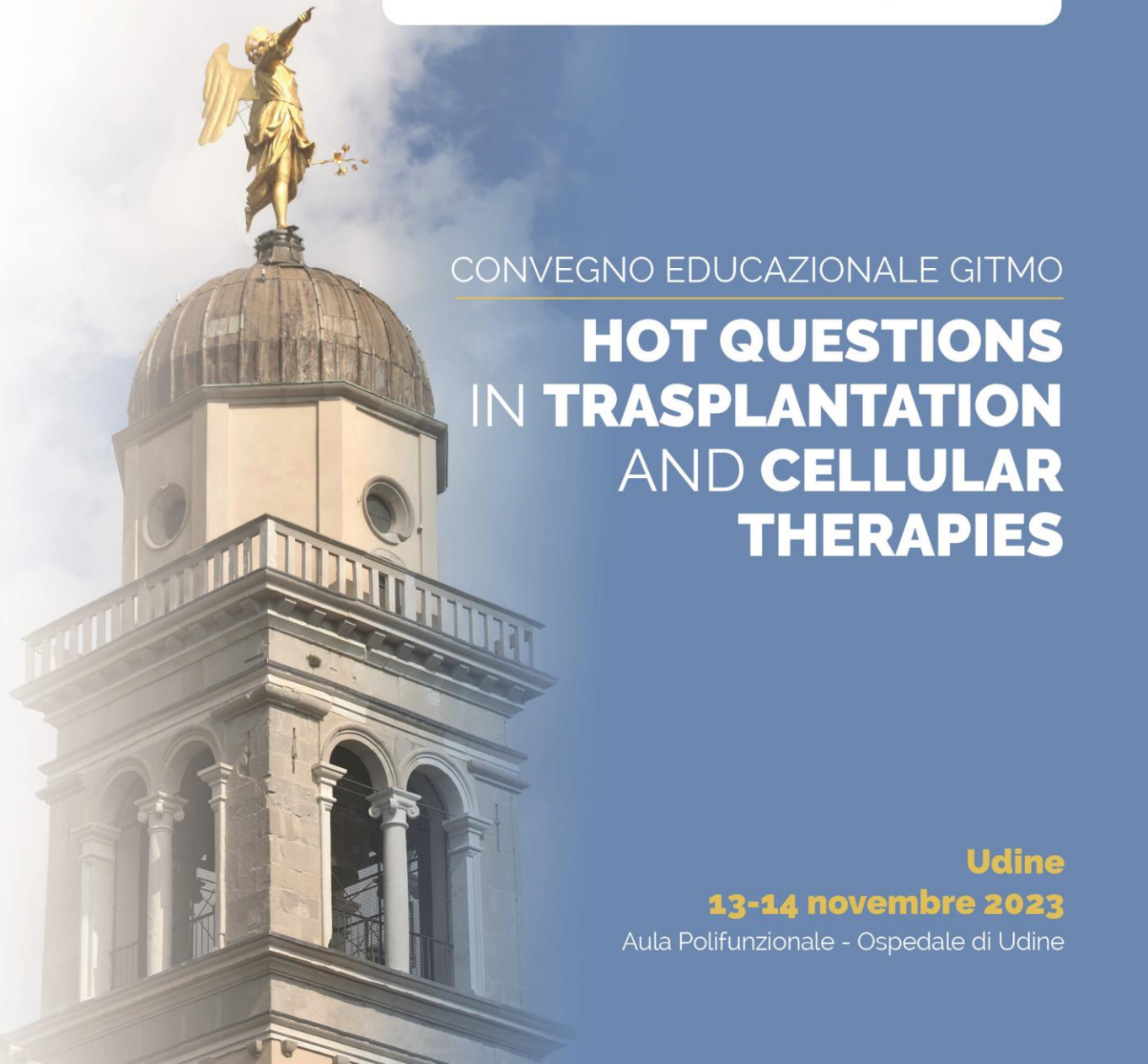
C’è una soglia di età anagrafica al di sopra della quale un paziente non dovrebbe essere candidato alla Terapia Cellulare CART?

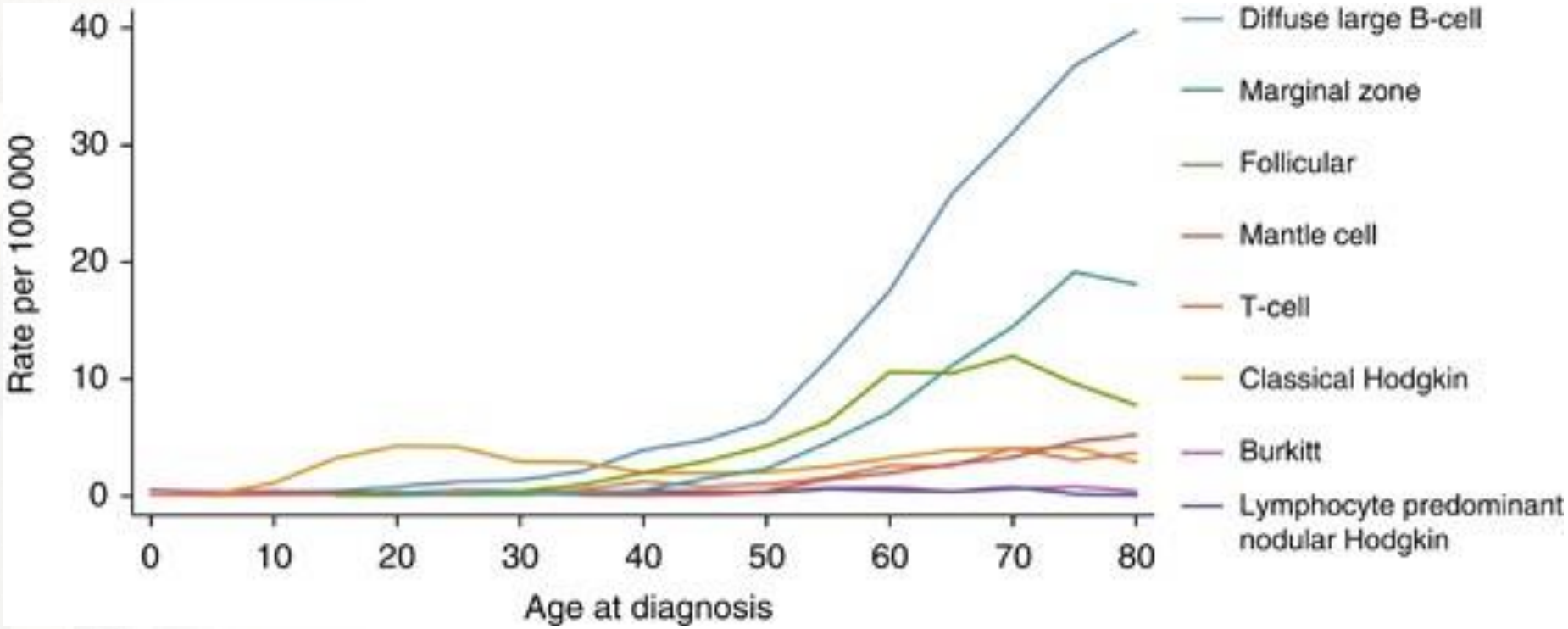
LE RAGIONI DEL NO

Michele Malagola

Cattedra di Ematologia, Università degli Studi di Brescia
Unità di Teraèie Cellulari e Trapianto di Midollo Osseo
ASST Spedali Civili di Brescia

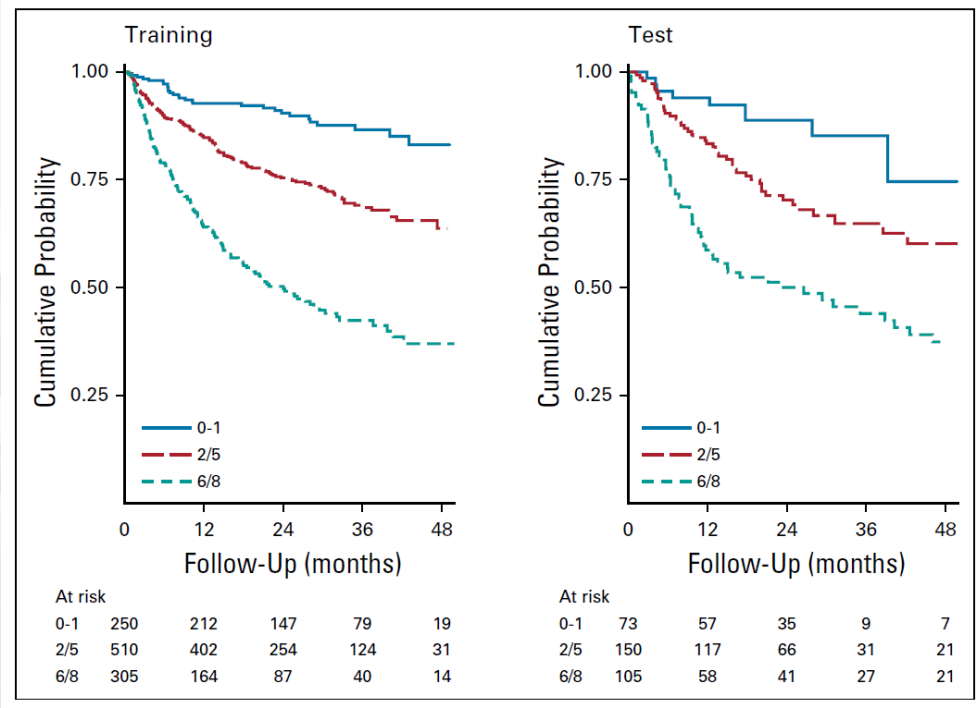


LYMPHOMAS' INCIDENCE BY AGE



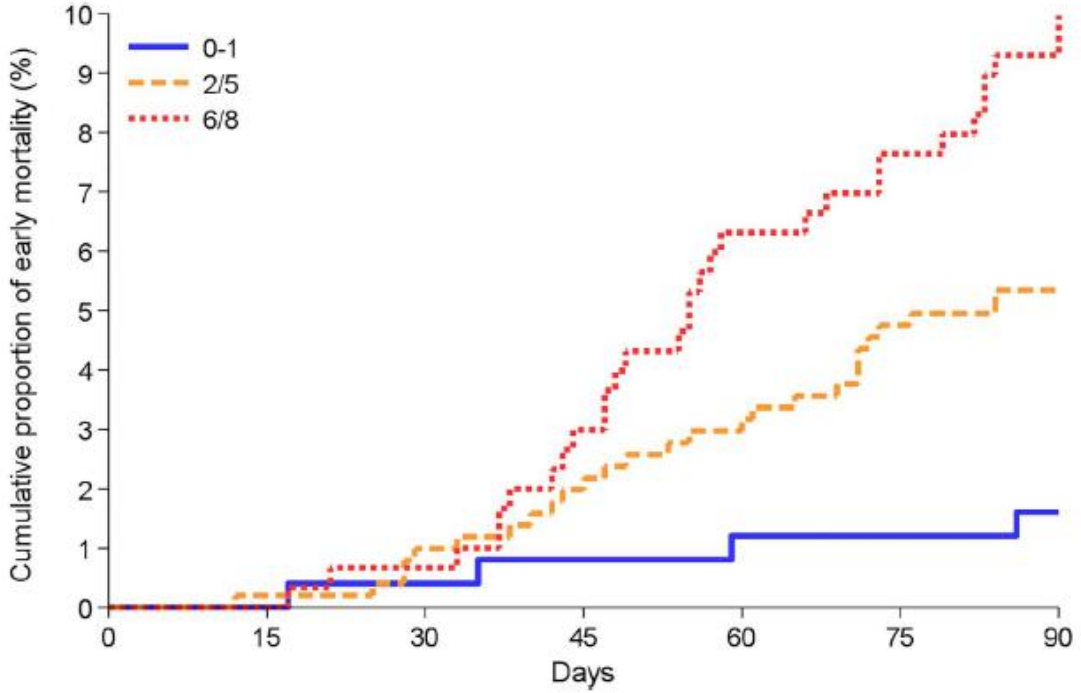
OUTCOME BY FITNESS

EPI = IPI + FIL score (CIRSG/Age/ADL/IADL) + Hb

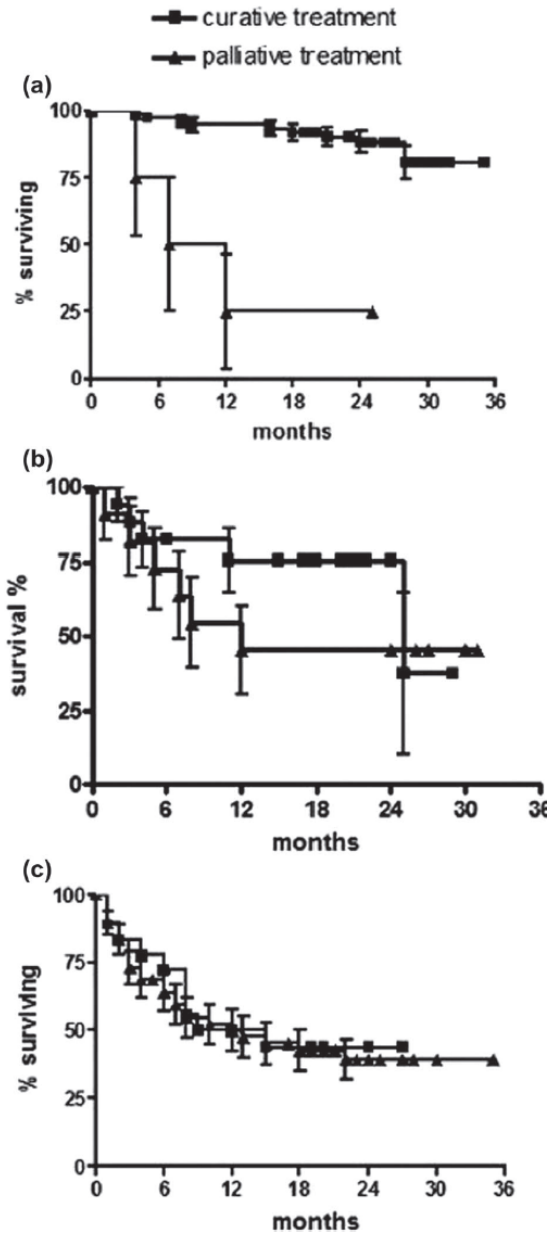


Merli et al, JCO 2021

(B) EPI model
Risk groups (score)
Low (0-1)
Intermediate (2-5)
High (6-8)



Cencini E et al, Hematol Oncol 2023



FIT

UNFIT

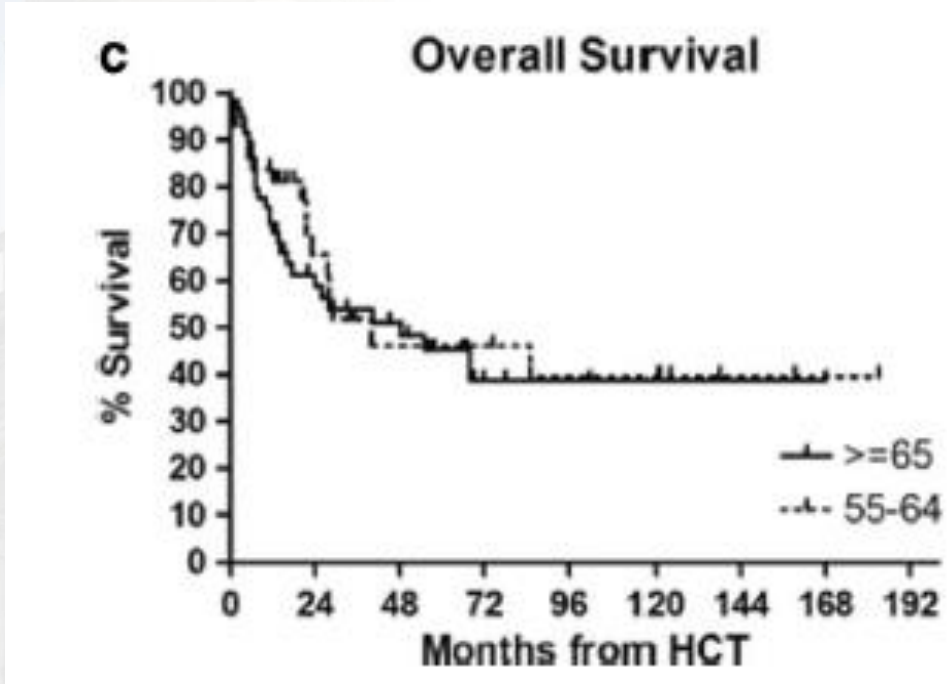
FRAIL

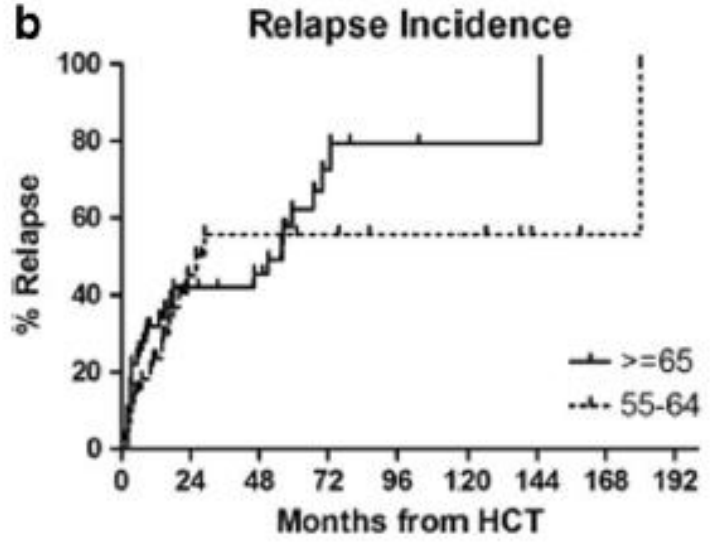
Tucci et al, Leuk Lymph 2013

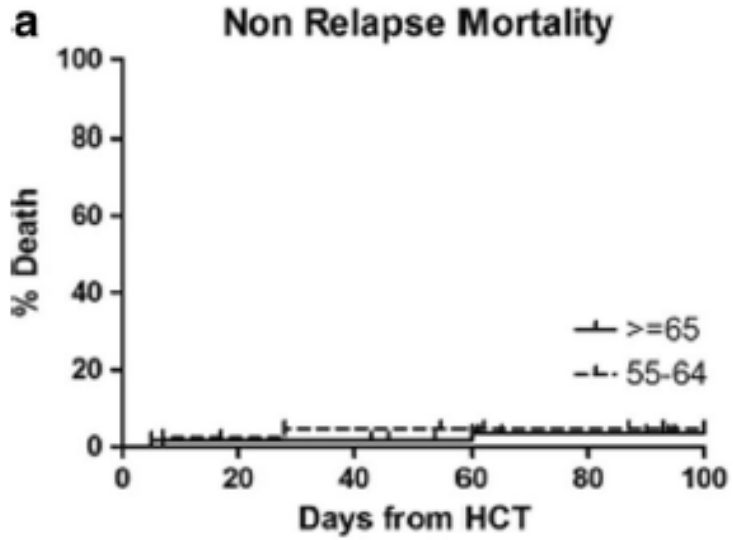
Toxicity and efficacy of autologous hematopoietic cell transplantation in elderly patients with aggressive lymphoma: a historical prospective study

Marina Davidov[1] · Chava Perry[1,2] · Yair Herishanu[1,2] · Nadav Sarid[1,2] · Esti Rom[2] · Odelia Amit[1,2] · Rinat Eshel[1,2] · Ella Naparstek[1,2] · Irit Avivi[1,2] · Ron Ram[1,2]

Annals of Haematol 2018







THE OLD STORY OF PATIENTS' SELECTION FOR INTENSIVE THERAPY

……AGE AND…….

