22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

Frail/Older Patients With DLBCL: A Persistent Challenge

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Disclosures

Consultancy fees: Seagen, Pfizer, AbbVie, Bristol-Myers Squibb, TG Therapeutics, ADC Therapeutics, Genentech, GenMab and Lilly Oncology

Challenges/Questions in Care of Older Adults

Functionomics

How to identify and utilize functional age?

Therapeutics

- How to optimize 1L therapy in unfit/frail patients?
- Can novel therapeutics move the needle in 2L+ setting?

Aging Biology

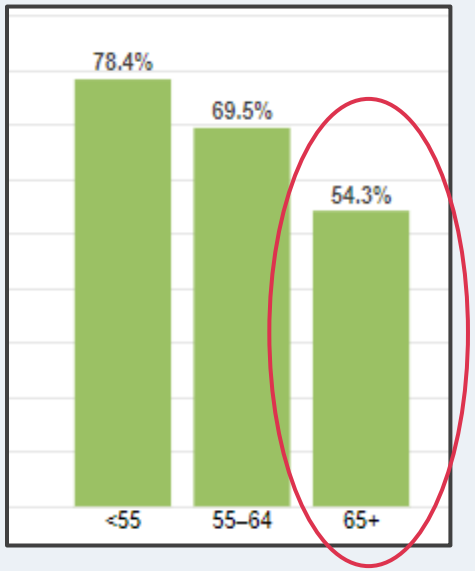
Can aging biology be leveraged to improve outcomes?

Value Based Care

How to study and incorporate:
-Time Toxicity
-Quality of life
-Patient Preferences into decision making?

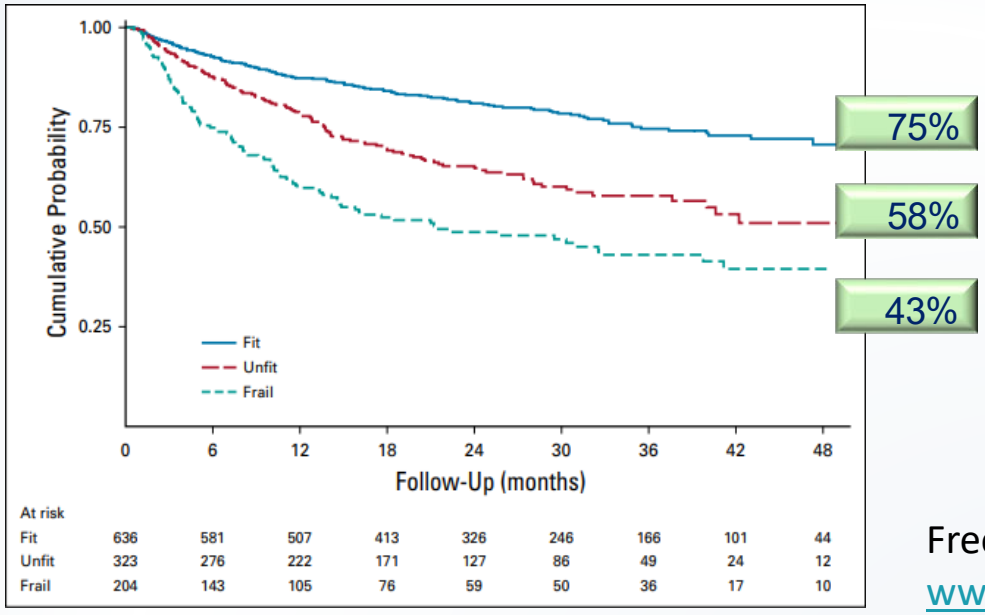
Importance of *Functionomics*

Older adults with DLBCL have worse outcomes



5-year Relative Survival

Simplified Geriatric Assessment (sGA)
The FIL tool allows risk stratification based on biological age



75%
58%
43%

3-year OS: 65% in entire cohort

Free Online Calculator:
www.filinf.it/epi

Simplified Geriatric Assessment				
Criteria	**Fit**	**Unfit (<80)**	**Unfit (≥80)**	**Frail**
ADL	≥5	<5	6	<6
IADL	≥6	<6	8	<8
CIRS-G	No comorbidities with score 3-4 ≤8 with score 2	≥1 with score 3-4 >8 with score 2	No comorbidities with score 3-4 <5 with score 2	≥1 with score 3-4 ≥5 with score 2
Age –years	<80	<80	≥80	≥80
1163 pts	55%	28%		18%

SEER database 2020
Akhtar...Torka et al. J Geriatr Oncol. 2022
Merli et al. JCO 2021 39:11, 1214-1223

