21ST INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM™

Elderly/Older patients...with DLBCL

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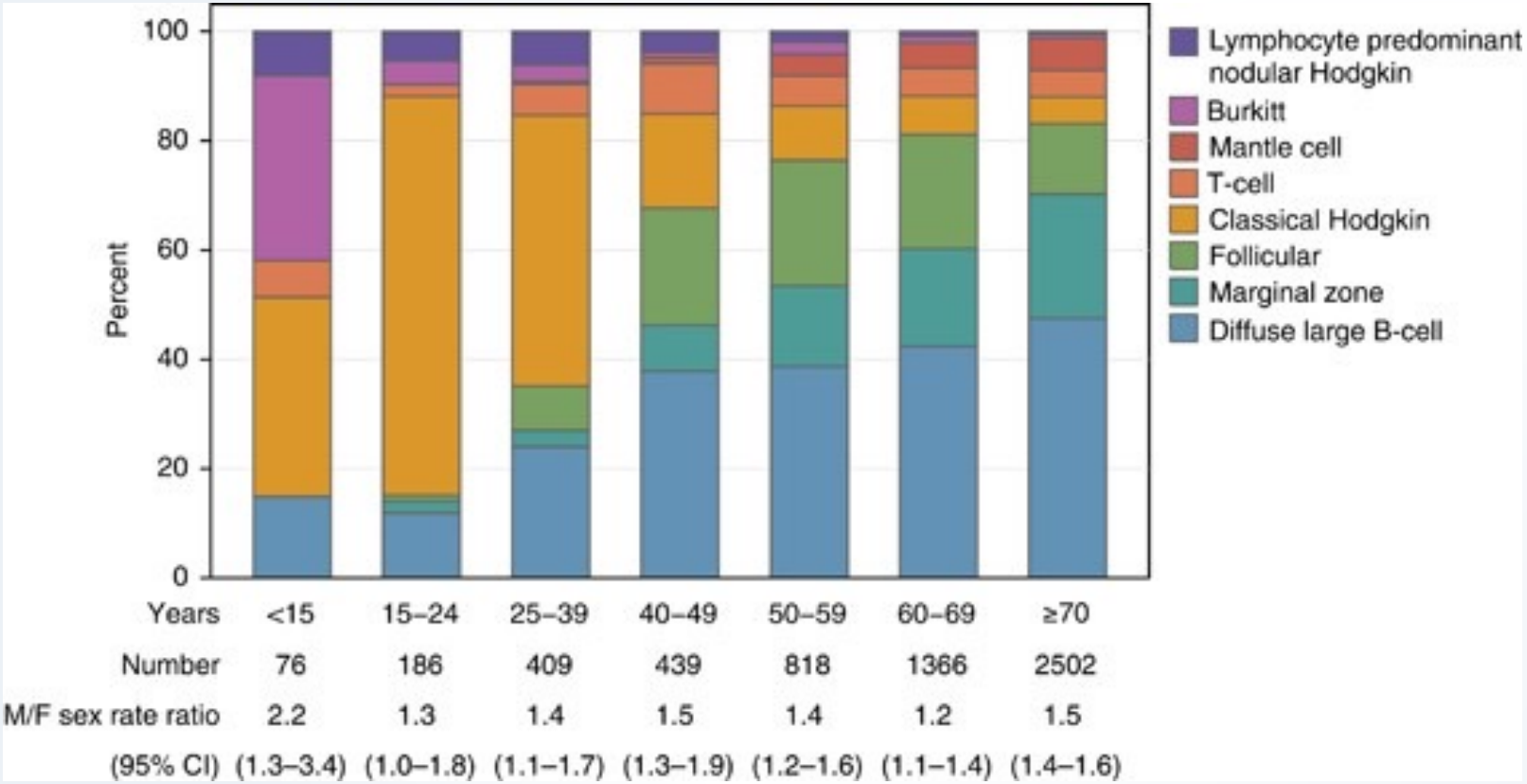
Disclosures

I hereby declare the following potential conflicts of interest concerning my presentation:

- Consultancy: Roche, BMS, Jannsen, Gilead, Regeneron, Genmab, Sobi, Incyte, Novartis, Abbvie
- Research Funding: none
- Honoraria: none
- Patents and Royalties: none
- Membership on an Entity's Board of Directors or Advisory Committees: none
- Discussion of off-label drug use:none

Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network



Years	<15	15–24	25–39	40–49	50–59	60–69	≥70
Number	76	186	409	439	818	1366	2502
M/F sex rate ratio	2.2	1.3	1.4	1.5	1.4	1.2	1.5
(95% CI)	(1.3–3.4)	(1.0–1.8)	(1.1–1.7)	(1.3–1.9)	(1.2–1.6)	(1.1–1.4)	(1.4–1.6)

Smith, A. *et al. Br J Cancer* **112**, 1575–1584 (2015).

Aggressive B cell Lymphomas in the elderly (WHO Haem5)

DLBCL, NOS

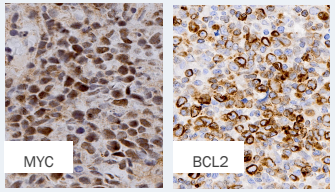
High frequency of ABC subtypes (up to 50%). Mareschall et al. Haematol 2011

Higher genomic complexity (vs young). Klapper et al Blood 2012

More frequent rates: gains of 1q21, 18q21, 7p22, 7q21, 3q27

Less frequent : IRF4-breaks

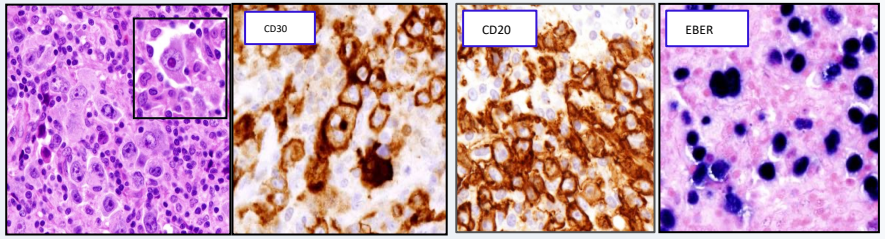
Double hit lymphoma (DHL)



EBV-DLBCL,

Immune senescence (Iatrogenic or congenital)

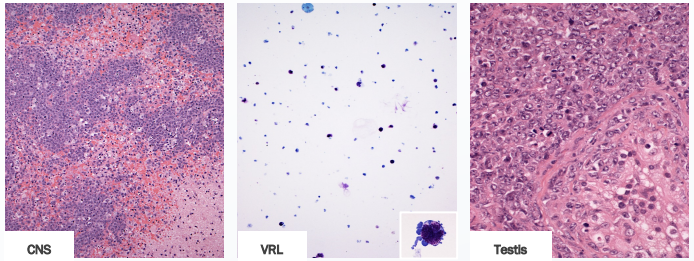
Low mutational burden but STAT3 mutations



Primary effusion lymphomas (PEL)

(HHV8+, immunocompromised pt, very aggressive)

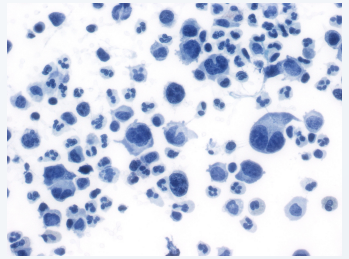
LBCL of immune-privileged sites



Plasmablastic Lymphoma

Fluid overload-associated LBCL

(HHV8 neg, elderly pts, no immunodeficiency, better outcomes vs PEL)

