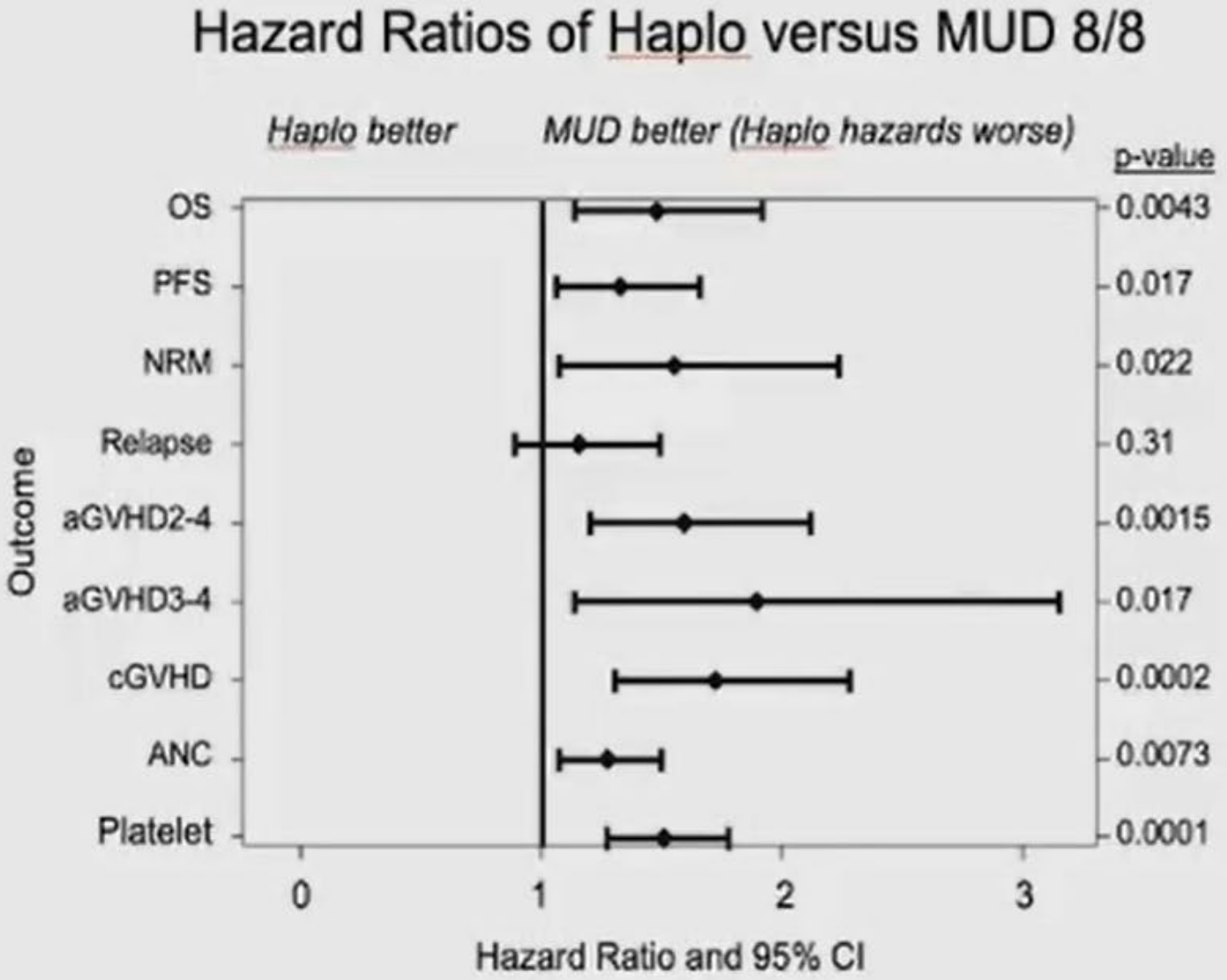
Multivariate Analysis

	Number	HR	95% CI Lower Limit	95% CI Upper Limit	P-Value
Platelets recovery day+28					
Haplo	1657	1.00			
MUD	259	1.47	1.25	1.72	<0.01
Neutrophil recovery day+28					
Haplo	1765	1.00			
MUD	294	1.25	1.06	1.46	<0.01
aGVHD (II-IV)					
Haplo	1697	1.00			
MUD	279	0.64	0.49	0.85	<0.01
aGVHD (III-IV)					
Haplo	1711	1.00			
MUD	286	0.55	0.33	0.90	<0.01
cGVHD					
Haplo	1724	1.00			
MUD	277	0.60	0.46	0.78	<0.01

Multivariate Analysis



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Conclusions

1. PTCy was not able to neutralize differences between MUD and Haplo donors.
2. When using PTCy, MUD 8/8 has better outcomes in terms of OS, PFS, NRM, aGVHD grade 2-4, aGVHD grade 3-4, cGVHD, neutrophil and platelets recovery.
3. Whenever available, a MUD 8/8 should still be preferred over Haplo donor when using PTCy.
4. Haploidentical HCT vs. MUD 8/8 HCT with PTCy in lymphomas warrants randomized investigation

Romidepsin in Conditioning and Maintenance Mitigates Relapse Risk and Enhances NK-Cell Cytotoxicity in Patients Receiving Allogeneic Stem Cell Transplant for Aggressive T-Cell Malignancies: Results of a Phase I/II Clinical Trial

Hosing C[1], Braunstein Z[2], Alaa MA[2], Valdez BC[1], Andersson BS[1], Devine S[2], Popat UR[1], Vasu S[2], Larkin K[2], Penza S[2], Choe H[2], Saad A[2], de Lima M[2], Wei L[3], McLaughlin E[3], Nakkula R[4], Campbell A[4], Trikha P[4], Puto M[2], William B[2], Champlin RE[1], Lee DA[4], Brammer JE[2]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The Ohio State University James Comprehensive Cancer Center Blood and Marrow Transplant Program, Columbus, OH, [3]The Ohio State University Department of Biomedical Informatics, Columbus, OH, [4]Nationwide Children's Hospital at the Ohio State University, Columbus, OH

The James

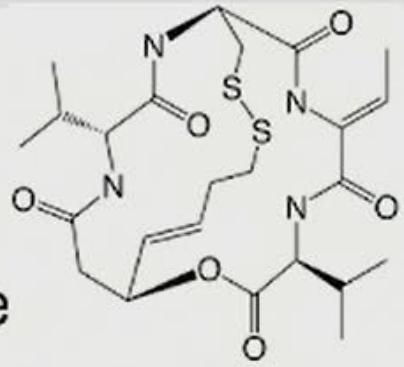
The Ohio State University

The University of Texas MD Anderson Cancer Center

Background

- T-cell malignancies are rare disease entities with high relapse rates ranging from 50-75% even after allogeneic stem cell transplant (allo-SCT)
- No trials using allo-SCT specifically targeting T-cell malignancies have ever been conducted
- Unlike B-cell malignancies, novel salvage therapies such as CAR-T cells for T-cell malignancies are limited
- Relapses are often early, before the Graft-versus-tumor effect can occur, and uniformly fatal
- Improving outcomes of T-cell malignancies of allo-SCT is a priority of the ASTCT

Rationale



- DNA hypermethylation and histone are known pathways for resistance of T-cell leukemias and lymphomas to therapy
- Romidepsin (Istodax) is an HDAC inhibitor (HDACi), approved for the treatment of PTCL and CTCL
- In pre-clinical studies, Romidepsin combined with fludarabine, clofarabine, and busulfan leads to synergistic cytotoxicity T-cell lymphoma/leukemia cell lines and patient samples (Valdez et al, Leuk Res, 2016)
- HDACis have been found to promote generation/function of T-regulatory cells (T-regs), while preserving graft-versus-lymphoma effect (GVL), so romidepsin may have similar effect

Hypothesis

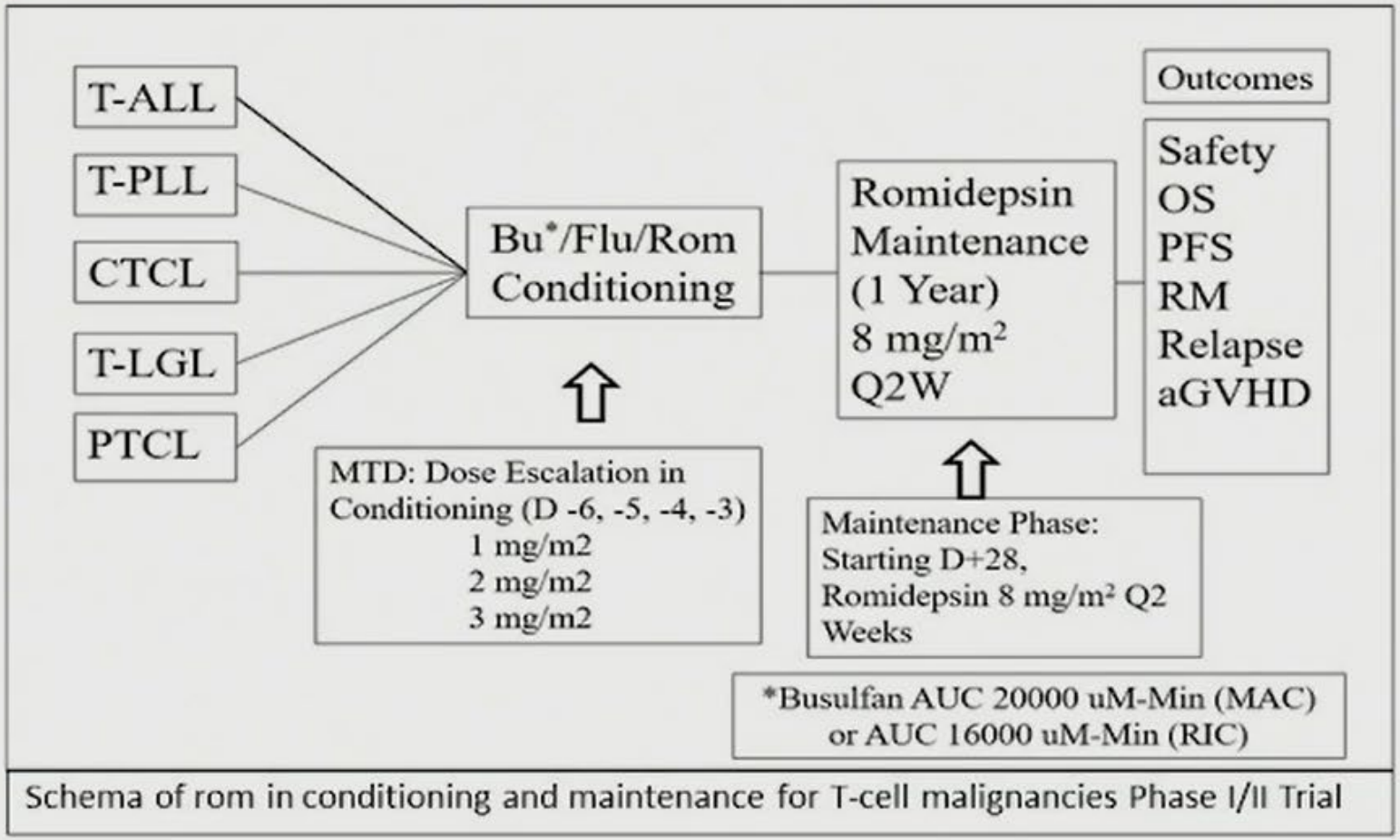
- We hypothesize that the introduction of romidepsin into the conditioning therapy, followed by romidepsin maintenance therapy will decrease disease relapse in patients with T-cell malignancies by stimulate the graft-versus-lymphoma effect through increased NK-cell cytotoxicity.

Study Design

- Phase I/II Trial testing escalating doses of romidepsin (1 mg/m^2, 2 mg/m^2, 3 mg/m^2) in combination with standard busulfan/fludarabine (BuFlu) conditioning
- Once recommended phase 2 dosage was determined, an expansion cohort of up to 30 total patients was included
- MUD or MRD
- GVHD prophylaxis was with tacrolimus/mini-Methotrexate and ATG for MUD
- Primary Endpoints: RP2D (Phase I), and Relapse at 1 year (Phase II)-pre-specified overall relapse rate of 55% (targeted at 15% decrease)

*RIC Arm added to protocol to improve enrollment, decrease NRM in those with HCT-CI >/= 4

Study Schema



Schema of rom in conditioning and maintenance for T-cell malignancies Phase I/II Trial

- Starting D+35 to D+100, patients in remission were initiated on romidepsin maintenance (m-rom) for 1 year at 8 mg/m^2 q2 weeks, with option 2nd year
- Built in dose reductions for toxicity were included (4 and 2 mg/m^2)

Patient Characteristics

Variable (Baseline)	N (%)
Total	21 (100)
Disease	
PTCL	6 (29)
CTCL	2 (10)
T-ALL	7 (33)
T-PLL	5 (24)
ATLL	1 (5)
Male Gender	11 (52)
Median Age	51 (21-67)
Remission Status at Transplant	
CR1	13 (62)
CR2+	4 (19)
PR	4 (19)
MRD+	10 (48)

*MTD was determined to be 2 mg/m^2; one DLT observed (VOD)

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Comprehensive Cancer Center

Patient Transplant Characteristics

Variable (Transplant)	N (%)
Total	21 (100)
Donor	
MUD	15 (71)
MRD	6 (29)
AUC (umol-min)	
MAC (5000)	16 (76)
RIC (4000)	5 (24)
ATG	
Yes	13 (62)
No	8 (38)
Marrow Source	
Peripheral Blood	13 (62)
Marrow	8 (38)
Romidepsin Dose	
1 mg/m^2	3 (14)
2 mg/m^{2*}	18 (86)

*MTD was determined to be 2 mg/m^2; one DLT observed (VOD)

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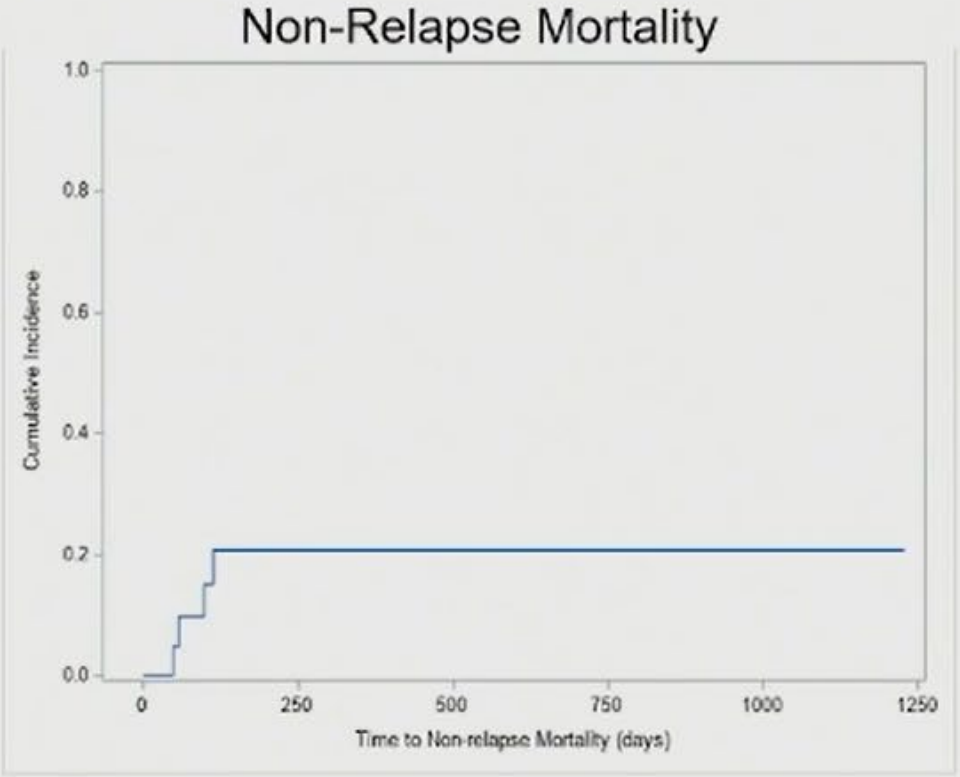
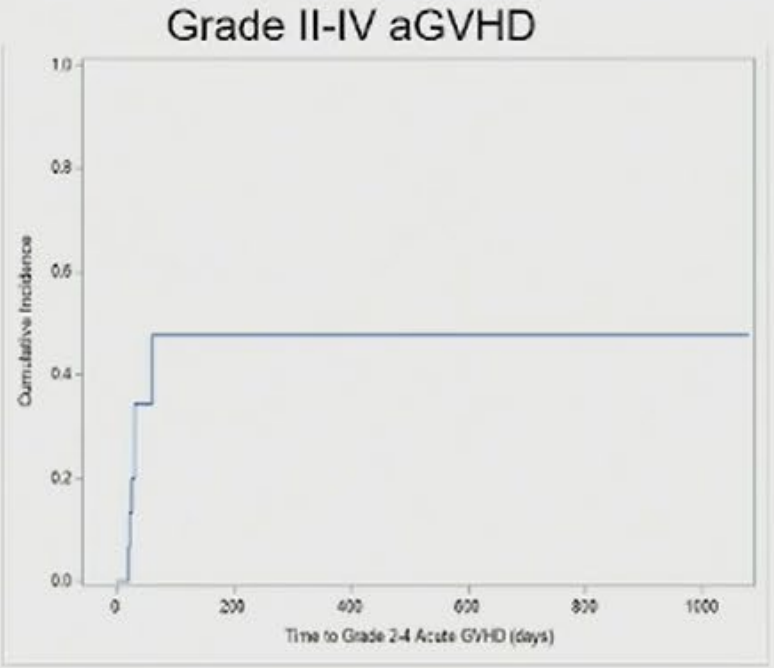
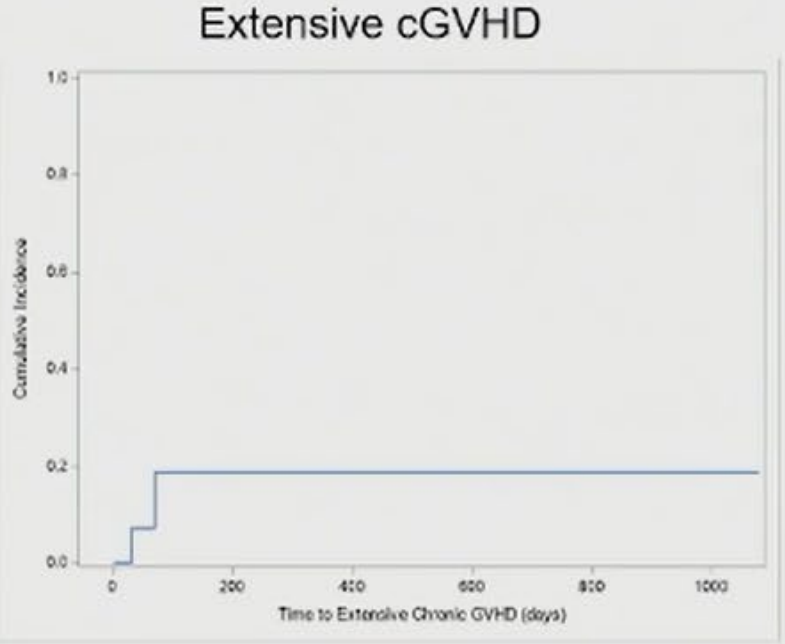
Cumulative Incidence of NRM/GVHD