Patient Characteristics vs Chemotherapy Dosing

R-CHOP vs R-mini-CHOP

Many datasets have now shown similar outcomes in ≥80 yrs

- UK data
- Danish data
- Flatiron data

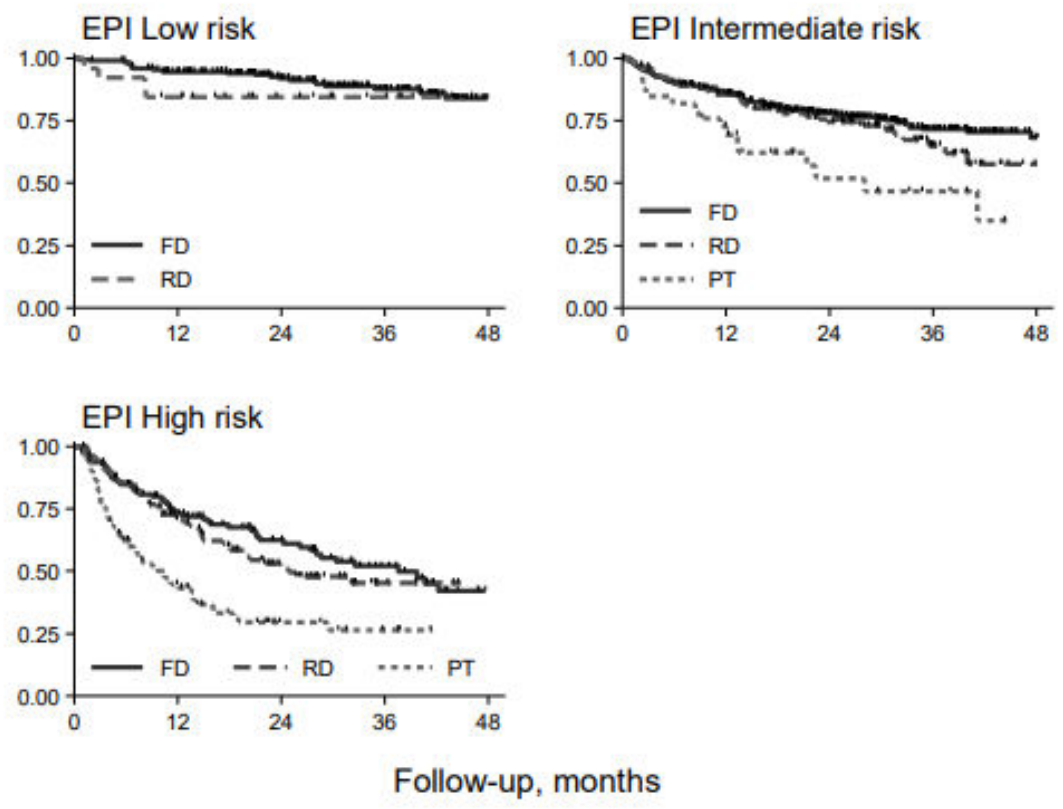
70-79 yrs: Full dose intensity is better than Reduced dose intensity

BUT

This difference is lost when patients are stratified by Elderly Prognostic Index (EPI)

Need more robust data

Overall Survival according to EPI risk groups and type of therapy



EPI: Elderly Prognostic Index

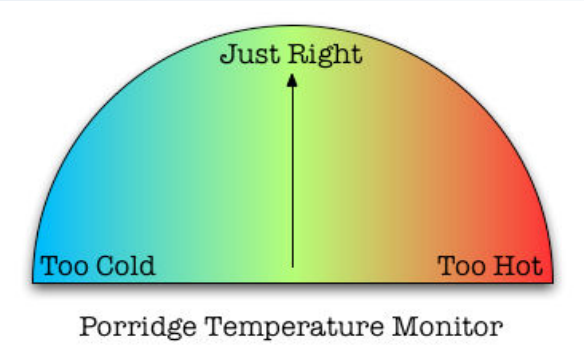
FD: full dose; RD: reduced dose, PT: palliative treatment

Two low-risk cases with palliative treatment excluded.

Eyre et al. J Intern Med 2019; 285: 681– 692
Juul et al. Eur J Cancer. 2018;99:86-96
Tucci et al. Haematologica 2022;108(4):1083-1091
Bair et al. Abs #68, ASH 2023

The Dilemma of Dosing

Use of reduced intensity treatment regimens can minimize toxicity but might also lead to poorer outcomes due to reduced disease control.



Porridge Temperature Monitor

Toxicity is more common in older adults, and those who experience it derive less benefit from treatment.

Prospective identification of pts at greatest risk of toxic events may allow tailored dose reductions in those vulnerable individuals and mark them for closer monitoring during therapy

- **Is FIL sGA the best tool?**
  - Still not widely used due to logistic barriers
  - Lack of validation in other populations
  - Does not allow patients less than 80 years of age to be classified as frail irrespective of other parameters
  - Cross comparison with other GA tools (e.g. CARG tool) challenging due to heterogeneity of instruments
  - Fitness is dynamic

Eyre et al. J Intern Med 2019; 285: 681– 692
Juul et al. Eur J Cancer. 2018;99:86-96
Tucci et al. Haematologica 2022;108(4):1083-1091.
Torka et al, JCO 43, 985-993(2025).