A LOOK AT THE HISTORICAL COMPARATOR

ALLO-SCT

Transplantation and Cellular Therapy 28 (2022) 96.e1–96.e11

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article

Allogeneic – Adult

GITMO Registry Study on Allogeneic Transplantation in Patients Aged ≥60 Years from 2000 to 2017: Improvements and Criticisms

Michele Malagola[1,*], Nicola Polverelli[1], Vicky Rubini[1], Massimo Martino[2], Francesca Patriarca[3], Benedetto Bruno[4], Luisa Giaccone[4], Giovanni Grillo[5], Stefania Bramanti[6], Paolo Bernasconi[7], Marco De Gobbi[8], Annalisa Natale[9], Elisabetta Terruzzi[10], Attilio Olivieri[11], Patrizia Chiusolo[12], Angelo Michele Carella[13], Marco Casini[14], Chiara Nozzoli[15], Patrizio Mazza[16], Simona Bassi[17], Francesco Onida[18], Adriana Vacca[19], Sadia Falcioni[20], Mario Luppi[21], Anna Paola Iori[22], Vincenzo Pavone[23], Cristina Skert[24], Paola Carluccio[25], Carlo Borghero[26], Anna Proia[27], Carmine Selleri[28], Nicoletta Sacchi[29], Sonia Mammoliti[30], Elena Oldani[31], Fabio Ciceri[32], Domenico Russo[1], Francesca Bonifazi[33]

Tab. 1	
Total	277
Median age at HSCT [IQR]	62.90 [61.37, 64.87]
Diagnosis	
CLL	72 (26.0%)
Hodgkin Lymphoma	8 (2.9%)
NHL	197 (71.1%)
HCT- CI	
>=3	44 (22.1%)
1_2	59 (29.6%)
0	96 (48.2%)
KPS	
<=70	29 (12.1%)
80	52 (21.8%)
90	103 (43.3%)
100	54 (22.7%)
Lines of therapy	
0	5 (2.6%)
1	18 (9.4%)
2	42 (22.0%)
3	67 (35.1%)
>=4	59 (30.8%)
Status at HSCT	
CR	92 (35.1%)
Frontline	2 (0.8%)
NR	70 (26.7%)
PR	98 (37.4%)
Patient sex	
F	95 (34.3%)
M	182 (65.7%)
Year of HSCT	
2000-2005	41 (14.8%)
2006-2011	116 (41.9%)
2012-2017	120 (43.3%)

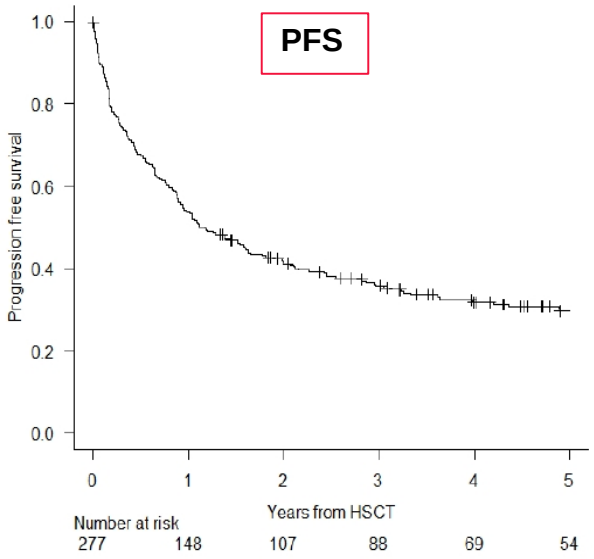
97 aggressive (49%)
60 indolent (30%)
40 missing (21%)

~90%

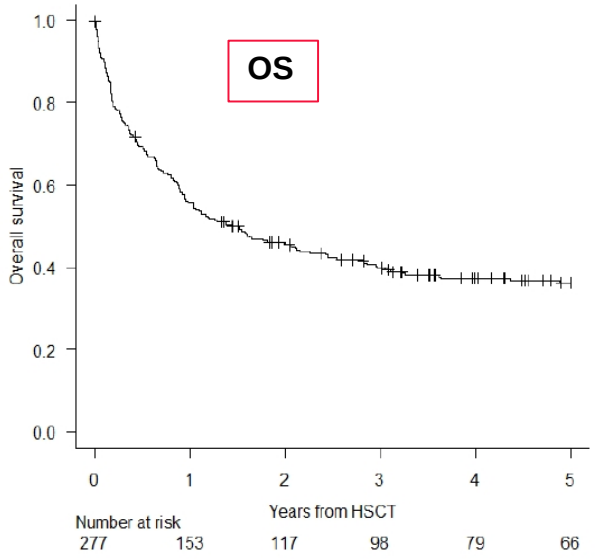
~65%

Tab. 2	Colonna1
Source of HSC	
BM	56 (20.3%)
PB	215 (77.9%)
UCB	5 (1.8%)
Intensity	
RIC	228 (83.2%)
MAC	46 (16.8%)
CMV d to R	
0	159 (67.9%)
1	75 (32.1%)
GVHD prophylaxis	
CnI +/- MMF without ATG	123 (49.4%)
CTX	29 (11.6%)
In vivo T-depletion (ATG or Campath)	90 (36.1%)
Other	7 (2.8%)
HLA match	
HAPLO	42 (16.2%)
MMUD	42 (16.2%)
MRD	110 (42.5%)
MUD	65 (25.1%)
SEX F to M	
0	199 (74.8%)
1	67 (25.2%)

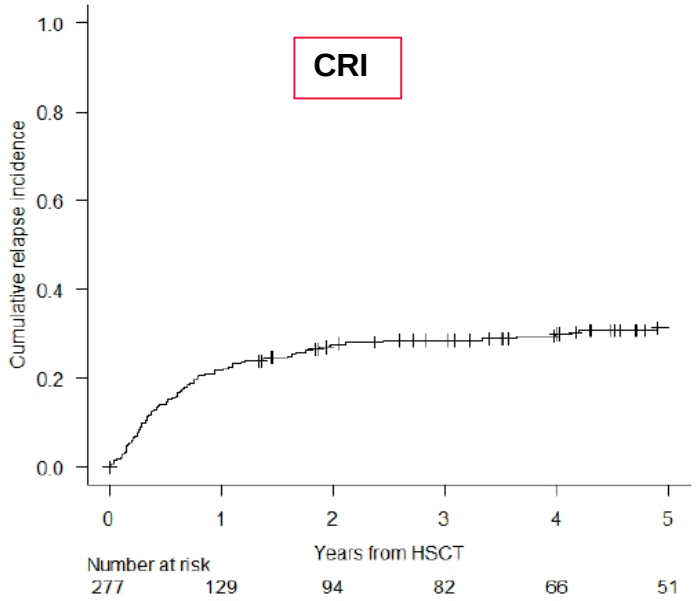
PFS



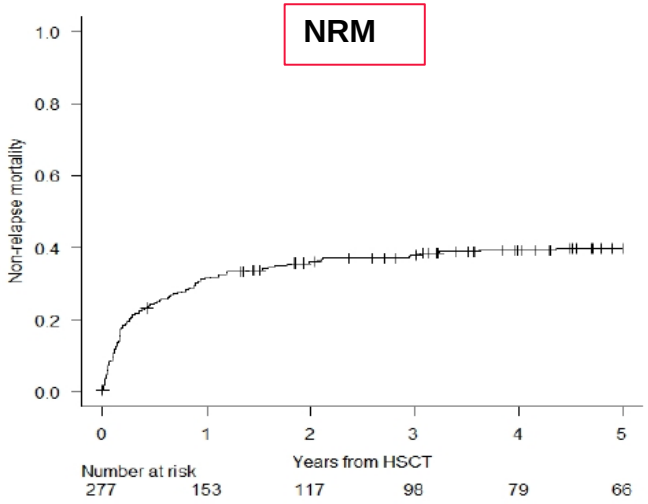
OS



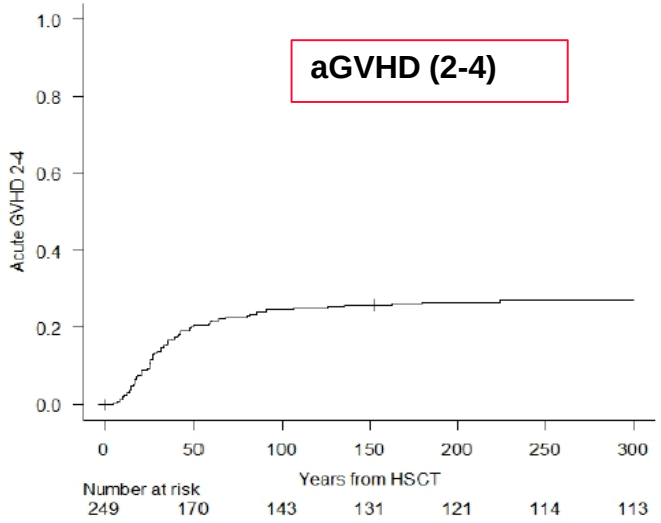
CRI



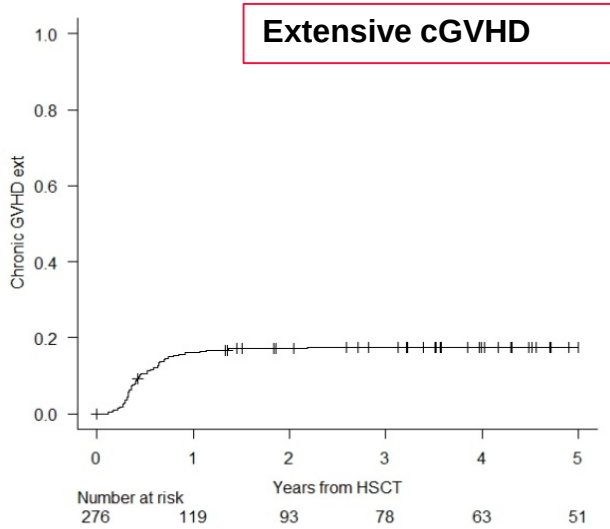
NRM



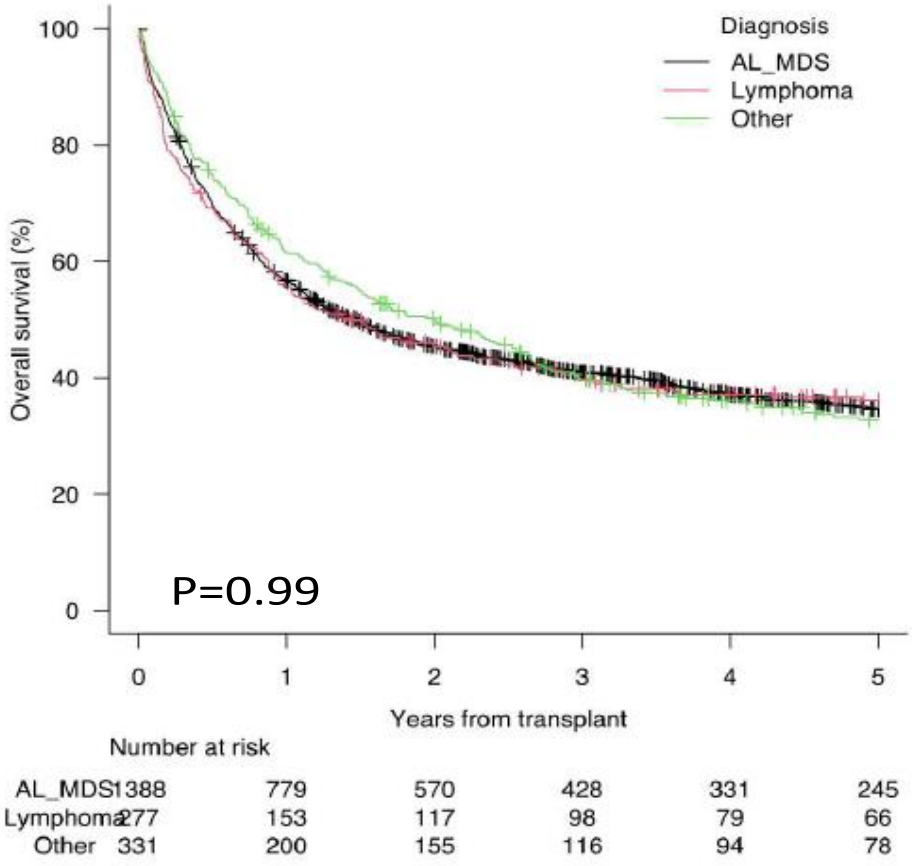
aGVHD (2-4)



Extensive cGVHD



OVERALL SURVIVAL AND DIAGNOSIS



OS at 1y 56.7% vs 55.7% vs 61.7%
OS at 2y 45,4% vs 45.3% vs 49,9%
OS at 5y 34.6% vs 36.1% vs 32.8%