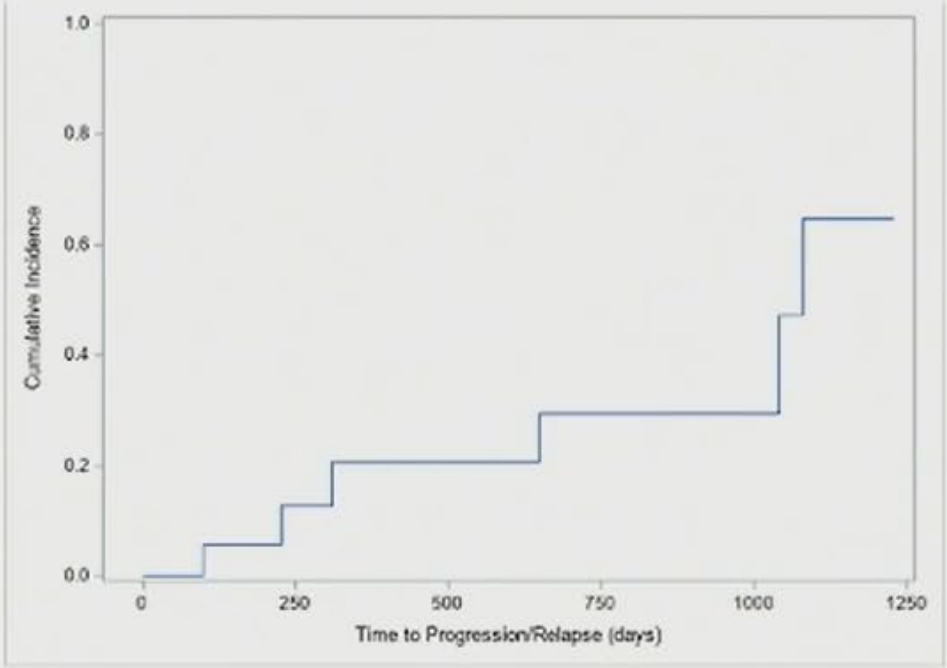






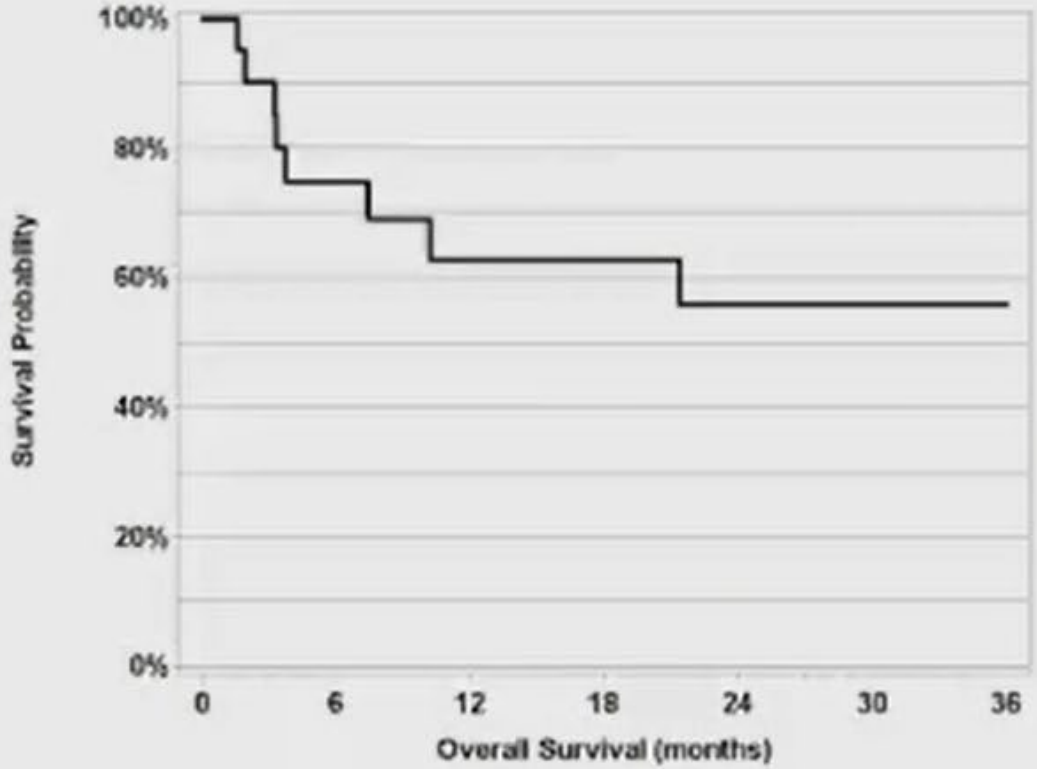
- CI NRM: Day 100: 14.8%, 1-year: 20%
- CI grade II-IV aGVHD: 47.6%
- CI extensive cGVHD: 18.5%
- No Impact on Engraftment (ANC Recovery median 12 days, platelet recovery 11 days)

Cumulative Incidence of Relapse



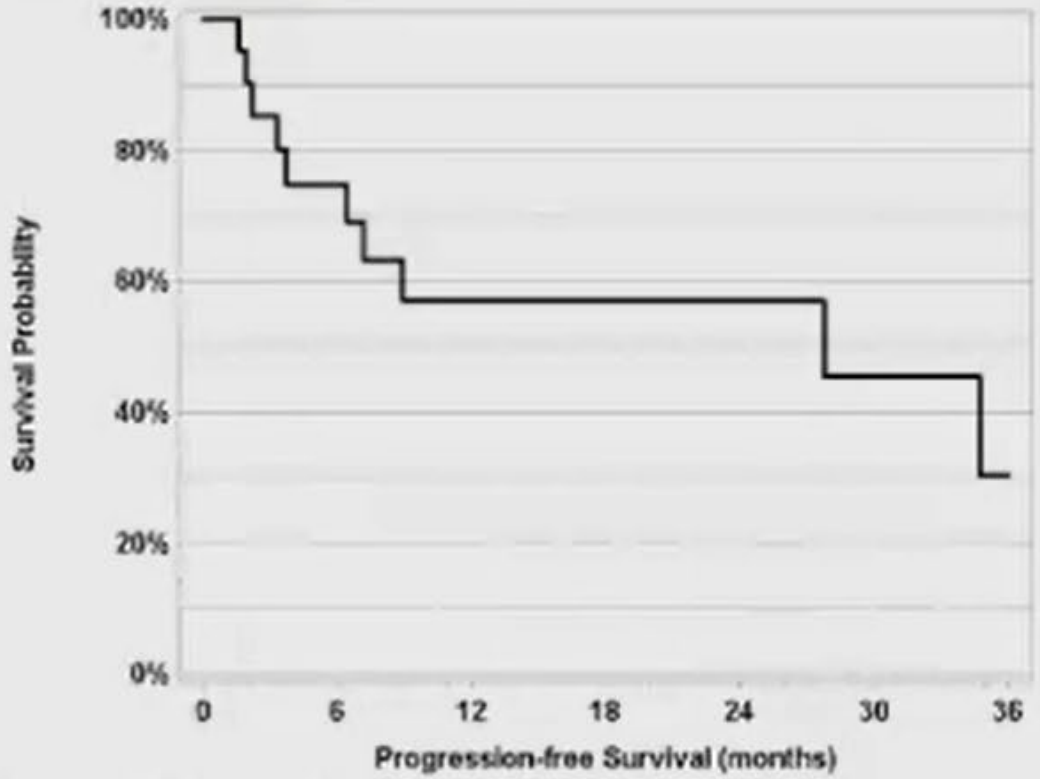
- Cumulative Incidence of Relapse at 1 year was 22.8% (95% CI 6.6-44.9%)
- Superior to pre-specified estimated 55% relapse rate for all diseases (note: leukemia included)

Overall Survival



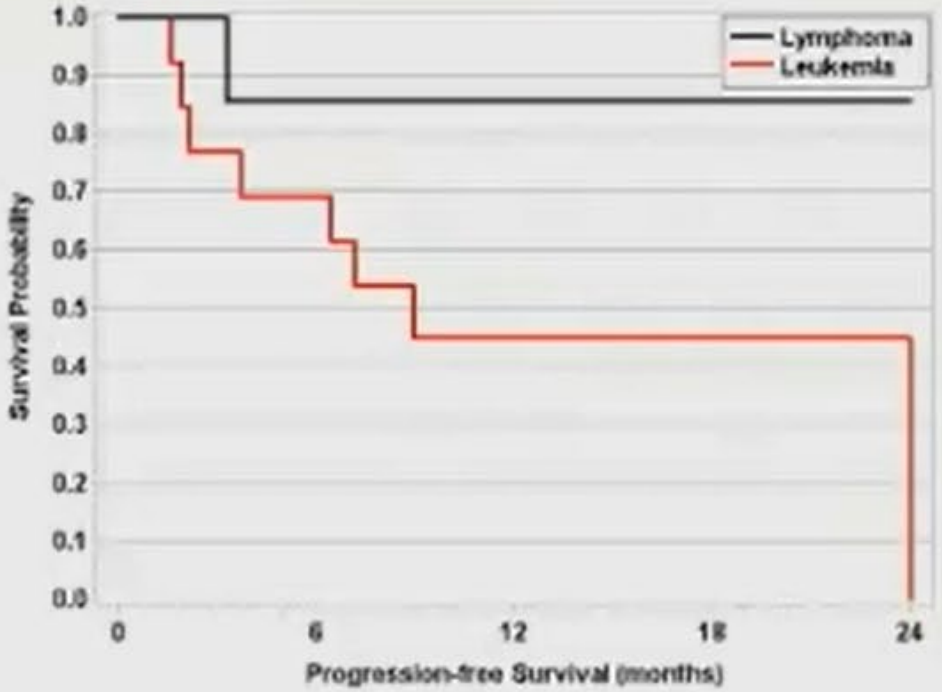
- Median OS has not been reached
- 1 and 3-year OS probability 62.8% and 55.8%

Progression-Free Survival



- Median follow-up time 10.1 months
- Median PFS 28.2 months
- 1 and 3 year PFS: 57% and 30.4%
- **No difference in PFS among those with MRD vs those without MRD prior to transplant (p=0.96)**

Progression-Free Survival (By Disease)



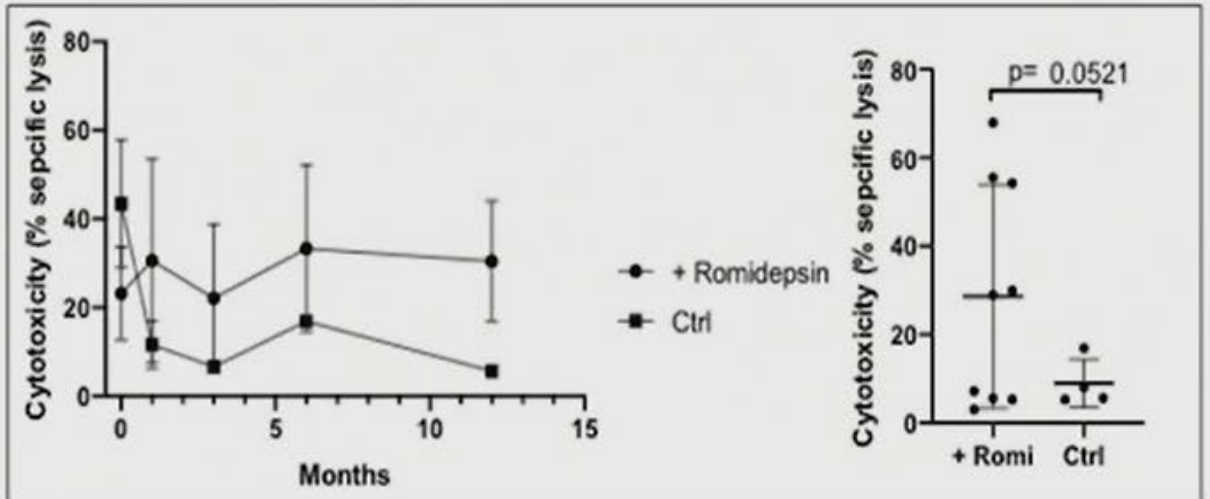
- PFS was substantially better for those with lymphoma (PTCL/CTCL) than leukemia (T-PLL, ATLL, T-ALL); 85.7% vs 44% p=0.049).
- CI Relapse was also higher for the leukemia group (0% vs 32.1%, p=0.05)
- No patients with PTCL relapsed; 3/5 patient with T-PLL are alive, disease free

Maintenance Romidepsin (m-rom)

- 13/21 (62%) of patients received m-rom with a median of 10 cycles (range 1-41)
- 7 patients experienced grade 3/4 AEs, though no patients discontinued m-rom due to toxicity

Subject	Disease	Maintenance (Cycles)	Reason for DC or Not Initiating
MDACC1	MF/ALCL	8	Pt Preference
MDACC2	T-ALL	1	Cytopenias
MDACC3	T-ALL	23	End of Treatment
MDACC4	SPLTCL	1	Pt Declined
OSU9	ATLL	10	Relapse
OSU10	T-PLL	16	End of Treatment
OSU13	T-PLL	12	Deceased (NRM)
OSU14	T-ALL	41	On Therapy
OSU15	T-ALL	8	Relapse
OSU16	SPLTCL	16	cGVHD
OSU18	T-ALL	12	On Therapy
OSU19	PTCL	8	On Therapy
OSU20	CTCL	2	On Therapy

NK-Cytotoxicity Correlative Analysis



M-Rom increased NK-cytotoxicity post allo-SCT at all time points (left) and in pooled analysis (right) compared to those without m-rom

- Using the celcein-AM assay, NK-cytotoxicity was higher at each time point in patients who received m-rom compared to those who did not (left), though there were insufficient samples to reach statistical significance
- When NK-cytotoxicity was assessed between the two groups after starting m – ROM, NK-cytotoxicty was significantly higher in the m-Rom group (right)

Conclusions

- BuFluRom with m-rom is effective at decreasing relapse in patients with T-cell malignancies, with 1-year CI relapse below expected relapse rates for these diseases
- Toxicities were similar to standard BuFlu alone and RP2D of rom in conditioning was 2 mg/m^2
- BuFluRom mitigated the poor outcomes of patients with MRD prior to transplant
- Early data suggests m-rom enhances NK-cell cytotoxicity post allo-SCT, potentially augmenting the GVL effect and accounting for decreased relapsed rates
- Long-term follow-up is needed to evaluate these results
- BuFluRom with m-rom could become a new options for patients with T-cell malignancies to mitigate relapse

Characterizing Safety in Patients With Hematologic Malignancies Receiving Allogeneic Stem Cell Transplant Following Pembrolizumab Therapy

P. Armand[1]; J. Kuruvilla[2]; A. F. Herrera[3]; V. Ribrag[4]; P. Brice[5]; C. Thieblemont[5]; B. von Tresckow[6]; E. Kim[7]; R. Orlowski[7]; S. Chakraborty[7]; P. Marinello[8]; P. L. Zinzani[8]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]UHN Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]City of Hope Medical Center, Duarte, CA, USA; [4]Gustave Roussy, Cancer Campus, Villejuif, France; [5]Saint-Louis Hospital, University of Paris, Paris, France; [6]University Hospital Cologne, University of Cologne, and West German Cancer Center, Essen University Hospital, University of Duisburg-Essen, Essen, Germany; [7]Merck & Co., Inc., Kenilworth, NJ, USA; [8]IRCCS University Hospital of Bologna, Seràgnoli Institute of Hematology, and Department of Specialized, Diagnostic and Experimental Medicine, University of Bologna, Bologna, Italy

Study Design and Analysis

All-patients-as-treated population[a]
N = 631

Patients who received an allo-SCT after study dose of pembrolizumab
n = 78

N = 70

KEYNOTE-013
n = 20
Pembrolizumab
10 mg/kg Q2W or
200 mg Q3W

KEYNOTE-087
n = 31
Pembrolizumab
200 mg Q3W

KEYNOTE-170
n = 5
Pembrolizumab
200 mg Q3W

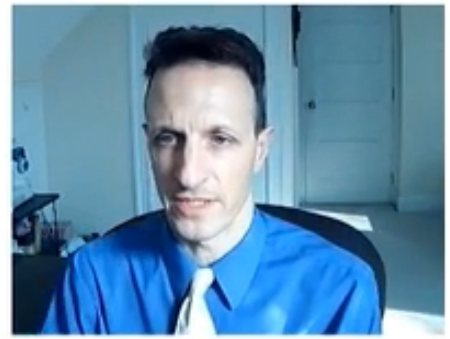
KEYNOTE-204
n = 14
Pembrolizumab
200 mg Q3W

Safety analysis for up to 18 months after allo-SCT

Primary End Point
Incidence and severity of complications in patients who received allo-SCT after pembrolizumab therapy

Allo-SCT, allogeneic stem cell transplant.
[a]Defined as all randomly assigned patients who received ≥1 dose of study drug.

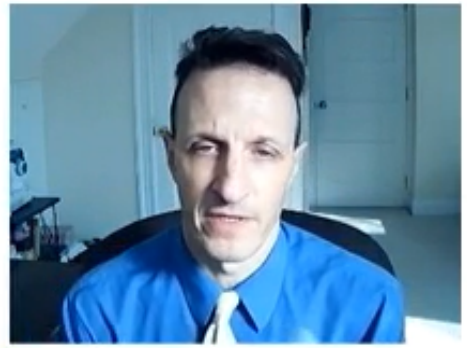
Patient Characteristics



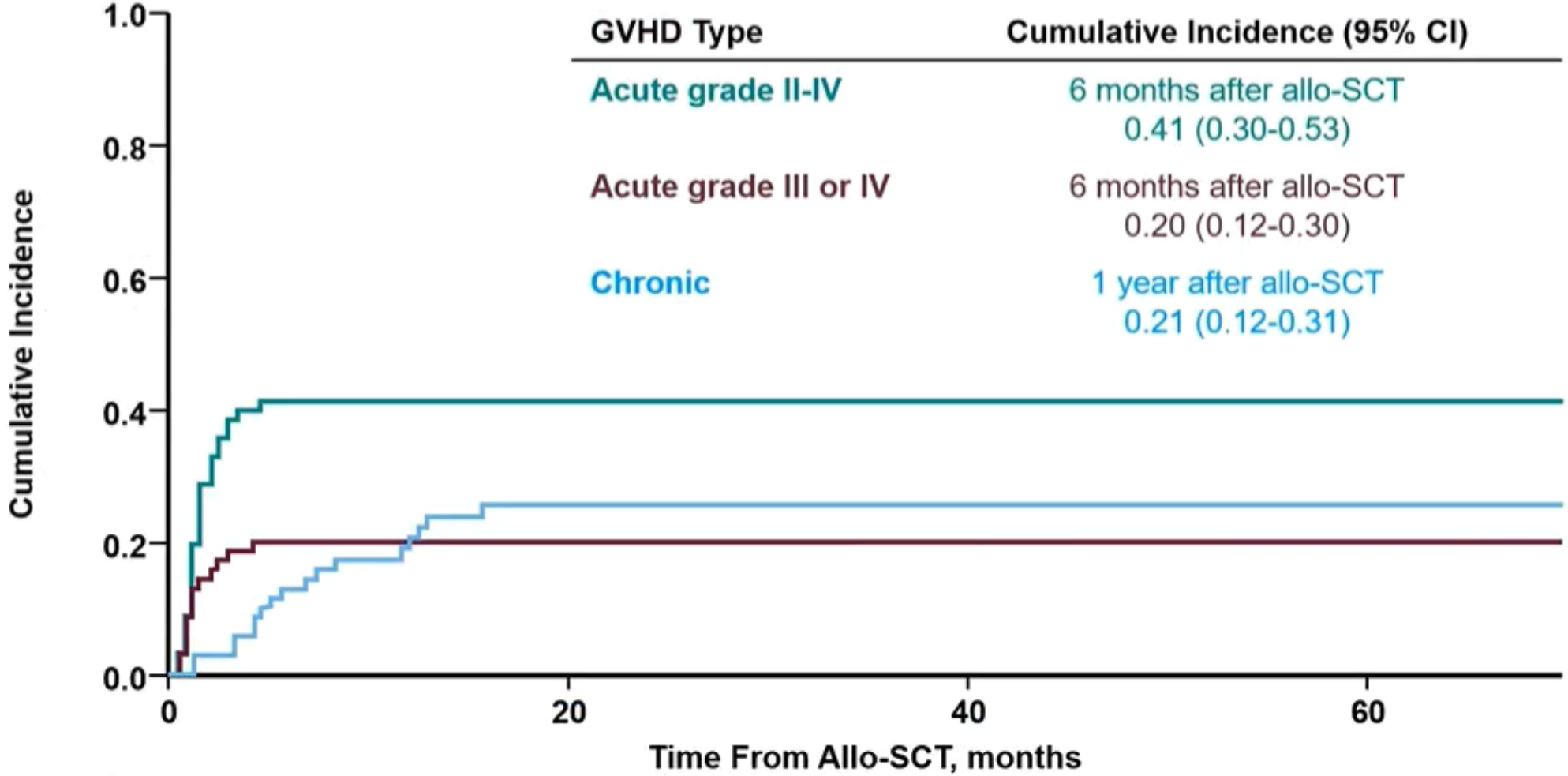
n (%)	All Patients N = 70
Age, median (range), years	30 (18-65)
Duration of on-study pembrolizumab, median (range), months	5.3 (0.7-29.6)
Time from last study dose of pembrolizumab to first allo-SCT, median (range), months	4.6 (1-20)
Disease type, n (%)	
cHL	57 (81.4)
PMBCL	5 (7.1)
RS	3 (4.3)
MM	2 (2.9)
Other[a]	3 (4.2)
Received intervening therapy[b]	49 (70.0)

n (%)	All Patients N = 70
Disease status at first allo-SCT	
Active	34 (48.6)
Remission	31 (44.3)
Status unknown	5 (7.1)
Allo-SCT donor source	
Matched sibling	18 (25.7)
Mismatched related	1 (1.4)
Matched unrelated	22 (31.4)
Mismatched unrelated	4 (5.7)
Haploidentical	22 (31.4)
Umbilical Cord blood	1 (1.4)
Missing	2 (2.9)

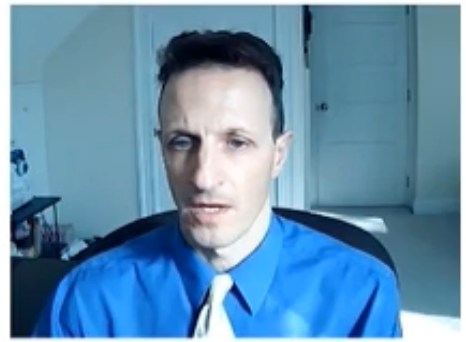
GVHD Cumulative Incidence After Allo-SCT