Comprehensive GA and Cancer and Aging Research Group Chemotherapy Toxicity Tool (CARG-TT)

may potentially improve prediction of chemotoxicity, while CGA better identifies patients at risk of poorer survival.

Tang et al, Abs#3660, ASH 2024

Vulnerable Elders Survey- 13 (VES-13)

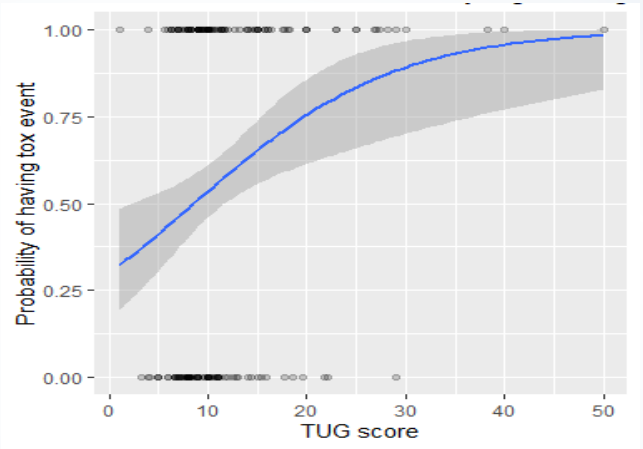
Can identify older adults with high rates of unplanned hospitalization, grade 3+ toxicity, dose reductions, and disease progression/death

Johnson et al, Abs#400, ASH 2024

Outcome	Not Vulnerable (N=57)	Vulnerable Patients (N=48)
Grade 3+ non-hematologic toxicity	23% (13/57)	40% (19/47)
Dose reduction	16% (9/57)	31% (15/48)
Early therapy cessation	7% (4/57)	13% (6/46)
Unplanned hospitalization	30% (17/57)	48% (23/48)
Intensive care unit admission	7% (4/57)	8% (4/48)
Quality of life decline	16% (8/49)	37% (13/35)
PFS, median, mo (95% CI)	Not reached	33.9 (29.6-not reached)
Death within 1 year	0% (0/57)	17% (8/48)