Median AL_MDS OS 1,48
Median Lymphoma OS 1,42
Median other OS 2,00

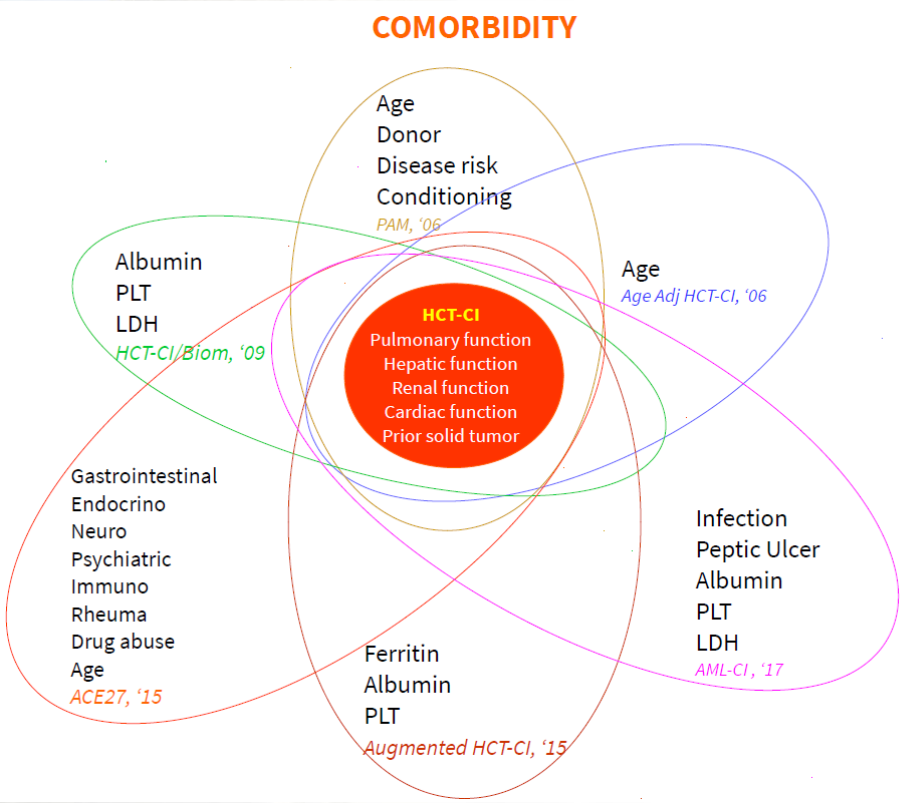
Malagola M et al, TCT 2022

PATIENTS' SELECTION

1. Comorbidities
2. Frailty

MULTIDIMENSIONAL GERIATRIC ASSESSMENT

COMORBIDITY



FRAILTY and COMPREHENSIVE GERIATRIC ASSESSMENT

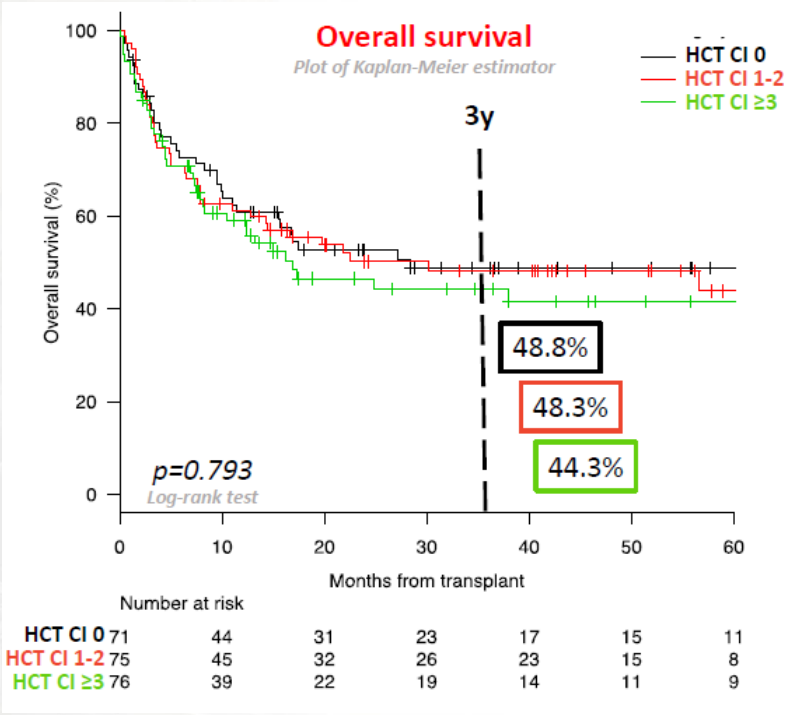
Ware JE 1992	- SF-36 PCS / SF-26 MCS	→	36 item (QoL) for physical assessment 26 item (QoL) for mental assessment
Podsiadlo 1991	– TUG (Time Up and Go)	→	time for 3 m walking (two ways)
McDowell 1997	– ADL (Activities of Daily Life)	→	from 0 to 6 for daily living
Graf 2008	– IADL (Instrumental Activities of Daily Life)	→	from 0 to 8 for daily activities
Beelman 1997	– CES-D (Center for Epidemiologic Studies on Depression)	→	items for depression assessment
Saliba 2001	– VES13 (Vulnerable Elders Survey)	→	13 items for geriatric assessment
Bland 2001	– 3-MS (Mini-Mental State Examination)	→	test for dementia
Fried 2001	- FFI (Fired Frailty Index)	→	5 parameters (self reported and PS)
Rantanen 2003	– SPPB (Short Physical Performance Battery)	→	test for physycal performance
Rockwood 2005	– CFS (Clinical Frailty Scale)	→	9 point-scale (from very fit to terminal)
Rejesky 2008	- PAT-D (Pepper Assessment Tool for Disability)	→	23 items on mobility+ADL+IADL
Hurria 2009	- DT (Distress Thermometer)	→	1 item for level of distress (0 to 10)
Bellera 2012	– G8 (Geriatric 8)	→	8 items (food, weight, mobility, BMI,…)
Bonanad 2015	- GAH scale (Geriatric Assessment in Hematology)	→	30 items (medications, ADL, nutrition,..)
Palumbo 2015	– IMWG Frailty Score (Int Myeloma WG)	→	30 item including CCI

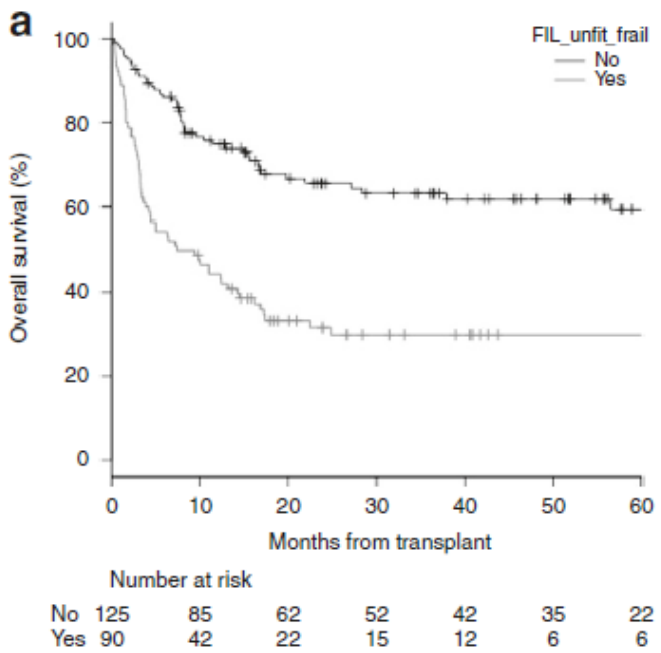
Bone Marrow Transplantation
https://doi.org/10.1038/s41409-020-0[illegible]2020

ARTICLE

Multidimensional geriatric assessment for elderly hematological patients (≥60 years) submitted to allogeneic stem cell transplantation. A French–Italian 10-year experience on 228 patients

Nicola Polverelli[1] · Paolo Tura[1,2] · Giorgia Battipaglia[2] · Michele Malagola[1] · Simona Bernardi[1,3] · Lisa Gandolfi[1] · Tatiana Zollner[1] · Camilla Zanaglio[1,3] · Mirko Farina[1] · Enrico Morello[1] · Alessandro Turra[1] · Mohamad Mohty[2] · Domenico Russo[1]





Comorbidities Predict Inferior Survival in Patients Receiving Chimeric Antigen Receptor T Cell Therapy for Diffuse Large B Cell Lymphoma: A Multicenter Analysis

TCT 2021 – Ohio - USA

Adam S. Kittai[1,*], Ying Huang[1], Max Gordon[2], Nathan Denlinger[1], Agrima Mian[3], Lindsey Fitzgerald[4], Jennifer Bishop[2], Sarah Nagle[2], Deborah M. Stephens[4], Samantha Jaglowski[1], Brian Hill[3], Alexey V. Danilov[5]

- 130 pts (commercial CART)
- 57 pts → CIRS ≥ 7
- 56 pts → ≥ CIRS 3

Table 4
Multivariable Analysis of CIRS ≥7 or CIRS-3+ Accounting for Patient Characteristics*

Characteristic	PFS		OS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
CIRS ≥7 or CIRS-3+	1.70 (0.94-3.06)	.08	2.39 (1.10-5.20)	.03
Age, 10-yr increase	.86 (.96-1.06)	.15	.82 (.65-1.04)	.10
Previous therapy, 1-unit increase	.87 (.71-1.06)	.17	.90 (.71-1.13)	.35
ECOG PS, 1-unit increase	1.43 (.99-2.05)	.05	1.63 (1.06-2.51)	.03
HGBCL*	.87 (.46-1.63)	.66	.97 (.45-2.09)	.94
Complex cytogenetics*	1.15 (.58-2.26)	.69	1.10 (.45-2.67)	.84
GCB vs non-GCB*	.99 (.59-1.66)	.96	1.08 (.58-2.02)	.81
Axi-cel vs tisa-cel	.60 (.34-1.05)	.07	.61 (.31-1.20)	.15

* From combining results across 50 imputed datasets.

CRITERI AIFA_DLBCL :

1.Linfoma recidivato/refrattario ad almeno 2 linee
2.ETA' (≥ 18y ≤ 75)
3.ECOG: 0-1
4.Test di gravidanza negativo
5.Aspettativa di vita ≥ 12 settimane
6.Paziente NON candidabile ad ASCT
7.Se precedente alloSCT: NO GVHD attiva, Tp immunosoppressiva interrotta da > 6 settimana; tempo >1 anno da trapianto;
8.Precedente terapia anti CD19 (allora bisogna dimostrare espressione CD19 alla biopsia)
9.NO Infezione attiva HBV, HCV, HIV
10.NO coinvolgimento SNC della Malattia o altri disturbi neurologici autoimmuni/infiammatori (es. Guillain-Barré, SLA) o altre (epilessia, demenza, malattia cerebrovascolari)
11.Storia di malattia autoimmune con danno d'organo
12.Adeguata funzionalità renale (clearance > 60 ml/min)
13.Adeguata funzionalità epatica (AST e ALT > 2.5 volte il limite, bilirubina >1.5 mg/dl, escluso Gilbert)
14.Adeguata funzionalità cardiaca (EF 50% o alterazioni significative ECG), NO storia di IMA, angioplastica, STENT nei precedenti 12 mesi
15.Adeguata funzionalità polmonare (sat 02 in aa >92%)
16.Adeguata riserva midollare (N>1000/mmc, Hb>8g/dl, Plts>75000, L>300 (Kymriah) o >100 (Yescarta)
17.NO Storia di TVP negli ultimi 6 mesi

CRITERI AIFA_MCL :

1.Linfoma recidivato/refrattario ad almeno 2 linee di cui una comprendente inibitori di BTK
2.ETA' (≥ 18y)
3.ECOG: 0-1
4.Test di gravidanza negativo
5.Aspettativa di vita ≥ 12 settimane
6.Paziente NON candidabile ad ASCT
7.Se precedente alloSCT: NO GVHD attiva, Tp immunosoppressiva interrotta da > 6 settimana; tempo >1 anno da trapianto;
8.Precedente terapia anti CD19 (allora bisogna dimostrare espressione CD19 alla biopsia)
9.NO Infezione attiva HBV, HCV, HIV
10.NO coinvolgimento SNC della Malattia o altri disturbi neurologici autoimmuni/infiammatori (es. Guillain-Barré, SLA) o altre (epilessia, demenza, malattia cerebrovascolari)
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14.Adeguata funzionalità cardiaca (EF 50% o alterazioni significative ECG), NO storia di IMA, angioplastica, STENT nei precedenti 12 mesi
15.Adeguata funzionalità polmonare (sat 02 in aa >92%)
16.Adeguata riserva midollare (N>1000/mmc, Hb>8g/dl, Plts>75000, Ly>100)
17.NO Storia di TVP negli ultimi 6 mesi

CRITERI AIFA_FL :

1.Linfoma follicolare recidivato/refrattario ad almeno 2 linee
2.ETA' (≥ 18y)
3.ECOG: 0-1
4.Test di gravidanza negativo
5.Aspettativa di vita ≥ 12 settimane
6.Se precedente alloSCT: NO GVHD attiva, Tp immunosoppressiva interrotta da > 6 settimana; tempo >1 anno da trapianto;
7.Precedente terapia anti CD19 (allora bisogna dimostrare espressione CD19 alla biopsia)
8.NO Infezione attiva HBV, HCV, HIV
9.NO coinvolgimento SNC della Malattia o altri disturbi neurologici autoimmuni/infiammatori (es. Guillain-Barré, SLA) o altre (epilessia, demenza, malattia cerebrovascolari)
10.Storia di malattia autoimmune con danno d'organo terminale o che abbiano richiesto terapia sistemica immunosoppressiva o «disease modifying» nei due anni precedenti
11.Adeguata funzionalità renale (clearance > 60 ml/min)
12.Adeguata funzionalità epatica (AST e ALT > 2.5 volte il limite, bilirubina >1.5 mg/dl, escluso Gilbert)
13.Adeguata funzionalità cardiaca (EF >45% o alterazioni significative ECG), NO storia di IMA, angioplastica, STENT nei precedenti 6 mesi
14.Adeguata funzionalità polmonare (sat 02 in aa >92%)
15.Adeguata riserva midollare (N>1000/mmc, Hb>8g/dl, Plts>50.000, Ly>300)

Drugs & Aging (2023) 40:685–689
https://doi.org/10.1007/s40266-023-01047-z

LEADING ARTICLE

Minnesota - USA

Age is No Barrier: CAR-T Therapy in Older Adults

Joseph E. Maakaron[1] · Basem M. William[2]

Table 1 Summary of published references outlining safety and efficacy in older adults.

	Age (total)	CRS	ICANS	CRS 3+	ICANS 3+	ORR	CR
BCMA [22]	< 70 (61)	78%	13%			89%	59% MRD (–)
San Francisco - USA	≥ 70 (22)	77%	9%			82%	50% MRD (–)
ZUMA-1 [16]	< 65 (44)	91%	71%	11%	39%		
MD Anderson - USA	≥ 65 (17)	83%	58%	18%	29%		
Israeli RWD [17]	< 70 (41)	69%	17%	7%	5%	78%	59%
Tel Aviv	≥ 70 (41)	69%	28%	9%	3%	63%	46%
GLA [20]	< 65 (216)			13%	9%	58%	31%
Heidelberg	≥ 65 (140)			10%	16%	69%	43%

Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma

Sattva S. Neelapu,[1] Caron A. Jacobson,[2] Olalekan O. Oluwole,[3] Javier Munoz,[4] Abhinav Deol,[5] David B. Miklos,[6] Nancy L. Bartlett,[7,8] Ira Braunschweig,[9] Yizhou Jiang,[10] Jenny J. Kim,[10] Lianqing Zheng,[10] John M. Rossi,[10] and Frederick L. Locke[11]

Median age 69 (65-76)

Efficacy outcomes	≥65 y (n = 24)	<65 y (n = 77)
Investigator-assessed ORR, n (%)	22 (92)	62 (81)
Complete response	18 (75)	41 (53)
Partial response	4 (17)	21 (27)
Ongoing response, n (%)ll	10 (42)	29 (38)
24-Mo overall survival rate, %	54	49

Blood 2020 (MD Anderson)

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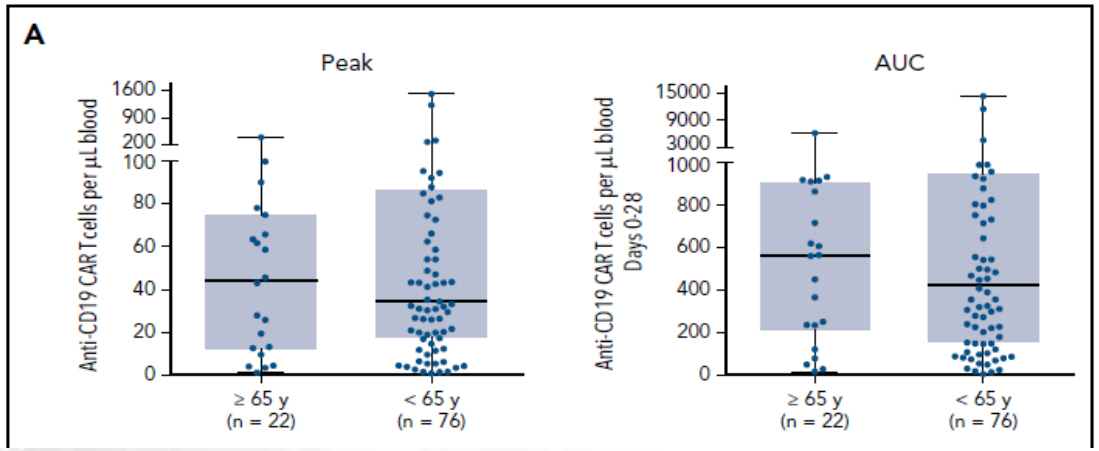
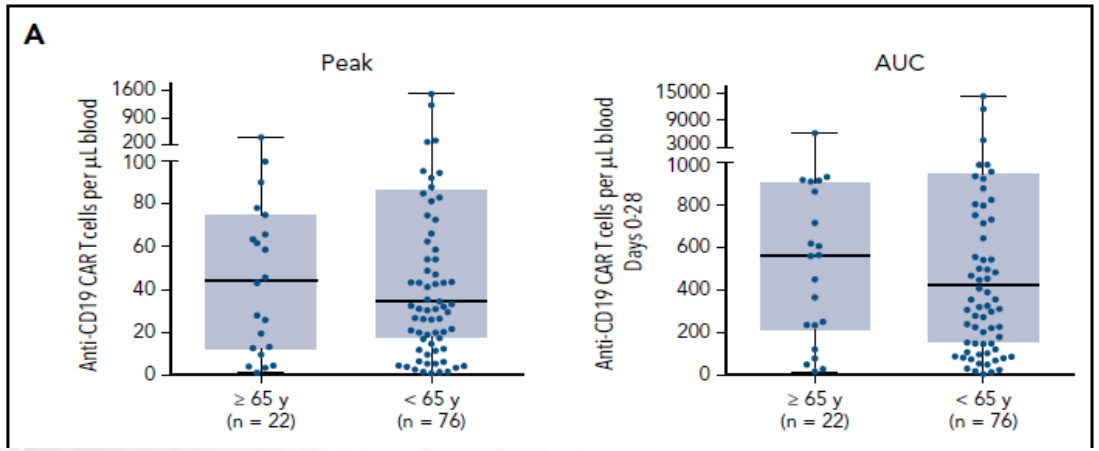
Ongoing response, n (%)‖	10 (42)	29 (38)
24-Mo overall survival rate, %	54	49