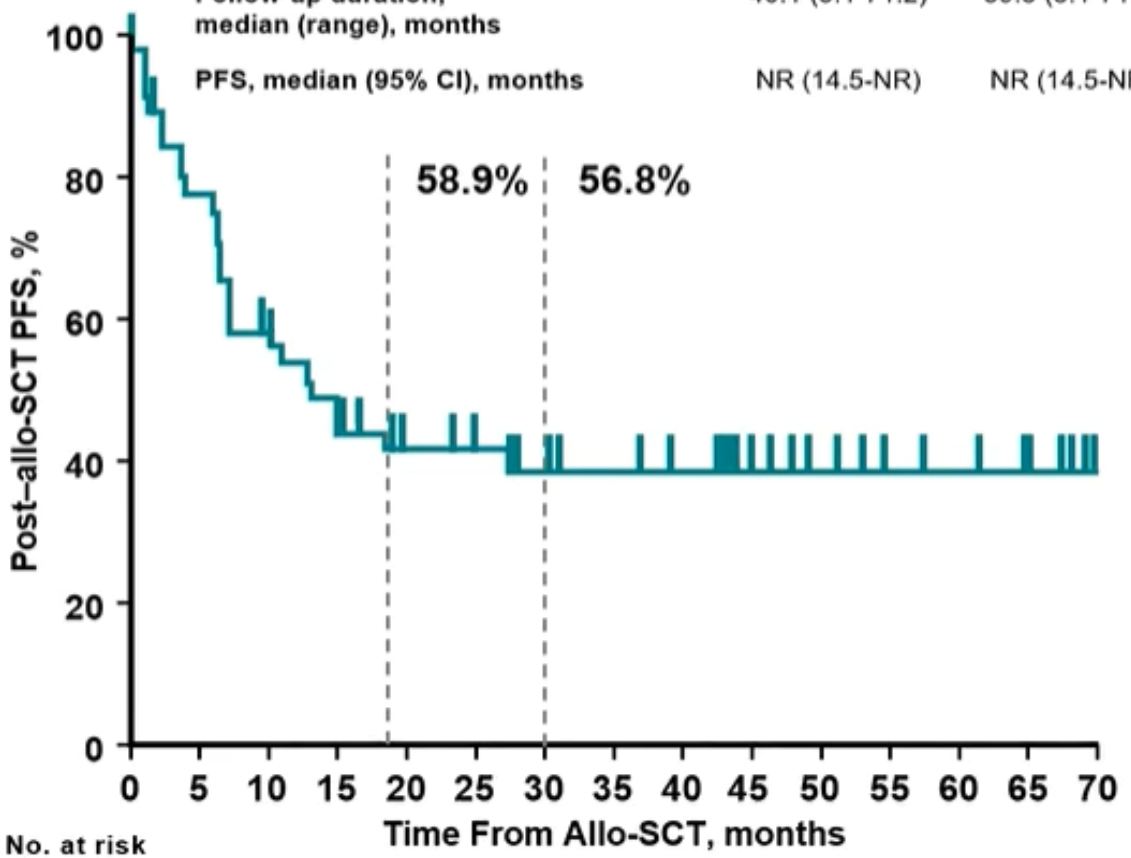
GVHD Type	Cumulative Incidence (95% CI)
Acute grade II-IV	6 months after allo-SCT 0.41 (0.30-0.53)
Acute grade III or IV	6 months after allo-SCT 0.20 (0.12-0.30)
Chronic	1 year after allo-SCT 0.21 (0.12-0.31)



PFS and OS



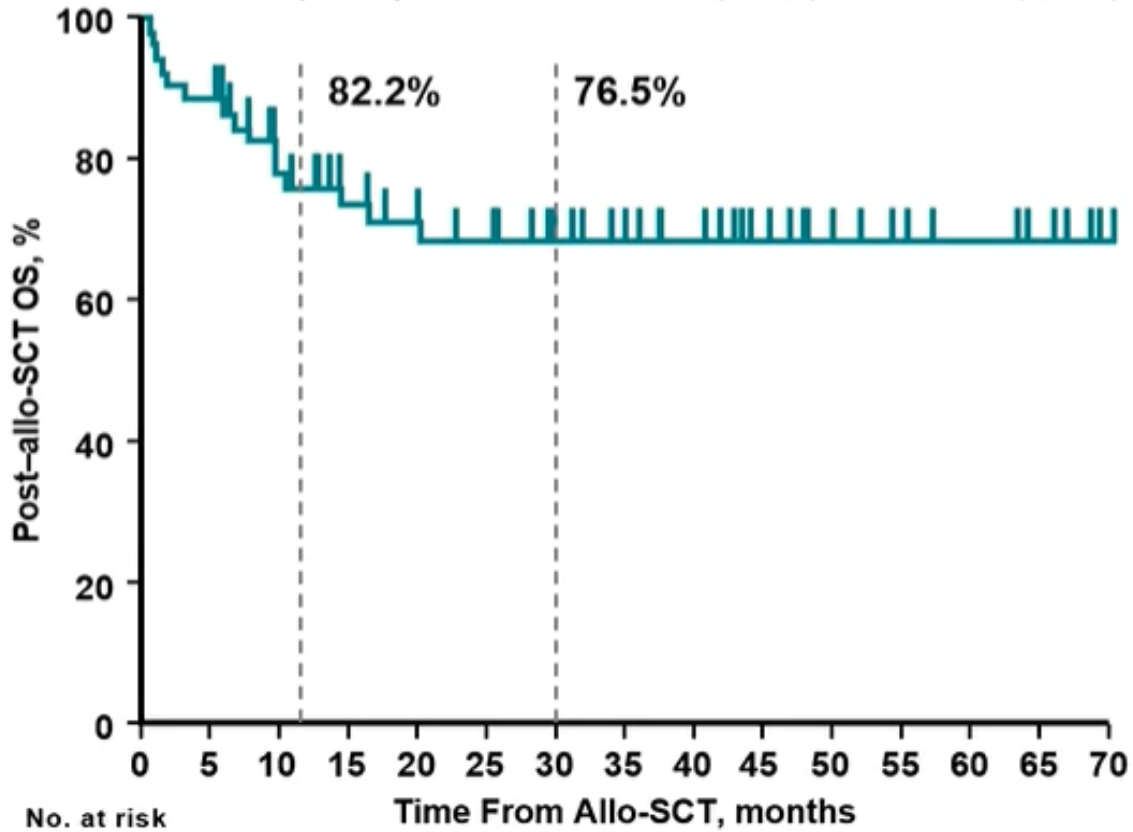
	Total (N = 70)	cHL (n = 57)
Follow-up duration, median (range), months	40.1 (5.1-71.2)	39.5 (5.1-71.2)
PFS, median (95% CI), months	NR (14.5-NR)	NR (14.5-NR)



No. at risk

70 50 39 34 29 27 23 22 20 14 10 8 6 4 0

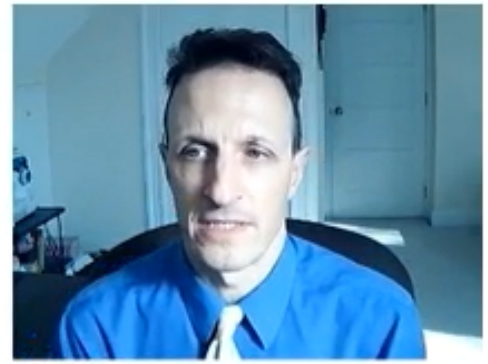
	Total (N = 70)	cHL (n = 57)
OS, median (95% CI), months	NR (NR-NR)	NR (NR-NR)



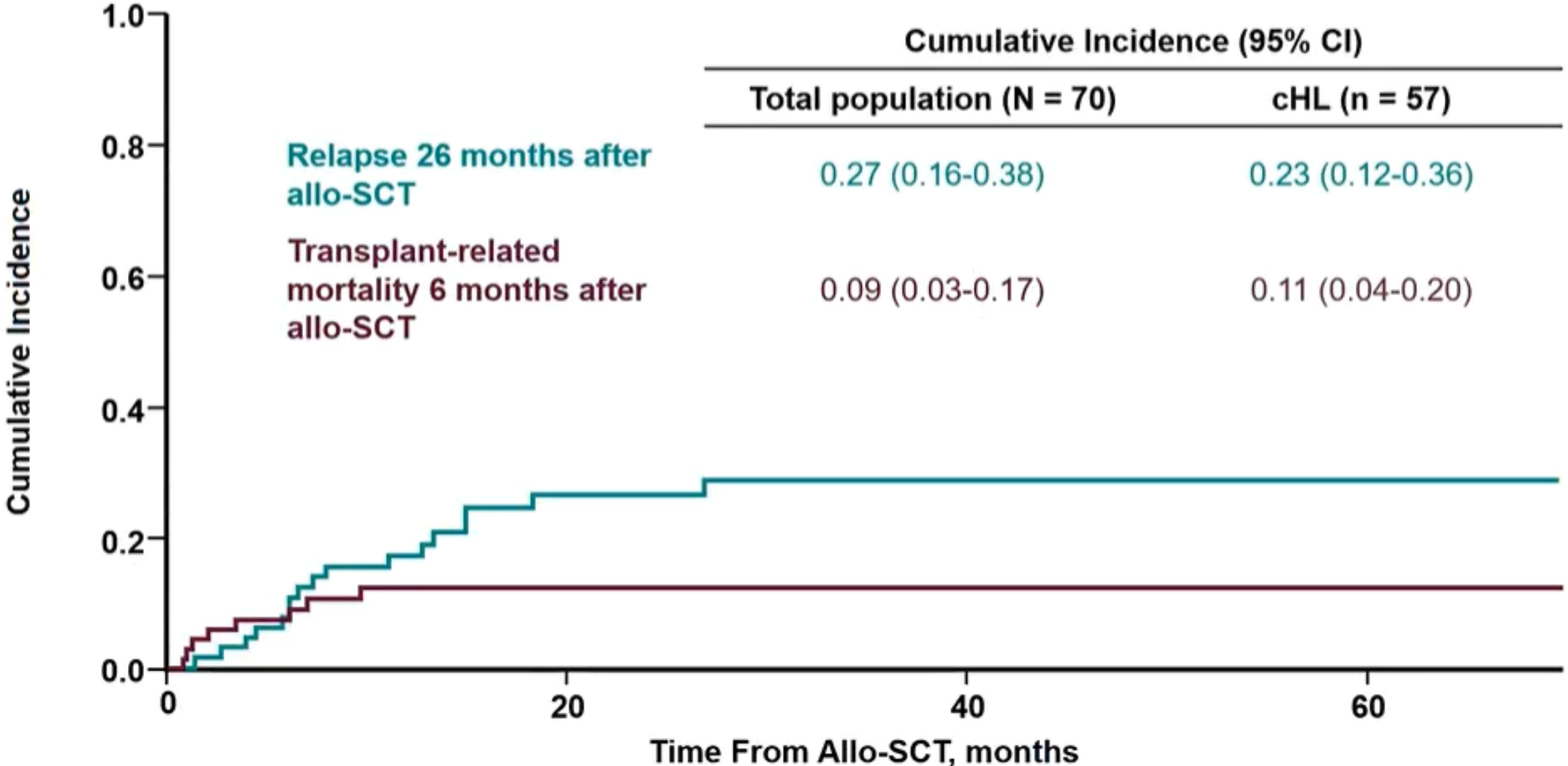
No. at risk

70 64 53 44 41 38 33 29 26 19 13 9 8 5 0

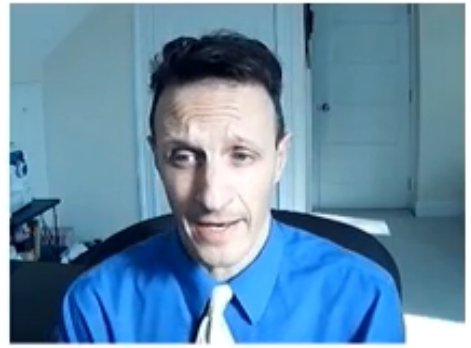
Cumulative Incidence of Relapse and Transplant-Related Mortality



	Cumulative Incidence (95% CI)	
	Total population (N = 70)	cHL (n = 57)
Relapse 26 months after allo-SCT	0.27 (0.16-0.38)	0.23 (0.12-0.36)
Transplant-related mortality 6 months after allo-SCT	0.09 (0.03-0.17)	0.11 (0.04-0.20)



Conclusions



- The cumulative incidence of acute grade II-IV GVHD (41% of patients) and chronic GVHD (21% of patients) observed after receiving an allo-SCT were similar to those from historical data (40%-80% and 30%-70% of patients, respectively)[1,2]
  - Incidence of severe acute GVHD (20% of patients) may be higher than for a typical modern allo-SCT series
- Treatment-related mortality was low and compares favorably with expected results in other populations
- The rate of patients with cHL who achieved PFS ≥1 year (58.9%) was favorable compared to historical series of patients without prior PD-1 blockade therapy (45%-48%)[3,4]
- OS at 1 year was 82.2% and comparable to historical 1-year OS data (>80% for patients with a matched sibling donor)[5]
- This analysis provides reassurance that allo-SCT is feasible for patients after PD-1 blockade therapy, with PFS outcomes that may in fact be better than historical benchmarks

1. Harris AC et al. *Biol Blood Marrow Transplant*. 2016;22:4-10. 2. Zeiser R, Blazar BR. *N Engl J Med*. 2017;377:2565-2579. 3. Sureda A et al. *Haematologica*. 2012;97:310-317.
4. Rivas MM et al. *Bone Marrow Transplant*. 2020;55:117-125. 5. Phelan R et al. CIBMTR US summary slides, 2020. Accessed October 29, 2021.
https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/Documents/Forms/AllItems.aspx

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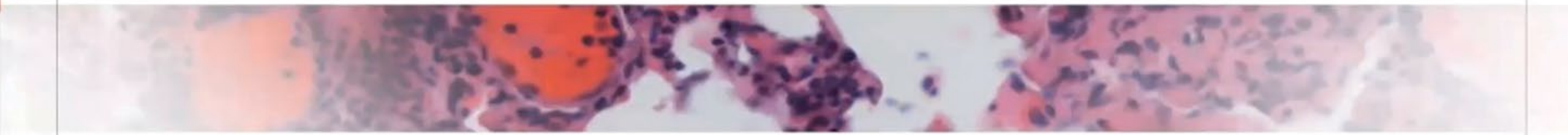

Clinical Significance of Clonal Hematopoiesis in the Setting of Autologous Stem Cell Transplantation for Lymphoma

Sharon Ben Barouch,[1,2] Tracy Lackraj,[3] Jessie J F Medeiros,[3] Mehran Bakhtiari,[3] Kit Tong,[3] Jesse Joynt,[3] Andrea Arruda,[3] Mark Minden,[3] Mily Alvarez,[3] John Kuruvilla,[3] Sita Bhella,[3] Vishal Kukreti,[3] Michael Crump,[3] Anca Prica,[3] Chris Chen,[3] Armand Keating,[3] John Dick,[3] Sagi Abelson,[4] Robert Kridel[3]

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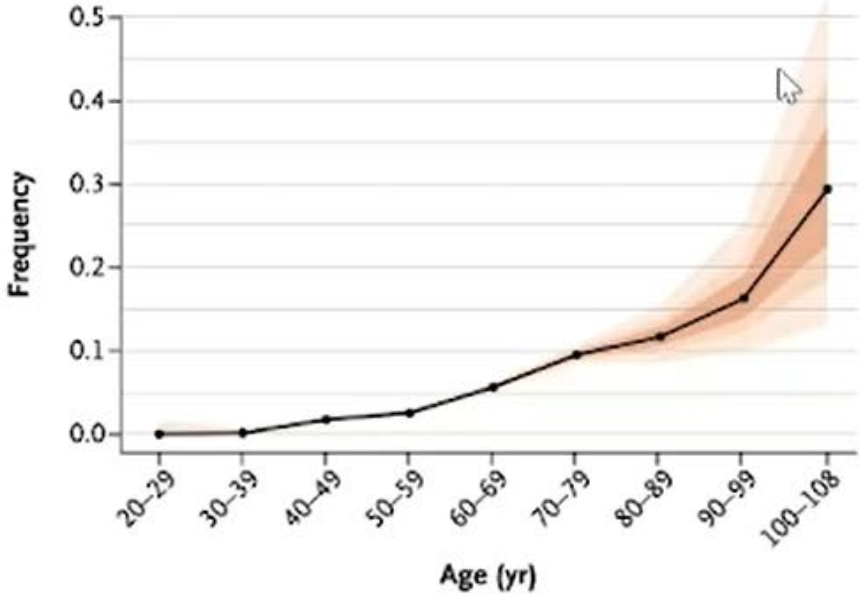
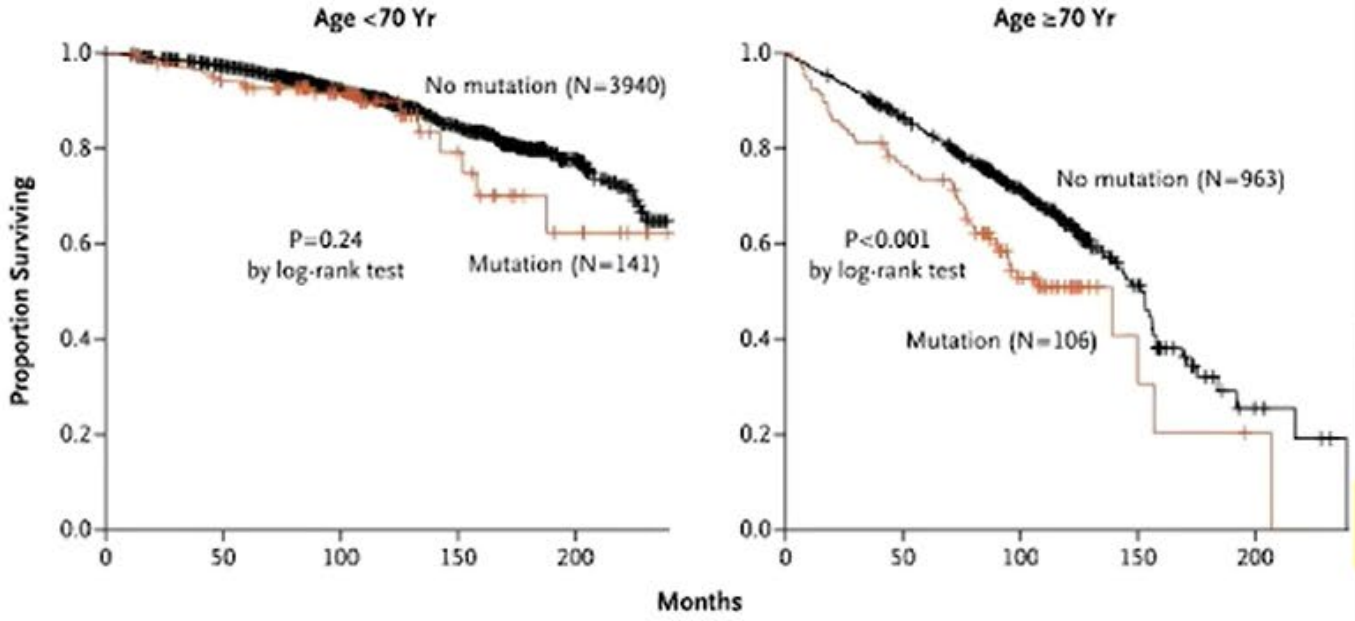
[2]Faculty of Medicine, Ben Gurion University of the Negev, Beer Sheva, Israel.
[3]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada.
[4]Ontario Institute for Cancer Research, Toronto, Canada.

Introduction

- The frequency of CH increase with advancing age[1] and is associated with inferior survival due to increased incidence of hematological malignancies[2,3], adverse cancer outcomes[4] and cardiovascular disease[5].