Timed-Up and Go (TUG) Time was Independently Associated with Toxicity

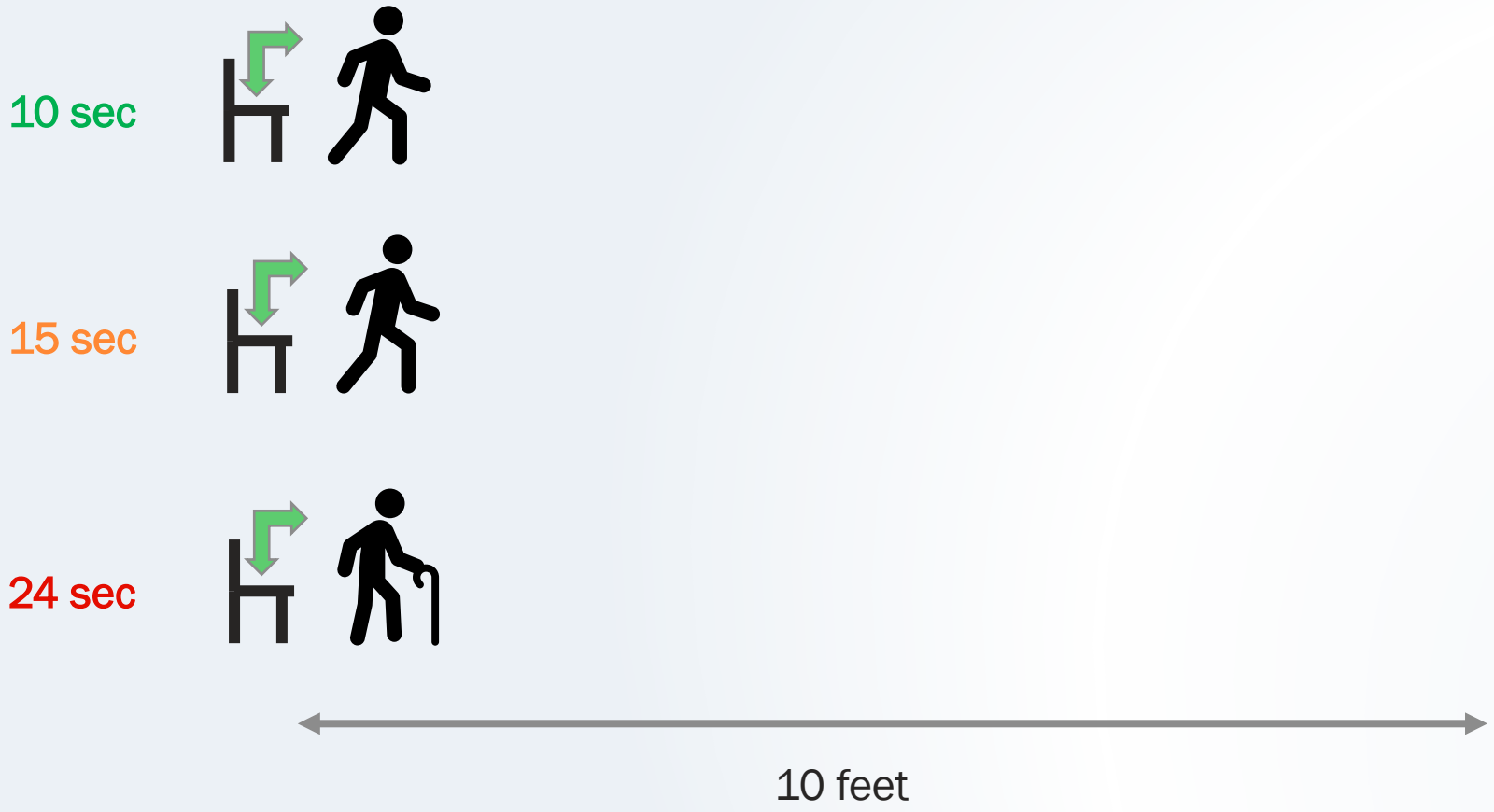
Torka et al, Abs#4474, ASH 2024



- For each 1-sec increase in TUG score, the odds of an event increased by a factor of 1.1 (10%).
- A 5-second increase would increase odds by a factor of 1.6, and a 10-second increase would increase odds by a factor of 2.6.
- Change in TUG time between cycles was not significant in predicting Stox.
- The actual TUG score itself had the effect at any given cycle.
- Effect was similar to that of the TUG baseline score analysis.

Practical Implications

Predicted Probability of Primary Toxicity Endpoint by Baseline TUG Score



Toxicity Risk by TUG Time

53 %

66 %

84 %

TUG score	Predicted risk
2	0.33
3	0.35
4	0.37
5	0.40
6	0.43
7	0.45
8	0.48
9	0.51
10	0.53
11	0.56
12	0.58
13	0.61
14	0.64
15	0.66
16	0.68
17	0.71
18	0.73
19	0.75
20	0.77
21	0.79
22	0.80
23	0.82
24	0.84
25	0.85
26	0.86
27	0.88
28	0.89
29	0.90
30	0.91

Torka et al, Abs#4474, ASH 2024

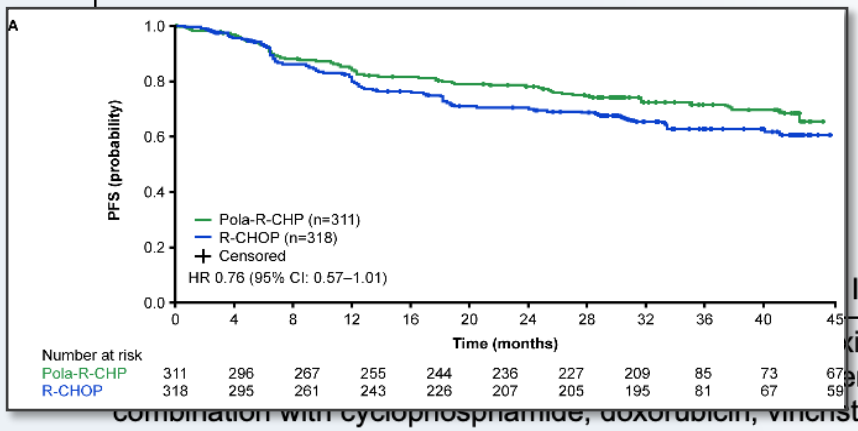
Current Approach to 1L Management of Older Adults with DLBCL

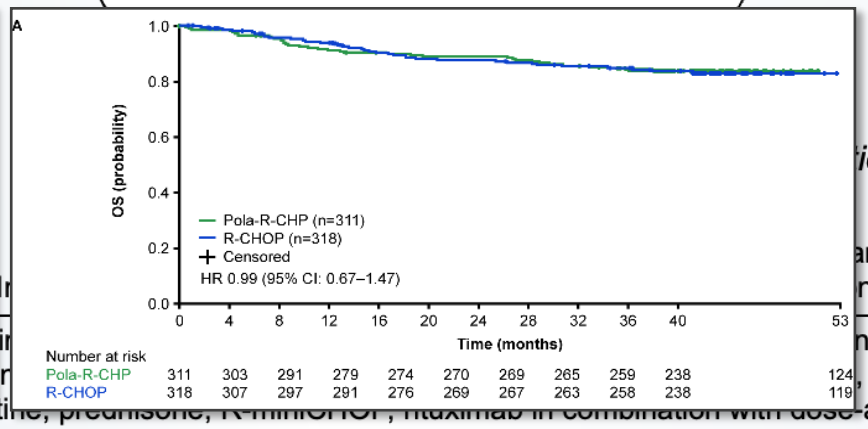
Older adult with newly diagnosed DLBCL (age≥65)

Fitness evaluation: sGA, TUG, Referral to Geriatric clinic as needed
Prephase therapy
Clinical Trial Screening*

Deaths related to treatments during treatment period seems to be reduced by introduction of prephase in LNH-09-7B protocol (8.3% [10/149] in LNH-03-7B versus 0% [0/120] in LNH-09-7B.