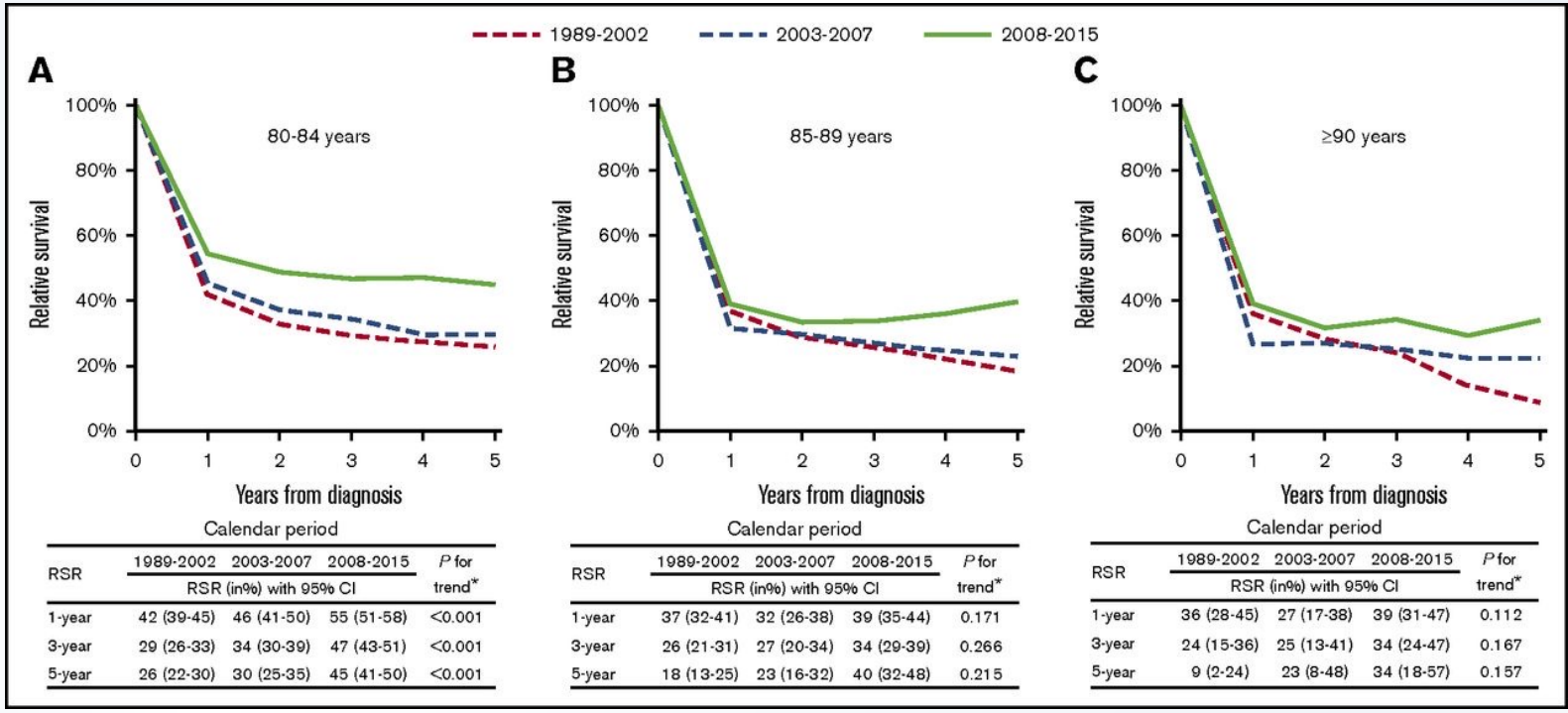


Alaggio et al. Leukemia 2022

Courtesy of A. Carbone

DLBCL in the elderly. A curable disease in a difficult patient

- Improved outcomes with immunochemotherapy
- R-CHOP
  - Is standard therapy until 80yo
  - Is the reference therapy also for pts older than 80y



Calendar period

RSR	1989-2002	2003-2007	2008-2015	*P* for trend*
	RSR (in%) with 95% CI			
1-year	42 (39-45)	46 (41-50)	55 (51-58)	<0.001
3-year	29 (26-33)	34 (30-39)	47 (43-51)	<0.001
5-year	26 (22-30)	30 (25-35)	45 (41-50)	<0.001

Calendar period

RSR	1989-2002	2003-2007	2008-2015	*P* for trend*
	RSR (in%) with 95% CI			
1-year	37 (32-41)	32 (26-38)	39 (35-44)	0.171
3-year	26 (21-31)	27 (20-34)	34 (29-39)	0.266
5-year	18 (13-25)	23 (16-32)	40 (32-48)	0.215

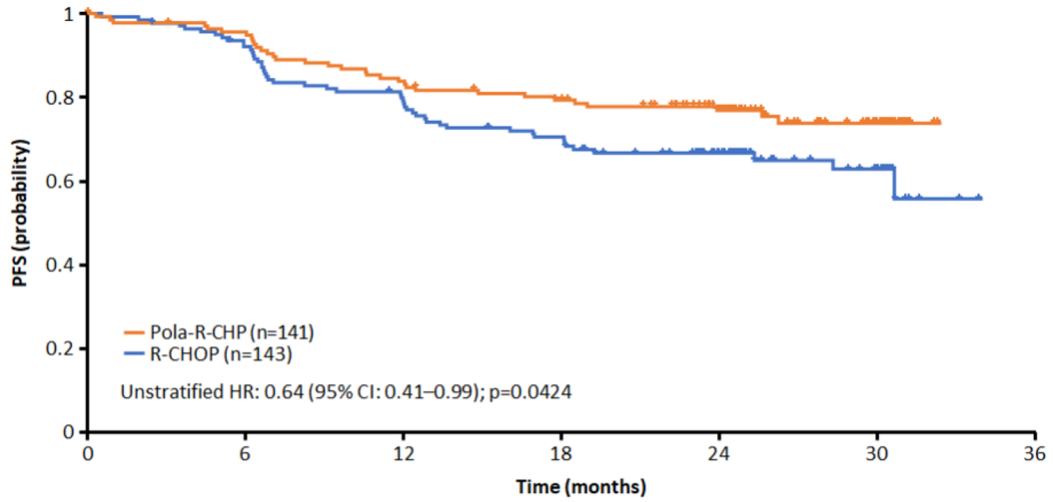
Calendar period

RSR	1989-2002	2003-2007	2008-2015	*P* for trend*
	RSR (in%) with 95% CI			
1-year	36 (28-45)	27 (17-38)	39 (31-47)	0.112
3-year	24 (15-36)	25 (13-41)	34 (24-47)	0.167
5-year	9 (2-24)	23 (8-48)	34 (18-57)	0.157

Avinash G. Dinmohamed, Blood Adv, 2017, Figure 1.

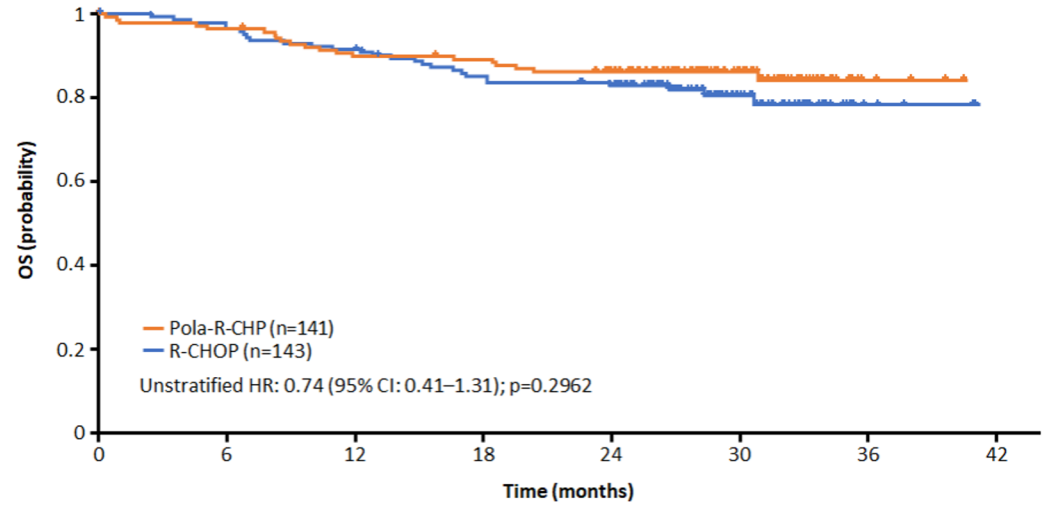
Polatuzumab + R-CHP in elderly patients (POLARIX trial)

PFS for Pola-R-CHP vs R-CHOP



Number at risk							
Pola-R-CHP	141	131	115	106	82	29	
R-CHOP	143	129	110	97	70	26	

OS for Pola-R-CHP vs R-CHOP



Number at risk							
Pola-R-CHP	141	134	124	122	113	50	4
R-CHOP	143	136	129	117	111	41	5

The risk of **progression, relapse or death** was **lower with Pola-R-CHP** vs R-CHOP (unstratified HR 0.64; 95% CI: 0.41–0.99); **OS data** were immature but **showed trend for reduction** in the risk of death with **Pola-R-CHP** versus R-CHOP (unstratified HR 0.74; 95% CI: 0.41–1.31)

Hu et al: DOI: 10.1200/JCO.2023.41.16_suppl.7518 *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) 7518-751

Lancet Oncol 2011; 12: 460–68
Published Online
April 8, 2011

Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial

*Frédéric Peyrade, Fabrice Jardin, Catherine Thieblemont, Antoine Thyss, Jean-François Emile, Sylvie Castaigne, Bertrand Coiffier, Corinne Haioun, Serge Bologna, Olivier Fitoussi, Gérard Lepeu, Christophe Fruchart, Dominique Bordessoule, Michel Blanc, Richard Delarue, Maud Janvier, Bruno Salles, Marc André, Marion Fournier, Philippe Gaulard, Hervé Tilly, for the Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators**

N=149

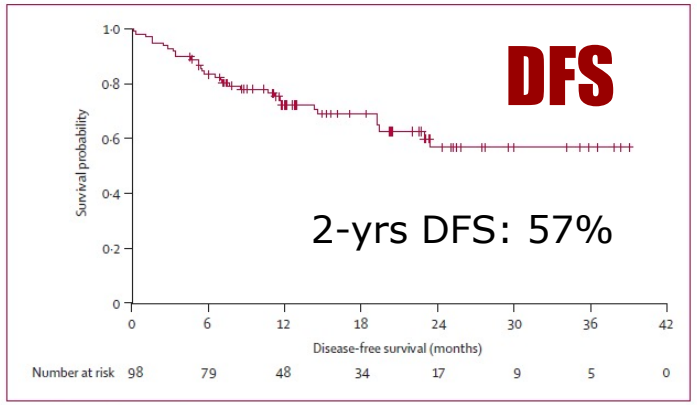
RminiCHOP (6 cy. every 21)