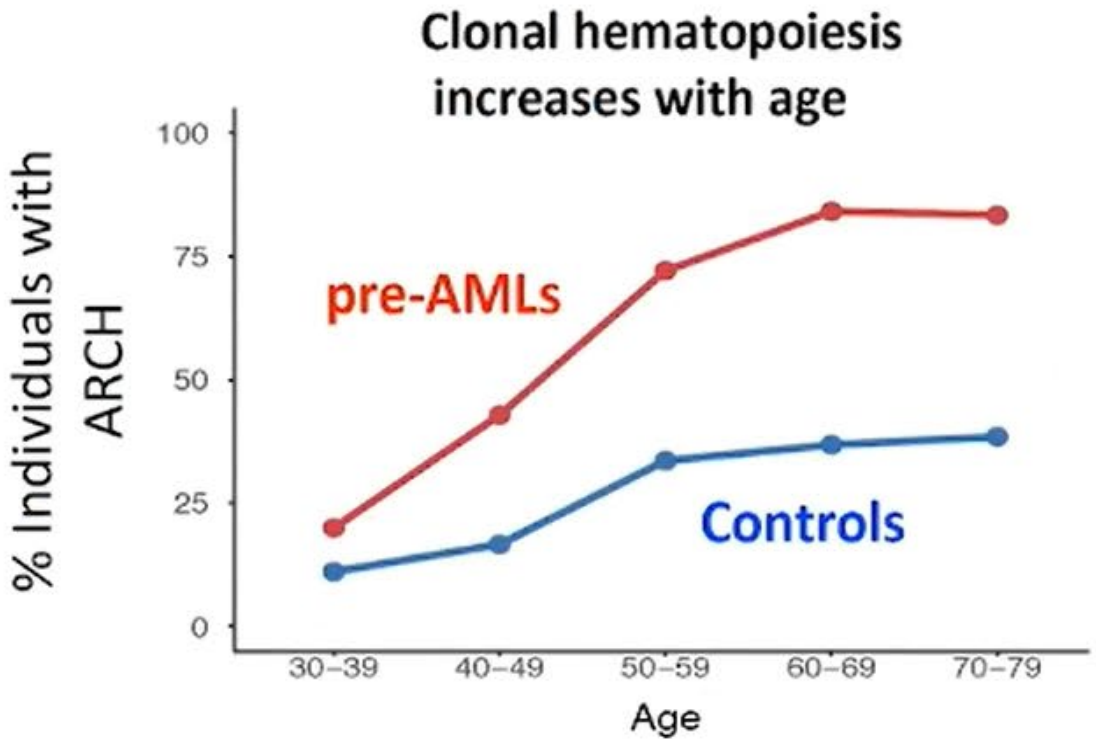




1. Jaiswal et al, NEJM 2014
2. Genovese et al, NEJM 2014
3. Xie et al, Nat Med. 2014
4. Coombs et al, Cell Stem Cell 2017
5. Jaiswal et al, NEJM 2017

CH and Hematological malignancies

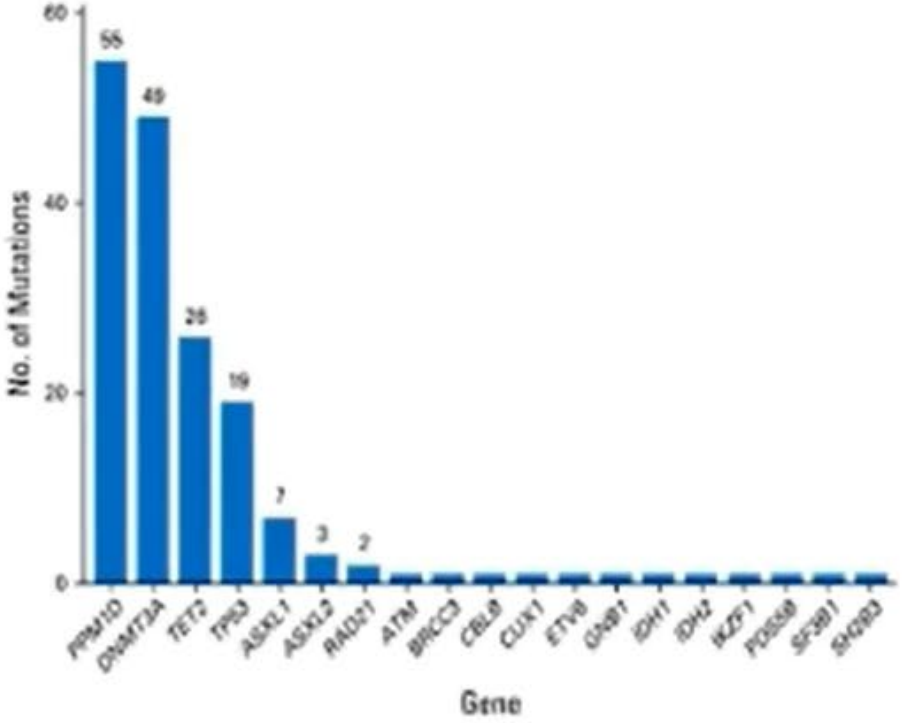
- The most common genes mutated in CH include *DNMT3A, TET2, ASXL1, JAK2, TP53* and *SF3B1*.
- These genes are associated with the development of myeloid malignancies[1,2] and mature lymphoid malignancies such as chronic lymphocytic leukemia and T-cell lymphoma[3,4]
- Abelson et al - CH was found in 73.4% of the pre-AML cases at a median of 7.6 years prior to AML diagnosis

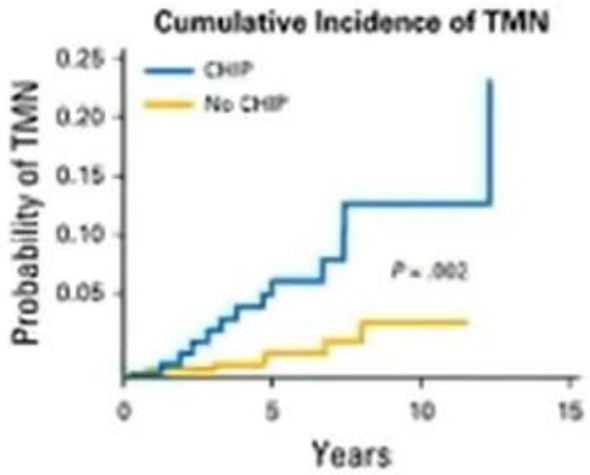


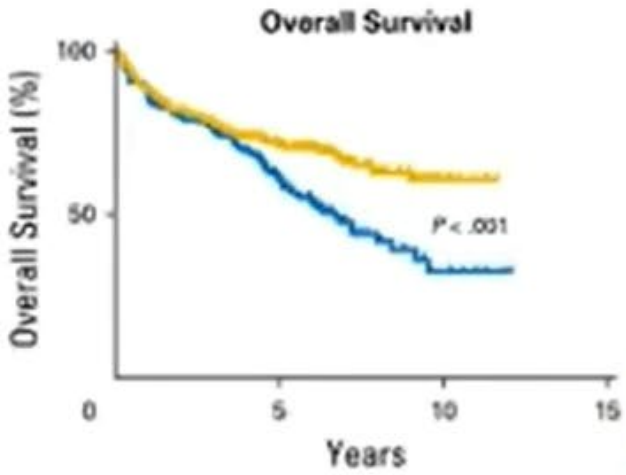
1. Shlush et al, Nature 2014.
2. Abelson et al, Nature 2019
3. Loh et al, Nature 2018
4. Terao et al, Nature 2020

CH and Lymphoma

- In the lymphoma context, this effect has mostly been observed in patients who had previously undergone autologous stem cell transplantation (ASCT).[1-3]
- Gibson et al:
  - The most frequently mutated genes - *PPM1D, DNMT3A, TET2 and TP53.*
  - The prevalence of CH was 30%.
  - CH was associated with increased risk of therapy-related myeloid neoplasms (TMN) and increased mortality.







1. Gibson et al, JCO, 2017
2. Husby et al, Leukemia 2020
3. Eskelund et al, Blood 2020

Study Design – Rationale

- Based on the existing literature, the outcome implications of CH in the ASCT setting remains controversial.
- If CH is truly associated with TMNs – should those patients undergo ASCT, or should they be referred to newer therapeutic approaches?
- Thus, robust understanding of the magnitude of potential risks associated with CH is critical to guide potential preventative strategies.

Methods – patients and samples

- Patients were **retrospectively** identified at **Princess Margaret Cancer Centre** as all those patients who underwent ASCT for lymphoma between 2002 and 2018 and for which an apheresis product was available.
- Genomic DNA was extracted using the Qiagen QIAamp DNA Mini kits.
- The study was approved by the University Health Network Research Ethics Board.

Methods - Statistical analyses

- **Primary endpoint:**
  - Overall survival (OS) from the time of ASCT
- **Secondary endpoints:**
  - OS from the time of relapse
  - Time to progression (TTP)
  - Time to neutrophil and platelets engraftment
  - TMN prevalence

Patients Characteristics

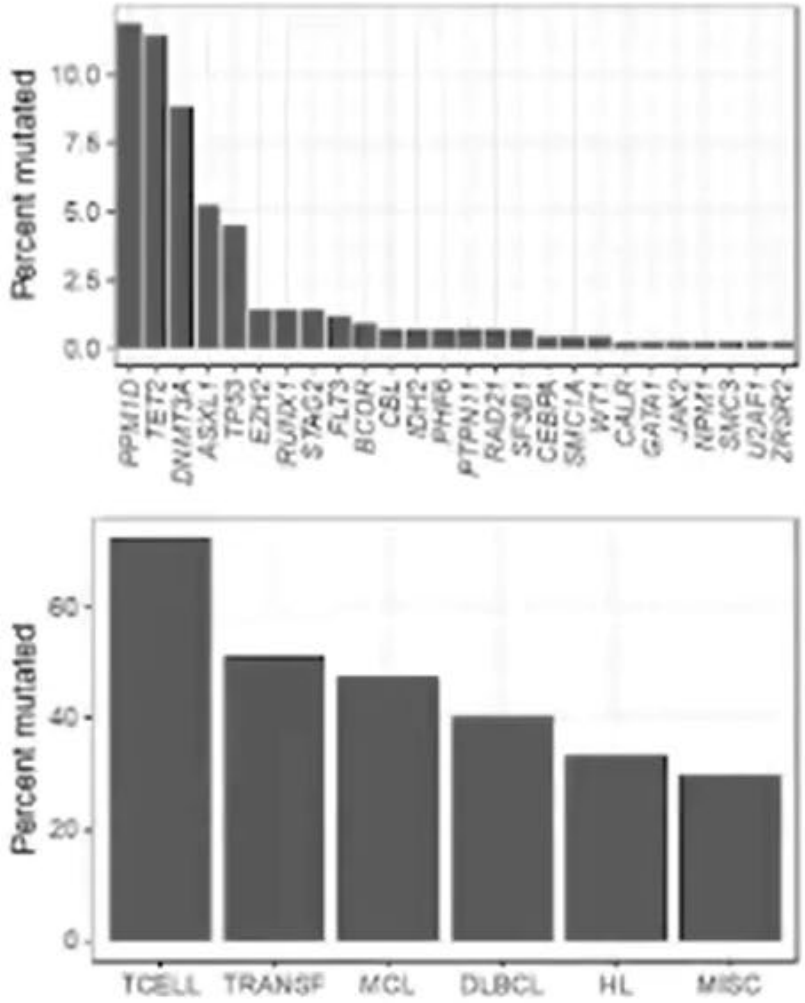
DNA was obtained from 420 residual apheresis products

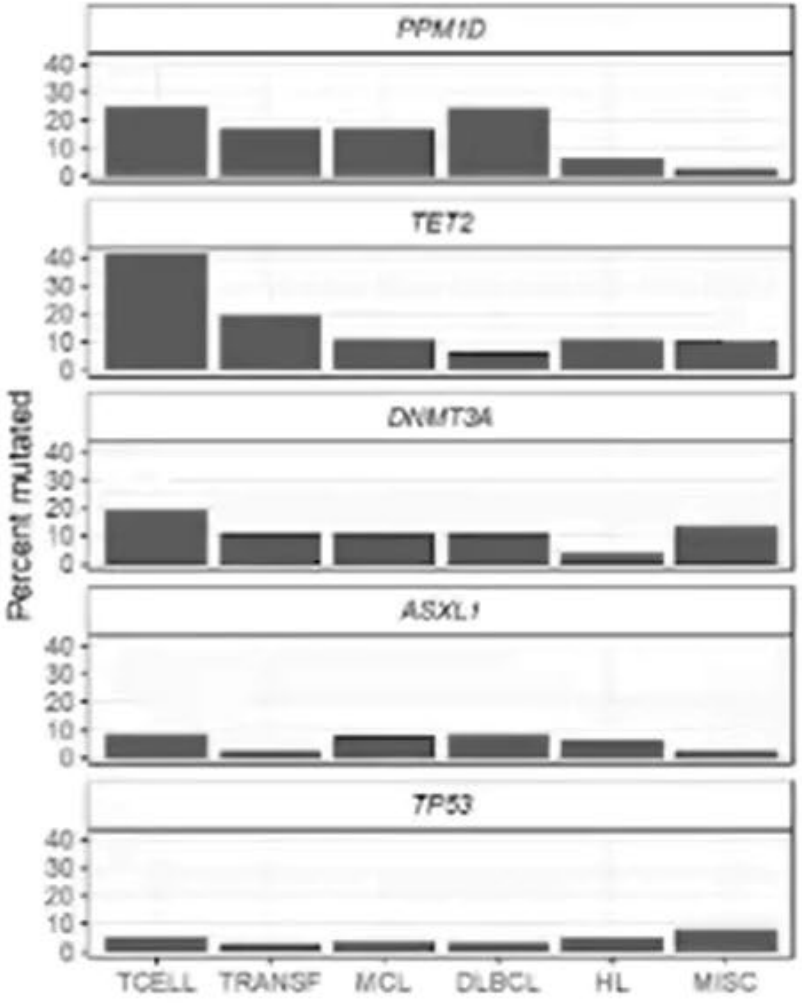
The median follow-up for living patients was 4.7 years.

Age at ASCT (median number of years, IQR)	53 (40-60)	-
Sex, n (%)		
Male	280	66.7%
Female	140	33.3%
Histology, n (%)		
Diffuse large B-cell lymphoma	114	27.1%
Transformed indolent lymphoma	35	8.3%
Mantle cell lymphoma	99	23.6%
Hodgkin lymphoma	99	23.6%
T-cell lymphoma	36	8.6%
Miscellaneous	37	8.8%
Salvage chemotherapy*		
GDP	196	61.3%
R-GDP or O-GDP	31	9.7%
DHAP	34	10.6%
R-DHAP	16	5.0%
R-CHOP	8	2.5%
HD-MTX-based	8	2.5%
Other	28	8.4%
Proceeded with ASCT		
Yes	373	88.8%
No	47	11.2%

Detection of CH

- CH was identified in 181/420 samples **(43.1%)**
- 35% (64/181) had more than one mutation.
- The median variant allele frequency was 0.029
- *PPM1D>TET2>DNMT3A>ASXL1 >TP53*
- High proportion of TCL cases was mostly due to *TET2* mutations, with 9/9 AITL cases harboring *TET2* mutations.



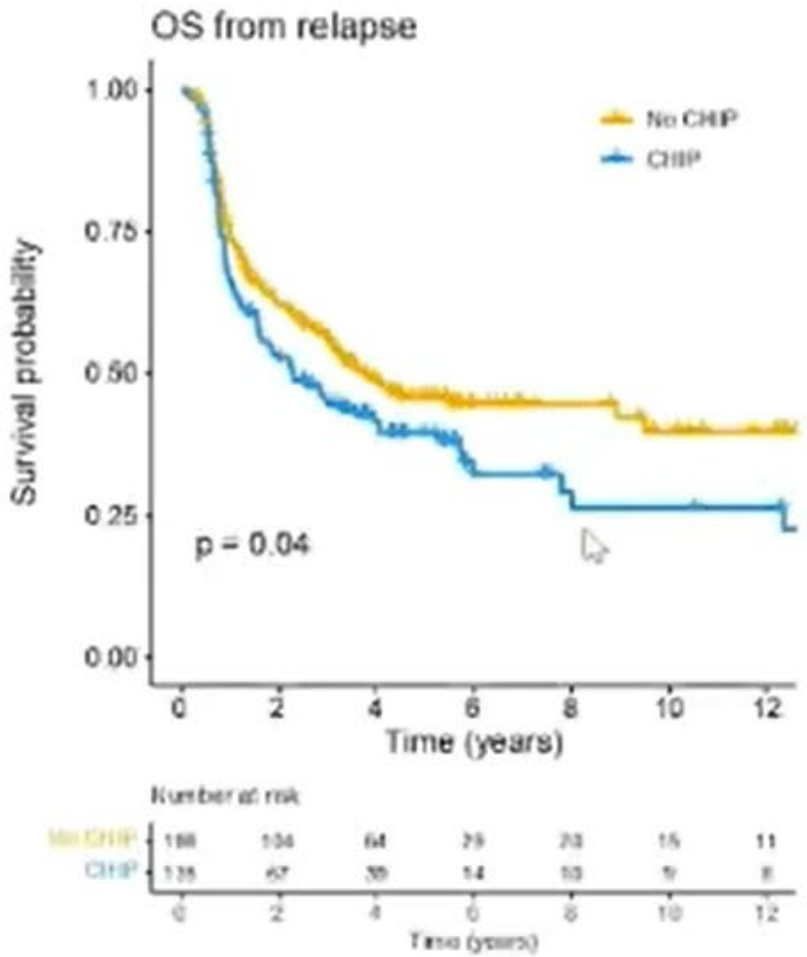


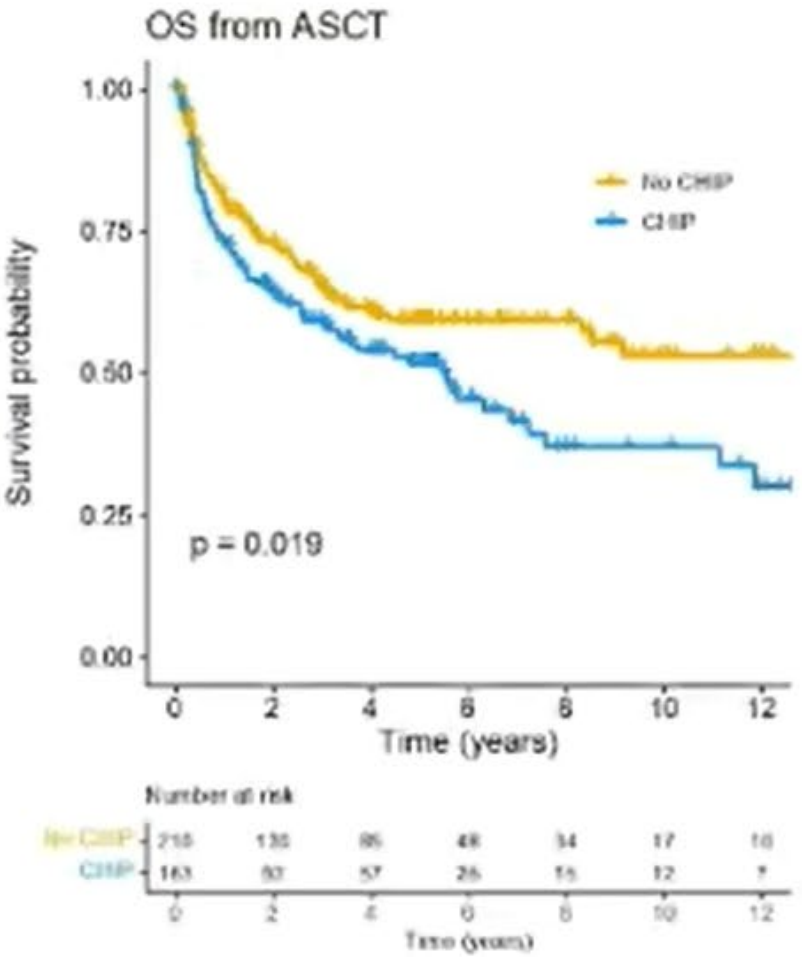
Association of CH with patient characteristics

	No CH	CH	P
Age at ASCT (median number of years, IQR)	51.0 (37.0-59.0)	55.0 (44.0-61.0)	**0.002**
Sex, n (%)			0.651
Male	162 (67.8%)	118 (65.2%)	
Female	77 (32.2%)	63 (34.8%)	
Histology, n (%)			
Diffuse large B-cell lymphoma	68 (28.5%)	46 (25.4%)	
Transformed indolent lymphoma	17 (7.1%)	18 (9.9%)	
Mantle cell lymphoma	52 (21.8%)	47 (26.0%)	
Hodgkin lymphoma	66 (27.6%)	33 (18.2%)	
T-cell lymphoma	10 (4.2%)	26 (14.4%)	**< 0.001**
Miscellaneous	26 (10.9%)	11 (6.1%)	
Lines of therapy prior to salvage, n (%)*			0.367
1	228 (95.4%)	167 (92.2%)	
2	10 (4.2%)	11 (6.7%)	
3	1 (0.4%)	2 (1.1%)	
Salvage chemotherapy, n (%)*			0.924
GDP	117	79	
R-GDP or O-GDP	19	12	
DHAP	20	14	
R-DHAP	8	8	
R-CHOP	4	4	
HD-MTX-based	4	4	
MISC	14	14	
Previous radiation, n (%)			1
Yes	62 (25.9%)	47 (26.0%)	
No	177 (74.1%)	134 (74.0%)	

Impact of CH on OS

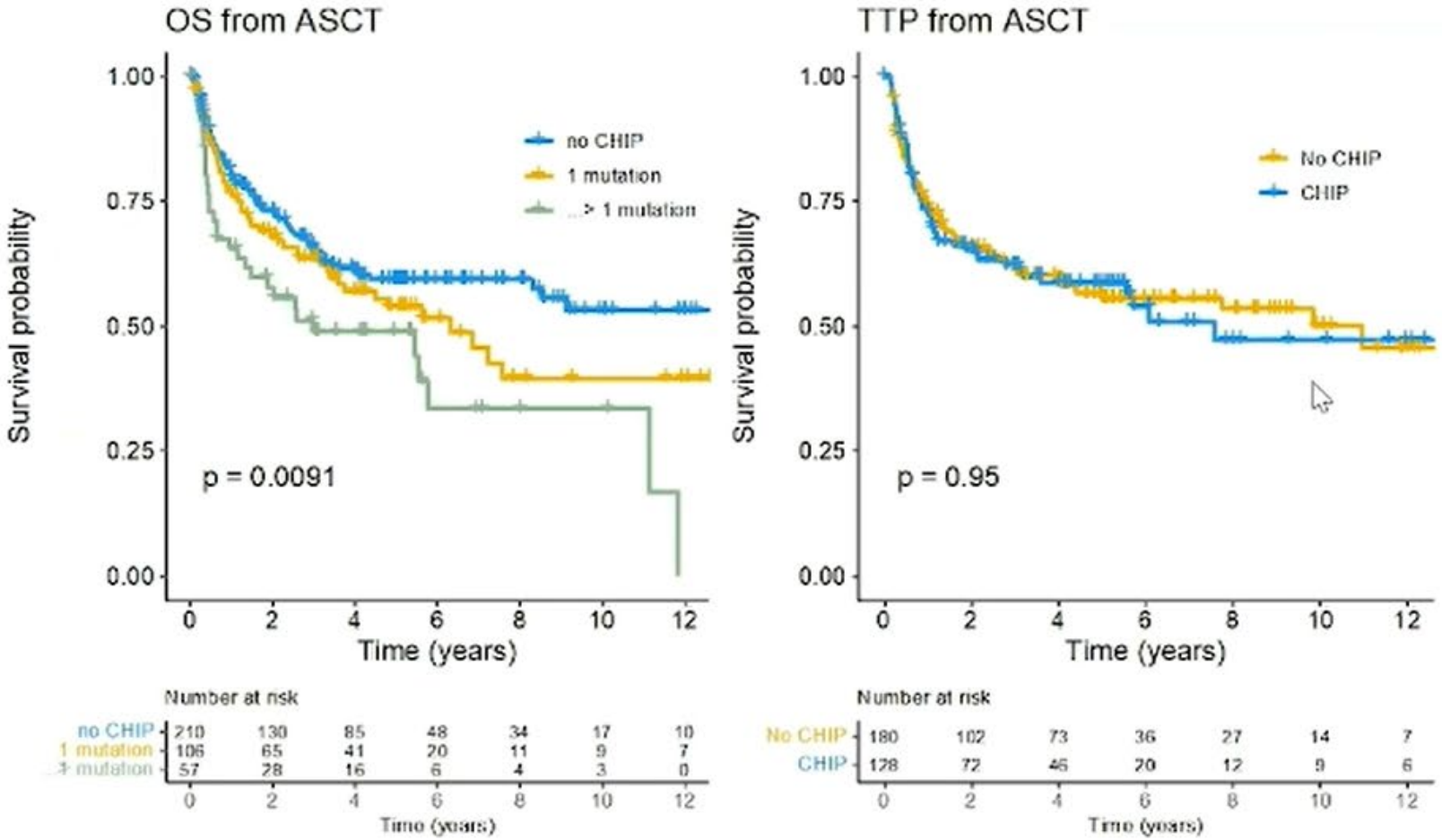
- Patients with CH have inferior OS from the time of relapse (5-year OS 39.4% vs. 45.8%, n = 321) and from the time of ASCT (5-year OS 51.9% vs. 59.3%, n=373).