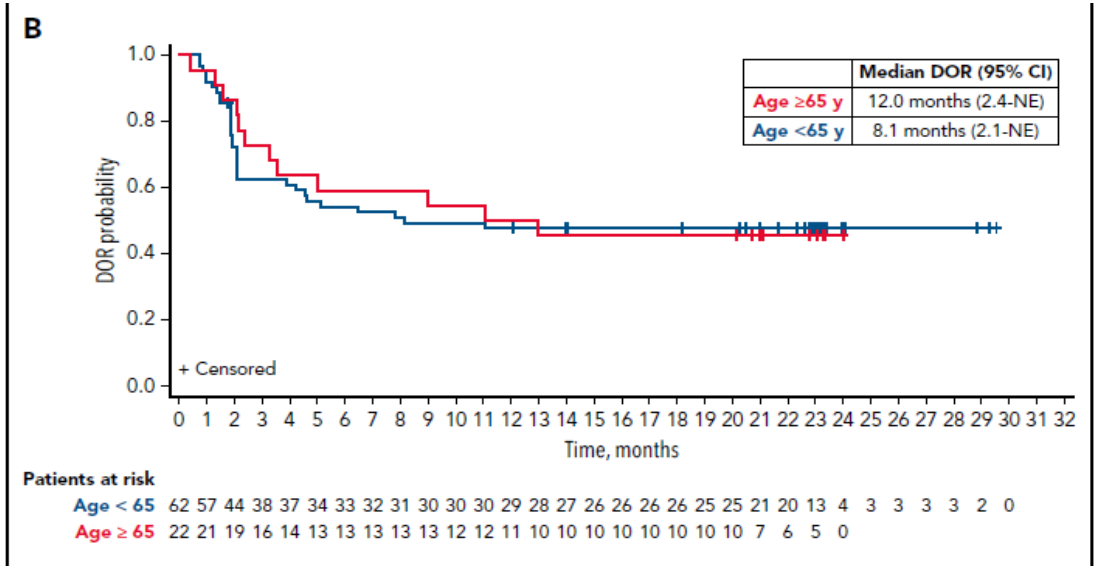
Characteristic	≥65 y (n = 27)	<65 y (n = 81)
Median age (range), y	69 (65-76)	55 (23-64)
Male, n (%)	22 (81)	51 (63)
ECOG performance status 1, n (%)	16 (59)	46 (57)
Disease stage III/IV, n (%)	22 (81)	68 (84)
IPI score 3-4, n (%)	19 (70)	29 (36)
≥3 Prior therapies, n (%)	18 (67)	58 (72)
Median tumor burden by SPD (range), mm^2	3790 (600-16764)	3574 (171-23297)
Disease type, n (%)		
DLBCL	20 (74)	64 (79)
PMBCL	0	8 (10)
TFL	7 (26)	9 (11)
Prior ASCT, n (%)	5 (19)	24 (30)
Refractory subgroup before enrollment, n (%)		
Primary refractory	1 (4)	2 (2)
Refractory to second-line or later therapy	21 (78)	59 (73)
Relapse after ASCT	5 (19)	20 (25)
Grade ≥3 AEs*		
Any grade ≥3 AE, n (%)	27 (100)	79 (98)
Neutropenia†	20 (74)	66 (81)
Anemia	13 (48)	36 (44)
Thrombocytopenia‡	12 (44)	31 (38)
Decreased white blood cell count	9 (33)	22 (27)
Encephalopathy	8 (30)	17 (21)
Lymphocyte count decreased	8 (30)	14 (17)
Grade ≥3 infection		
Infection, n (%)	5 (19)	25 (31)
Grade ≥3 CRS§		
Any grade ≥3 CRS, n (%)	2 (7)	10 (12)
Pyrexia	3 (12)	9 (12)
Hypotension	2 (8)	8 (11)
Hypoxia	3 (12)	6 (7)
Grade ≥3 neurologic event§		
Any grade ≥3 neurologic event, n (%)	12 (44)	23 (28)
Encephalopathy	8 (30)	17 (21)
Confusional state	2 (7)	8 (10)
Aphasia	0	8 (10)
Agitation	3 (11)	2 (2)
Delirium	3 (11)	0

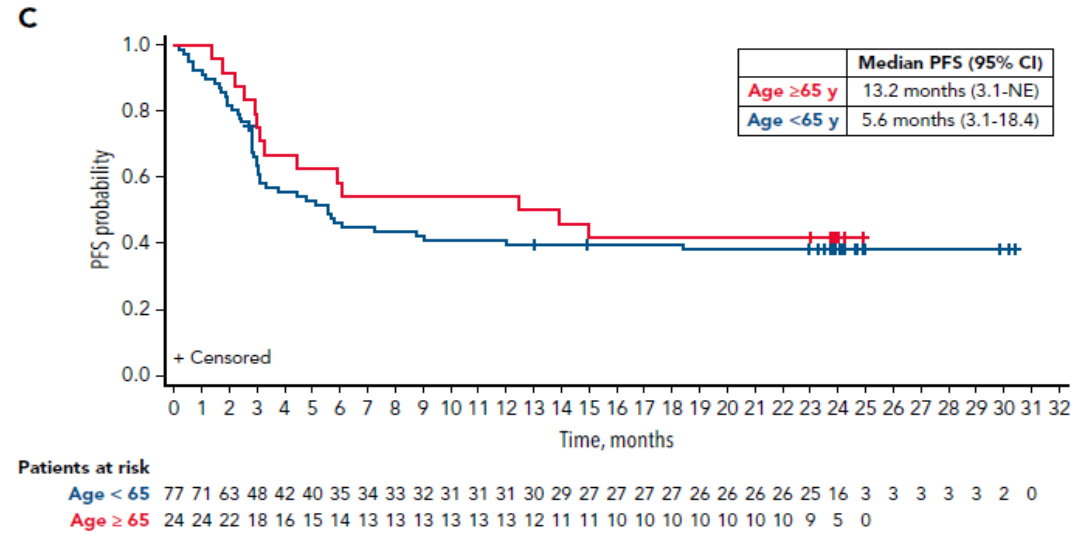
Blood 2020 (MD Anderson)



Neelapu, Blood 2020







Neelapu, Blood 2020

Age defining immune effector cell associated neurotoxicity syndromes in aggressive large B cell lymphoma patients treated with axicabtagene ciloleucel

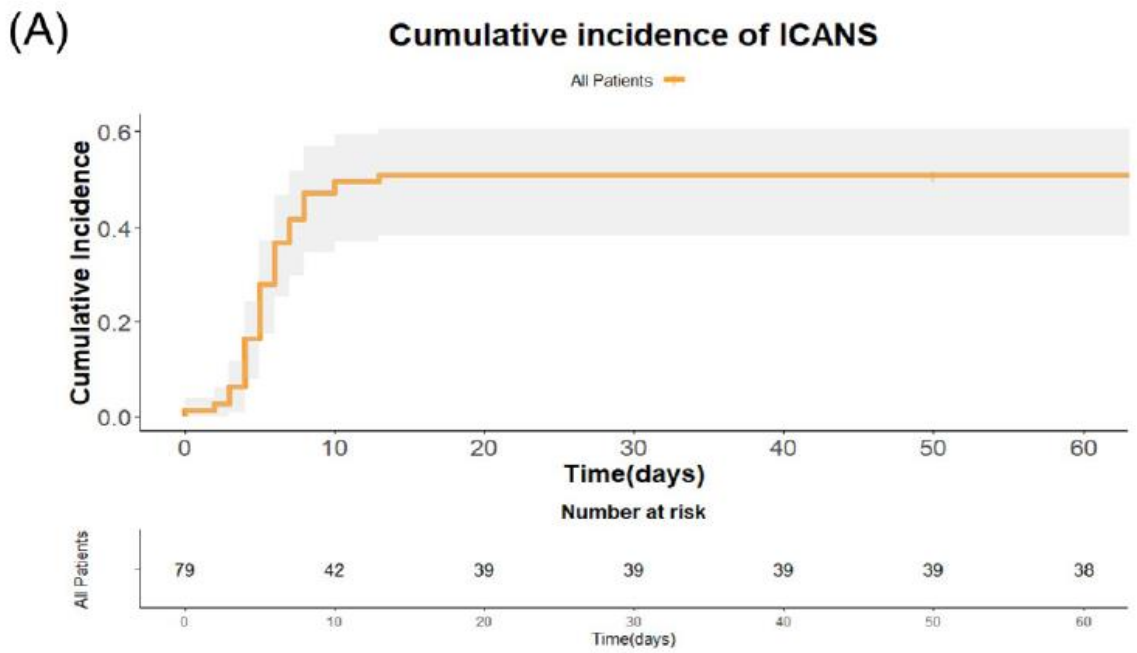
- 47 pts < 60 yrs
- 32 pts > 60 yrs
- AXICEL (2016-2020)

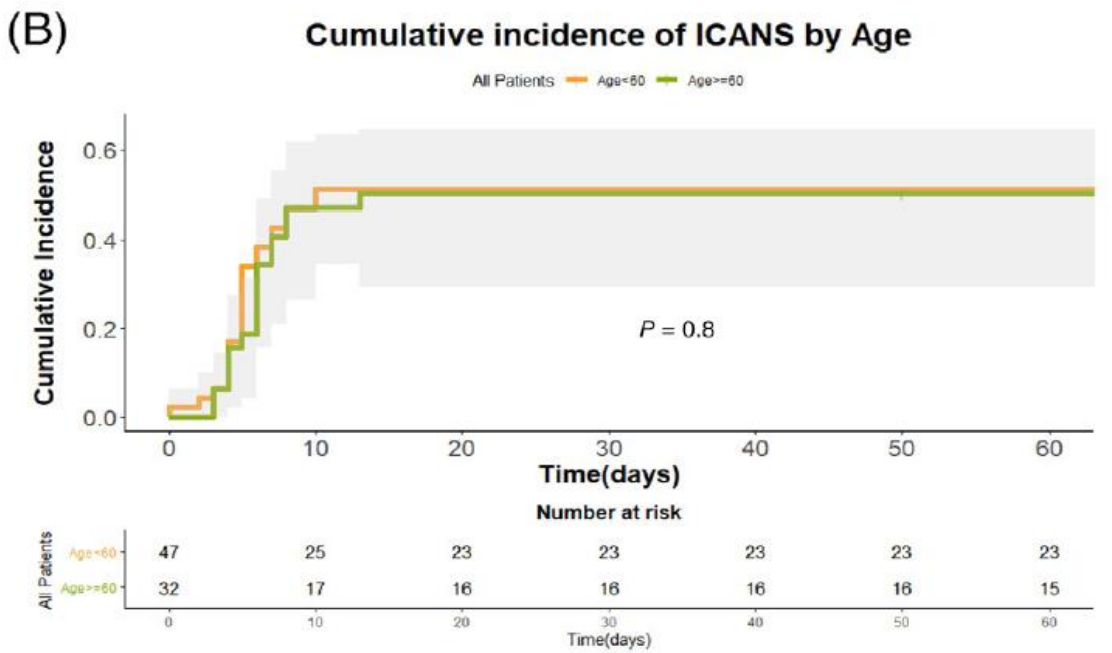
→ Median age 58 (27-76)

40 pts developed ICANS (51,3%)

↓

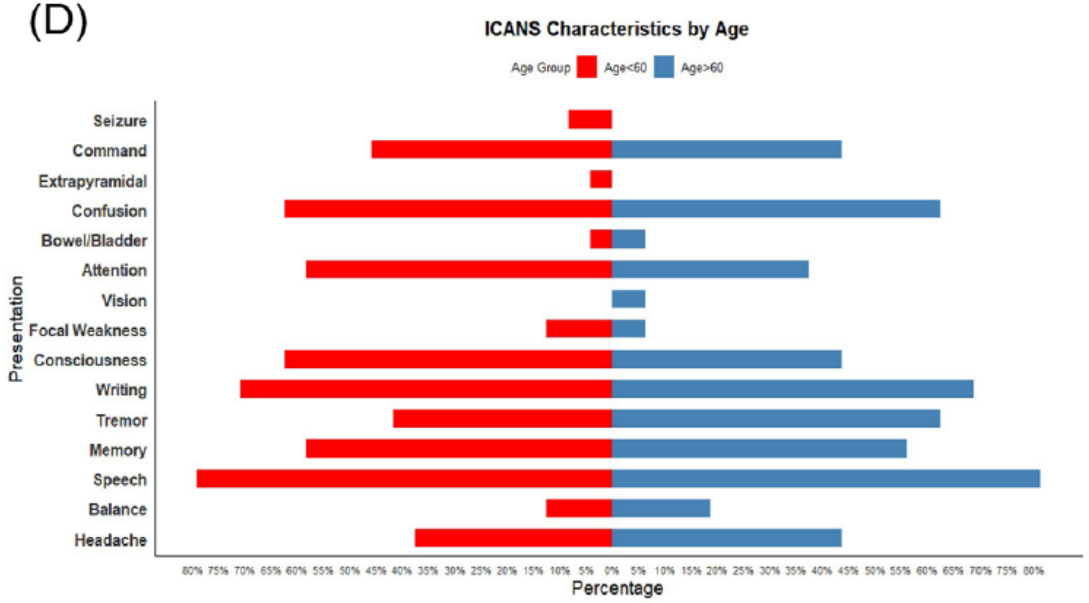
50% older vs 52% younger





Wudhikarn et al, AJH 2020 (Mayo)

(D)



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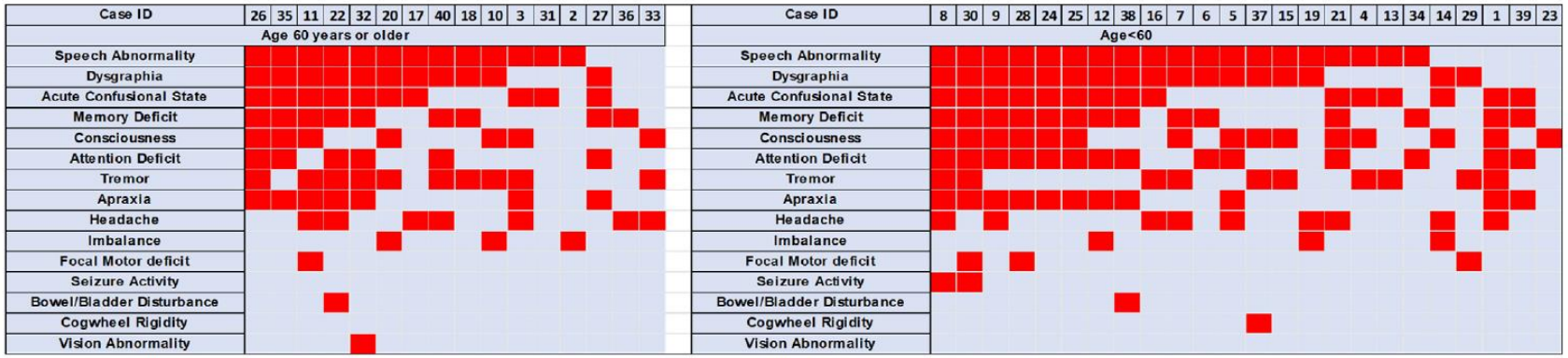

Wudhikarn et al, AJH 2020 (Mayo)

Real-world adverse events associated with CAR T-cell therapy among adults age ≥ 65 years

Marjorie E. Zettler, Bruce A. Feinberg, Eli G. Phillips Jr, Andrew J. Klink, Sonam Mehta, Ajeet Gajra *

Cardinal Health Specialty Solutions, Cardinal Health, Dublin, OH, United States of America

J Ger Oncol 2020

- 804 FDA reports on AEs for Tisacel/Axicel up to 2019

WARNING

- only reported Aes
- No grading according to CTCAE

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Table 1
Characteristics of post-marketing adverse event cases associated with CAR T-cell therapy, by age.