- Rituximab 375 mg/mq
- Doxorubicin 25 mg/mq
- Cyclophosphamide 400 mg/mq
- Vincristine 1 mg total
- Prednisone 40 mg/mq (oral)

6 cycles in 108 pts (median DI 97%)

Complete response	59 (40%)
Unconfirmed complete response	34 (23%)
Partial response	16 (11%)
Stable disease	2 (1%)
Progression during treatment	8 (5%)
Death	27 (18%)
Not assessed	3 (2%)

Table 5: **Response at end of treatment**



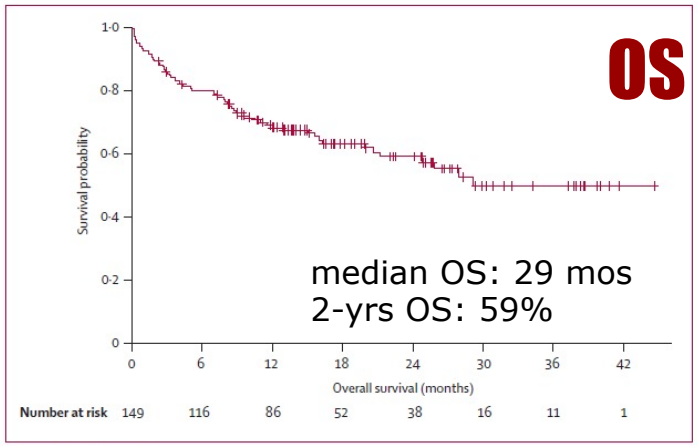
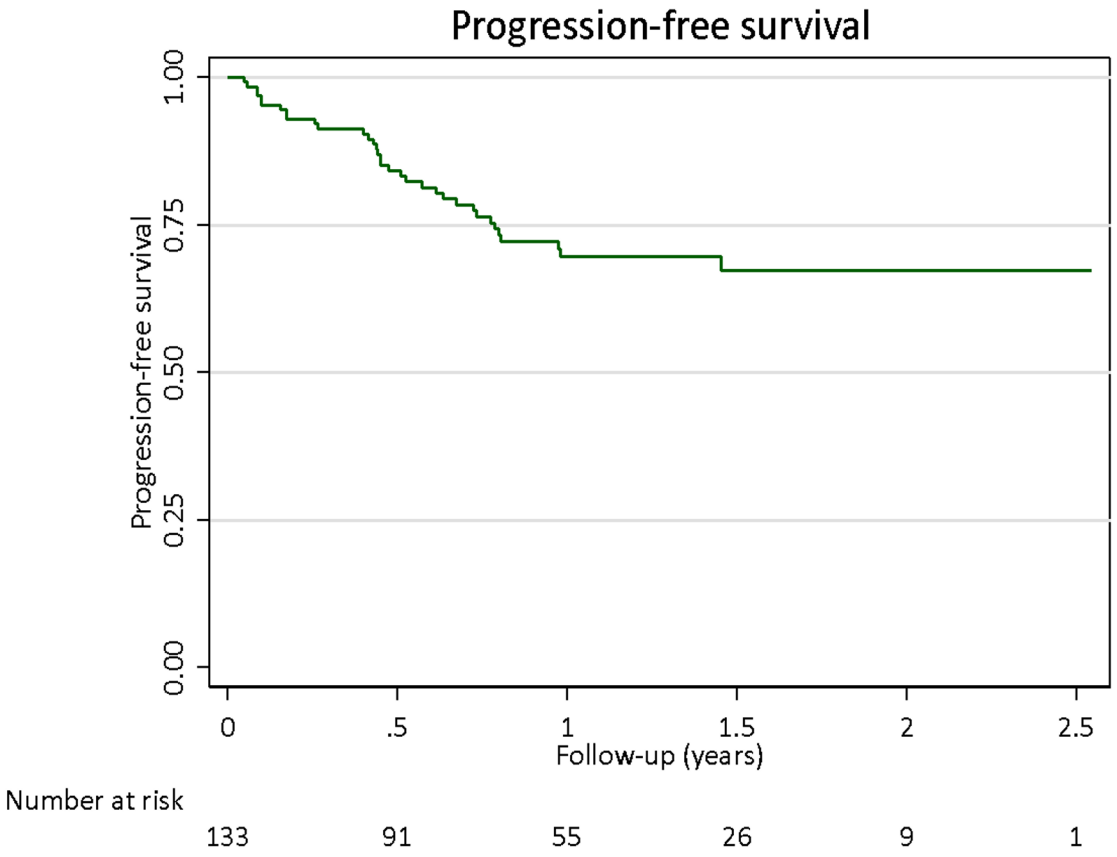
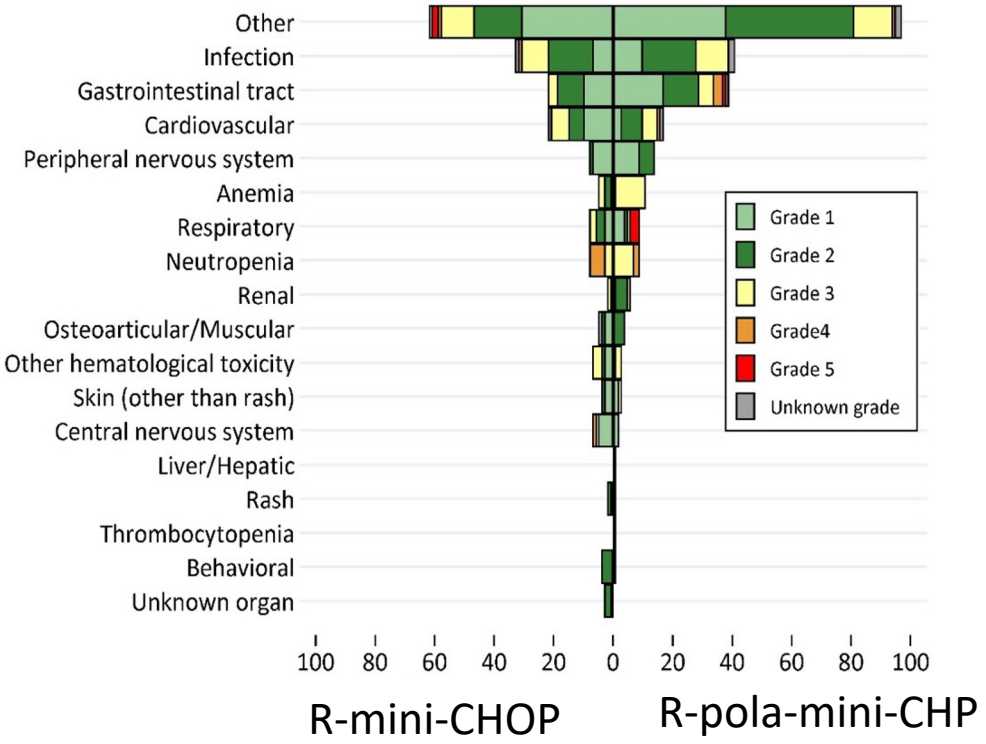


Figure 2: **Overall survival**

References

INITIAL SAFETY DATA FROM THE PHASE 3 POLAR BEAR TRIAL IN ELDERLY OR FRAIL PATIENTS WITH DIFFUSE LARGE CELL LYMPHOMA





Median follow-up 1.1 years

Jerkeman et al. ASH 2023

Clinical trial data can hardly be generalized to the general population of old patients with lymphoma

Old patients are under-represented in Clinical trials

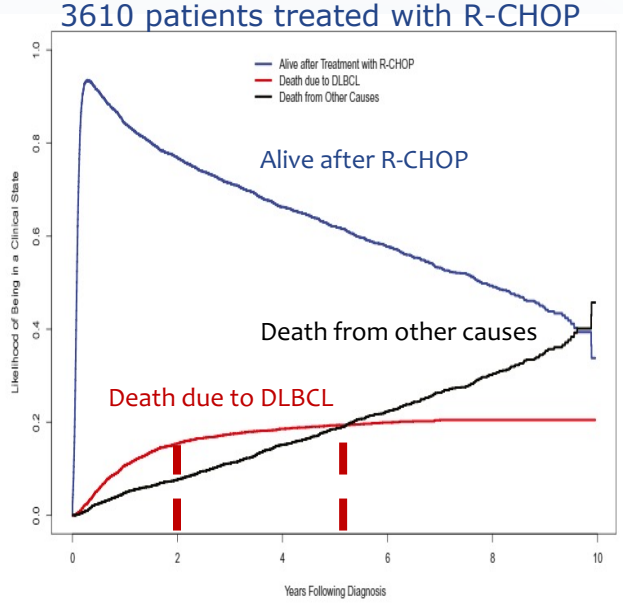
	Clinical Trial Participants (2005-2015)	Cancer Incidence (2013)
<65	138077 (60%)	559949 (44%)
65-69	38664 (17%)	174886 (14%)
70-74	27578 (12%)	162483 (13%)
75-79	17544 (8%)	169510 (13%)
80+	9678 (4%)	209949 (16%)