Impact of CH on OS

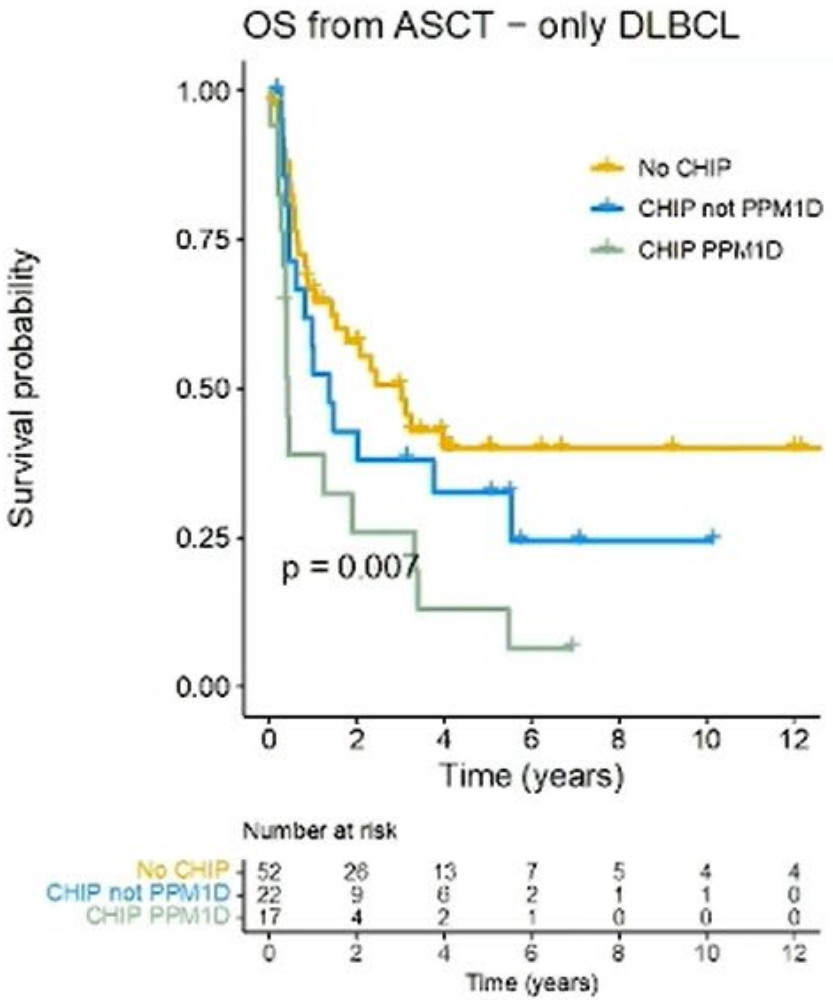
- Patients with more than one CH mutation had inferior OS compared to patients with one mutation or none (5-year OS 48.9% vs. 53.9% vs. 59.3%, log-rank P = 0.009).
- The presence of CH did not have an impact on the risk of post-ASCT relapse.



Impact of CH on OS – individual gene mutations

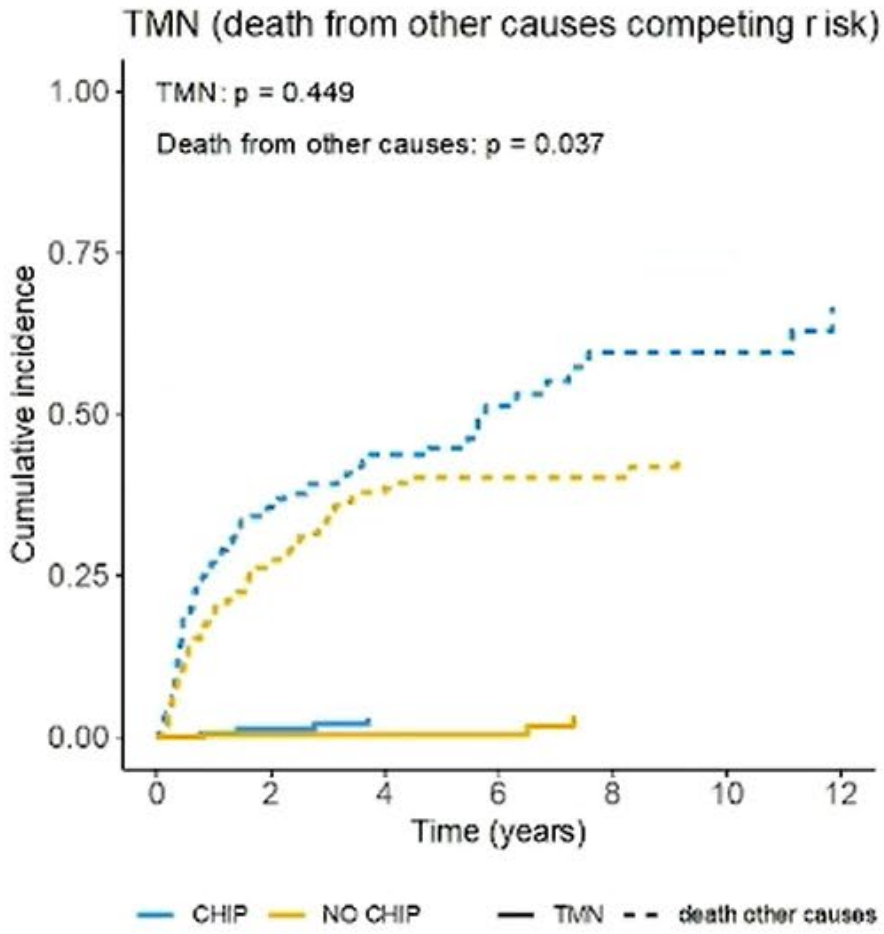
- In a further **subgroup analysis**, CH was associated with adverse outcome post-ASCT only in patients with **DLBCL** (HR 1.81, 95% CI 1.08-3.03, *P* = 0.025).

- Within the DLBCL sub-group, poor CH-related survival could be attributed mostly to *PPM1D* mutations (HR 2.42, 95% CI 1.34-4.38, *P* = 0.007).



Impact of CH on the incidence of TMN

- **Only 7/420 patients (1.7%) developed TMN** – compared favorable to a previously reported cohort from our center.[1]



1. Seshadri et al, Leuk Lymph 2009

Conclusion

- CH is common in lymphoma patients undergoing ASCT and associated with an increased risk of death after ASCT that cannot be explained by lymphoma relapse.
- The prognostic association was mostly seen in DLBCL patients whose stem cell products harbored *PPM1D* mutations.
- The prevalence of CH in our study was higher compared to previous reports (43%).
- The risk of TMN was low in our cohort (1.7%).
- Our findings support identification of CH and aggressive management of non-lymphoma-related illness in the post-ASCT survivorship.

1. Gibson et al, JCO, 2017
2. Husby et al Leukemia 2020

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Phase I Dose-Escalation Study of Venetoclax Plus BEAM Followed By Autologous Stem Cell Transplant (ASCT) for Chemoresistant or High-Risk Relapsed/Refractory Non-Hodgkin Lymphoma (NHL)

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University of Minnesota

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Background

- Relapsed/Refractory NHL still represents an unmet need despite recent advances
- BCL-2 family members are antiapoptotic and associated with tumor initiation, disease progression and chemotherapy resistance
- BCL-2 overexpression is a major contributor to the pathogenesis of certain lymphoid malignancies
- Antagonism of BCL-2 may enhance response to therapy and overcome resistance to therapy
- Venetoclax is a highly selective BCL-2 inhibitor
  - Approved for CLL
  - Active in NHL as a single agent and in combination with chemotherapy

Preclinical models

- Combination of venetoclax and cytotoxic chemotherapies potentiates their cytotoxicity
  - The combination of venetoclax with doxorubicin or cytarabine has a synergistic cell kill effect on double-hit lymphoma
  - Venetoclax and etoposide or doxorubicin led to decreased 48-hour cell viability compared to each agent alone in 4 different DLBCL cell lines
  - Venetoclax synergizes with etoposide in apoptosis induction in leukemia cell lines

Johnson-Farley, N., et al., Leukemia & Lymphoma, 2015. **56**(7): p. 2146-2152.
McConnell, I., E. Anderson, and V. Yazbeck, Cancer Research, 2017. **77**(13 Supplement): p. 2770-2770.

Methods

- Open-label, single-center, phase I trial (NCT03583424) + dose expansion
- Venetoclax is given D-10 → D-1 before ASCT with a ramp-up
- Three dosing cohorts (400, 800, 1200 mg), 3+3 design
- Primary outcome is safety/maximal tolerated dose (MTD)
- Adverse events (AEs) were recorded using CTCAE v 4.1 between days -10 to -6 then the Bearman scale was used from day -6 until engraftment

Inclusion Criteria

- Age greater than 18
- KPS greater than 80
- All B-NHL histologies with the exception of CLL/SLL
  - Relapsed less than 6 months following primary chemotherapy
  - Partial response or less to primary or salvage chemotherapy
  - Required 3 or more lines of chemotherapy regardless of response
- Good organ function and ability to tolerate high-dose chemotherapy and ASCT

Exclusion Criteria

- CR on PET (5-PS ≤ 3) to chemotherapy except if relapsed within 6 months
- Active or treated CNS disease
- Deemed not a candidate for HDC/ASCT by PI or delegate
- Uncontrolled active illness or infection
- Allergy to study drugs
- Pregnancy

Schema

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
D -17	D -16	D -15	D -14	D -13	D -12	D -11
Allopurinol	Mobilization and collection					
D -10	D -9	D -8	D -7	D -6	D -5	D -4
V 100 8 AM TLS at 4 PM	V 200 8 AM TLS at 4PM	V 400 8 AM TLS at 4PM	V 400/800 Admission	V 400/800/1200 BCNU	V VP/AraC	V VP/AraC
D -3	D -2	D -1	D 0			
V VP/AraC	V VP/AraC	V Mel	SC Infusion			

- TLS mitigation strategy if K, Cr, PO4 increase by certain thresholds
- Cytopenias are expected

Results

	Total (n=19)	Cohort A (n=3)	Cohort B (n=5)	Cohort C (n=11)
Age, median (range)	61 (41-72)	64 (55-69)	52 (49-64)	61 (41-72)
Male, n(%)	15 (79)	3 (100)	2 (67)	10 (77)
Race, n(%)				
African American	1 (5)	0 (0)	1 (33)	0 (0)
White	18 (95)	3 (100)	2 (67)	13 (100)
Stage at Diagnosis				
II	3 (16)	2 (67)	0(0)	1 (8)
III	1 (5)	1 (33)	0(0)	0(0)
IV	15 (79)	0(0)	3 (100)	12(92)
Disease Type				
Anaplastic Large cell Lymphoma	1 (5)	0(0)	0(0)	1 (8)
DLBCL	9 (47)	3 (100)	1 (33)	5 (38)
Follicular Lymphoma	2 (11)	0(0)	2 (67)	0 (0)
MCL	7 (37)	0(0)	0(0)	7 (54)
Disease Status				
CR1	6(32)	0(0)	0(0)	6(46)
PR1	1(5)	0(0)	0(0)	1(8)
Primary Refractory	7(37)	1 (33)	1 (33)	5(38)
Relapsed	5(26)	2 (67)	2 (67)	1(8)

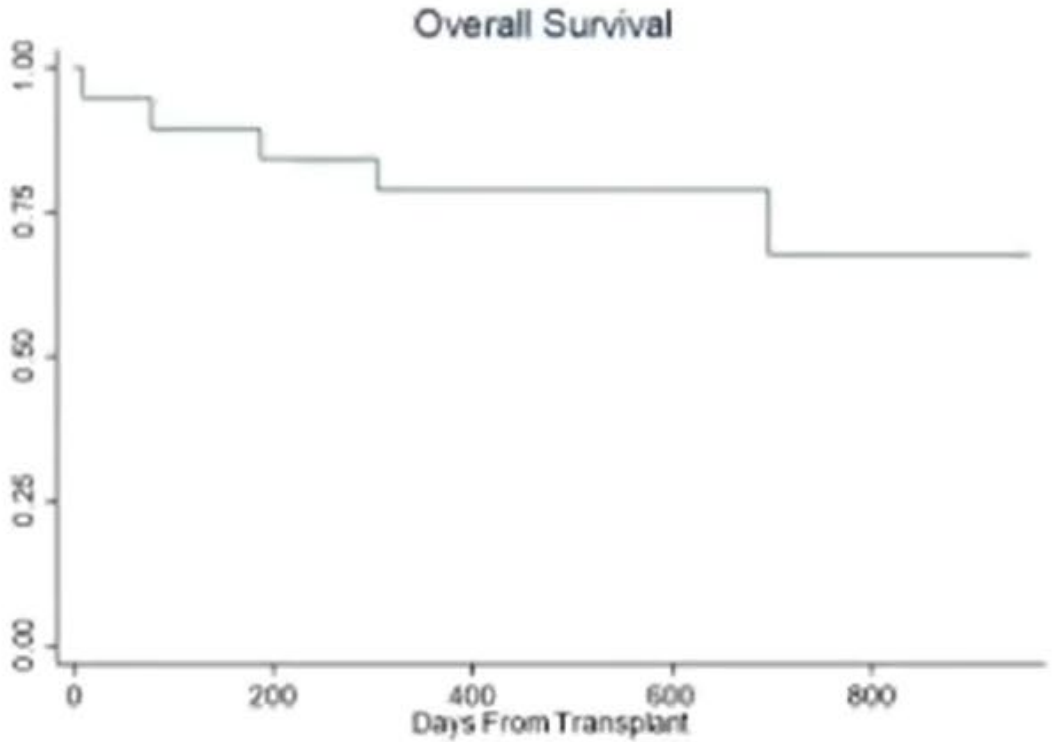
- Dose-escalation proceeded with no DLT
- 19 patients were accrued across three cohorts
- Majority
  - > 60 years
  - Male
  - Aggressive histologies
  - Stage IV
  - Relapsed/Refractory

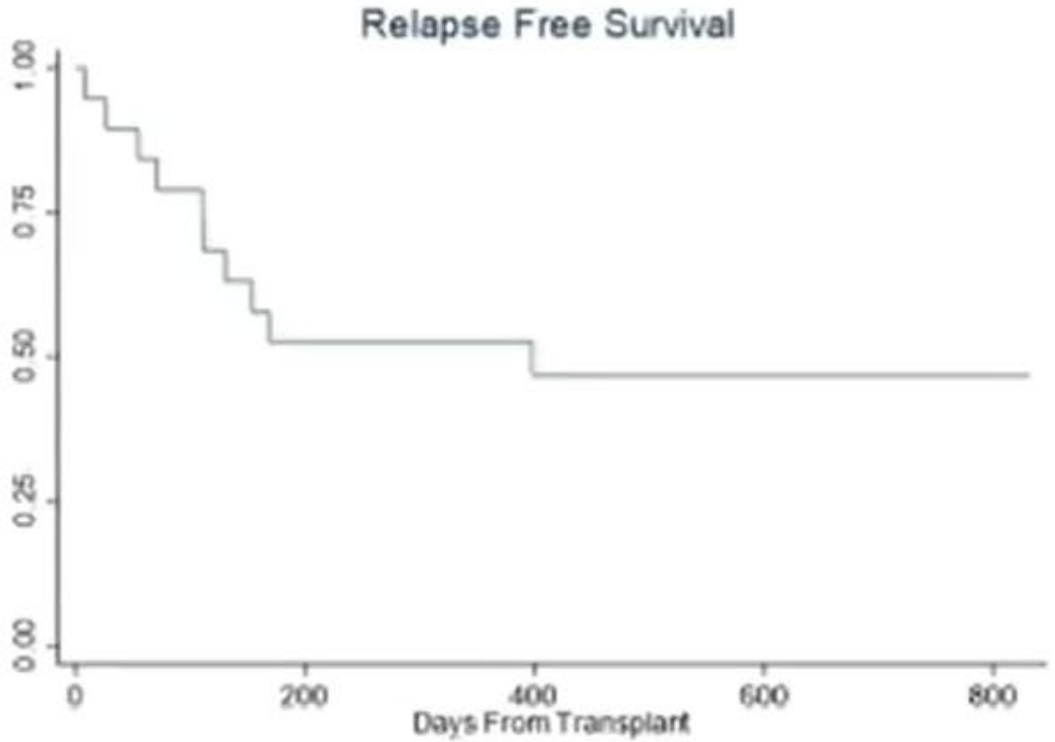
Results

	Total (n=19)	Cohort A (n=3)	Cohort B (n=5)	Cohort C (n=11)
Days to Neutrophil Engraftment	10 (9-12)	10 (10-11)	10 (9-12)	9 (9-12)
Days to Platelet Engraftment	19 (13-35)	20 (18-34)	19 (18-21)	19 (13-35)
Length of Stay	19 (14-35)	18 (17-20)	19 (17-27)	19 (14-35)
Response at day 100				
CR	12 (63)	1 (33)	2 (67)	9 (69)
SD	2 (11)	1(33)	0(0)	1(8)
PD	4 (21)	1(33)	1(33)	2(15)
Death with no disease	1 (5)	0(0)	0(0)	1(8)
Response at 1 year				
CR	9 (47)	0(0)	3 (100)	6 (46)
PD	5 (26)	3 (100)	0(0)	2 (15)
Death with disease	3 (16)	0(0)	0(0)	3 (23)
Death with no disease	1 (5)	0(0)	0(0)	1 (8)
Not reached 1YR	1 (5)	0(0)	0(0)	1 (8)

- No serious AEs were observed d-10 → d-6
- No TLS
- Engraftment was as expected
- Post-transplant, on the Bearman scale
  - 0 grade III toxicities
  - 5 grade II toxicities
  - 8 grade I toxicities
- In cohort 3, one patient died prior to engraftment due to sepsis
- CR rates were 47% at 1-yr