Variable (n, %)	Age < 65 years (n = 471)	Age ≥ 65 years (n = 333)	P value
Therapy			
Axi-cel	392 (83%)	245 (74%)	<0.01
Tis-cel	79 (17%)	88 (26%)	
Sex			
Female	181 (38%)	121 (36%)	0.55
Male	274 (58%)	202 (61%)	
Not specified	16 (3%)	10 (3%)	
Outcome			
Death	62 (13%)	61 (18%)	<0.05
Disabled	9 (2%)	2 (1%)	0.12
Life-threatening	39 (8%)	22 (7%)	0.38
Hospitalization	181 (38%)	96 (29%)	<0.01
Reaction term			
Cytokine release syndrome	302 (64%)	197 (59%)	0.15
CAR T-cell-related encephalopathy syndrome	20 (4%)	25 (8%)	<0.01
Neurotoxicity	171 (36%)	142 (43%)	0.07
Pyrexia	156 (33%)	75 (23%)	<0.01
Hypotension	63 (13%)	41 (12%)	0.66
Hypoxia	28 (6%)	25 (8%)	0.38
Tachycardia	48 (10%)	17 (5%)	<0.01
Atrial fibrillation	10 (2%)	15 (5%)	0.06
Febrile neutropenia	18 (4%)	11 (3%)	0.70
Pneumonia	9 (2%)	10 (3%)	0.32
Sepsis	5 (1%)	11 (3%)	0.02
Thrombocytopenia	20 (4%)	5 (2%)	0.03
C-reactive protein increased	13 (3%)	5 (2%)	0.23
Serum ferritin increased	11 (2%)	5 (2%)	0.40
Hemophagocytic lymphohistiocytosis	9 (2%)	10 (3%)	0.32
Hypogammaglobulinemia	22 (5%)	25 (8%)	0.09
Infusion related reactions	6 (1%)	2 (1%)	0.34
Hemoglobin decreased	31 (7%)	44 (13%)	<0.01
Hematocrit decreased	29 (6%)	41 (12%)	<0.01
Blood fibrinogen decreased	1 (0.2%)	5 (2%)	0.04
Blood creatinine increased	1 (0.2%)	5 (2%)	0.04
Rash	0 (0%)	5 (2%)	<0.01

Impact and safety of chimeric antigen receptor T-cell therapy in older, vulnerable patients with relapsed/refractory large B-cell lymphoma

Richard J. Lin,[1,2] Stephanie M. Lobaugh,[3] Martina Pennisi,[1] Hei Ton Chan,[1,] Yakup Batlevi,[1] Josel D. Ruiz,[1] Theresa A. Elko,[1] Molly A. Maloy,[1] Connie L. Batlevi,[2,4] Parastoo B. Dahi,[1,2] Sergio A. Giralt,[1,2] Paul A. Hamlin,[2,4] Elena Mead,[2,5] Ariela Noy,[2,4] M. Lia Palomba,[2,4] Bianca D. Santomasso,[2,6] Craig S. Sauter,[1,2] Michael Scordo,[1,2] Gunjan L. Shah,[1,2] Beatriz Korc-Grodzicki,[2,7] Soo Jung Kim,[7] Mari Lynne Silverberg,[1] Chelsea A. Brooklyn,[1] Sean M. Devlin[3] and Miguel-Angel Perales[1,2]*

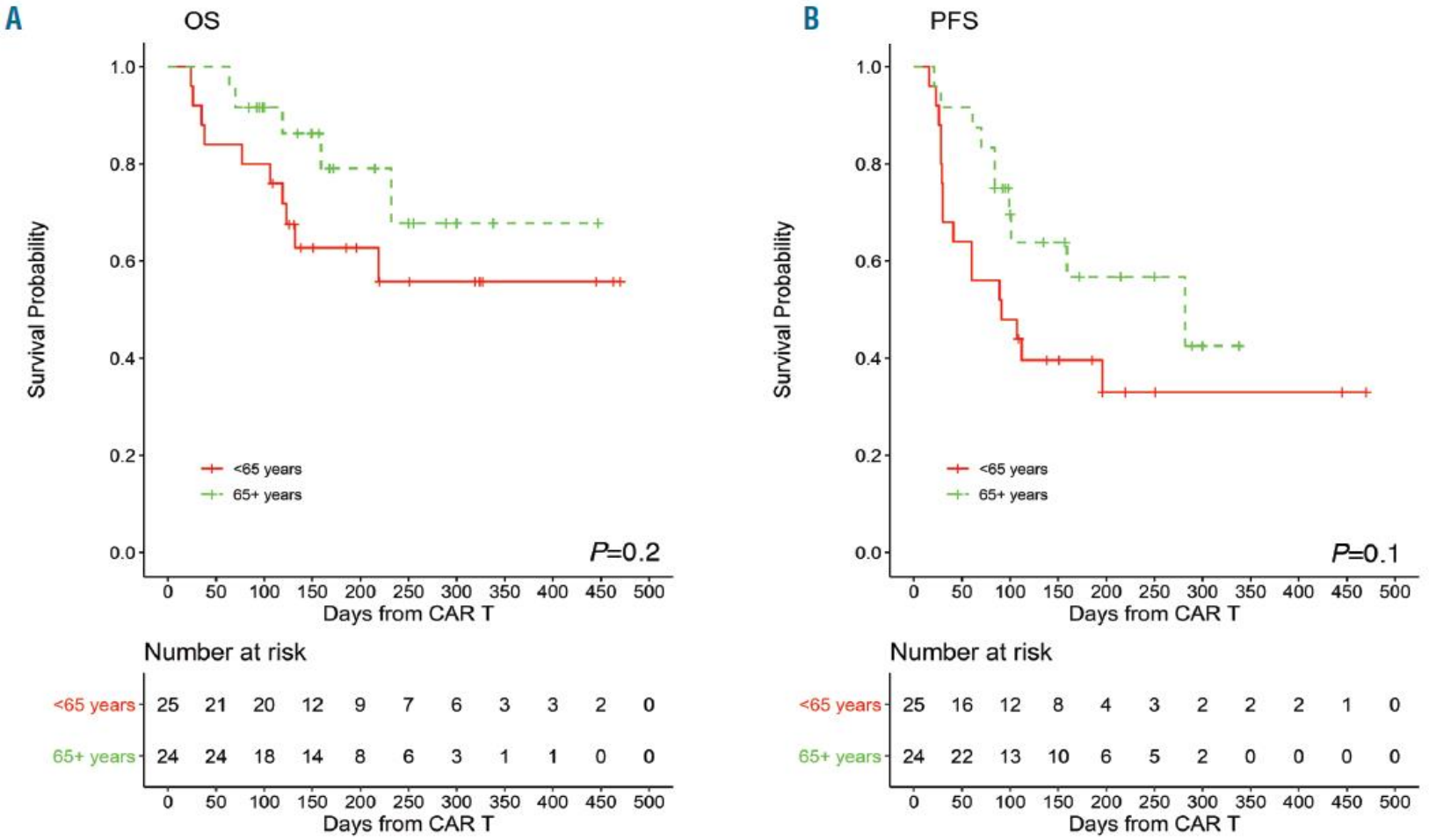
Hematol 2021 (MSK)

- 24 DLBCL ≥ 65 yrs
- 25 pts < 65 yrs

Tisacel/Axicel (2018 - 2019)

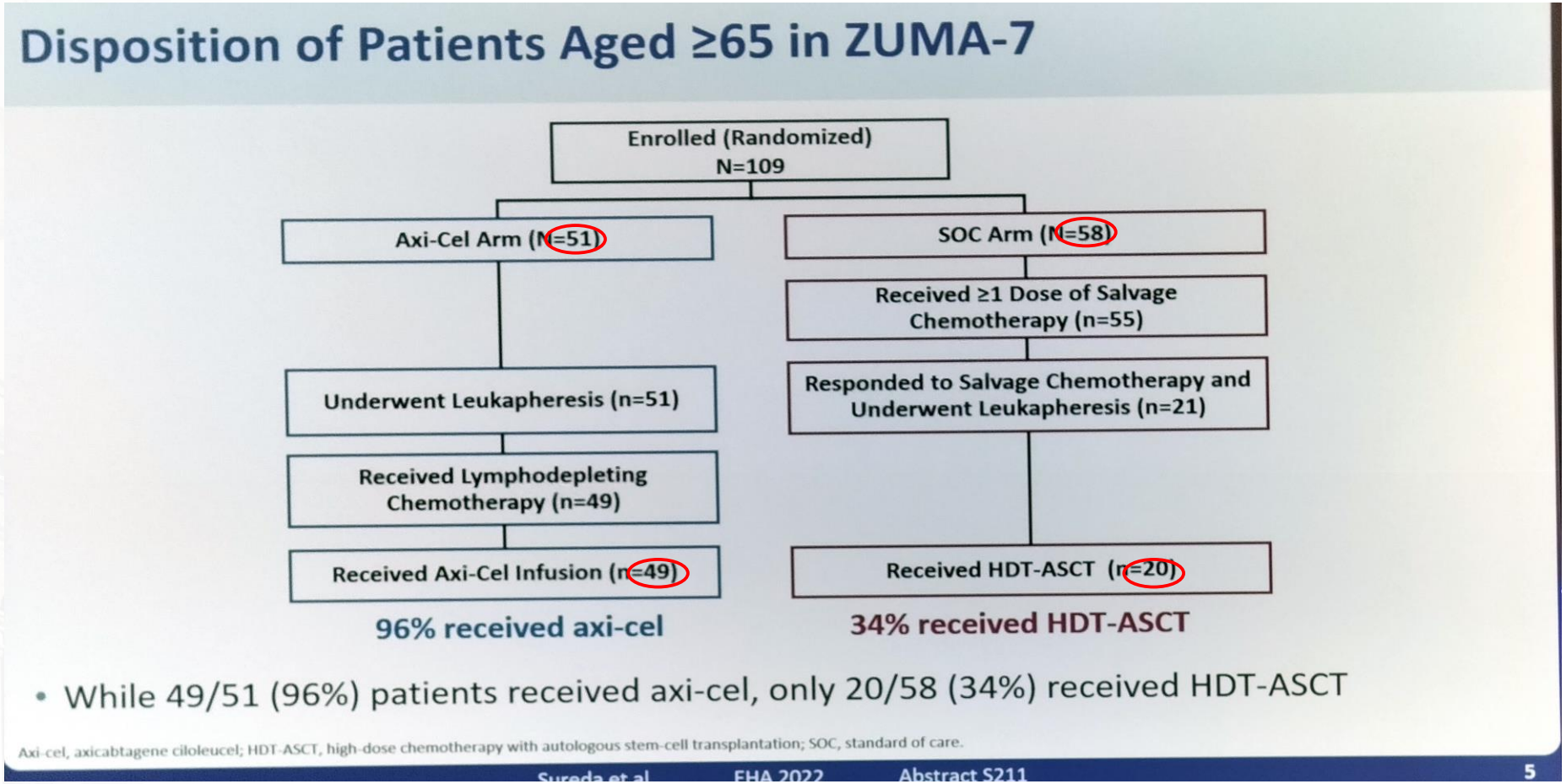
Table 1. Characteristics and toxicities of lymphoma patients treated with chimeric antigen receptor T-cell therapy.

	Younger patients (<65 years, n=25)	Older patients (≥65 years, n=24)	P
Age in years, median (range)	56 (20 – 64)	72 (67 – 86)	
Female gender, n (%)	2 (8)	13 (54)	<0.001
CAR T, n (%)			0.11
Axicabtagene ciloleucel	21 (84)	15 (63)	
Tisagenlecleucel	4 (16)	9 (37)	
Advanced stage at CAR T, n (%)	14 (56)	14 (58)	0.78
Prior lines, median (range)	3 (2 – 9)	3 (2 – 9)	0.81
Baseline LDH, median (range)	298 (128 – 3722)	240 (146 – 1409)	0.12
Time to CAR T, median (range)	75 days (43 – 175)	92 days (33 – 272)	0.54
DCI/CCI, median, (range)	2 (2 – 4)	3 (2 – 7)	0.04
KPS <80, n (%)	7 (28)	9 (38)	0.55
Functional limitation, n (%)	5 (20)	8 (33)	0.35
Cognitive impairment, n (%)	8 (32)	11 (46)	0.76
Prior fall, n (%)	7 (28)	7 (29)	>0.99
Weight loss, n (%)	8 (32)	5 (21)	0.52
ICU admission, n (%)	9 (36)	6 (25)	0.54
CRS, n (%)			0.61
No CRS	7 (28)	4 (17)	
Grade 1-2 CRS	15 (60)	18 (75)	
Grade >2 CRS	3 (12)	2 (8)	
ICANS, n (%)			0.60
No ICANS	16 (60)	11 (46)	
Grade 1-2 ICANS	6 (24)	7 (29)	
Grade >2 ICANS	4 (16)	6 (25)	
Infections, ≥G3, n (%)	15 (60)	10 (42)	0.26
Prolonged cytopenia, n (%)	16 (64)	10 (42)	0.16
Metabolic toxicities, ≥ grade 3, n (%)	3 (12)	8 (33)	0.10
Other toxicities, ≥ grade 3, n (%)	9 (36)	12 (50)	0.39



Lin, Hematol 2021

SUBANALYSIS OF PATIENTS > 65 YEARS (ZUMA-7)



Sureda A, EHA 2022 - ORAL

Baseline Characteristics for Patients Aged ≥65 Years

Characteristic	Axi-Cel N=51	SOC N=58	Overall N=109
Median age (range), years	70 (65-80)	69 (65-81)	69 (65-81)
Sex, male, n (%)	28 (55)	39 (67)	67 (61)
Disease stage III-IV, n (%)	42 (82)	44 (76)	86 (79)
sAAIPI of 2-3[a], n (%)	27 (53)	18 (31)	45 (41)
Response to 1L therapy[a], n (%)			
Primary refractory	37 (73)	39 (67)	76 (70)
Relapse ≤12 months of 1L therapy	14 (27)	19 (33)	33 (30)
Disease type per investigator, n (%)			
DLBCL not specified	27 (53)	40 (69)	67 (61)
T-cell/histiocyte-rich LBCL	0 (0)	1 (2)	1 (1)
Large cell transformation from follicular lymphoma	7 (14)	9 (16)	16 (15)
HGBL with/without *MYC* and *BCL2* and/or *BCL6* rearrangement	17 (33)	8 (14)	25 (23)
Elevated LDH level, n (%)[b]	31 (61)	24 (41)	55 (50)

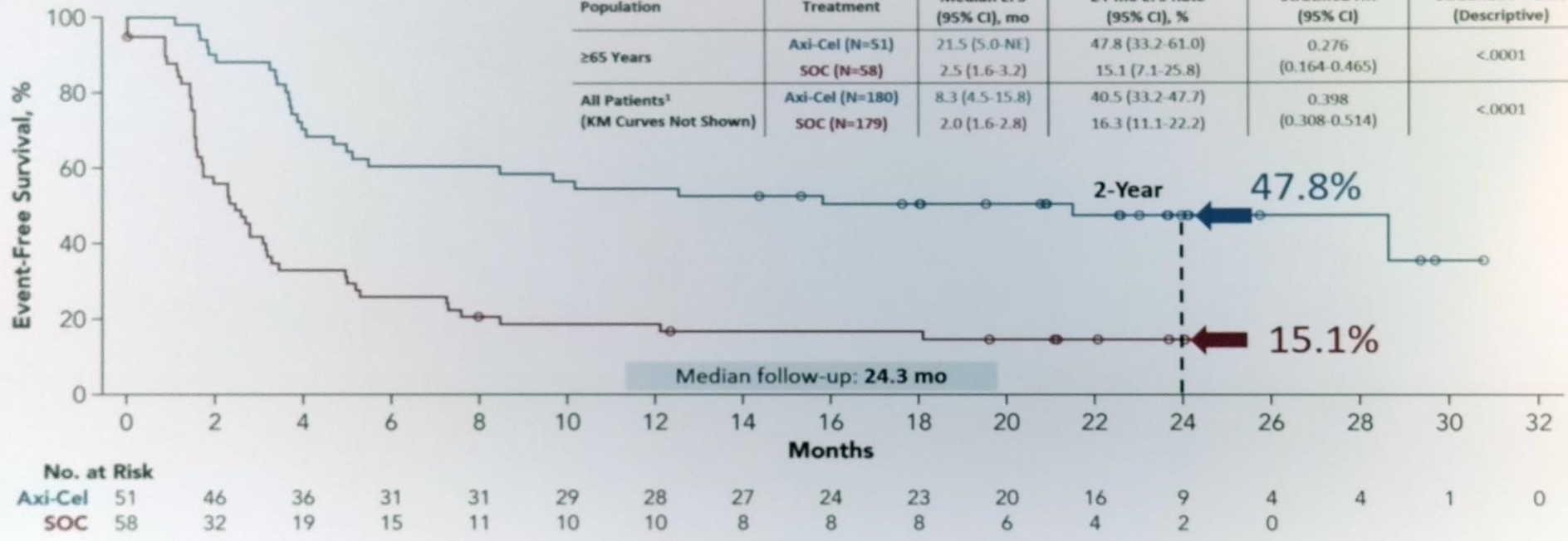
- Compared with SOC patients, more axi-cel patients had high-risk features at baseline

As reported by investigator at the time of randomization via Interactive Voice/Web Response System. [b] LDH level greater than upper limit of normal per local laboratory reference range.
L, first-line; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; sAAIPI, second-line age-adjusted
nternational Prognostic Index; SOC, standard of care.