Harpreet Singh et al, ASCO 2017

Inclusion criteria usually based on subjective and non reproducible criteria

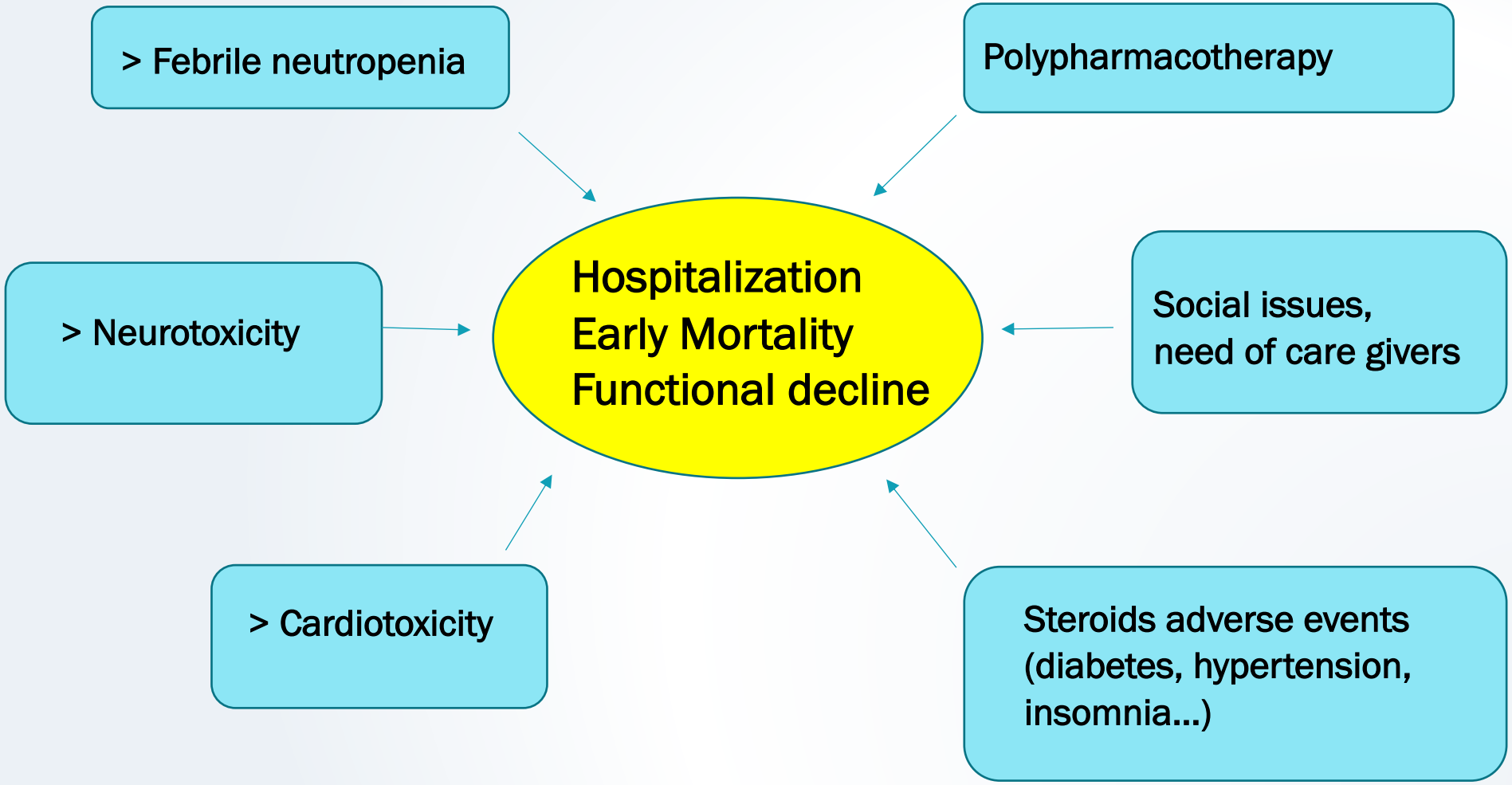
Even if a cure is possible, additional risks have a significant impact in reducing outcomes

3610 patients treated with R-CHOP



Caglayan C et al Cancer 2019

«Treating ELDERLY patients with aggressive lymphoma poses the DILEMMA of balancing potential cure while minimizing toxicity»

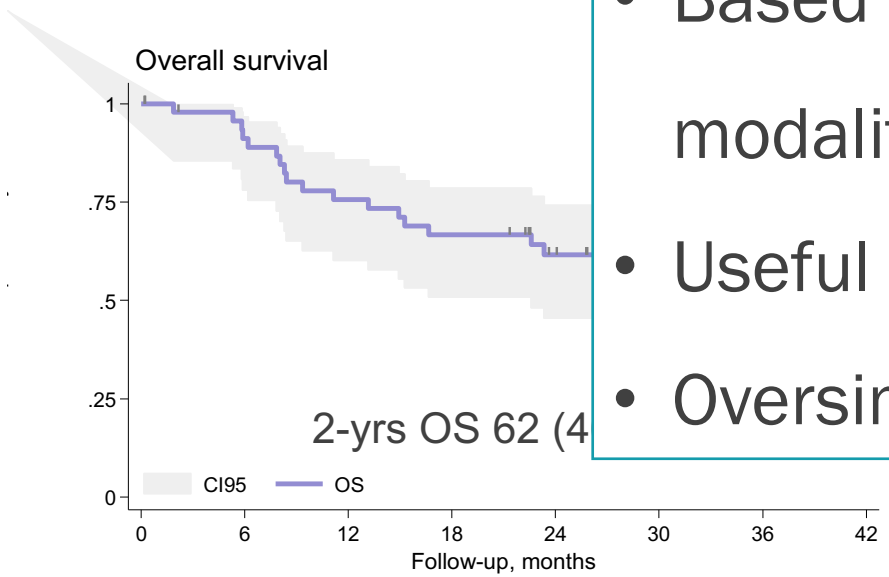


N. Bartlett ASH Education Program 2020

The easy approach: organ based

R-COMP for DLBCL patients and Moderate/Severe Heart Disease

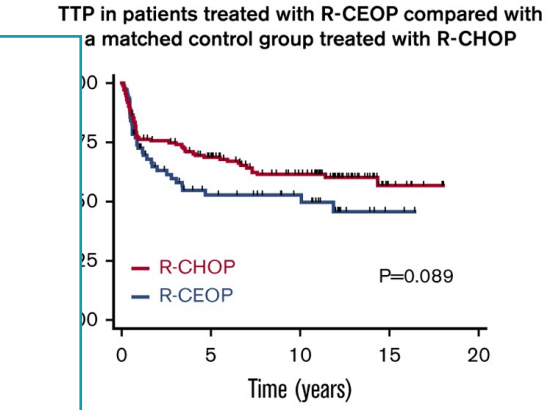
N=50 (med age 76yr
Full Treatment
CR rate

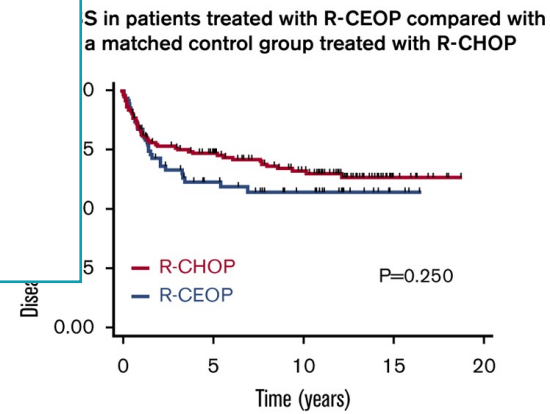


Luminari et al. Hematol Oncol 2017

- Mostly phase II studies
- Based on full dose curative modality
- Useful for few patients
- Oversimplified approach

R-CEOP for DLBCL Patients with Contraindication to Anthracyclines Demonstrates Curative Potential