Fit patients	**Unfit patients**	**Frail patients**
Standard of care		
Curative chemotherapy R-CHOP Pola-R-CHP DA-EPOCH (in select cases)	**Attenuated chemotherapy** May intensify if fitness improves with therapy R-miniCHOP Pola-R-miniCHOP	# **Consider palliative therapy**





Major unmet need
-High risk of toxicity
…ious introduction of novel agents

…rticipate in clinical trials when available
…n patient preferences and goals of care

…ne, prednisone; Pola-R-miniCHOP,
…, rituximab; R-CHOP, rituximab in
…combination with cyclophosphamide, doxorubicin, vincristine, prednisone; R-miniCHOP; rituximab in combination with dose-attenuated cyclophosphamide, doxorubicin, vincristine, prednisone; sGA, simplified geriatric assessment; TUG, timed up and go test

Unfit and frail older adults with DLBCL: Recent and Upcoming studies ‘Chemo-based’

Trial	POLAR-BEAR	S1918	ARCHED/ GLA 2022-1	MSKCC GLORY	ZR2-MiniCHOP
Intervention	R-miniCHOP vs Pola-R-miniCHP	R-miniCHOP +/- oral azacitidine (CC-486)	R-miniCHOP +/- acalabrutinib	Glofit+Pola+R-miniCHP PET adapted	ZR2 induction→ miniCHOP x 4-6
Pt population	≥75 yrs and frail ≥80 yrs	≥75 yrs	>60 yrs and unfit for full dose R-CHOP >80 yrs	≥65 yrs Unfit Anthracycline eligible	65-80 yrs ECOG ≥2 >80 yrs
GA based enrollment	Yes	No	Investigator assessment after sGA	Yes	No
Phase	3	3	3	2	2
Status	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
ORR/CR (%)	NA	NA	NA	NA	95/90
Survival	NA	NA	NA	NA	2y PFS 78% 2y OS 83% No CNS relapse
Toxicity	G3/4 heme tox same in both arms More G1-2 GI Aes with pola	NA	Serious infn and bleeding similar. More cardio SAE in acala arm.	NA	Mainly heme

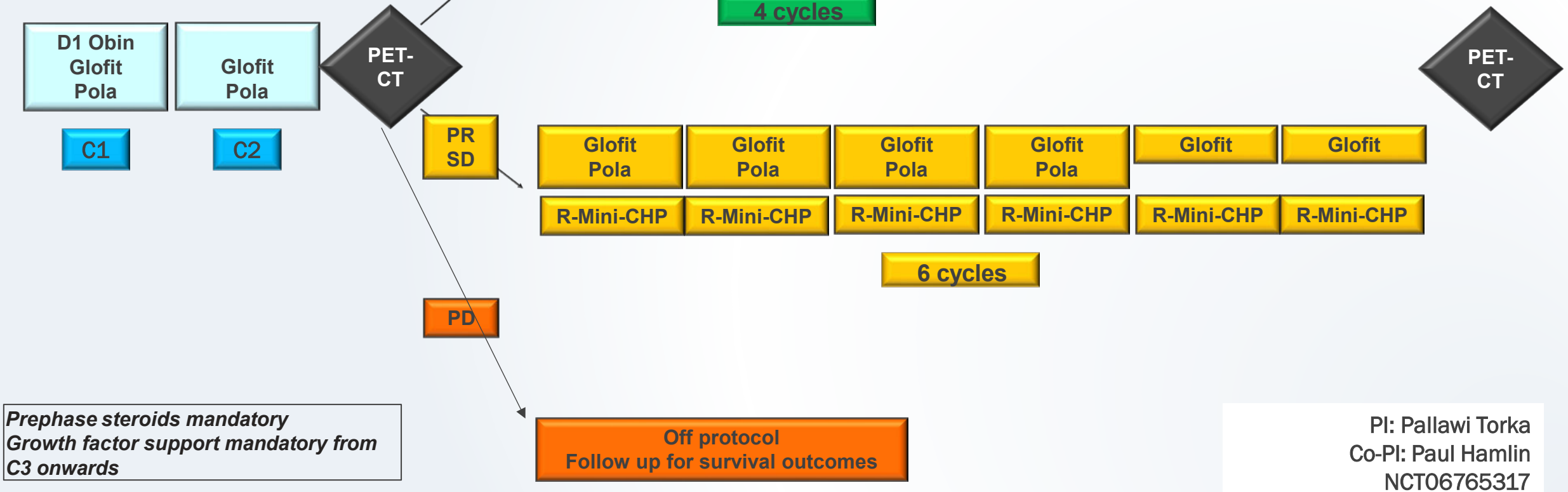
Jerkeman et al, EHA 2023, Brem et al, JGO 2022, Christofyllakis et al, Abs#4498, ASH 2024, Sun et al, Abs#1733, ASH 2024