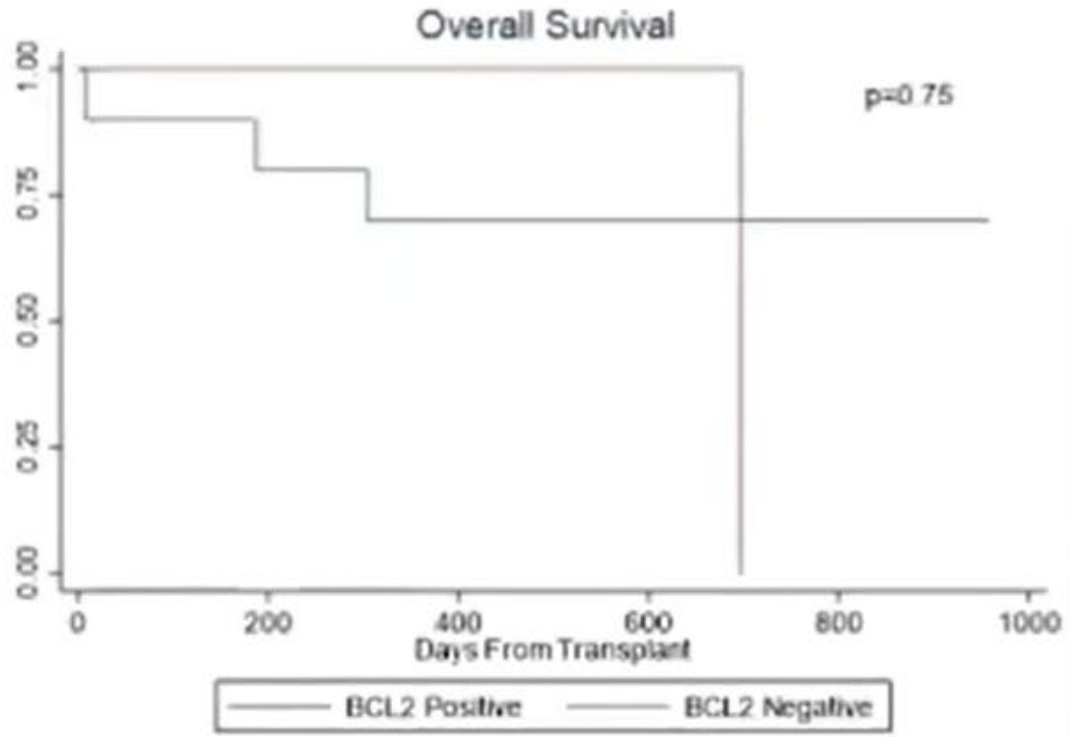
Results

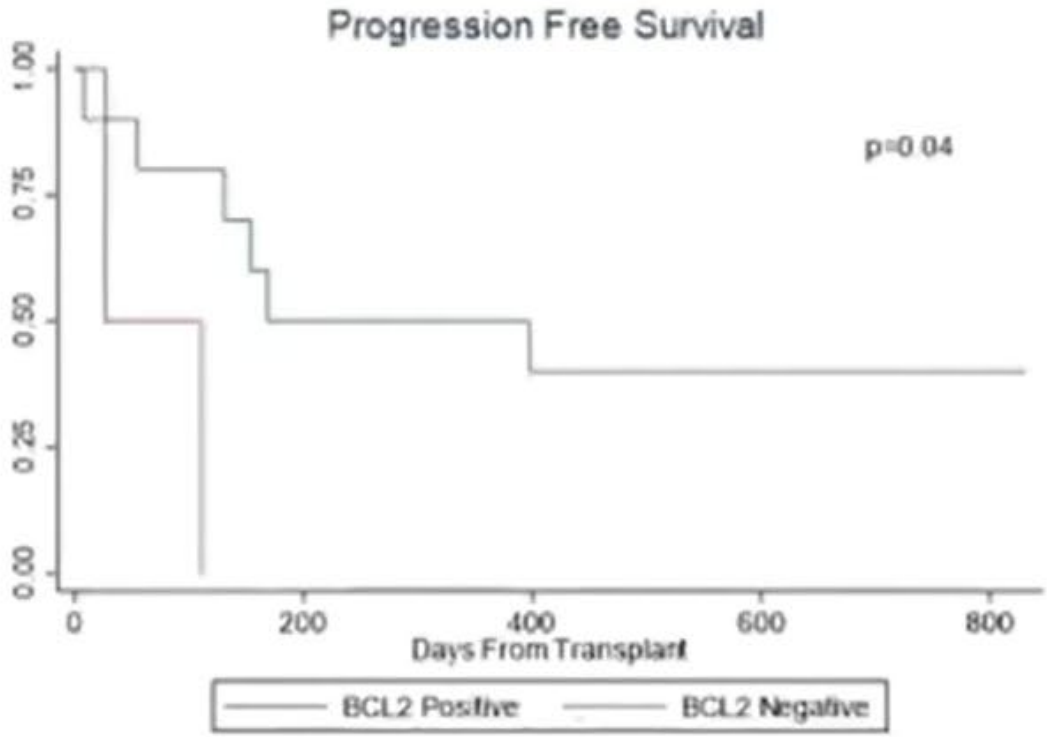




- Median follow-up of 654 (335-957) days, median PFS was 398 days and median OS was not reached
- Six patients went on to receive CD19 chimeric antigen receptor T-cell (CAR-T) therapy

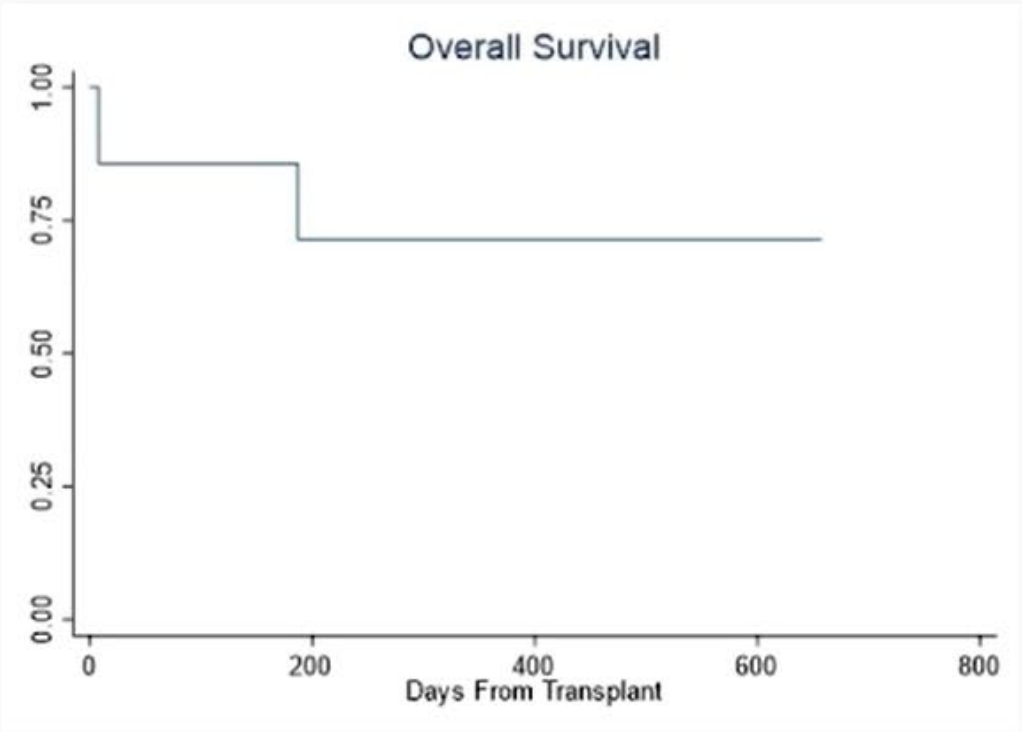
Response by BCL-2 Expression

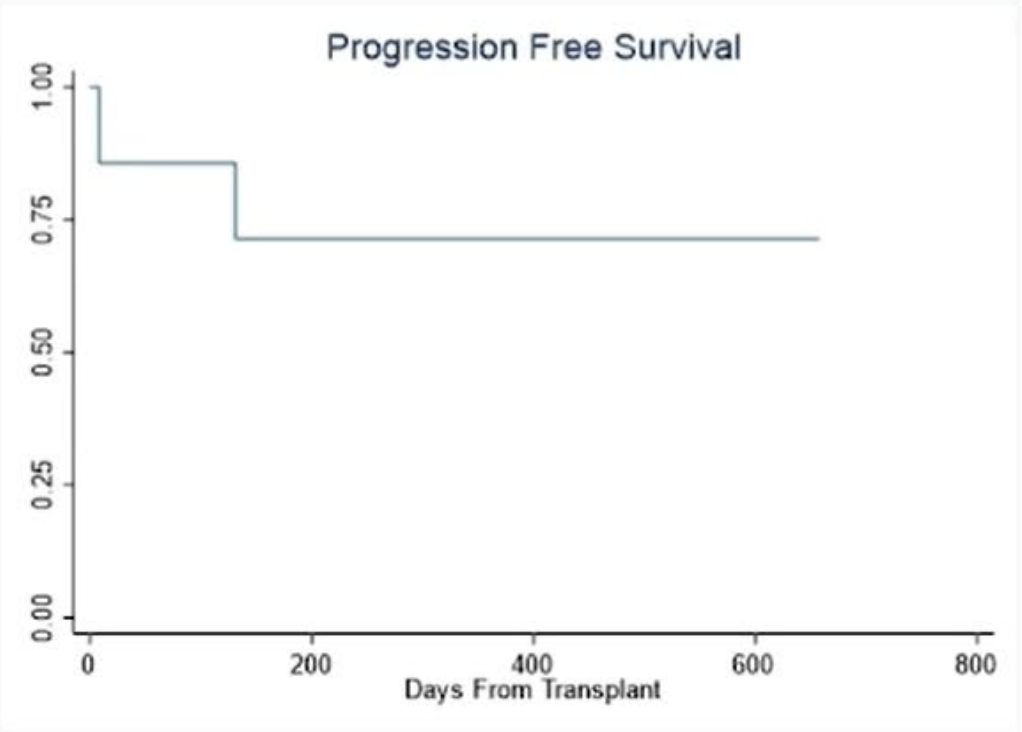




- Biopsies reviewed for BCL-2 expression by IHC in 13 patients
- "Positive" ≥ 50% expression by IHC (2/13 patients) had a significantly longer PFS

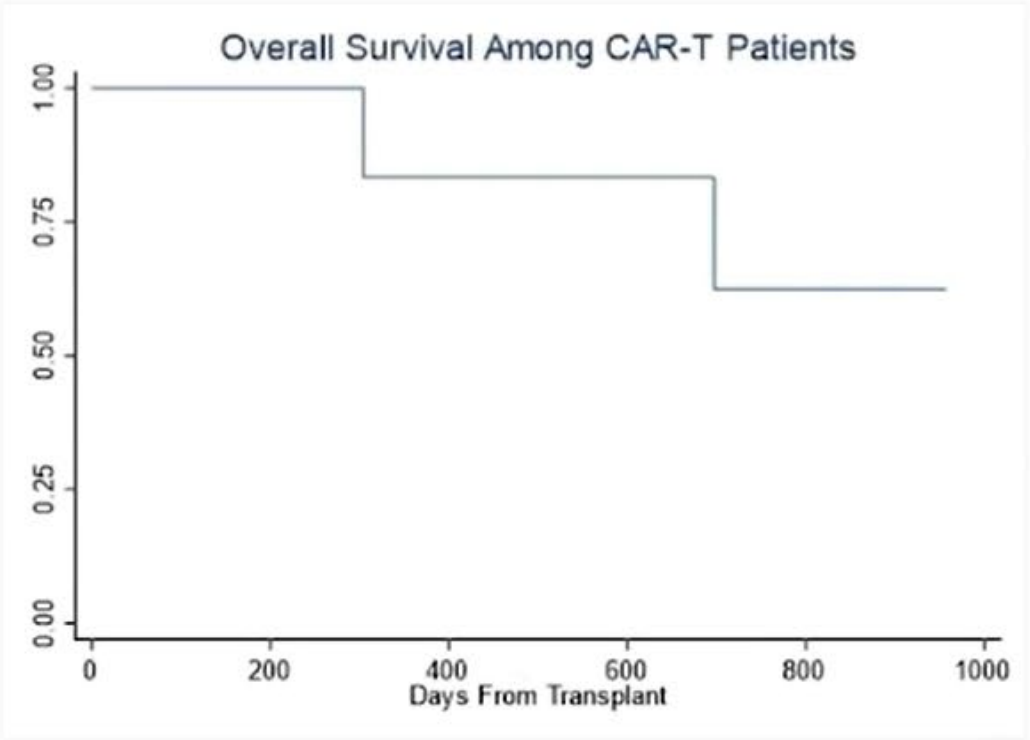
MCL Results

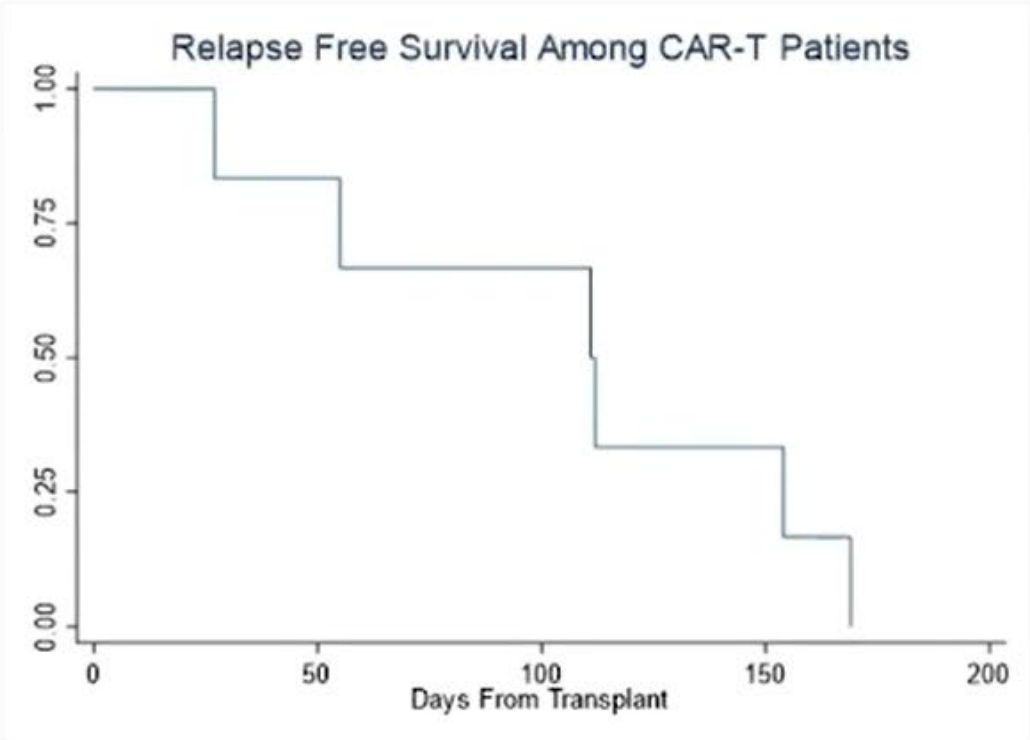




- In patients with MCL, CR at day 100 = 86% (6/7). One died prior to day 100 in remission
- 1-yr CR=57% (4/7) with one relapse and one not reached 1-yr staging

Results after CAR-T Salvage





- Six patients went on to receive CD19 auto-CAR-T (axi-cel = 2; tisa-cel = 4)
- Median time from ASCT to CAR-T was 208 (88-250) days
- Median OS was not reached and median PFS was 111 days

Discussion

- The addition of Venetoclax to BEAM conditioning appears to be safe and feasible with no additional toxicities from those seen with BEAM
- Two signals of efficacy appear to be patients with tumors overexpressing BCL-2 and patients with MCL
- This trial was conceived in 2016 prior to CAR-T approvals for r/r NHL but provides proof of concept for augmenting BEAM conditioning

AB-205 (E-CEL®) Cell Therapy in Older Subjects with Lymphoma Undergoing High-Dose Therapy and Autologous Hematopoietic Cell Transplantation (HDT-AHCT)

Michael Scordo[1], Lihua E Budde[2], Mehrdad Abedi[3], Carolyn Mulroney[4], Bita Fakhri[5], Attaphol Pawarode[6], Bhagirathbhai Dholaria[7], Geoffrey Shouse[2], Edward Kavalerchik[8], Sanjay K. Aggarwal[8], Muzaffar H. Qazilbash[9], Paul Finnegan[8], and Sergio A Giralt[1]

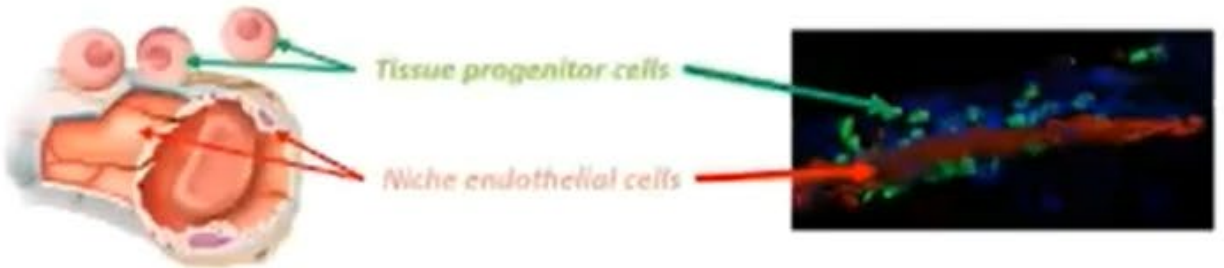
[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]City of Hope National Medical Center, Duarte, CA; [3]UC Davis Medical Center, Sacramento, CA; [4]UCSD Moores Cancer Center, La Jolla, CA; [5]University of California, San Francisco, CA; [6]University of Michigan, Ann Arbor, MI; [7]Vanderbilt University, Nashville, TN; [8]Angiocrine Bioscience, San Diego, CA; [9]MD Anderson Cancer Center, Houston, TX

63rd ASH Annual Meeting and Exposition, December 13th, 2021

Severe Regimen-Related Toxicities (SRRT)

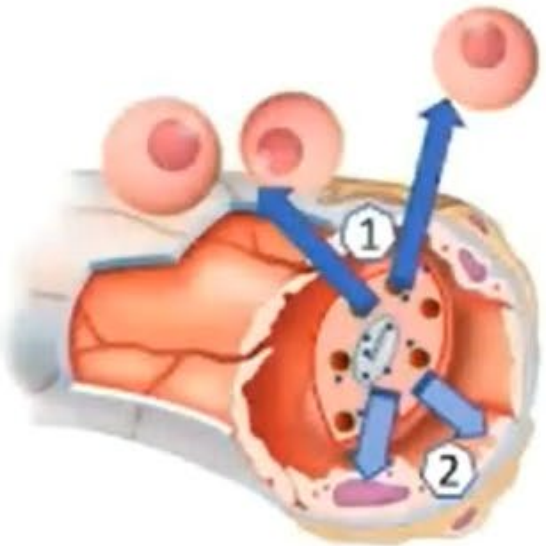
- Myeloablative chemotherapy is potentially curative for high-risk (relapsed), chemo-sensitive lymphomas; however, severe toxicities can limit wide application
  - In the process of eradicating cancer, non-target healthy tissues are injured
- Severe toxicities are thought to occur when the organ's vascular stem cell niches are injured
  - Most frequent toxicities involve the marrow and the alimentary tract
  - Marrow and the alimentary tract are known to possess constantly active vascular stem cell niches
- Rate of SRRT increases with age
  - Aging is a known factor related to dysfunction of organ vascular niches
- SRRT acknowledged as 'severe unmet need' by FDA
  - RMAT and Orphan Designations granted to AB-205 in setting of myeloablative chemotherapy and HCT

Stem cell vascular niche



Chow et al., JCO 2006; Gyurkocza et al. Blood 2014; Stansborough et al., Int J Radiat Biol 2016; Dahi et al., Blood Advances, 2021

AB-205 E-CEL Therapy to Reduce SRRT



AB-205 E-CEL Cells: engineered human endothelial cells

1. Human umbilical cord vein endothelial cells
2. Transduced with pro-survival gene *E4ORF1*

- ❖ Releases reparative angiocrine factors in injury/disease states
  - Complex and dynamically expressed mixture of factors
  - Over 100 angiocrine factors identified

Reparative angiocrine factors expressed by E-CEL Cells act on:

1. endogenous adult organ stem/progenitor cells
2. endogenous niche endothelial cells

- ❖ Paracrine effect

Phase 1b/2 AB-205 Study Design

Key Eligibility Criteria

- Adults with NHL and HL
- 1st AHCT
- Eligible for HDT-AHCT (adequate organ function)
- Localized radiation and post-HCT maintenance permitted
- ECOG ≤ 1

Cohorts enrolled sequentially, following safety assessment of previous cohort

Cohort 1:
5 × 10^6 E-CEL/kg on D0

Cohort 2:
10 × 10^6 E-CEL/kg on D0

Cohort 3:
20 × 10^6 E-CEL/kg on D0

Cohort 4:
20 × 10^6 E-CEL/kg
(Split: 50% D0 & 50% D2)

Cohort 5:
30 × 10^6 E-CEL/kg
(Split: 67% D0 & 33% D2)

DLT: occurring from AB-205 infusion until day +28
- G3-4 infusion related reactions.
- G3-4 AEs to vital organs that do not decrease to grade ≤ 2 within 7 days.
- G4 neutropenia that does not resolve to grade ≤ 3 within 28 days.
- G4 thrombocytopenia that does not resolve to grade ≤ 3 within 28 days.
- Acute GVHD grade ≥ 2 that does not resolve to grade ≤ 1 within 14 days.
- Any G5 toxicity not due to underlying malignancy or not clearly due to AB-205.