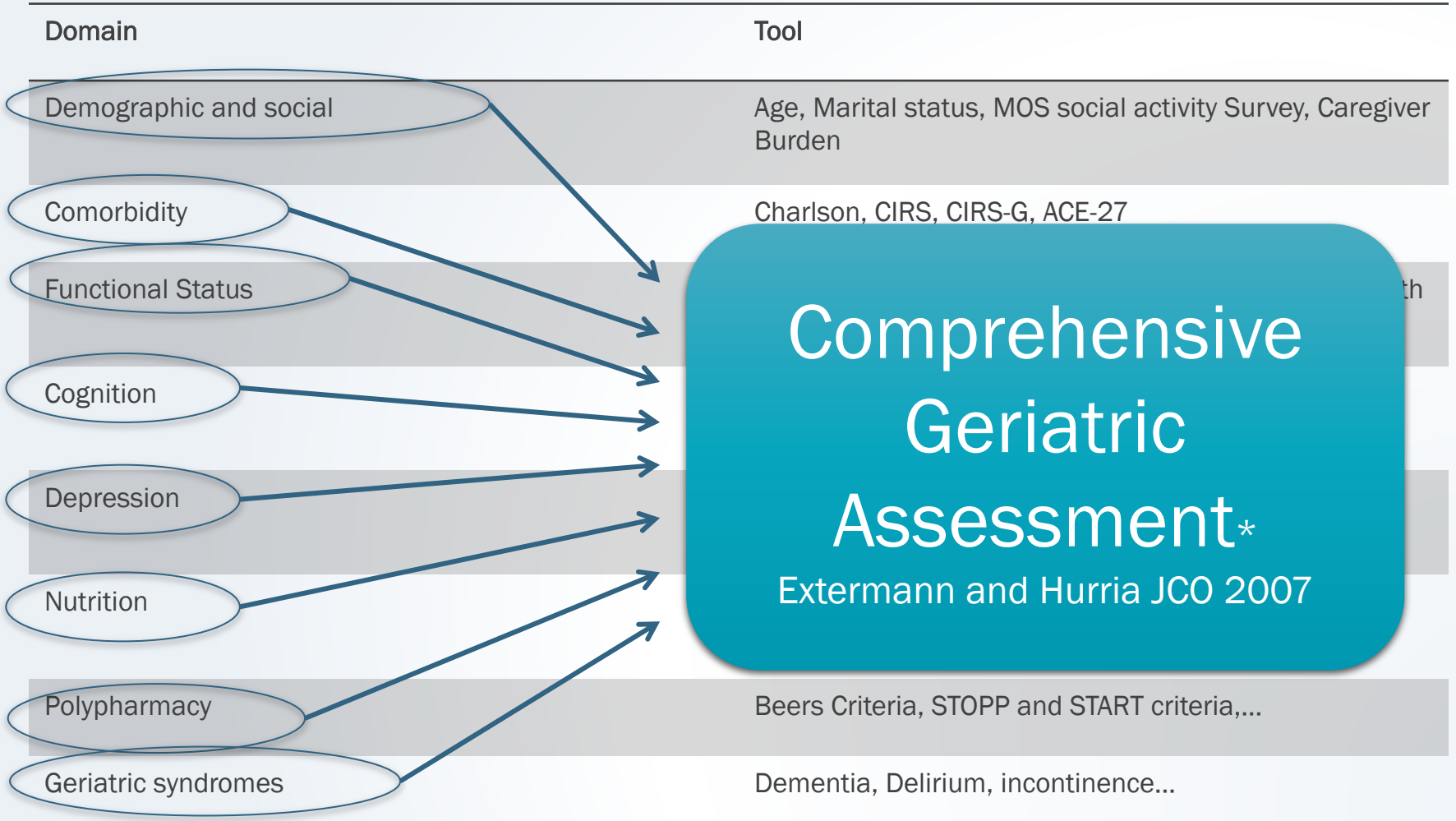




Alden A. Moccia, Blood Adv, 2021,

A COMPLEX PATIENT REQUIRES A COMPLEX SOLUTION

The geriatric approach to elderly patients



Modified from Wildiers et al. JCO 2014

Geriatric assessment and screening tools validated in NHL

Screening tool	Items	Time to administer	Correlation with outcomes
Simplified Geriatric Assessment (FIL)	ADL; IADL; Age; CIRS-G; IPI (EPI); Hemoglobin (EPI)	<10 min	Overall survival
ACA index and IADL- ACA	Age, Albumin (<3.7 g/dL), CCI IADL (IADL-ACA)	<10 min	Overall survival; Mean chemotherapy dose; Treatment toxicity and treatment-related mortality
Geriatric-8 (G8)	Nutritional Status; Polypharmacy; Age; Psychological Status; Health perception	<5 min	Overall Survival; Treatment toxicity
Vulnerable Elders Survey (VES-13)	Age; Self-rated health; Physical function; functional disabilities	<5 min	Overall Survival; Response rate
fTRST	Cognition; Living situation; Physical function; Polypharmacy	<5 min	Overall Survival; Treatment-related mortality
CRASH	Diastolic blood pressure; LDH; Functional status (IADL, Performance status); Nutritional status (MNA); Chemotherapy; Cognition (MMS)	<20 min	Treatment toxicity
CARG-TT	Age, Cancer type, Treatment, Hemoglobin, Kidney function, Physical function, IADL (medications), Falls, Hearing, Social activity	<5 min	Treatment toxicity*

O.S. Akhtar, et al. Journal of Geriatric Oncology 2022

Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: the prospective Elderly Project of the Fondazione Italiana Li

- N=1353, >65y, dec 2013 – dec 2017
- Mandatory sGA at enrollment
- Treatment choice independent from sGA results

Criteria for sGA assessment

	FIT	UNFIT		FRAIL
ADL	≥5*	< 5*	6*	<6*
IADL	≥6*	<6*	8*	<8*
CIRS-G	0 score =3-4, ≤8 score =2	1 score =3-4, > 8 score =2	0 score =3-4, <5 score =2	1 score =3-4, ≥5 score =2
Age	<80	<80	≥80	≥80

Abbreviations: ADL, activities of daily living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; IADL, instrumental ADL; sGA, simplified geriatric assessment.

*Number of residual functions.

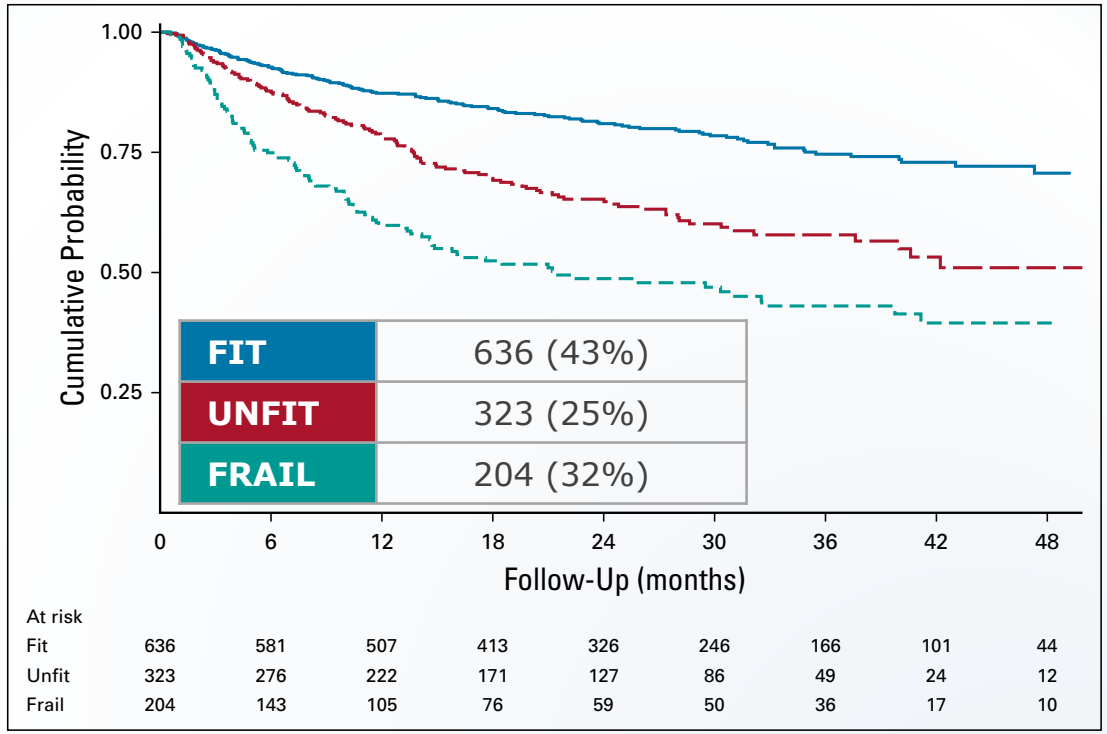


FIG 1. Overall survival by sGA in all patients with treatment details (N = 1,163). sGA, simplified geriatric assessment.

F. Merli et al. J Clin Oncol 2021

Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: the prospective Elderly Project of the Fondazione Italiana Linfomi.

(A)

Factors	HR (95% CI)	z-score	Ratio*	Weight	P value
FIT	1.00	-	-		-
UNFIT	1.93 (1.49 to 2.50)	4.97	2.59	3	<0.001
FRAIL	2.74 (2.07 to 3.62)	7.09	3.69	4	<0.001
IPI 1	1.00				-
IPI 2	1.55 (0.99 to 2.44)	1.92	1.00	1	0.055
IPI 3-5	2.90 (1.93 to 4.35)	5.14	2.68	3	<0.001
Hb <12 g/dL	1.28 (1.02 to 1.60)	2.13	1.11	1	0.033

(B)

EPI model	N (%)	3-yr OS (95%CI)	HR (95%CI)	P value
Risk groups (Score)	1065	66 (62 to 69)	-	-
Low (0-1)	250 (23)	87 (81 to 91)	1.00	-
Intermediate (2-5)	510 (48)	69 (63 to73)	2.57 (1.72 to 3.84)	<0001
High (6-8)	305 (29)	42 (36 to 49)	6.21 (4.17 to 9.25)	<0.001
High vs Intermediate	-		2.41 (1.91 to 3.05)	<0.001