Sureda A, EHA 2022 - ORAL

Primary Endpoint: Event-Free Survival per Blinded Central Review in Patients Aged ≥65 Years

Population	Treatment	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %	Stratified HR (95% CI)	Stratified *P* Value (Descriptive)
≥65 Years	Axi-Cel (N=51)	21.5 (5.0-NE)	47.8 (33.2-61.0)	0.276 (0.164-0.465)	<.0001
	SOC (N=58)	2.5 (1.6-3.2)	15.1 (7.1-25.8)		
All Patients[1] (KM Curves Not Shown)	Axi-Cel (N=180)	8.3 (4.5-15.8)	40.5 (33.2-47.7)	0.398 (0.308-0.514)	<.0001
	SOC (N=179)	2.0 (1.6-2.8)	16.3 (11.1-22.2)		

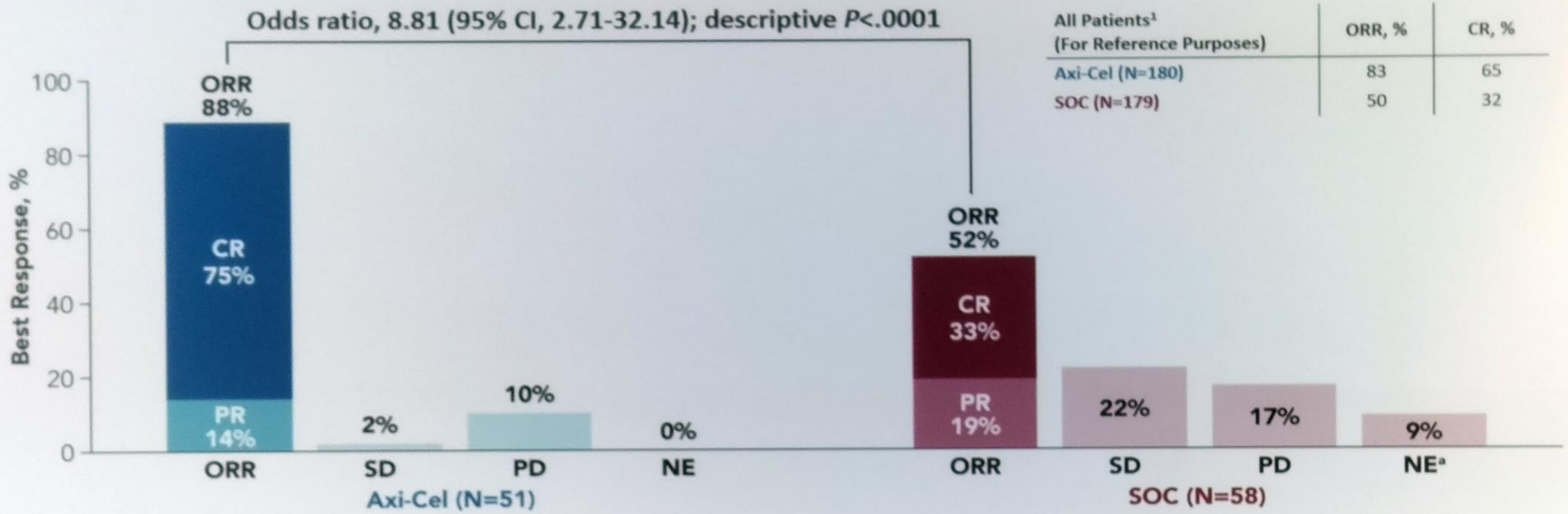


- Kaplan-Meier estimates of the 24-month EFS rates were higher for axi-cel than for SOC (47.8% vs 15.1%, respectively)

1. Locke FL, et al. *N Engl J Med*. 2022;386:640-654.
Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; HR, hazard ratio; KM, Kaplan-Meier; mo, month; NE, not evaluable; SOC, standard of care.

Sureda A, EHA 2022 - ORAL

Objective Response Rate in Patients Aged ≥65 Years



All Patients[1] (For Reference Purposes)	ORR, %	CR, %
Axi-Cel (N=180)	83	65
SOC (N=179)	50	32

- ORR was higher with axi-cel versus SOC (descriptive *P*<.0001), and CR rate of the axi-cel arm was over double that of the SOC arm (75% vs 33%, respectively)

[a] NE: In the SOC arm, there was 1 patient with undefined disease and 4 who did not have response assessments done.

1. Locke FL, et al. *N Engl J Med*. 2022;386:640-654.

Axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care.

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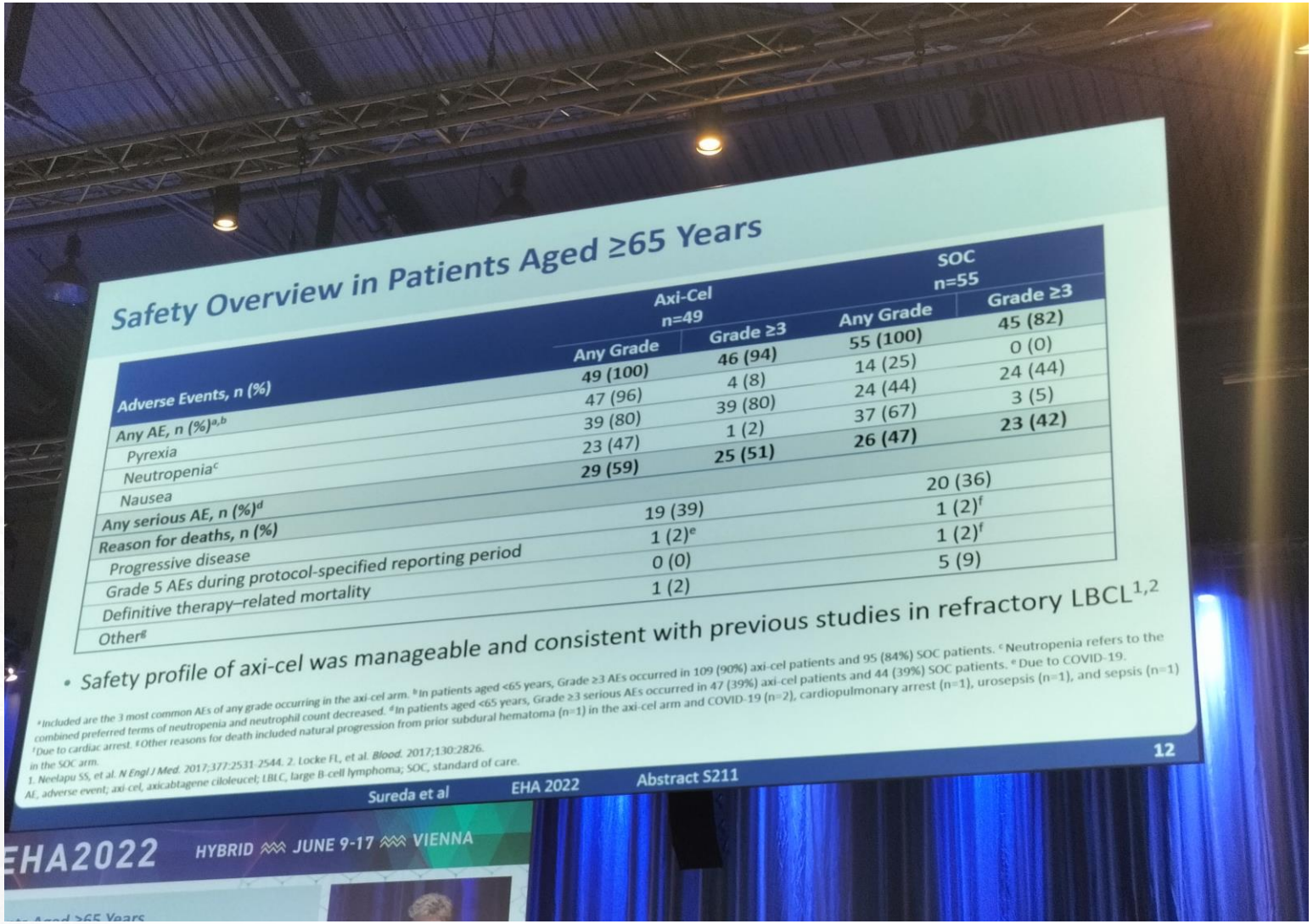

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CRS and Neurologic Events in Patients Aged ≥65 Years

	Axi-Cel n=49		SOC n=55	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS, n (%)[a,b]	48 (98)	4 (8)	-	-
CRS management,[c] n (%)				
Tocilizumab	33 (67)		-	
Corticosteroids	14 (29)		-	
Vasopressors	3 (6)		-	
Median time to onset, days	3		-	
Median duration of events, days	8		-	
Neurologic event, n (%)[d,e]	32 (65)	13 (27)	14 (25)	1 (2)
Management with corticosteroids,[c] n (%)	22 (45)		0 (0)	
Median time to onset, days	7		26	
Median duration of events, days	9		39	

- There were slightly higher rates of CRS and neurologic events, including Grade ≥3, in patients aged ≥65 years compared with the overall ZUMA-7 population[1]

[a] CRS was graded according to Lee et al.[2] [b] In patients aged <65 years, Grade ≥3 CRS occurred in 7 (6%) axi-cel patients. [c] Toxicity management followed ZUMA-1 pivotal cohorts. [d] Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.[3] [e] In patients <65 years, Grade ≥3 neurologic events occurred in 23 (19%) axi-cel patients and 0 (0%) SOC patients.

1. Locke FL, et al. *N Engl J Med*. 2022;386:640-654. 2. Lee DW, et al. *Blood*. 2014;124:188-195. 3. Topp MS, et al. *Lancet Oncol*. 2015;16:57-66.

Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; SOC, standard of care.

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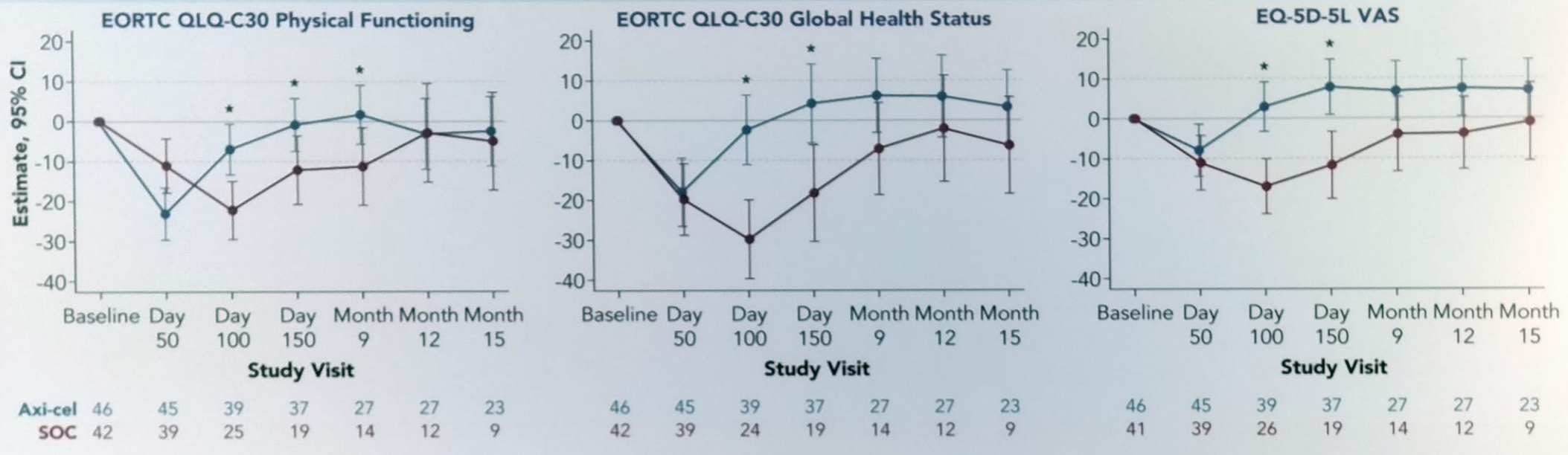
Changes From Baseline for Prespecified PRO Endpoints Were Clinically Meaningful at Day 100 in Favor of Axi-Cel in Patients ≥65 Years



- In the QoL analysis set comprising 46 axi-cel and 42 SOC patients, there was a clinically meaningful difference in mean change of scores from baseline at Day 100 in favor of axi-cel for EORTC QLQ-C30 Global Health (descriptive *P*<.0001), Physical Functioning (descriptive *P*=.0019), and EQ-5D-5L visual analogue scale (descriptive *P*<.0001)
- For all 3 domains, scores favored (descriptive *P*<.05) axi-cel over SOC at Day 150

*Descriptive *P*<.05.

Axi-cel, axicabtagene ciloleucel; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL five-dimension questionnaire using a five-level scale; PRO, patient-reported outcomes; QLQ-C30, Quality of Life Questionnaire-Core 30; SOC, standard of care; VAS, visual analogue scale.

Sureda et al EHA 2022 Abstract S211 14

Sureda A, EHA 2022 - ORAL

CORRESPONDENCE OPEN

Check for updates

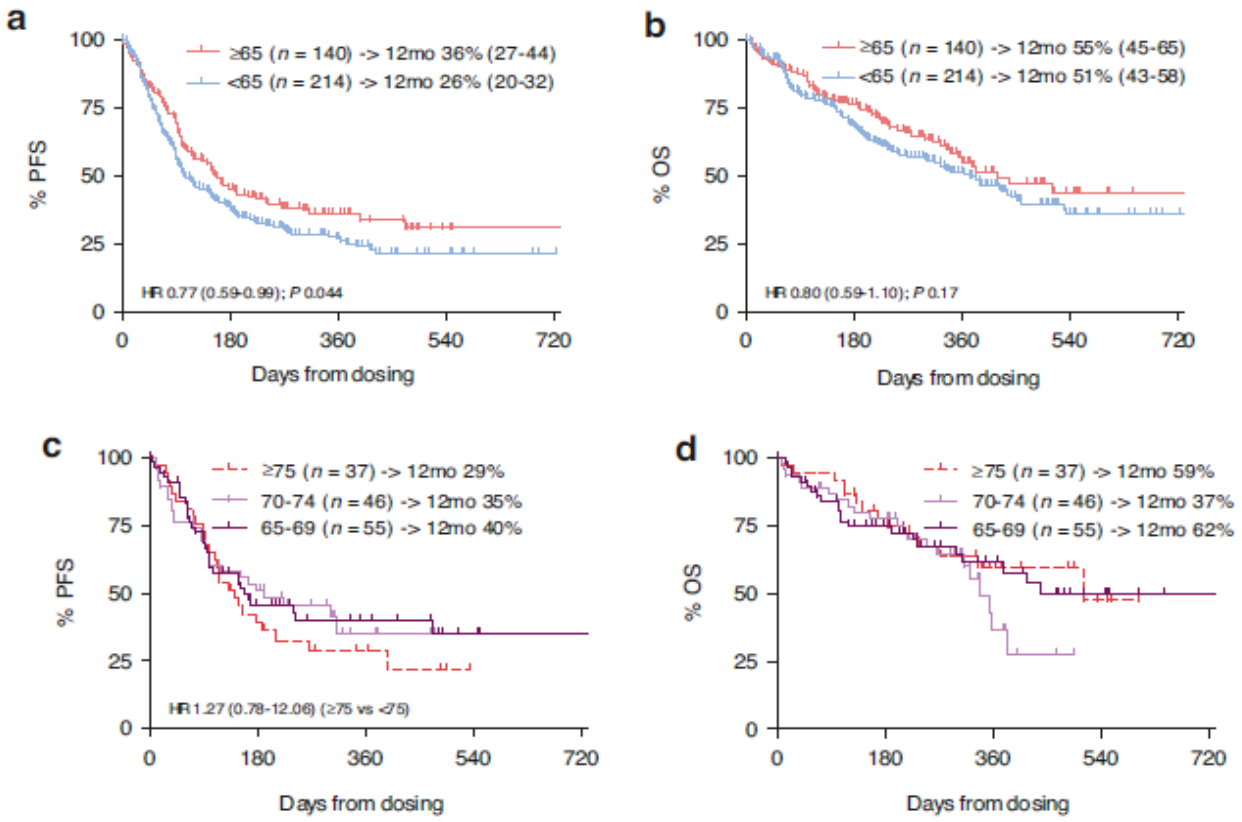
Impact of age on outcome of CAR-T cell therapies for large B-cell lymphoma: the GLA/DRST experience

Dreger P et a, BMT 2023 (Heidelberg)

- 356 CART → 173 pts AXI
  183 pts TISA
  140 ≥ 65 yrs

Table S2: Outcomes by age

	≥65 years (n=140)	<65 years (n=216)	P value*
Outcomes			
Neurotoxicity ≥3	21/131 (16%)	18/204 (9%)	0.055
Axi-cel	14/62 (23%)	13/105 (12%)	0.13
Tisa-cel	7/69 (10%)	5/98 (5%)	0.24
CRS ≥3	14/136 (10%)	28/210 (13%)	0.50
Axi-cel	5/63 (8%)	14/109 (13%)	
Tisa-cel	9/73 (12%)	14/101 (14%)	
Hospitalization days (median, range)	22 (8-95)	21 (9-128)	0.48
ORR	97 (69%)	125 (58%)	0.043
Axi-cel	54 (89%)	73 (70%)	0.0073
Tisa-cel	43 (61%)	52 (50%)	0.16
CR	60 (43%)	66 (31%)	0.023
Axi-cel	34 (56%)	36 (35%)	0.0094
Tisa-cel	26 (37%)	30 (29%)	0.33