MSKCC GLORY trial: Optimizing Frontline Therapy for DLBCL in Older Adults: A GLOfitamab-Based, Response-Adapted, Window-StYle Trial (GLORY)

- Patients ≥ 65 years
- Newly diagnosed DLBCL, HGBCL or transformed lymphoma
- Unfit or frail by sGA
- Stage 2B, 3 or 4 disease
- Any IPI score
- Anthracycline eligible

Primary Endpoints
- CRR at end of therapy
- CRR after 2 cycles of glofit-pola

Key Secondary Endpoints
- ORR, DOR, DOCR, PFS, OS
- Safety
- ctDNA kinetics



Prephase steroids mandatory
Growth factor support mandatory from C3 onwards

PI: Pallawi Torka
Co-PI: Paul Hamlin
NCT06765317

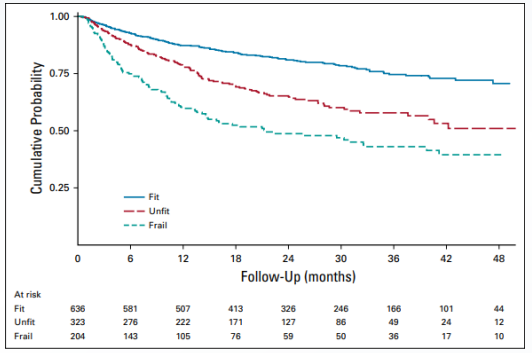
Unfit and frail older adults with DLBCL: 'Chemo-free' trials

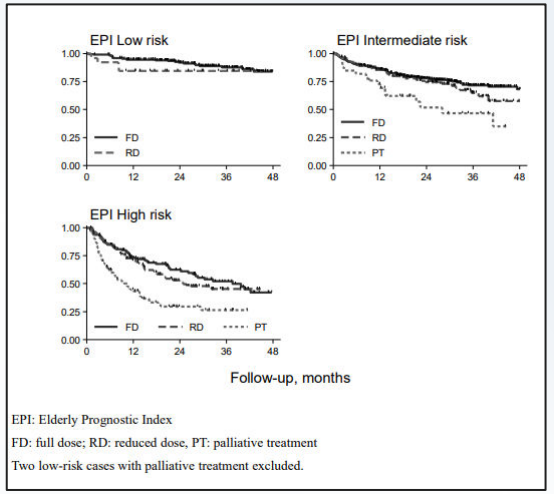
Trial	Mosun	Mosun+ Pola	LOTIS-9	EPCORE-DLBCL3	sR2	ZR2	Pola-R2	R-Pola-Glo
Intervention	Single agent BiAb-Mosunetuzumab	BiAb + ADC	Loncastuximab + Rituximab	Epcoritamab monotherapy x 1 year	Sintilimab, rituximab, lenalidomide x8 cycles→ Len maintenance x 2y	Zanubrutinib, rituximab, lenalidomide x 8 cycles→ Len maintenance	Polatuzumab, rituximab, lenalidomide x 8 cycles	BiAb+ADC+ R
Pt population	**>60 yrs with ECOG PS ≥ 2 or ≥80 yrs Ineligible for full dose CIT**	**65-79 yrs and unfit or ≥80 yrs Ineligible for full dose CIT**	**≥80 yrs Unfit or frail**	**≥75 yrs and comorbidities Or ≥80 yrs**	**>60 yrs with ECOG PS ≥ 2 or >70 yrs**	**≥75 yrs unfit or frail by sGA**	**≥70 years old unfit or frail by sGA**	**>60 yrs Ineligible for full dose CIT**
GA based enrollment	Yes	Yes	Yes	No	No	Yes	Yes	No
Phase	1/2	2	2	2	2	2	2	2
Status	Follow up	Follow up	Stopped	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Prelim data	54 pts 83 y (65-100)	108 pts 81 y (66-94)	40 pts	44 pts 81 y (77-95)	18 pts 75 y	24 pts 81.5 y	21 pts 79.5 y (73-90)	
ORR/CR (%)	**67.7/41.9**	**64.4/56.4**	**94.1/58.8**	**74/64**	**85.7/78.6**	**100/87.5**	**93/93**	**NA**
Survival	NA	PFS: 11.9 months	NA	NA	1y PFS 80.8% 1y OS 92.9%	NA	NA	NA
Toxicity	CRS 22.5% No G3+ CRS	CRS 20% G3 2% 16% deaths, mainly due to COVID pneumonia	Deaths due to fatal respiratory events	CRS 68% G3 5% ICANS 9% G3 2% 4 fatal TEAEs	Mainly heme	Mainly heme Pneumonia 11.5%	Data immature	12