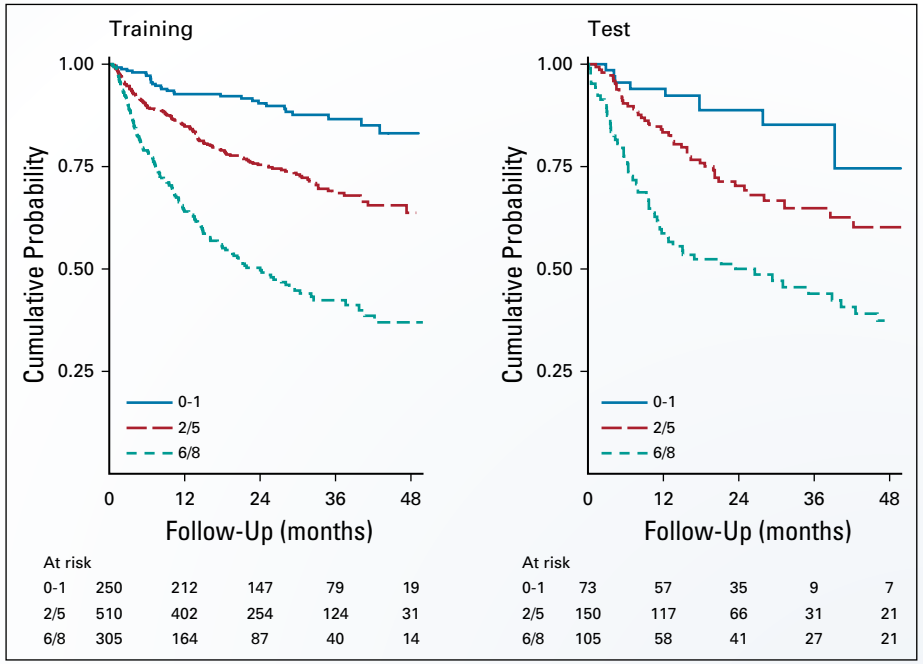


FIG 2. Overall survival stratified by the EPI in the training (A: 1,065 patients) and validation (B: 328 patients) samples. EPI, Elderly Prognostic Index.

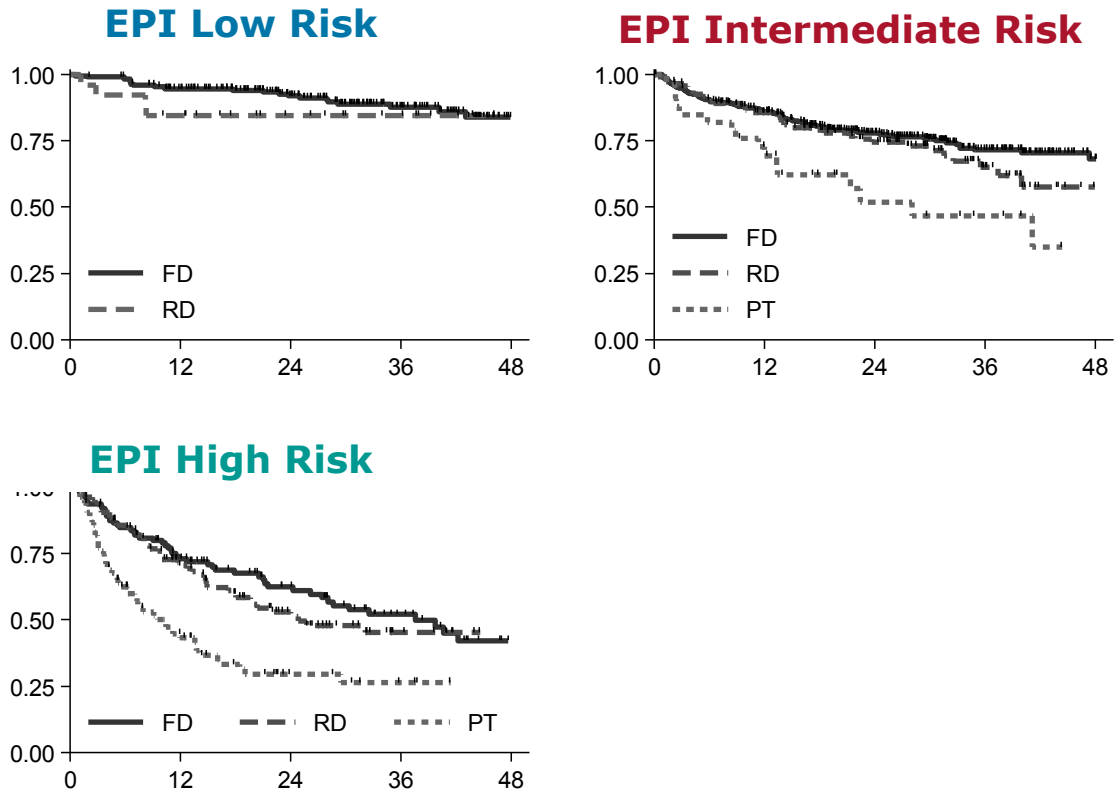
F. Merli et al. J Clin Oncol 2021

Simplified geriatric assessment and EPI are useful to define the risk risk/benefit profile of DLBCL therapy

According to anthracycline doses, treatment was classified as:

- FD: full dose (≥70%)
- RD: reduced dose (<70%)
- PT: palliative, no anthracycline

	EPI		
Treatment	Low	Int	High
FD	89%	79%	37%
RD	10%	24%	35%
PT	<1%	7%	35%

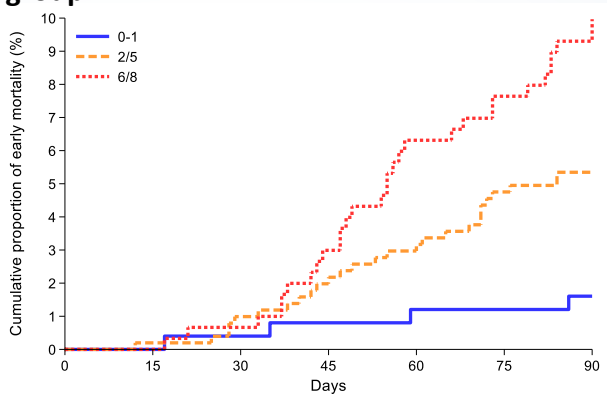


F. Merli et al. J Clin Oncol 2021

Simplified Geriatric assessment in elderly DLBCL (www.filinf.it/epi)

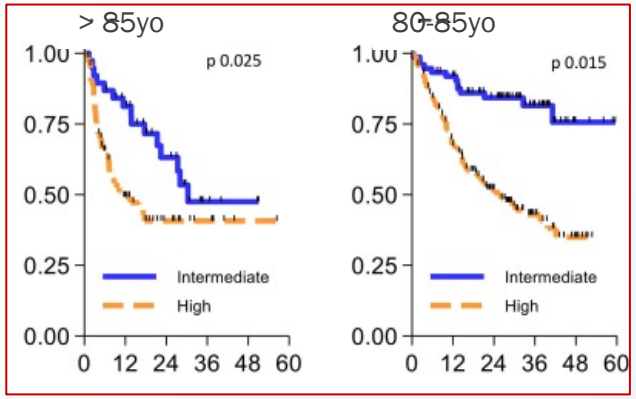
- EPI > sGA (+Bulky) predicts early mortality and non lymphoma related deaths (Cencini et al. Hematol Oncol 2022)

Cumulative incidence (%) of early deaths by EPI group



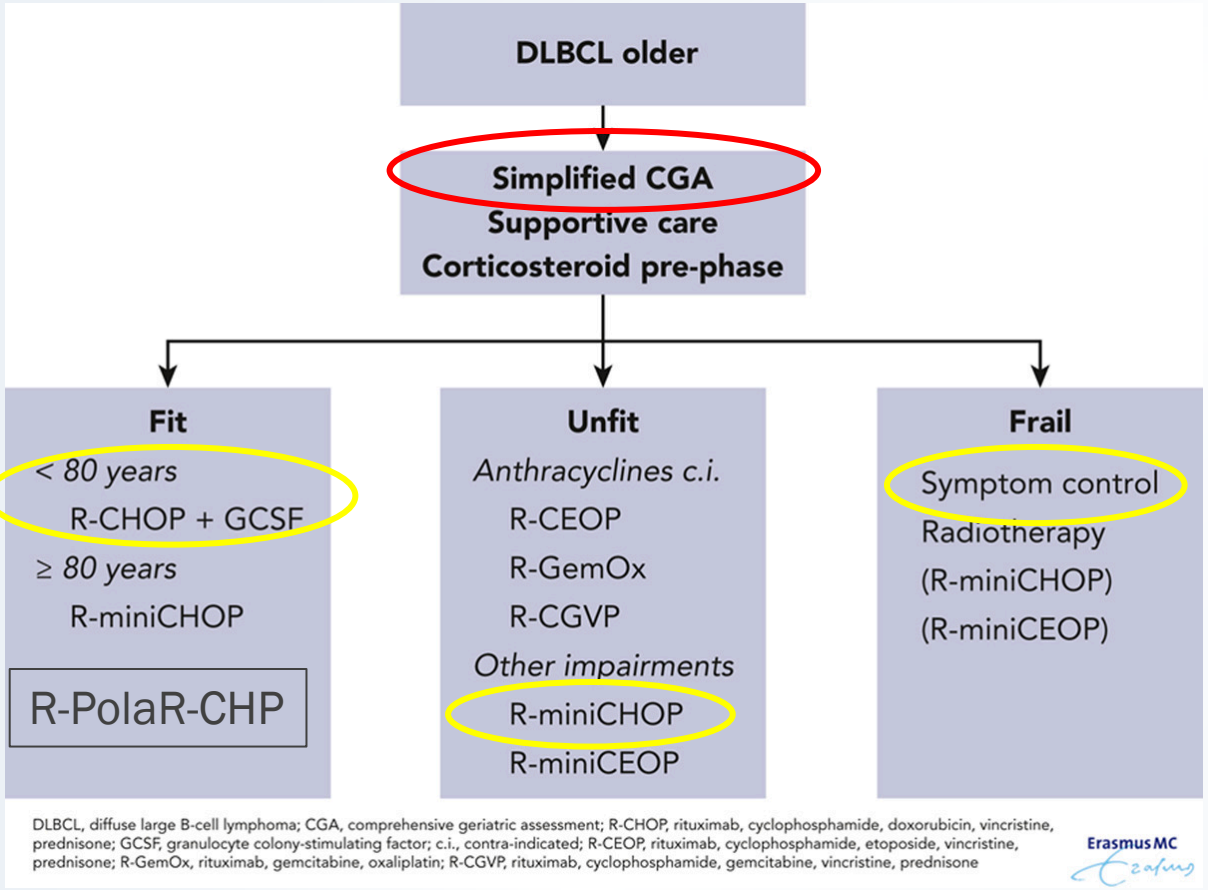
- Identifies different risk group also among very old patients (> 80 and >85 yo) (Tucci et al Haematologica 2022)