Primary Objective

- Safety of AB-205

Secondary Objectives

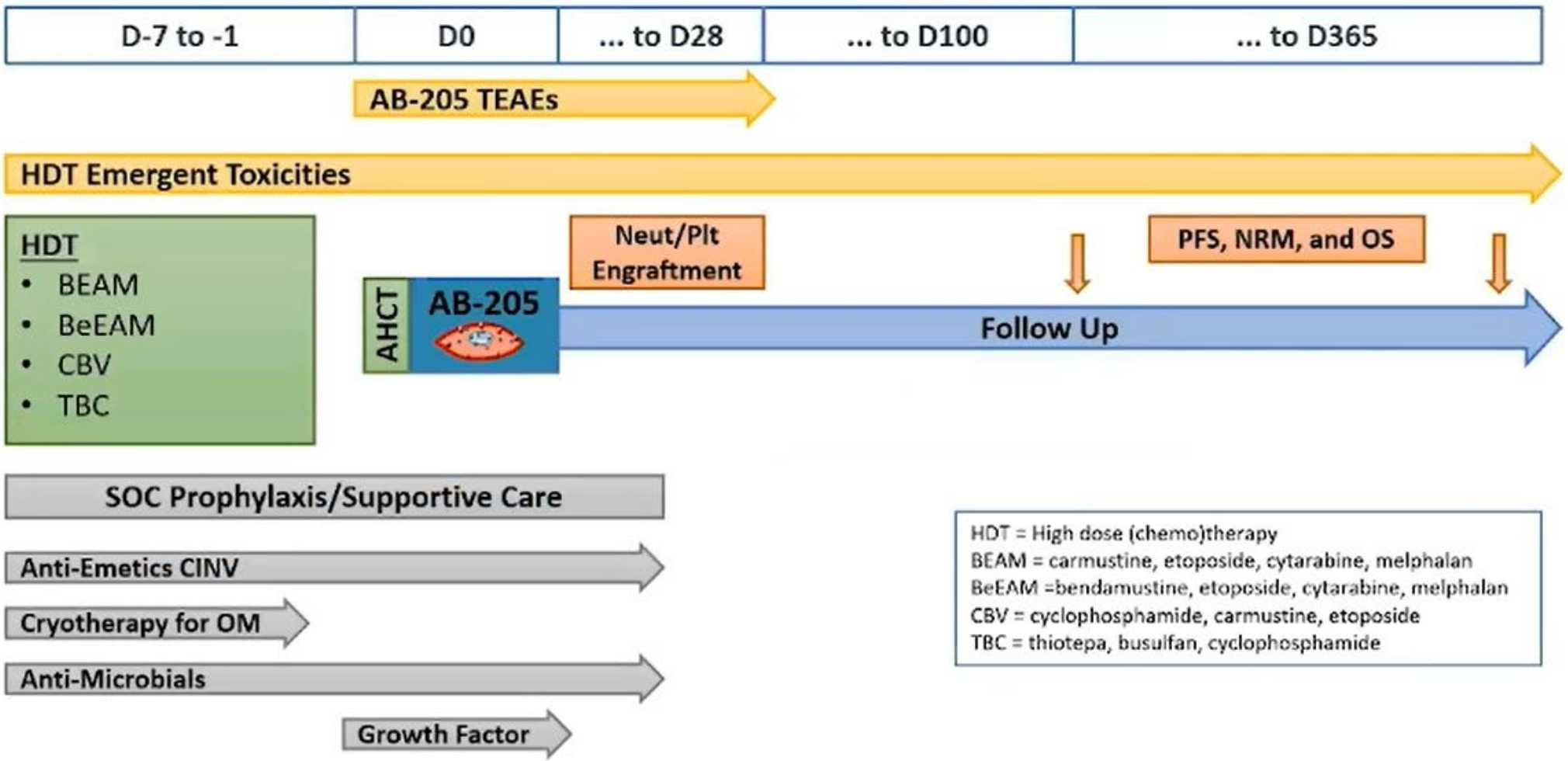
- Severity and duration of G≥3 Oral/GI toxicities including oral mucositis, nausea, vomiting, diarrhea
- Time to neutrophil and platelet engraftment

Exploratory Objectives

- PFS, NRM, OS
- Lymphoid recovery

ClinicalTrials.gov Identifier: NCT03925935

AB-205-001: Treatment Schedule



AB-205-001: Control Cohort

- Retrospective control cohort analysis
  - Data from two AB-205-001 clinical sites (City of Hope and UCSF)
  - Undergoing AHCT for systemic lymphoma
  - AHCT conditioning similar to trial: mostly BEAM
  - Age ≥ 40 yo (n=111)
  - Years 2019 to 2020
  - NCI CTCAE criteria (oral/GI SRRT rate, febrile neutropenia)
  - Conducted/supervised by PI or Co-PI at participating sites
- Concurrently performed alongside AB-205-001 trial
- Retrospective control cohort study adopted as comparator for:
  - RMAT Designation
  - End of Phase 2 Meeting

AB-205-001: Baseline Characteristics

Systemic Lymphoma Patients Undergoing HDT-AHCT	AB-205-001 Aged ≥ 40	Control Cohort Aged ≥ 40
N	28	111
Age, Median (range)	57 (40, 73)	61 (41, 77)
Male, %	54%	73%
Diagnosis, %		
HL	25%	14%
NHL	75%	86%
Prior lines, Median (range)	2 (1, 4)	2 (1, 4)
HDT Regimen, %		
BEAM	79%	98%
BeEAM	18%	2%
CBV	4%	-
CD34⁺ Count $\times 10^6$/kg, Median (range)	5.2 (2.9, 19.6)	4.2 (2.0, 19.6)

AB-205-001: Safety Summary

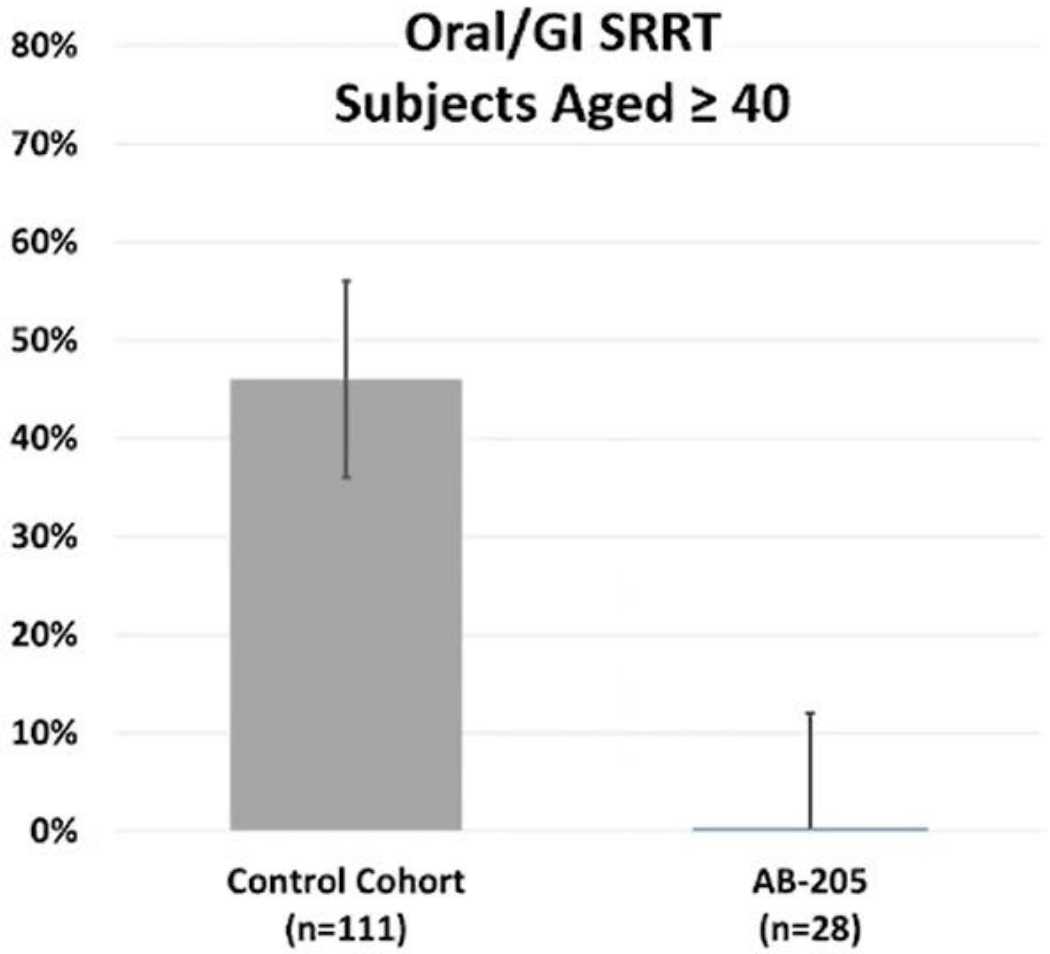
- AB-205 is well-tolerated: MTD not reached
- No clinically significant infusion-related reactions
- No immune reactions
- AEs on study are consistent with those expected in an AHCT population

All Grade Non-Hematologic TEAEs in ≥ 20%, n (%)	AB-205-001 Aged ≥ 40 (n=28)
Diarrhea	20 (71%)
Nausea	15 (53%)
Stomatitis	13 (46%)
Fatigue	11 (39%)
Decreased appetite	8 (29%)
Hypocalcemia	8 (29%)
Hypokalemia	8 (29%)
Vomiting	8 (29%)
Headache	6 (25%)

Grade ≥ 3 Non-Hematologic TEAEs, n	AB-205-001 Aged ≥ 40 (n=28)
Hypokalemia	3
Angina pectoris	1
Sepsis	1
Enterocolitis infectious (C. diff)	1
Depression	1
Epistaxis	1
Hypocalcemia	1
Hypophosphatemia	1
Septic shock	1

- Median duration of follow-up: 1.5 years
- No detrimental effect on survival seen:
  - PFS at 1 year: 83% (95% CI: 61%, 94%)
  - OS at 1 year: 91% (95% CI: 70%-98%)
- 2 deaths amongst 28 subjects aged ≥40 with systemic lymphomas
  - 66 yo female with high risk DLBCL
    - Relapsed D79; Died D171
  - 71 yo male with TCL
    - Lung infection; Died D131

AB-205-001: Efficacy on Oral/GI SRRT



Historical control cohort – *unpublished, forthcoming manuscript*

Oral/GI SRRT clinical composite

- 1 of 4 toxicities considered severe (NCI Grade ≥ 3)

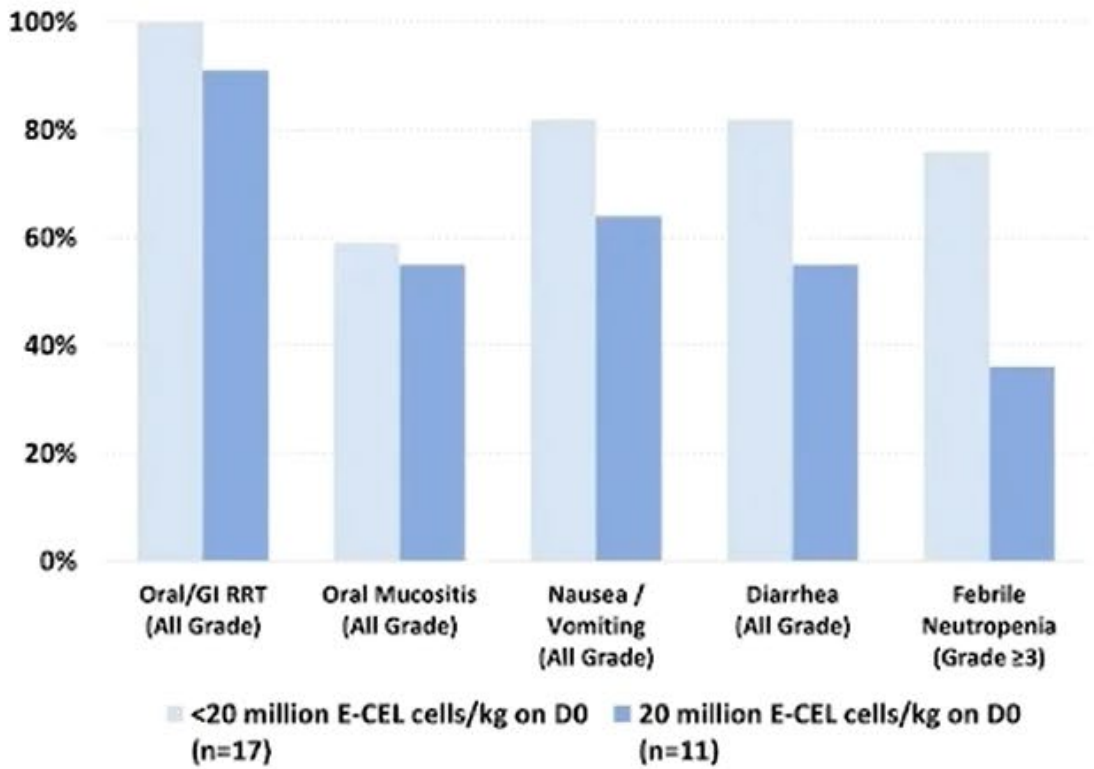
Oral/GI SRRT	CTCAE v5.0 Grade 3 Definition
Mucositis oral	Severe pain; interfering with oral intake
Nausea	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Diarrhea	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
Vomiting	Tube feeding, TPN, or hospitalization indicated

Occurring post-initiation of HDT despite use of:

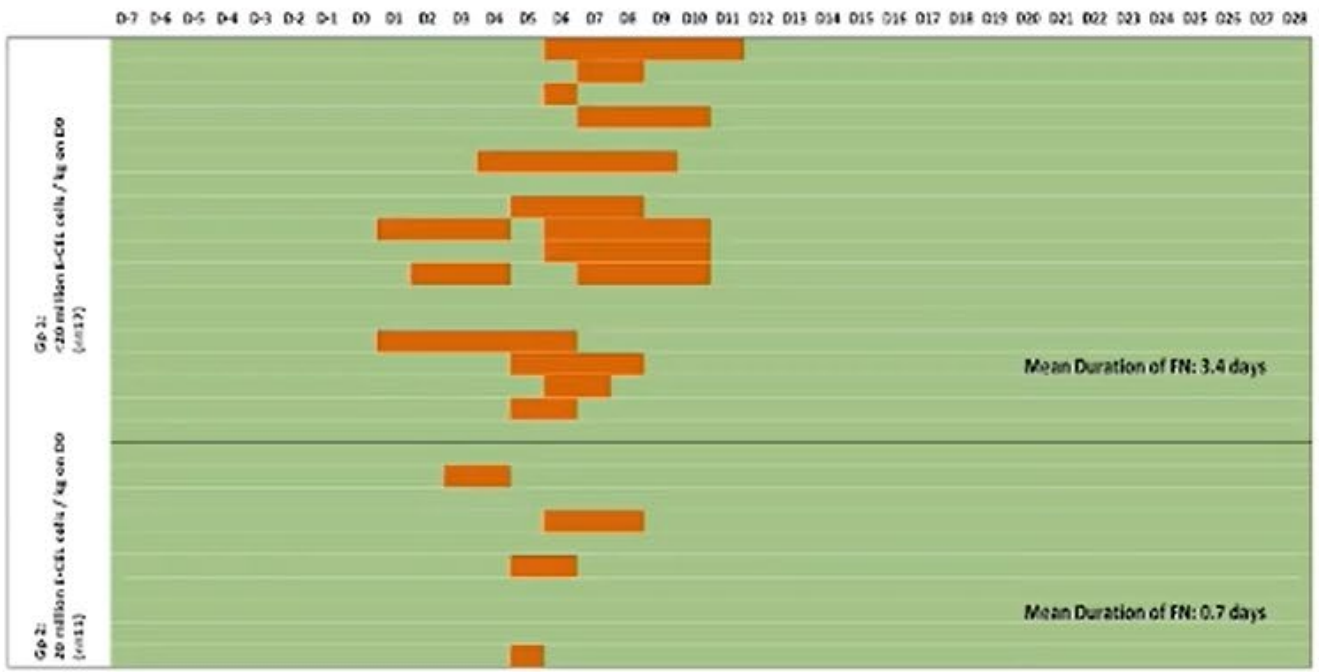
- Combination anti-emetics for CINV
- Oral ice chips to prevent OM
- Anti-diarrheals
- Antimicrobials

AB-205-001: Dose Response

Oral/GI Events (All Grade) and FN*



Duration of FN*



Positive dose response with AB-205

*Subjects Aged ≥ 40
FN = Febrile Neutropenia

AB-205-001: Engraftment and Length of Stay

Subjects Aged ≥ 40	AB-205 (N=28)
Neutrophil Engraftment, Median Days (IQR) The first of three consecutive days after AHCT of absolute neutrophil count (ANC) ≥ 500/µL	10 (9, 11)
Platelet Engraftment, Median Days (IQR) The first of seven consecutive days after AHCT of platelet count ≥ 20,000/µL without transfusion support	10 (10, 13)
Length of Stay, Median Days (IQR)	12 (10, 13)

Historical control cohort – *unpublished, forthcoming manuscript*

Conclusions & Next Steps

- AB-205 has significant potential to address a serious unmet need in patients undergoing HDT-AHCT
  - Serious unmet need acknowledged by US FDA through RMAT & Orphan designations
- 20 x 10^6 E-CEL/kg demonstrated robust effect on reduction of severe oral/GI toxicities and febrile neutropenia
  - Data provided justification for a single dose for the registration Phase 3 study
- Data from this study were the subject of an end-of-phase 2 meeting with FDA
  - Clearance from the FDA to initiate treatment in single registration randomized Phase 3
  - FPFV planned for Q1 2022

HDT = High Dose Therapy
AHCT = Autologous Hematopoietic Cell Transplantation

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1832: Predictors of Relapse and Survival Following Autologous Stem Cell Transplant in Patients with Diffuse Large B-Cell Lymphoma

AUTHORS: Marie Hu[1], Marcus P. Watkins[2], Qing Cao[3], Raya Saba[2], David A. Russler-Germain[2], Veronika Bachanova[1], Todd A. Fehniger[2], and Daniel Weisdorf[1]

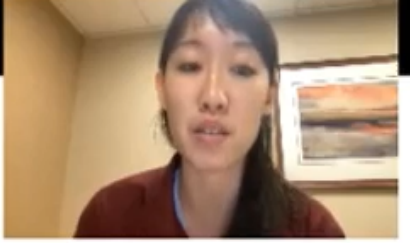
[1]University of Minnesota, Division of Hematology, Oncology, and Transplantation, Minneapolis, MN, [2]Washington University School of Medicine, Division of Oncology, St. Louis, MO, [3]Biostatistics Core, Masonic Cancer Center, University of Minnesota, Minneapolis, MN

Background

- 30-40% of patients with diffuse large B-cell lymphoma (DLBCL) will be refractory to or relapse after first line treatment
- Current standard of care is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT)
- Prior studies have largely examined clinical risk factors associated with higher risk of relapse after ASCT
  - Limited data integrating both pathologic and molecular features

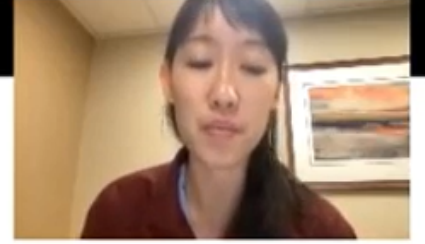
Objective

- To identify high-risk features associated with relapse after ASCT using a combination of clinical, molecular, pathologic, and transplant characteristics



Methods

- Retrospective study of all adult patients with DLBCL who underwent ASCT at University of Minnesota and Washington University in St. Louis from 2010 to 2020
- Excluded primary CNS lymphoma, primary mediastinal B-cell lymphoma, Burkitt lymphoma
- Analyzed demographics, clinical characteristics, cell of origin (COO) by immunohistochemistry (IHC), fluorescence in-situ hybridization (FISH) testing, and treatment/transplant characteristics



Methods

- Primary endpoints:
  - 3-year progression-free survival (PFS)
  - 3-year overall survival (OS)
- Kaplan-Meier method was used to estimate survival
- Univariate and multivariate Cox proportional hazards regression performed to identify factors associating with PFS and OS

Results

- 235 patients underwent ASCT between 2010 to 2020
- Median age 61, 63% male
- At dx: 80% advanced stage, 74% extranodal involvement, 65% elevated LDH
- 60% GCB, 40% non-GCB

Characteristic	Number (Percent
Median age at ASCT (years)	61 (range 25-75)
Age <60	131/235 (56%)
Age ≥60	104/235 (44%)
Male sex	149/235 (63%)
Stage at diagnosis	
I-II	46/234 (20%)
III-IV	188/234 (80%)
Extranodal involvement	
Yes	174/234 (74%)
No	60/234 (26%)
R-IPI at diagnosis	
0-3	163/195 (84%)
4-5	32/195 (16%)
Prior indolent lymphoma	
Yes	71/235 (30%)
No	164/235 (70%)
Cell of origin (COO) by IHC	
Germinal center (GCB)	115/191 (60%)
Non-GCB	76/191 (40%)

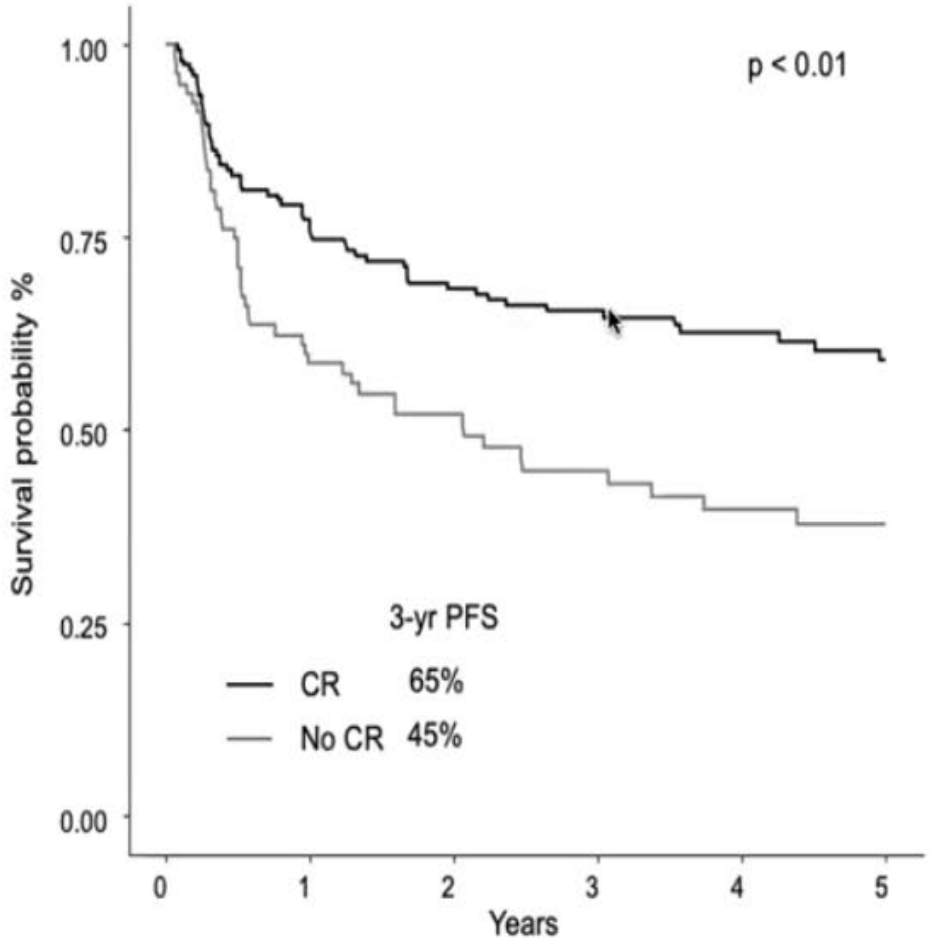
Results

- 10% single MYC-R, 22% double/triple hit
- 12% refractory, 62% relapsed at median of 12 months
- Median 2 lines of tx prior to ASCT (range 1-5)
- At ASCT: 66% CR, 32% PR