Olszewski et al, ICML 2023, Olszewski et al, ASH 2023, Westin et al, ASH 2022, Morschhauser et al, Abs#867 ASH 2024, Zou et al, Abs#1732, ASH 2024, Wei et al, Abs#3121 ASH 2024, Wang et al, Abs#1728, ASH 2024, Melchardt et al, ASH 2023

Unfit/frail Older Adult Clinical Trials: Some Observations

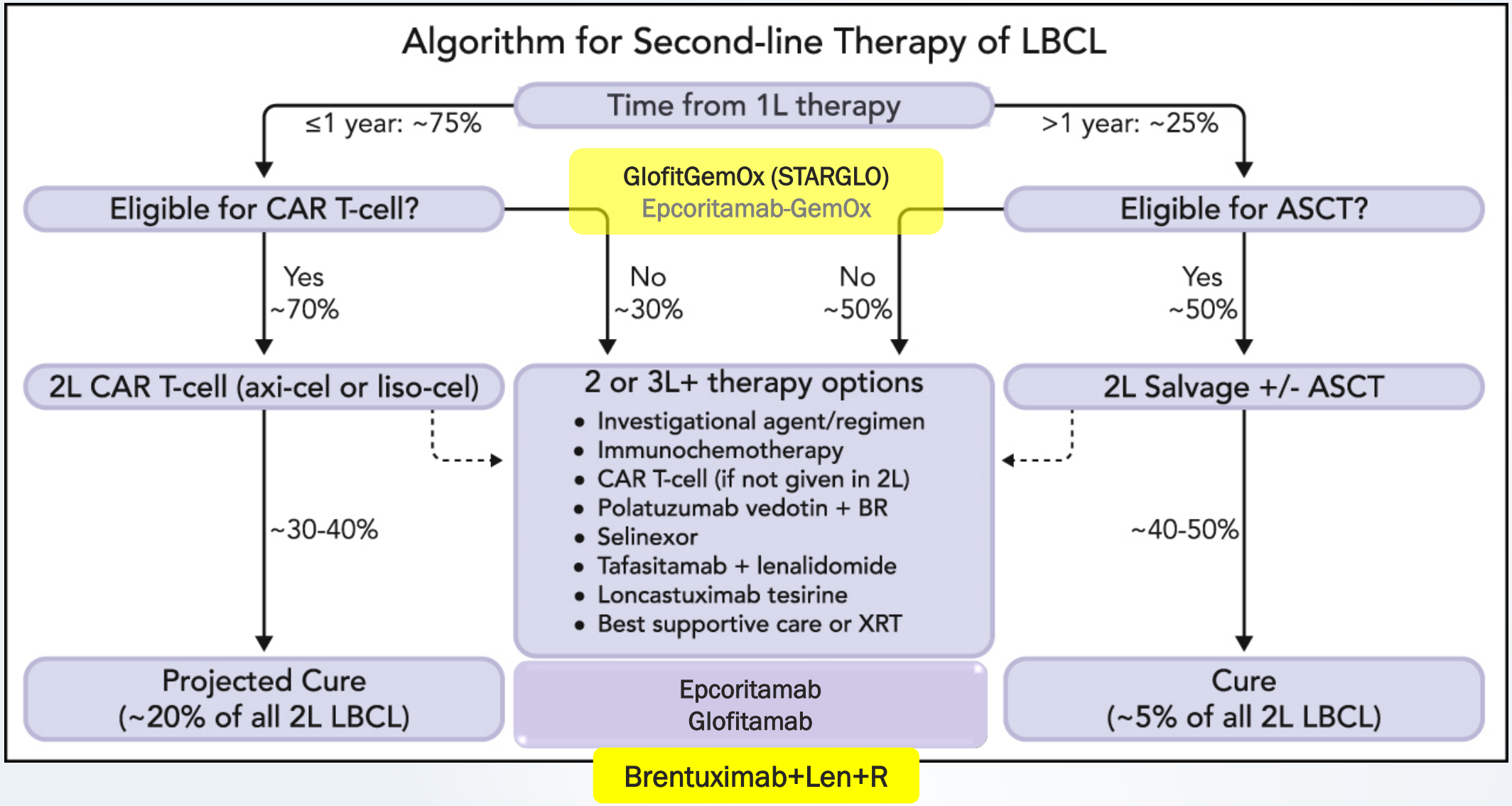
- Encouraging to see high response rates
- No formal criteria for fitness in some studies
- Investigator discretion to decide that patient is ineligible for full dose R-CHOP introduces bias
- Unfit and frail categories considered together
- Is it fair to deprive 'unfit' pts of proven 'curative' therapy?
- sGA is an 'imperfect' tool