Overall survival by EPI



- Is being validated in the SWOG 1918 trial for 80yo+ DLBCL pts(R-miniCHOP +/- Aza) (Brem et al. J Ger Oncol 2022)

How I treat older patients with DLBCL in the frontline setting



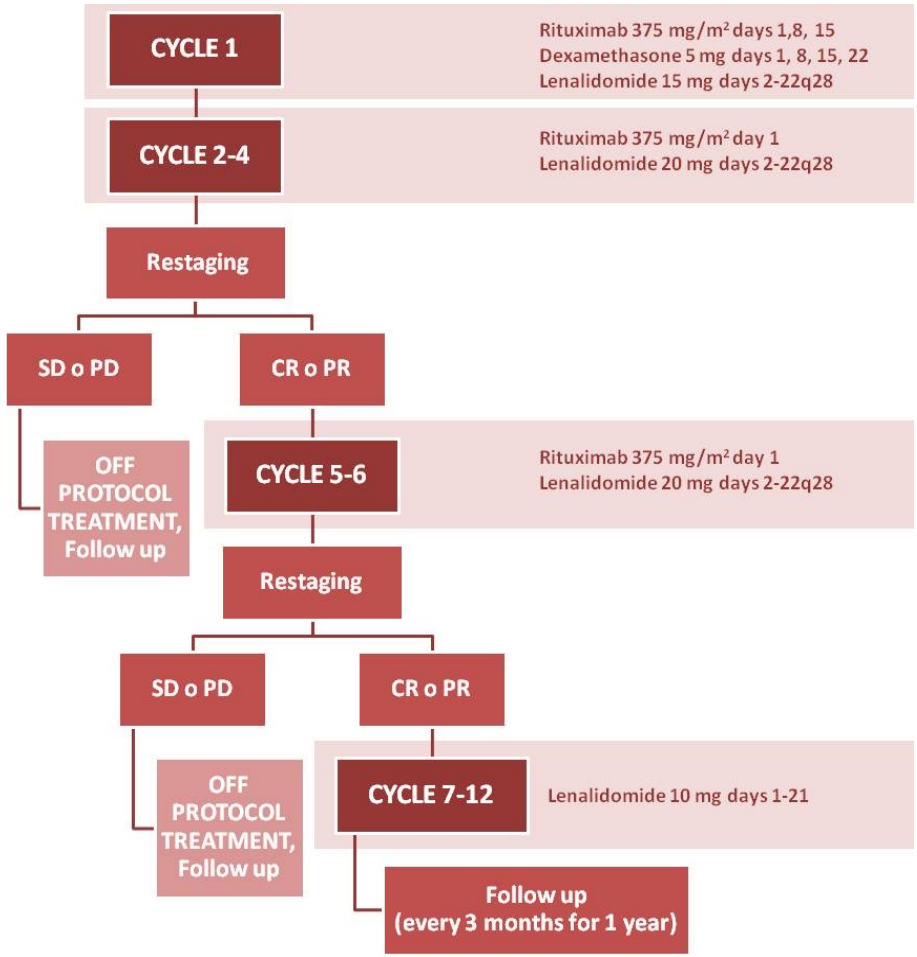
Orphan category with the highest unmet needs
Entry door for chemofree options?

Pieternella J. Lugtenburg,Pim G. N. J. Mutsaers
How I treat older patients with DLBCL in the frontline setting, Blood, May 2023

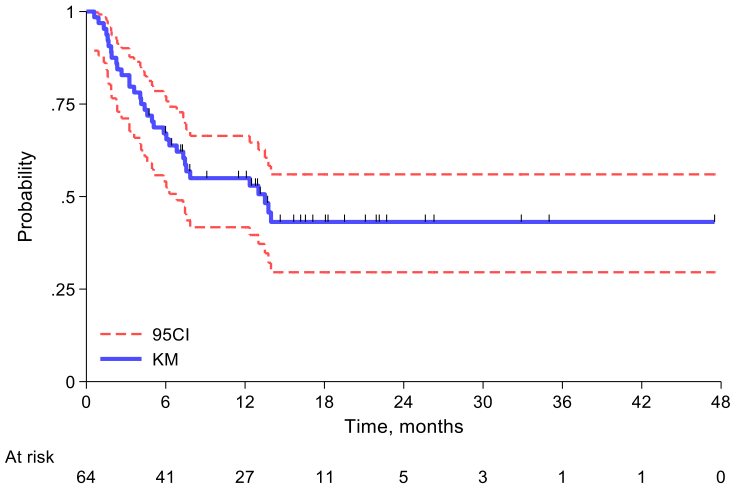
FONDAZIONE ITALIANA LINFOMI

Lenalidomide and Rituximab (ReRi) as front-line chemo-free therapy for elderly frail patients with Diffuse Large B-cell lymphoma. A phase II study of the Fondazione Italiana Linfomi

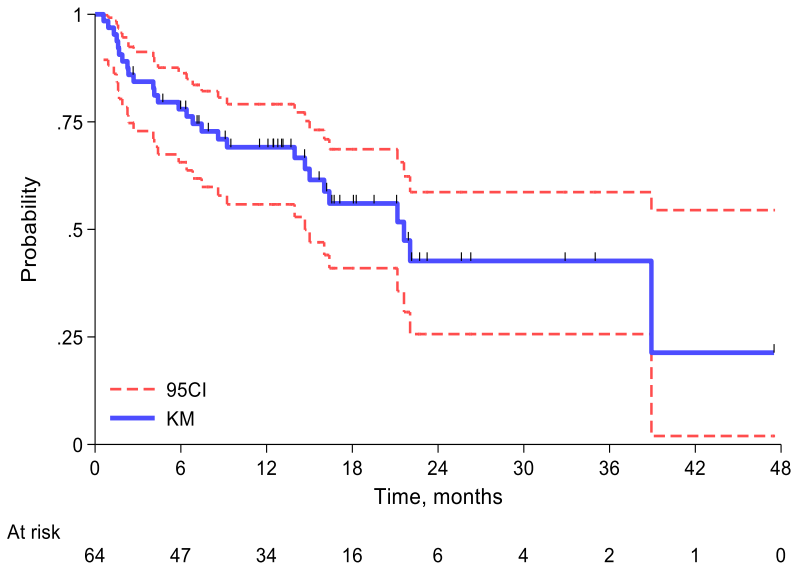
www.filinf.it



PFS



OS



68 enrolled pts,
(median age 83 y)
ORR 50% (27% CR)
Median PFS 14 m

Gini et al, Blood 2023

Mosunetuzumab monotherapy continues to demonstrate promising efficacy and durable complete responses in elderly/unfit pts with previously untreated DLBCL

Key inclusion criteria

- Previously untreated DLBCL or HGBL
- Age ≥80 years or 60–79 years with impairment in:
  - ≥1 ADL or
  - instrumental ADL or
  - inability to tolerate full dose chemoimmunotherapy

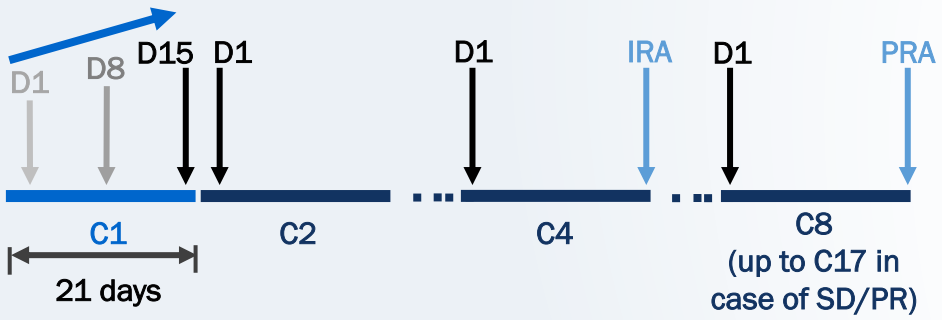
Study design

- Optional pre-phase treatment with prednisone ± vincristine
- Step-up dosing during C1
- Patients achieving a CR by C8 completed treatment
- Patients with a PR or SD at C8 could receive a further nine cycles (17 total)

Endpoints

- Primary endpoint: investigator-assessed objective response and ORR and CR rates by PET-CT[1]
- CRS was assessed by ASTCT criteria[2]

Mosunetuzumab dosing schedule



Median age, years (range)
83 (65–100)
<80 n 13 (24%)
≥80 n 41 (76%)

ECOG 0-1 65%

Best response, n (%) [95% CI]	N=54
ORR	30 (56) [41–69]
CR	23 (43) [29–57]
Response at EOT, n (%) [95% CI]	**N=54**
ORR	24 (44) [31–59]
CR	19 (35) [23–49]

*Re-treatment with mosunetuzumab was permitted if disease progression was subsequently observed.
IMC, independent monitoring committee; IRA, interim response assessment; PRA, primary response assessment.