CORRESPONDENCE OPEN

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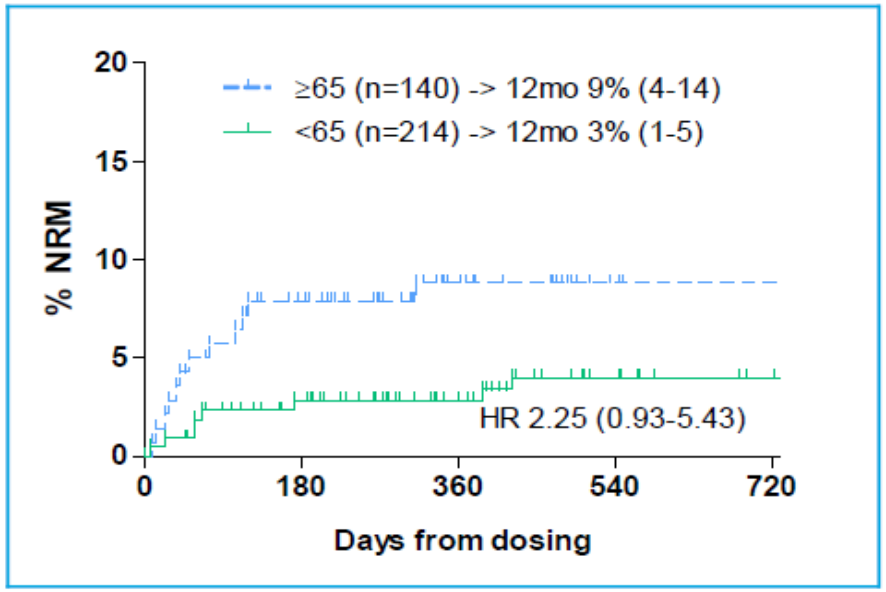
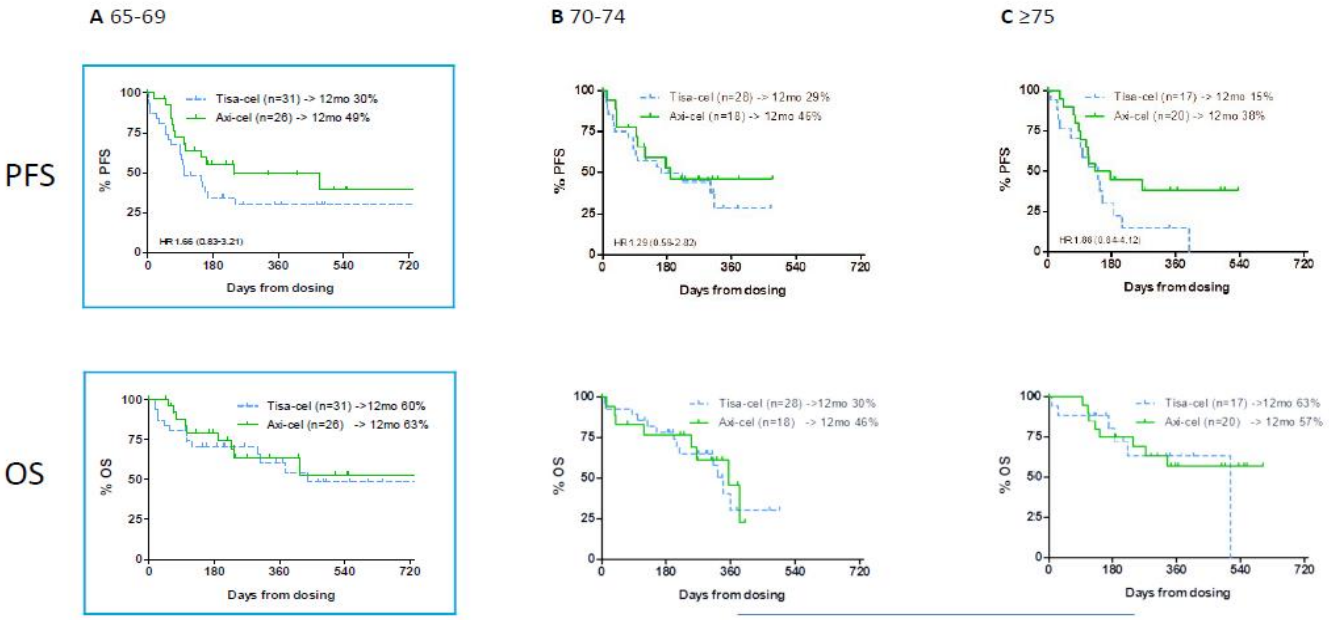
Dreger P et a, BMT 2023 (Heidelberg)

All





Toxicity and efficacy of chimeric antigen receptor T-cell therapy in patients with diffuse large B-cell lymphoma above the age of 70 years compared to younger patients – a matched control multicenter cohort study

Ron Ram,[1,2] Sigal Grisariu,[3] Liat Shargian-Alon,[2,4] Odelia Amit,[1,2] Yaeli Bar-On,[1,2] Polina Stepensky,[3] Moshe Yeshurun,[2,4] Batia Avni,[3] David Hagin,[2,5] Chava Perry,[1,2] Ronit Gurion,[2,4] Nadav Sarid,[1,2] Yair Herishanu,[1,2] Ronit Gold,[1] Chen Glait-Santar,[1,2] Sigi Kay[1,2] and Irit Avivi[1,2]

Hematol 2023 (Tel Aviv)

- 82 NHL → 41 pts ≥ 70 yrs
  41 pts < 70 yrs

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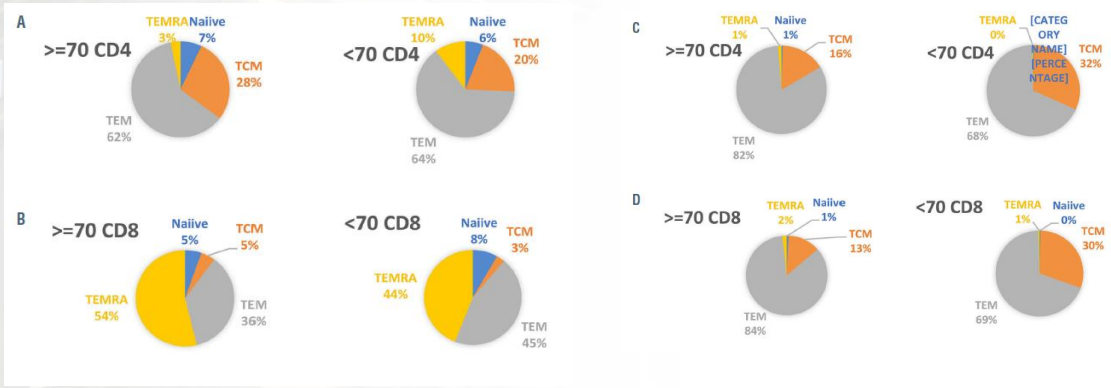

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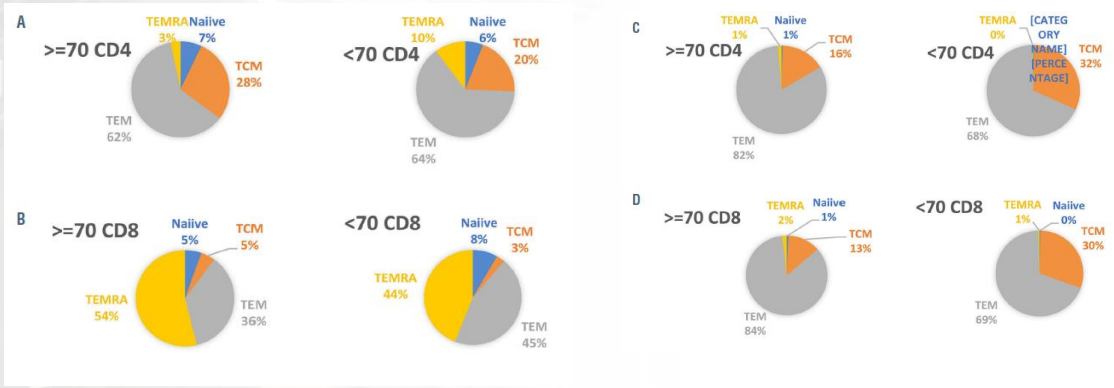

Table 1. **Characteristics of patients**

Domain	Study Cohort (n=41)	Control (n=41)	*P*-value
Age in years, mean (± S.D.)	76.2 (4.4)	55.4 (15)	<0.001
Sex – Female	24, 61%	23, 54%	0.674
Product			0.775
Tisa-cel	33 (80.5%)	34 (82.9%)	
Axi-cel	8 (19.5%)	7 (17.1%)	
Transformed indolent lymphoma	11 (26.8%)	8 (19.5%)	0.432
Non-GCB subtype	25 (61%)	21 (51%)	0.29
ECOG performance status			0.187
0	3 (7.3%)	1 (2.4%)	
1	13 (31.7%)	15 (36.6%)	
2	20 (48.8%)	9 (22%)	
3	5 (12.2%)	16 (39%)	
Specific comorbidities			
Ischemic heart disease	10 (24%)	7 (17%)	0.41
Hypertension	14 (34%)	8 (20%)	0.14
Diabetes mellitus	7 (17%)	9 (22%)	0.58
Smoker	3 (7.3%)	4 (9.7%)	0.69
Chronic kidney disease	4 (9.7%)	2 (4.9%)	0.39
Cerebrovascular attack	3 (7.3%)	1 (2.4%)	0.61
Dementia	1 (2.4%)	1(2.4%)	0.61
N lines prior to CAR-T			0.453
2	22 (53.7%)	20 (48.8%)	
3	13 (31.7%)	11 (26.8%)	
4	5 (12.2%)	4 (9.8%)	
5	0 (0%)	2 (4.9%)	
>5	1 (2.4%)	4 (9.8%)	
Previous autologous transplantation	3 (7.3%)	14 (34.1%)	0.003
Days from referring to collection, mean (±S.D.)	18.8 (11.3)	15.4 (8.9)	0.453
N cycles of collection, mean (±S.D.)	2.46 (0.64)	2.4 (0.75)	0.696
Collection efficiency, mean (±S.D.)	52.9 (15)	55.3 (13)	0.530
Days from collection to pick-up	4.1 (3.6)	5.5 (4.5)	0.232
Bridging to CAR-T infusion			0.417
None/steroids only	7 (17.1%)	12 (29%)	
Chemotherapy ± radiation	29 (70.7%)	23 (56%)	
Radiation	3 (7.3%)	5 (12.2%)	
Novel agents*	2 (4.9%)	1 (2.8%)	
Status prior to CAR-T infusion			**0.017**
Complete remission	7 (8.5%)	6 (14.6%)	
Partial remission	30 (34.1%)	6 (14.6%)	
Stable disease	3 (7.3%)	11 (26.8%)	
Progressive disease	20 (48.8%)	15 (36.6%)	
Not evaluated	3 (7.3%)	3 (7.3%)	
Days from apheresis to CAR-T infusion, mean (±S.D.)	36.5 (12)	38.7 (12)	0.453
High LDH prior to CAR-T infusion	18 (43.9%)	18 (43.9%)	1
LDH (in patients with elevated values) - median, range (U/L)	548 (380-2,041)	575 (382-1,891)	0.65

GCB: germinal center B cell; LDH: lactate dehydrogenase; S.D.: standard deviation.

Table 2. Toxicity and response to CAR-T cell therapy

Domain	Study Cohort (n=41)	Control (n=41)	*P*-value
Cytokine release syndrome			0.881
0	13 (31.7%)	13 (31.7%)	
1	9 (22%)	7 (17.1%)	
2	15 (36.6%)	18 (43.9%)	
3	4 (9.8%)	3 (7.3%)	
4	0 (0%)	0 (0%)	
Immune effector cell-associated neurotoxicity syndrome			0.475
0	29 (72.5%)	34 (82.9%)	
1	5 (12.5%)	3 (7.3%)	
2	5 (12.5%)	2 (4.9%)	
3	1 (2.5%)	2 (4.9%)	
4	0 (0%)	0 (0%)	
N Tocilizumab (dose/patient)	1.5	0.9	0.484
Patients given steroids	14 (32.5%)	10 (24.4%)	0.258
Need for GCSF on day 14	9 (22%)	15 (36.9%)	0.112
Early infections			0.301
CDI	5 (12%)	0	
MDI	6 (14.8%)	8 (19.5%)	
Organ dysfunction			1
Congestive heart failure	0 (0%)	0 (0%)	
Atrial fibrillation	3 (7.3%)	3 (7.3%)	
Acute kidney injury	3 (7.3%)	3 (7.3%)	
Days of hospitalization	23.4 (8)	24.6 (9.6)	0.547
Late pancytopenia	9 (22%)	11 (26.8%)	0.399
IgG levels < 4 gr/L*	5 (23.8%)	5 (33%)	0.398
Reactivation of CMV**	6 (18.8%)	5 (15.2%)	0.234
Reactivation of HHV6***	3 (15%)	1 (4.3%)	0.09
1- month PET/CT results			0.337
CR	19 (46%)	24 (59%)	
PR	7 (17%)	8 (19%)	
PD	13 (32%)	9 (22%)	
Progression-free survival (6 months)	39%	54%	0.209
Overall survival (6 months)	74%	76%	0.792

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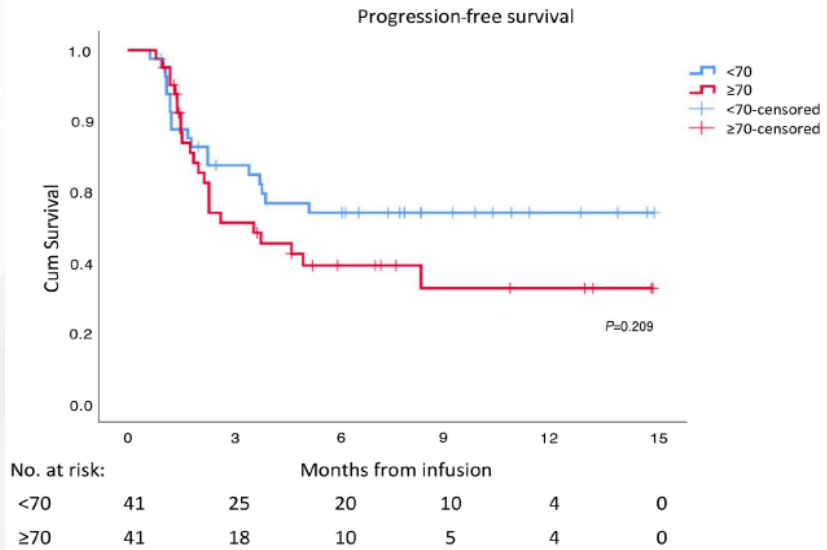

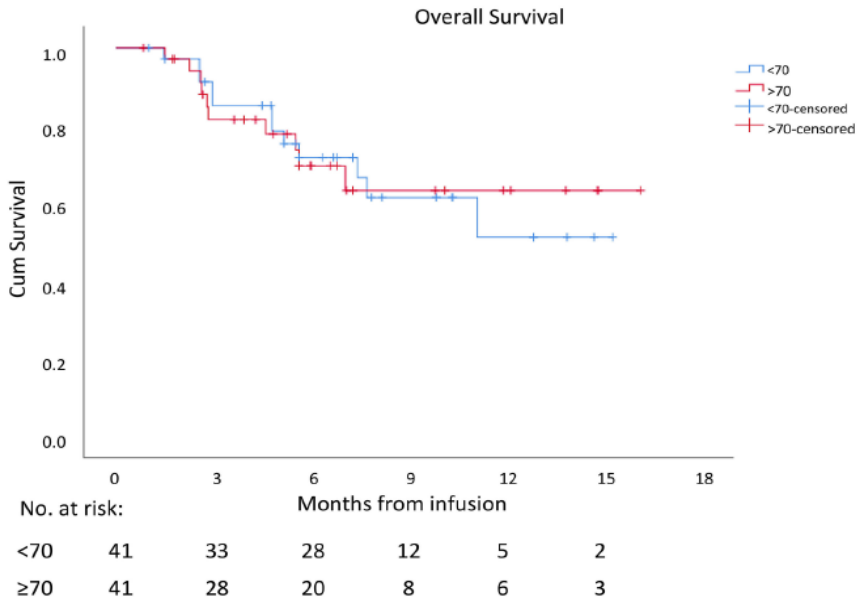

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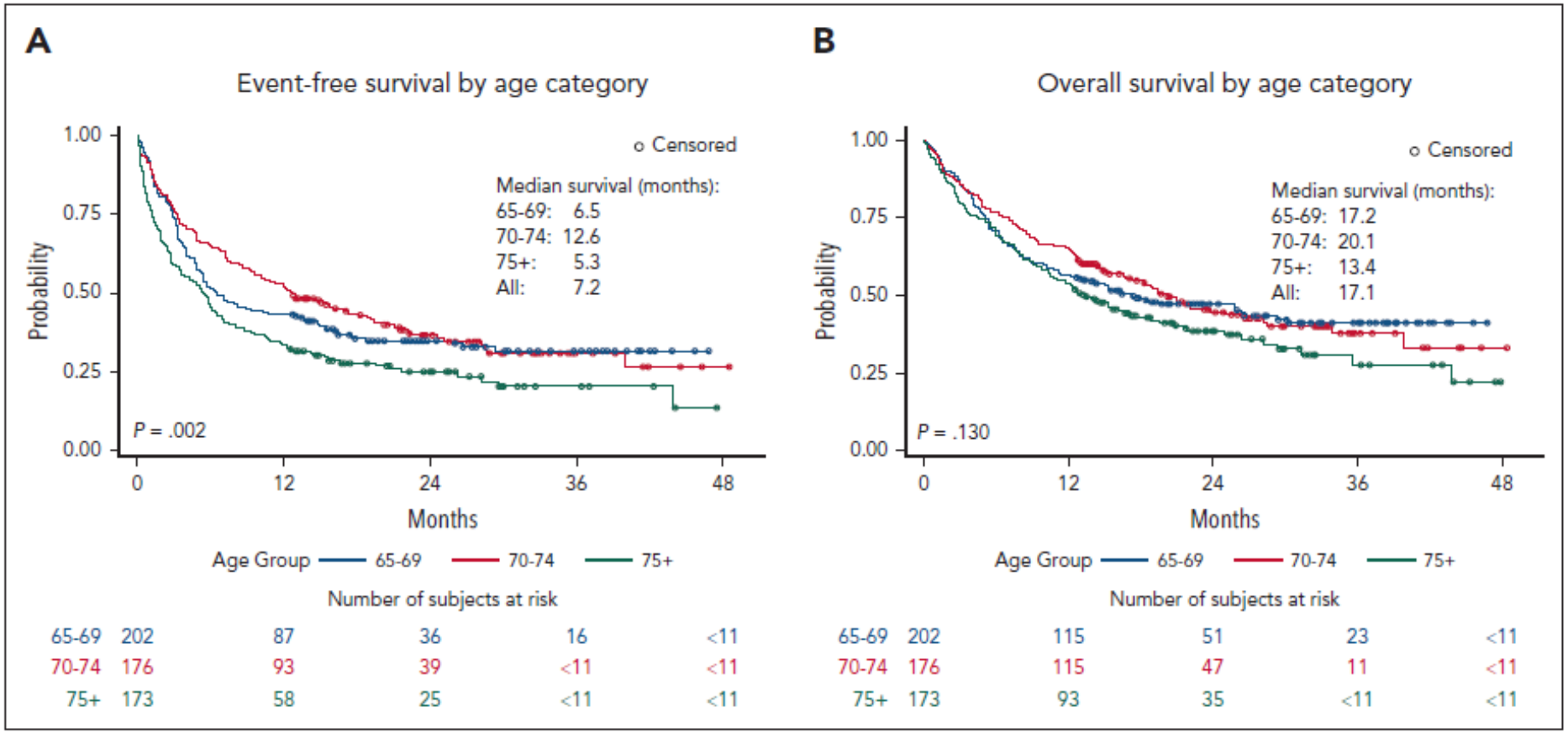
Real-world experience of CAR T-cell therapy in older patients with relapsed/refractory diffuse large B-cell lymphoma