Fit	Unfit *(anthracycline eligible)*	Frail *(anthracycline ineligible)*
Can be included in standard age-agnostic trials	Goal is to **preserve/increase cure rates with less toxicity**	Major unmet need
	Dose-attenuated chemo-based backbone	Chemo-free combinations
Biology based; response adapted therapies		

Treatment options for Relapsed/Refractory DLBCL



Westin et al. Blood. 2022 May 5;139(18):2737-2746, Abramson et al, Lancet 2024, Bartlett et al, JCO 2025,

Options for Tx-ineligible, CAR-T ineligible or post CAR-T progression

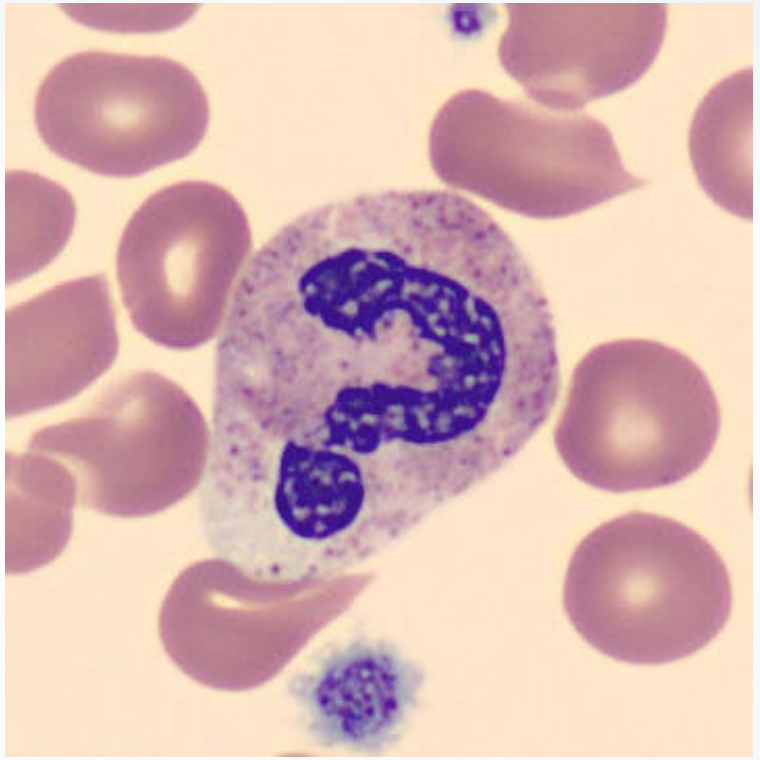
	Pola-BR vs BR	Tafasitamab-Lenalidomide	LoncaT	Epcoritamab	Glofitamab	Glofit-Gem-Ox vs R-Gem-Ox	Brentuximab-Len-R vs Len-R
Population	2L+	2-4L	3L+	3L+	3L+	2L+	3L+
N	40 vs 40	81	145	157	155	183 vs 91	112 vs 118
Age≥65	65% vs 58%	56% (>70y)	45%	49%	55%	63% vs 62%	71% vs 64%
Oldest patient	84 vs 86	76	-	83	90	NA	87 vs 89
ORR (CR)%	45 (40) vs 17.5 (17.5)	57.5 (40)	48.3 (24.1)	63 (40)	52 (39)	68.3 (58.5) vs 40.7 (25.3)	64 (40) vs 42 (19)
mPFS (m)	9.5 vs 3.7	11.6	4.9	4.4	4.9	13.8 vs 3.6	4.2 vs 2.6
mOS (m)	12.4 vs 4.7	33.5	9.9	18.5	12 mo 50%	25.5 vs 12.9	13.8 vs 8.5
Grade 3/4 AEs (>10%)	Cytopenias Infections	Cytopenias Febrile Neutropenia	Cytopenias	CRS 50% G3 3% ICANS 6%	CRS 64% G3 4%	CRS 44%	Cytopenias Diarrhea

Useful in rare circumstances: BTK inhibitors, Lenalidomide, Rituximab alone, Selinexor

Varma et al. Hematol Oncol. 2023 Jun;41 Suppl 1:92-106; Thieblemont et al, Leukemia 2024; Dickinson et al, NEJM 202; Abramson et al, Lancet 2024, Bartlett et al, JCO 2025.

Conclusions

- Unfit/frail older adults with DLBCL should be considered for curative anthracycline-based chemotherapy regardless of age.
- sGA, VES-13 and TUG time can assist with identifying vulnerable patients at highest risk of toxicities for pre-emptive interventions. TUG time is a dynamic tool that can be implemented prior to each cycle for risk assessment.
- Encouraging response rates seen in 1L with chemo-free combinations, data on durability eagerly awaited.
- CAR-T cell therapy remains the best option for older adults with R/R DLBCL.
- Outcomes remain suboptimal in 2L+ setting in CAR-T ineligible pts with current therapies, several ongoing trials are evaluating novel combinations (e.g. MSKCC ECLAT study with epco-tafa-len).



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