Olszewski A et al, presented at ASH 2022

Chemo-free trials in elderly/frail patients

Rituximab + new CELMODs (e.g. CC99282-golcadomide)

Rituximab + new BTKi (e.g. Zanubrutinib)

Lenalidomide + Tafasitamab (LYSA group trial NCT04974216)

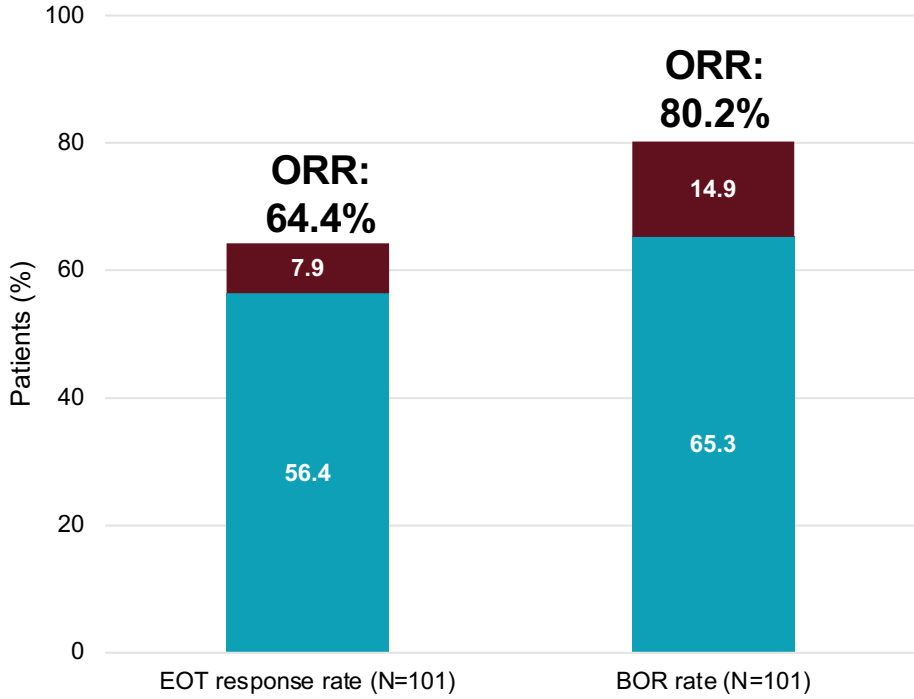
Bispecific MoAb +/- lenalidomide (e.g. epcoritamab + lena)

Bispecific MoAb in combination with other drugs (e.g. mosunetuzumab + polatuzumab)

Mosunetuzumab + Polatuzumab in untreated elderly unfit/frail DLBCL

n (%), unless stated otherwise		All N=108
Age in years	Median (range)	81 (66–94)
	≥80 years	66 (61.1)
Female		56 (51.9)
ECOG PS	0	31 (28.7)
	1	56 (51.9)
	2	21 (19.4)
Simplified geriatric assessment[1]*	Fit	1 (0.9)
	Unfit	64 (59.3)
	Aged <80 years	41 (38.0)
	Aged ≥80 years	23 (21.3)
	Frail	43 (39.8)

EOT response and BOR rates in Mosun-Pola target dose cohort



Almost all (107/108) pts were considered unfit or frail by simplified geriatric assessment[1] and had multiple comorbidities in addition to polypharmacy

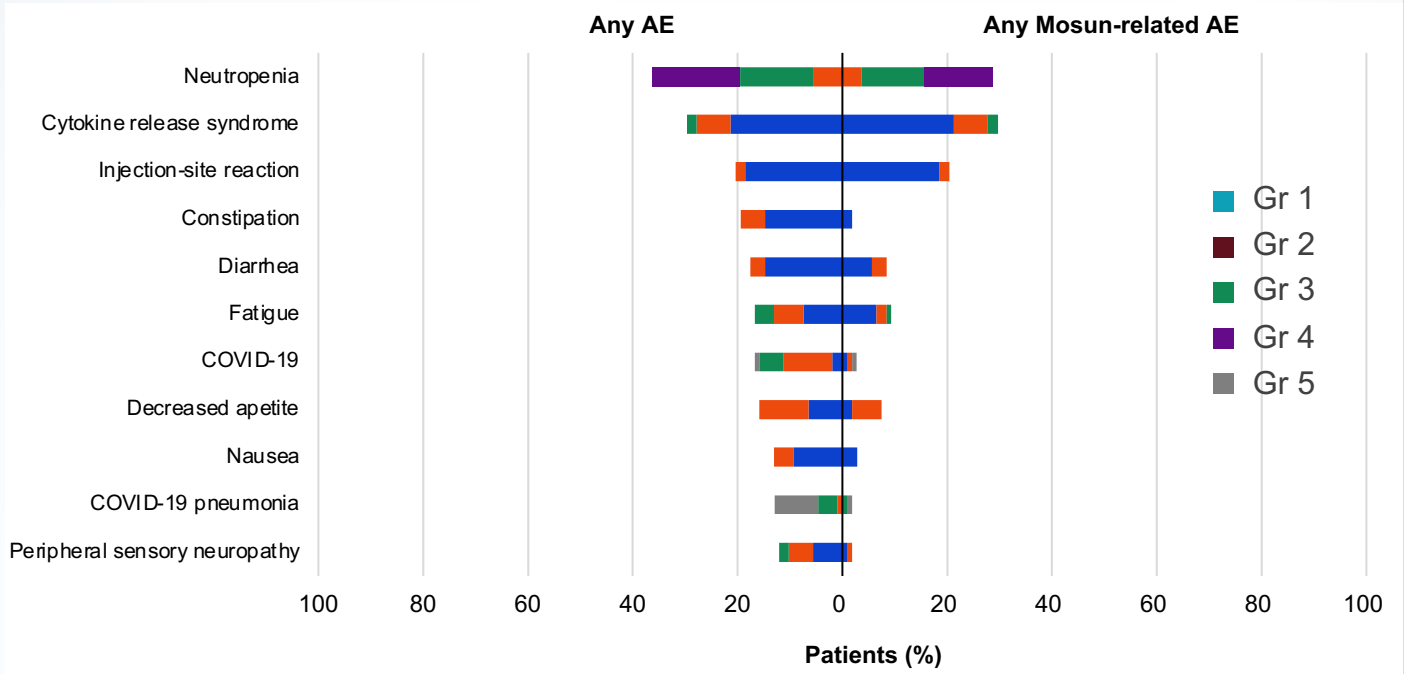
Data cut-off: August 5, 2023. *Includes assessments of ADL, IADL, CIRS-G, and MNA-SF. †Per local testing. aaIPI, age-adjusted International Prognostic Index; COO, cell of origin; DH, double hit; GCB, germinal center B cell; LDH, lactate dehydrogenase; MNA-SF, mini nutritional assessment-short form; TH, triple hit.

Olszewski et al., Oral presentation ASH 2023

AE summary

n (%)	All N=108
AE	107 (99.1)
Gr 3–4 AE	49 (45.4)
SAE	51 (47.2)
Gr 5 AE	18 (16.7)
AE leading to discontinuation	17 (15.7)
AE of interest	
Neutropenia*	39 (36.1)
Gr ≥3	33 (30.6)
Serious infection	27 (25.0)
Gr ≥3	25 (23.1)
ICANS-like events†	1 (0.9)
Gr ≥3	1 (0.9)‡

AEs by preferred term in ≥10% of patients by grade and relationship to study treatment



The safety profile of the Mosun-Pola combination was overall consistent with that of the individual drugs

Data cut-off: August 5, 2023. Multiple occurrences of the same AE in one patient are counted once at the highest grade; *31 pts (28.7%) received G-CSF; no febrile neutropenia was reported. †Defined as treatment-related neurological AEs potentially consistent with ICANS. ‡Gr 3 memory impairment occurred in one patient on Day 273 and was considered Mosun-related.
AE, adverse event; G-CSF, granulocyte-colony stimulating factor; Gr, Grade; ICANS, immune effector cell-associated neurotoxicity syndrome; SAE, serious AE.

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Conclusions

- Elderly/frail patients are hard to treat pts and require a multidimensional and personalized appoach
- Validated sGA and EPI are new tools to standardize clinical practice and research in older DLBCL patients
- Further development of GA is expected (longitudinal assessment, integration of novel items i.e. Sarcopenia, immune exhaustion?)
- High risk EPI and or frail pts at sGA represent a clinical unmet need that is currently addressed by clinical research (novel agents)