Characteristic	Number (Perc
Double/triple-hit lymphoma (DHL)	
Yes	35/158 (22%)
No	123/158 (78%)
Double-expressor lymphoma	
Yes	14/57 (25%)
No	43/57 (75%)
Disease category	
Primary refractory	29/178 (16%)
Early relapse (<12 mo)	71/178 (40%)
Late relapse (≥12 mo)	78/178 (44%)
Median lines of treatment	2 (range 1-5)
1-2 lines	196/235 (83%)
≥3 lines	39/235 (17%)
Disease status at ASCT	
CR	154/234 (66%)
PR	76/234 (32%)
SD/PD	4/234 (2%)
Conditioning regimen	
BEAM	165/235 (70%)
Cy/TBI	47/235 (20%)
Other	23/235 (10%)

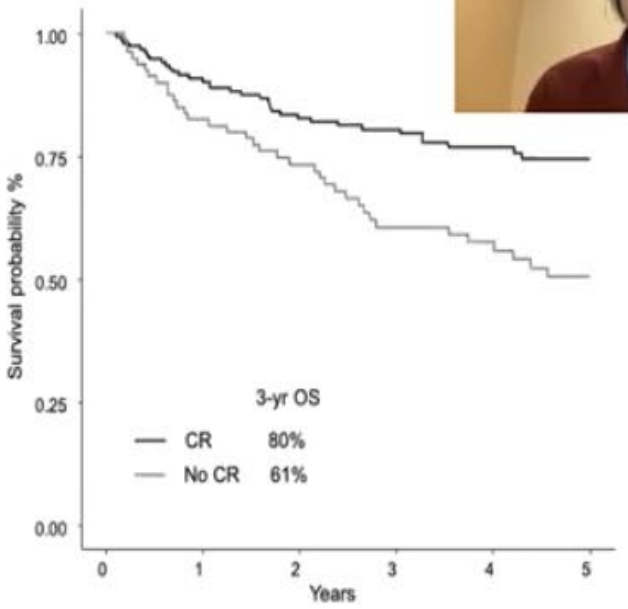
PFS regression analysis

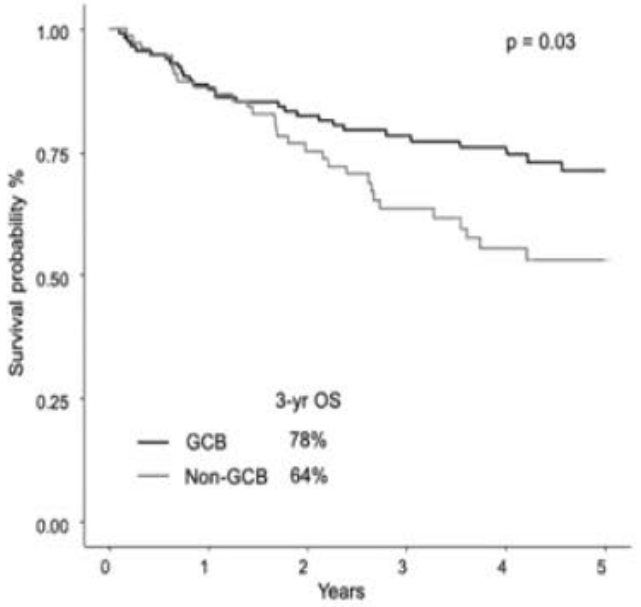
- **Overall 3-yr PFS 58%**
- Prognostic factors for worse PFS:
  - Univariate: 3+ lines of tx prior to ASCT, non-CR at ASCT, transformed disease
  - Multivariate: non-CR at ASCT



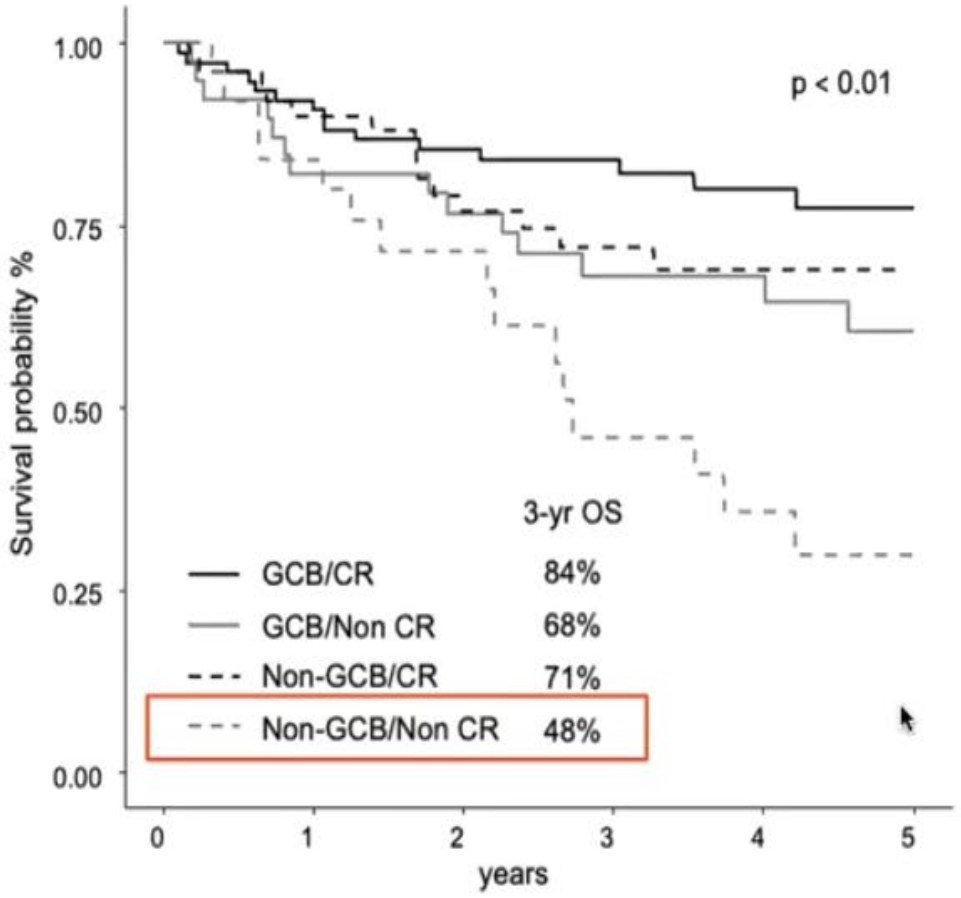
OS regression analysis

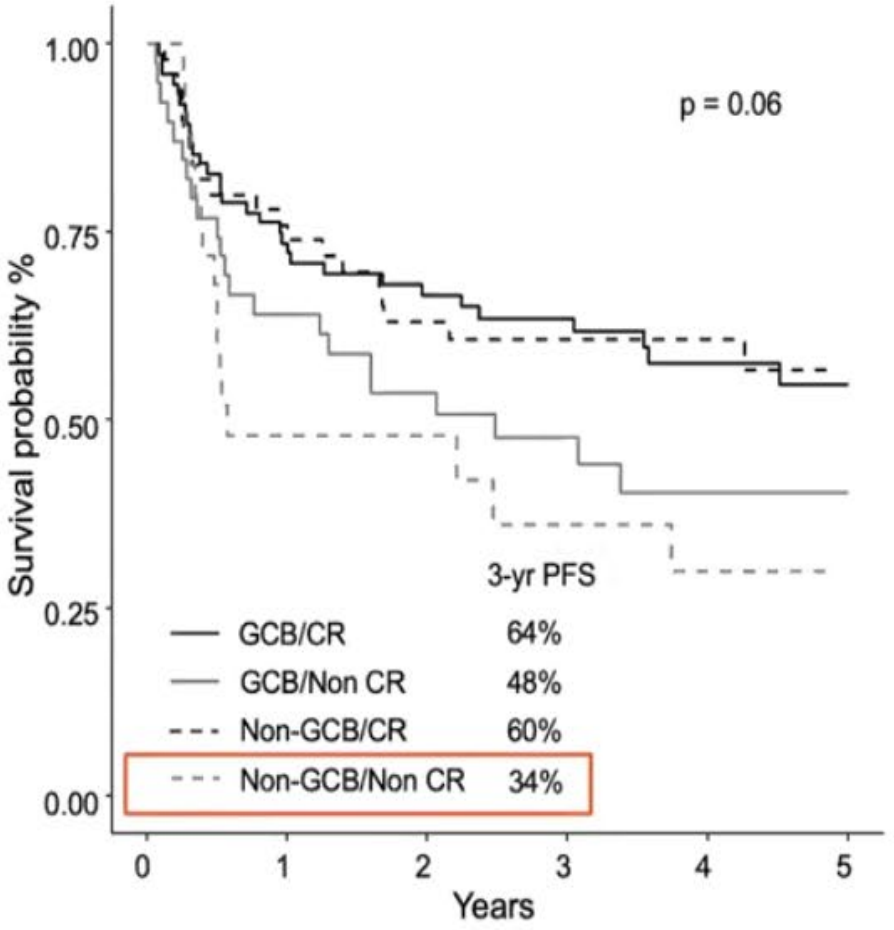
- **Overall 3-yr OS 74%**
- Prognostic factors for worse OS:
  - Univariate: 3+ lines of tx prior to ASCT, non-CR at ASCT
  - Multivariate: non-CR at ASCT, non-GCB COO, age >60





OS/PFS by COO and disease status





Conclusions

- Factors associated with OS after ASCT were disease status at time of transplant and COO, with non-GCB patients not in CR having the poorest outcomes
  - GCB patients not in CR were still able to be cured by ASCT at a high rate
- Molecular rearrangements including DHL/THL were not prognostic
- These findings may inform which patients should undergo ASCT, while the highest risk group may be better treated with alternatives including novel targeted agents or chimeric antigen receptor cell therapy

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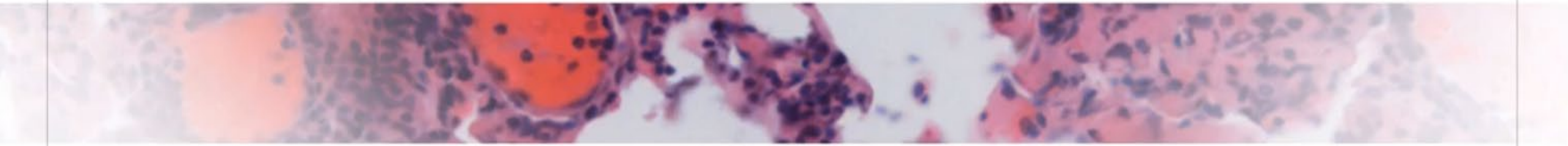
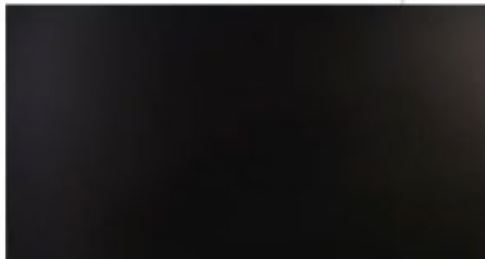


Autograft-Absolute Lymphocyte Count Infusion Predicts Survival in Double/Triple Hit Lymphomas Post-Autologous Peripheral Blood Hematopoietic Stem Cell Transplantation

Luis F. Porrata, David J. Inwards, Stephen M. Ansell, Ivana N. Micallef, Patrick B. Johnston, Jose Villasboas,
Jonas Paludo, Svetomir N. Markovic.
Bone marrow Transplant Program
Mayo Clinic, Rochester, MN

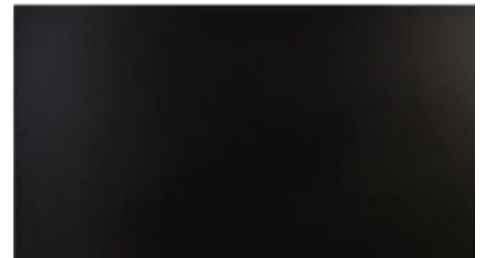


INTRODUCTION

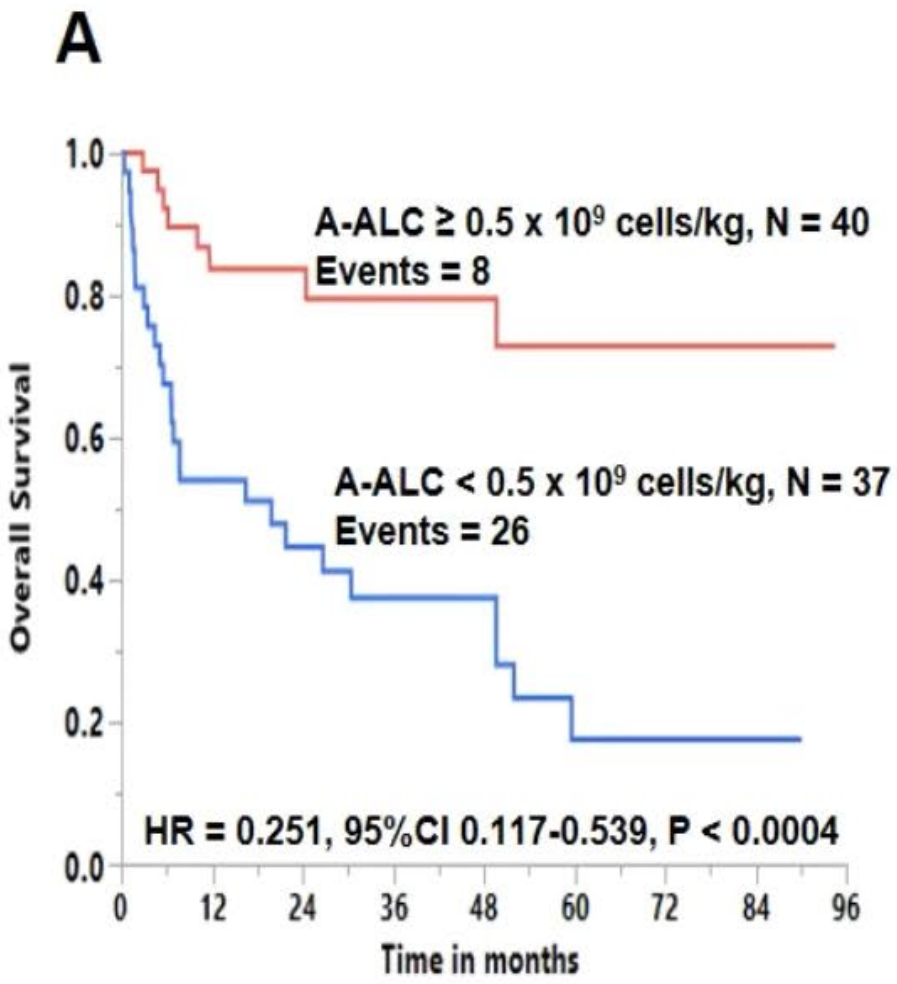
- The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasm established the diagnosis of double hit lymphoma/triple hit lymphoma (DHL/THL) based on the rearrangements of *MYC* and *BCL2* or *BCL6*, or both .

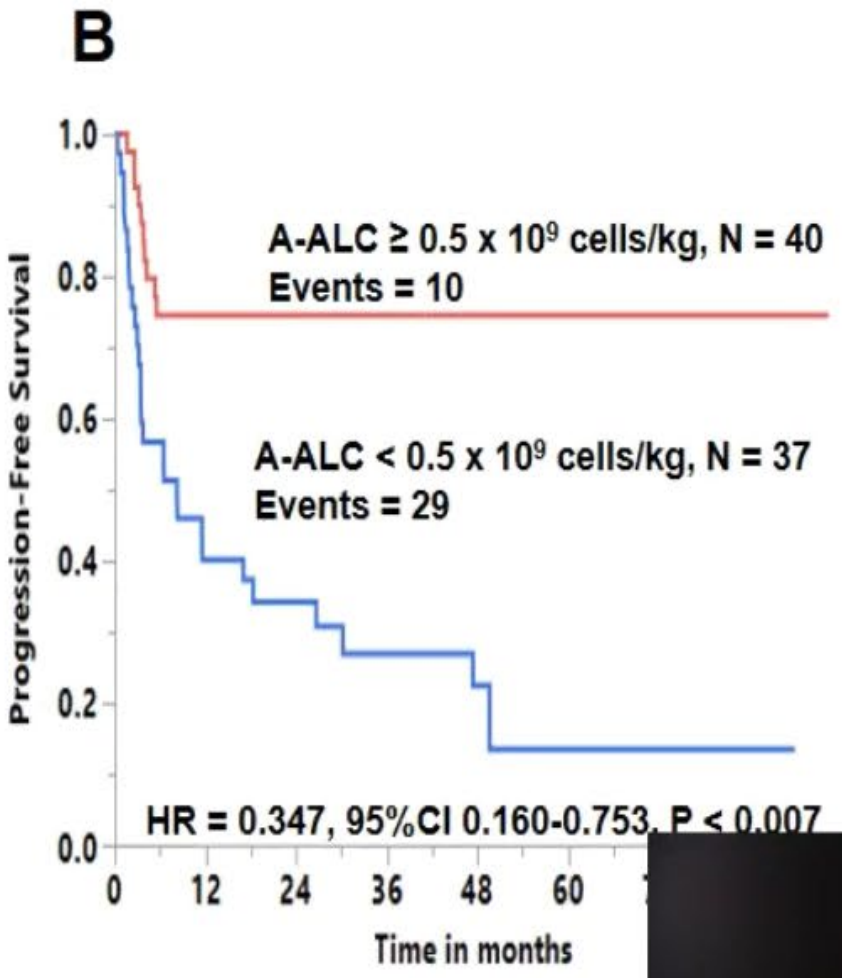
- The infusion of autograft-absolute lymphocyte count (A-ALC) has been reported to be a prognostic factor of clinical outcomes for lymphomas patients undergoing autologous peripheral blood hematopoietic stem cell transplantation (APBHSCT).

- However, A-ALC has not been specifically analyzed as a prognostic factor against DHL/THL patients. Thus, in this study, we evaluated if the A-ALC is a prognostic factor for OS and progression-free survival (PFS) in DHL/THL patients treated with APBHSCT.



SURVIVAL


A
1.0
0.8
0.6
0.4
0.2
0.0
Overall Survival
A-ALC ≥ 0.5 x 10⁹ cells/kg, N = 40
Events = 8
A-ALC < 0.5 x 10⁹ cells/kg, N = 37
Events = 26
HR = 0.251, 95%CI 0.117-0.539, P < 0.0004
0
12
24
36
48
60
72
84
96
Time in months


B
1.0
0.8
0.6
0.4
0.2
0.0
Progression-Free Survival
A-ALC ≥ 0.5 x 10⁹ cells/kg, N = 40
Events = 10
A-ALC < 0.5 x 10⁹ cells/kg, N = 37
Events = 29
HR = 0.347, 95%CI 0.160-0.753, P < 0.007
0
12
24
36
48
60
Time in months

Multivariate analysis for overall survival and progression-free survival including all the patients

	Overall Survival			Progression-Free Survival		
Variables	HR	95%CI	P	HR	95%CI	P
A-ALC ≥ 0.5 x10^9 cells/kg	0.178	0.052-0.614	<0.005	0.400	0.189-0.850	<0.02
Age, years ≤ 60	0.308	0.106-0891	<0.03			
Complete response prior to transplant	0.196	0.062-0.620	<0.006	0.322	0.139-0.747	<0.01
Extra-nodal disease < 2	0.651	0.317-6.128	0.6			
DHL vs THL	0.849	0.260-2.763	0.8			
Plerixafor use, yes vs no	0.349	0.101-1.208	0.1			
LDH (U/L) normal				0.160	0.020-1.266	0.1
IPI index < 3				0.830	0.421-1.636	0.6

Abbreviations: A-ALC = Autograft absolute lymphocyte count; DHL = double hit lymphoma; IPI = International Prognostic Index; LDH = Lactate dehydrogenase; and THL = triple hit lymphoma.

CONCLUSIONS

- A-ALC is an independent prognostic factor for OS and PFS in Double/Triple Hit lymphoma post- APBHSCT.
- Since 2017, it is the standard practice at Mayo Clinic, Rochester MN to collect both CD34 stem cells for hematologic engraftment and A-ALC for immunologic engraftment to improve clinical outcomes post-APBHSCT.

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