MD Anderson

Dai Chihara,[1] Laura Liao,[2] Joseph Tkacz,[3] Anjali Franco,[3] Benjamin Lewing,[3] Karl M. Kilgore,[3] Loretta J. Nastoupil,[1] and Lei Chen[2]

Table 1. Patient characteristics

Characteristic	Patients aged 65-69 y (n = 202)		Patients aged 70-74 y (n = 176)		Patients aged ≥75 y (n = 173)		All patients (n = 551)	
Age, median (range), y	67	(65-69)	72	(70-74)	78.6	(75-90)	72.2	(65-90)
Urban/suburban, n (%)	160	(79.2)	142	(80.7)	142	(82.1)	444	(80.5)
Male sex, n (%)	108	(53.5)	93	(52.8)	98	(56.6)	299	(54.3)
Baseline Charlson Comorbidity Index, mean (SD)*	5	(3.2)	5	(3.3)	5	(3.3)	5	(3.24)
Median (range)	4	(0-15)	4	(0-15)	4	(0-15)	4	(0-15)
Bridging therapies, n (%)†								
Any therapy	102	(50.5)	69	(39.2)	91	(52.6)	262	(47.5)
Chemotherapy or targeted therapy	64	(31.7)	41	(23.3)	55	(31.8)	160	(29.0)
Corticosteroids	<50	(~)	<50	(~)	23	(13.3)	73	(27.9)
Radiotherapy	<11	(~)‡	<11	(~)‡	13	(7.5)	29	(11.1)
CAR T-cell administration setting, n (%)								
Inpatient	171	(84.6)	155	(88.1)	130	(75.1)	456	(82.8)
Length of stay, mean (SD), d	19.7	(12.36)	24.2	(21.15)	20.5	(13.09)	21.4	(16.2)
Outpatient	31	(15.3)	21	(11.9)	43	(24.9)	95	(17.2)



Characteristic	Categories	EFS						OS					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age groups	≥75 vs 65-69 y	1.37	1.07-1.74	.011	1.41	1.10-1.82	.007	1.25	0.96-1.62	.105	1.2	0.91-1.58	.188
	≥75 vs 70-74 y	1.54	1.19-1.98	.001	1.46	1.13-1.89	.004	1.29	0.98-1.70	.066	1.2	0.90-1.58	.207
Sex	Male vs female	0.99	0.81-1.22	.943	0.92	0.75-1.14	.449	1.06	0.85-1.33	.577	1	0.80-1.26	.973
Urban/suburban residence	Rural vs urban	1.14	0.88-1.47	.317		—	—	1.22	0.93-1.60	.158		—	—
Bridging therapy	Present vs absent	1.34	1.09-1.64	.005	1.27	1.03-1.56	.028	1.49	1.19-1.86	<.001	1.39	1.11-1.75	.005
Charlson Comorbidity Index	≥5 vs 0-4	1.57	1.28-1.94	<.0001	1.56	1.26–1.92	<.0001	1.63	1.30-2.05	<.0001	1.58	1.26-1.99	<.0001

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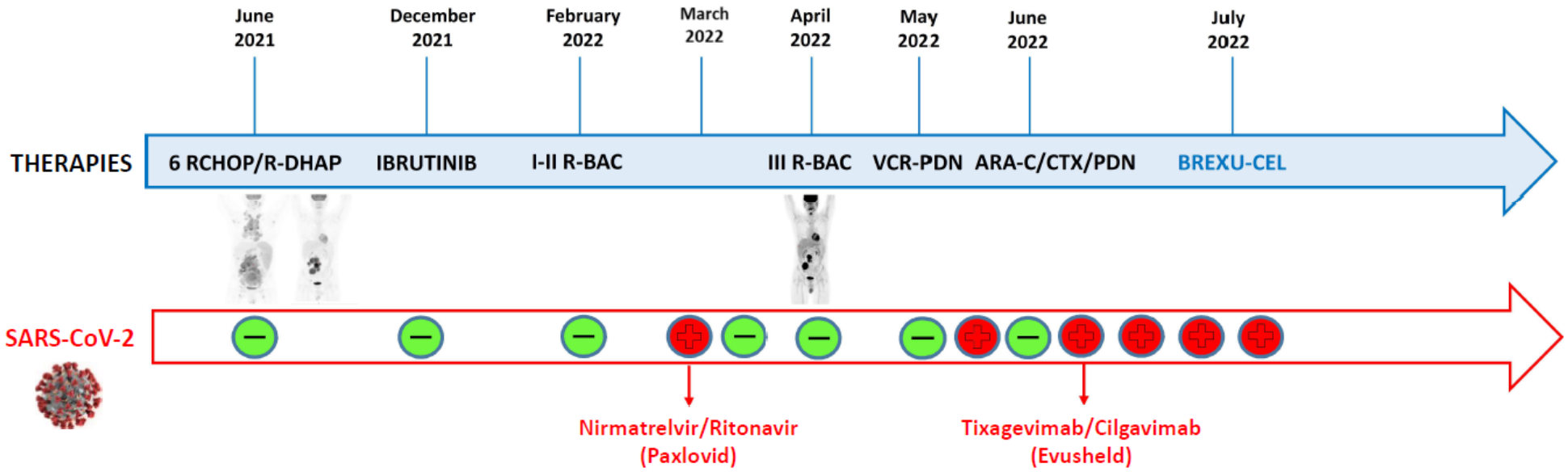
AGE ALONE MAY NOT BE SUFFICIENT TO PREDICT THE CLINICAL COURSE

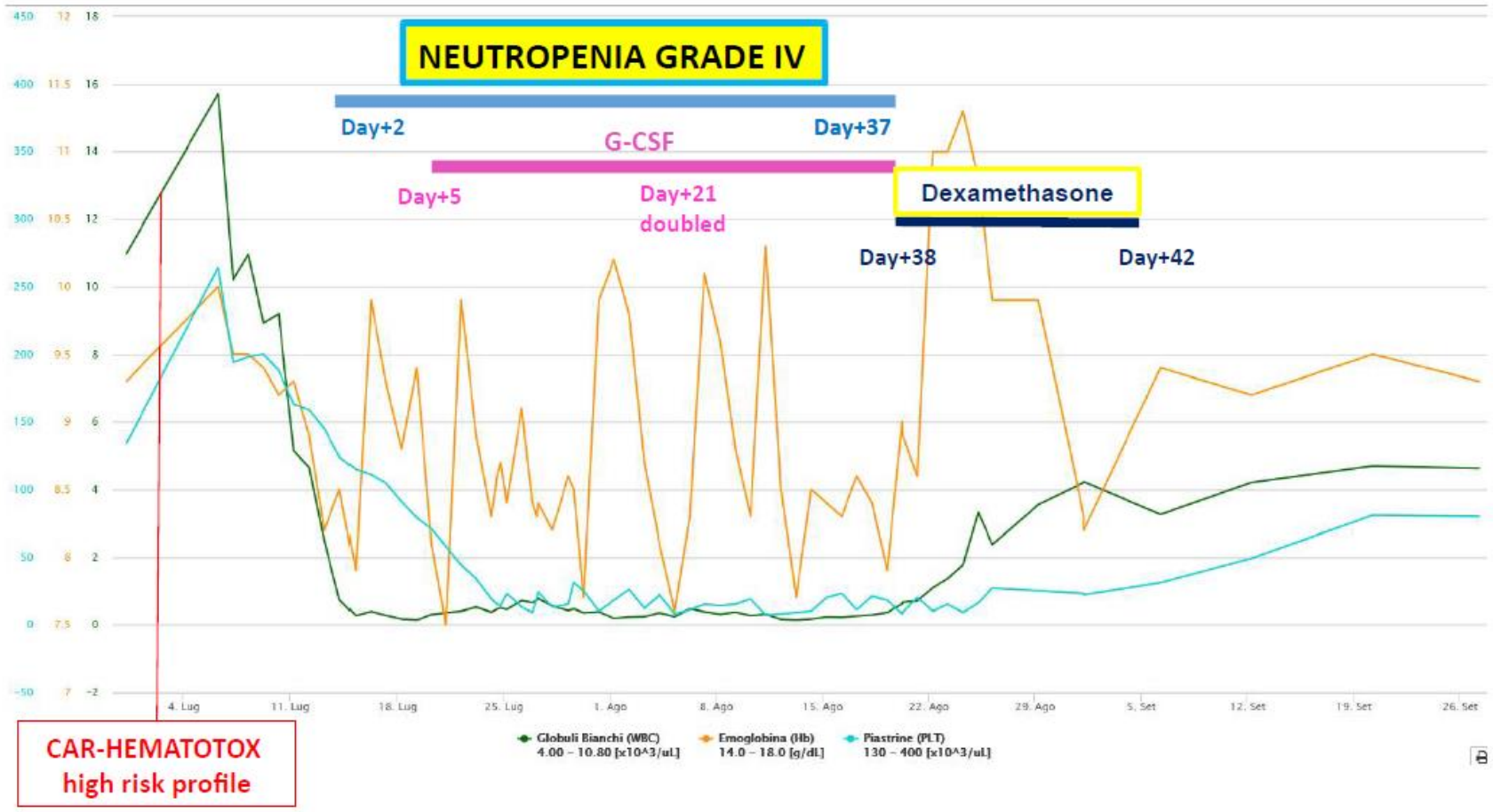
Case report

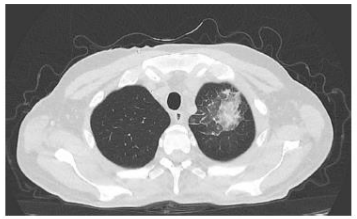
44 yrs old MCL, stage IV B, MIPI high risk

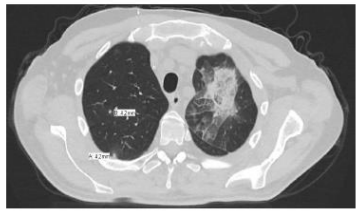
Due to his peculiar clinical condition, both lymphodepletion therapy (including fludarabine and cyclophosphamide) and Brexu-cel were administered in a negative-pressure room at the Department of Infectious Diseases on 12 July 2022

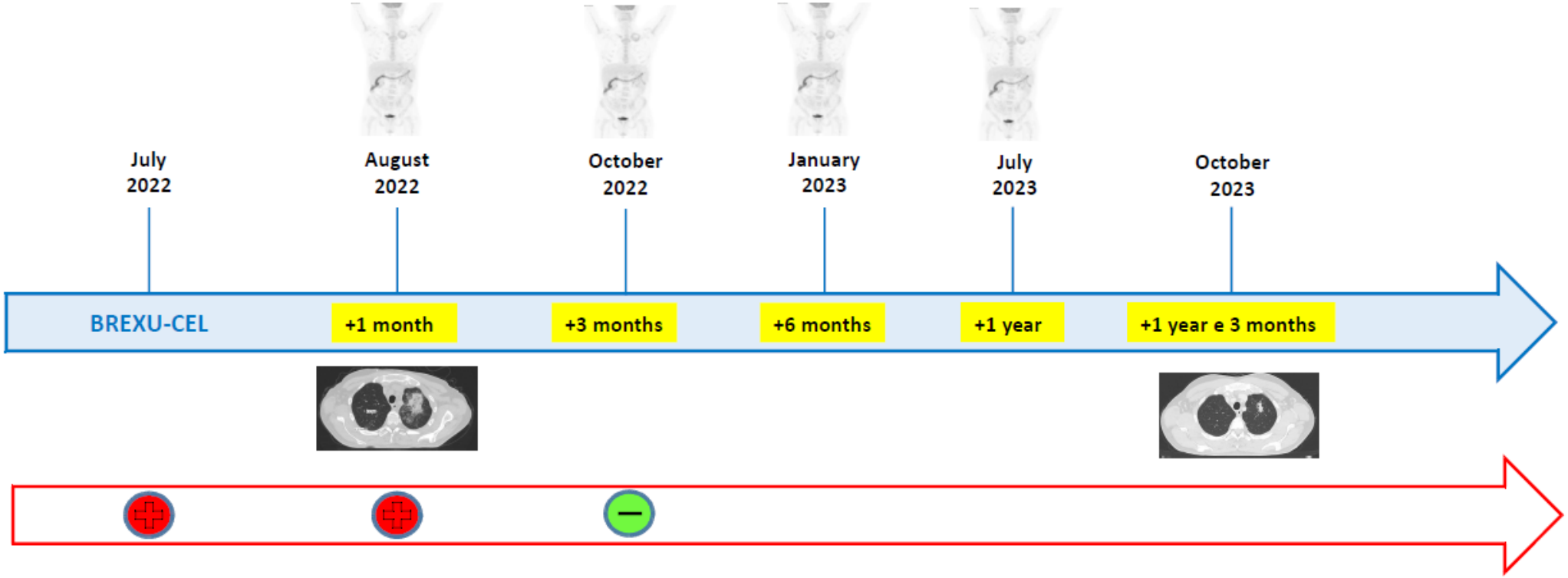


Radici V, *Front. Transplant*, 19 September 2023, Sec. Cell and Stem Cell Transplantation Volume 2 - 2023 | https://doi.org/10.3389/frtra.2023.1238494


NEUTROPENIA GRADE IV
Day+2
Day+37
G-CSF
Day+5
Day+21
doubled
Dexamethasone
Day+38
Day+42
CAR-HEMATOTOX
high risk profile
4. Lug
11. Lug
18. Lug
25. Lug
1. Ago
8. Ago
15. Ago
22. Ago
29. Ago
5. Set
12. Set
19. Set
26. Set
Globuli Bianchi (WBC)
4.00 – 10.80 [x10^3/uL]
Emoglobina (Hb)
14.0 – 18.0 [g/dL]
Piastrine (PLT)
130 – 400 [x10^3/uL]






July 2022
August 2022
October 2022
January 2023
July 2023
October 2023
BREXU-CEL
+1 month
+3 months
+6 months
+1 year
+1 year e 3 months

CONCLUSIONS

1. Age alone should not be considered a criteria for exclusion from CART

2. Always true? → up to the age of 65 yrs **Y**

   - 70 yrs **Y**
   - 75 yrs **Y**
   - 80 yrs **Y/N**
   - 85 yrs **N/Y**

CONCLUSIONS

1. Age alone should not be considered a criteria for exclusion from CART

2. Always true? → up to the age of

65 yrs	**Y**
70 yrs	**Y**
75 yrs	**Y**
80 yrs	**Y/N**
85 yrs	**N/Y**

} COSTS ?

3. Comorbidities

4. Frailty

5. Disease phase → optimal bridge

6. **PATIENTS' SELECTION** (CART vs other new drugs)

Variable	Aged 65-69 y (n = 168)		Aged 70-74 y (n = 143)		Aged ≥75 y (n = 134)		Total (n = 445)	
Total health care costs, $								
Mean (SD)*	311 699	(189 161)	296 192	(196 115)	271 767	(190 975)	294 692	(192 232)
Median	364 036		342 099		333 698		352 572	

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SPECIAL THANKS TO….

- **Prof Domenico Russo**
- All the Colleagues of the CART-team
- All the Colleagues of the Lab
- Nurses
- Patients