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Therapy of DLBCL in the elderly: the next 'victim' in becoming chemo free?

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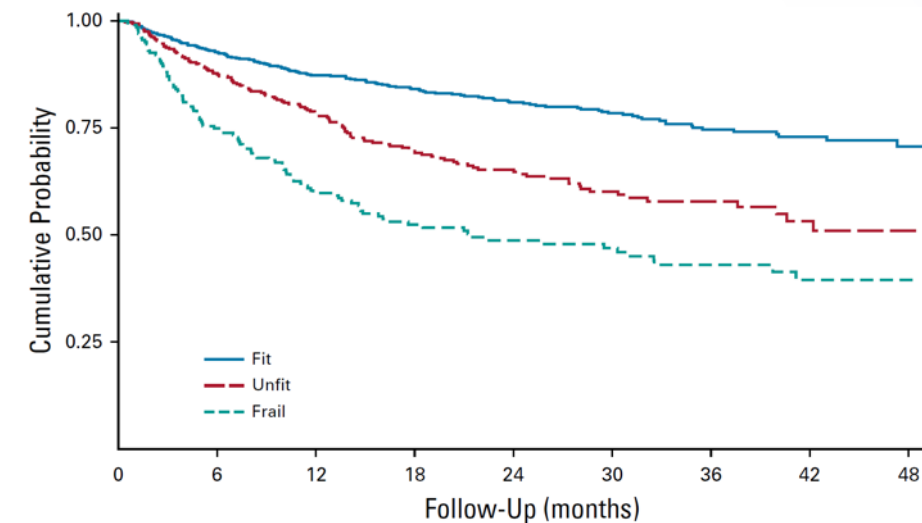
Who are “elderly” patients?

- Definition
 - 65: American Society of Clinical Oncology
 - 70: International Society of Geriatric Oncology
- Importance of assessment of functional status
 - Chronological age is less important
 - Geriatric assessment
 - **Not standardized**
 - Provides challenge in interpreting trial or research results
- SEER-Medicare study
 - 57% of patients age >85 only received palliative care or no treatment

How can we assess/define frailty?

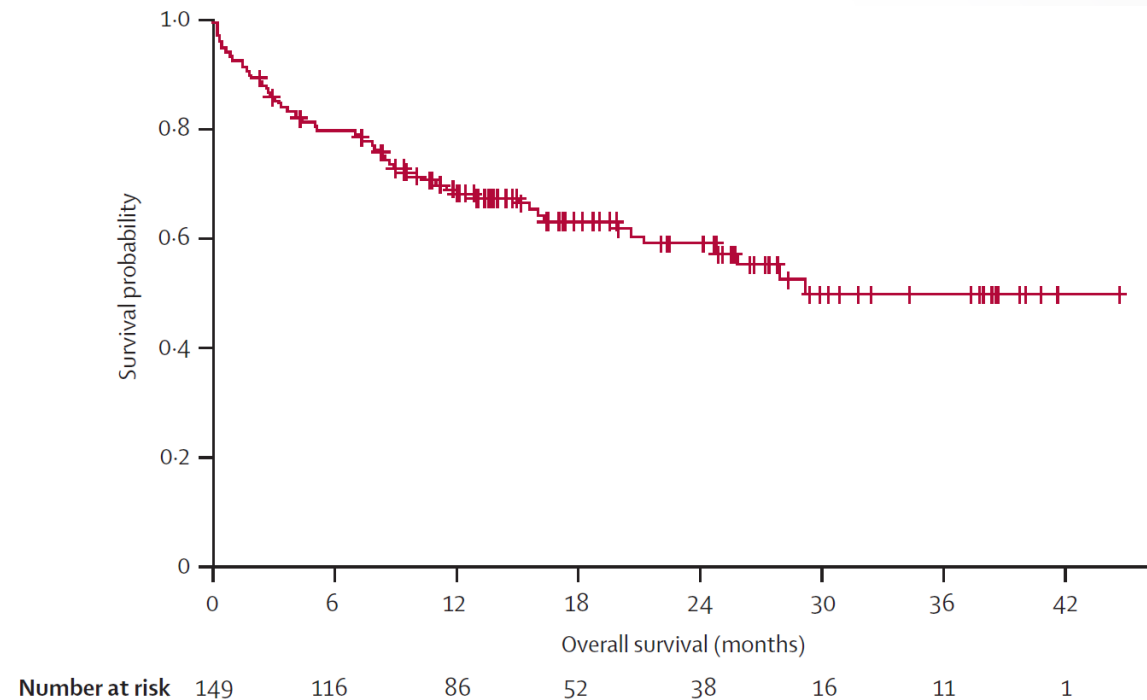
- FIL study
- “Simplified” Geriatric Assessment
- Prospective cohort
- 1,163 patients with age ≥ 65
- Significantly correlates with OS
 - 3-year OS
 - Fit: 75%
 - Unfit: 58%
 - Frail: 43%
- Can be used as an eligibility criteria (cumulative)

	FIT	UNFIT	FRAIL
ADL	6	5*	$\leq 4^*$
IADL	8	7-6*	$\leq 5^*$
CIRS-G	0 of score 3-4 < 5 of score 2	0 of score 3-4 5-8 of score 2	≥ 1 of score 3-4 >8 of score 2
Age	-	≥ 80 FIT	≥ 80 UNFIT



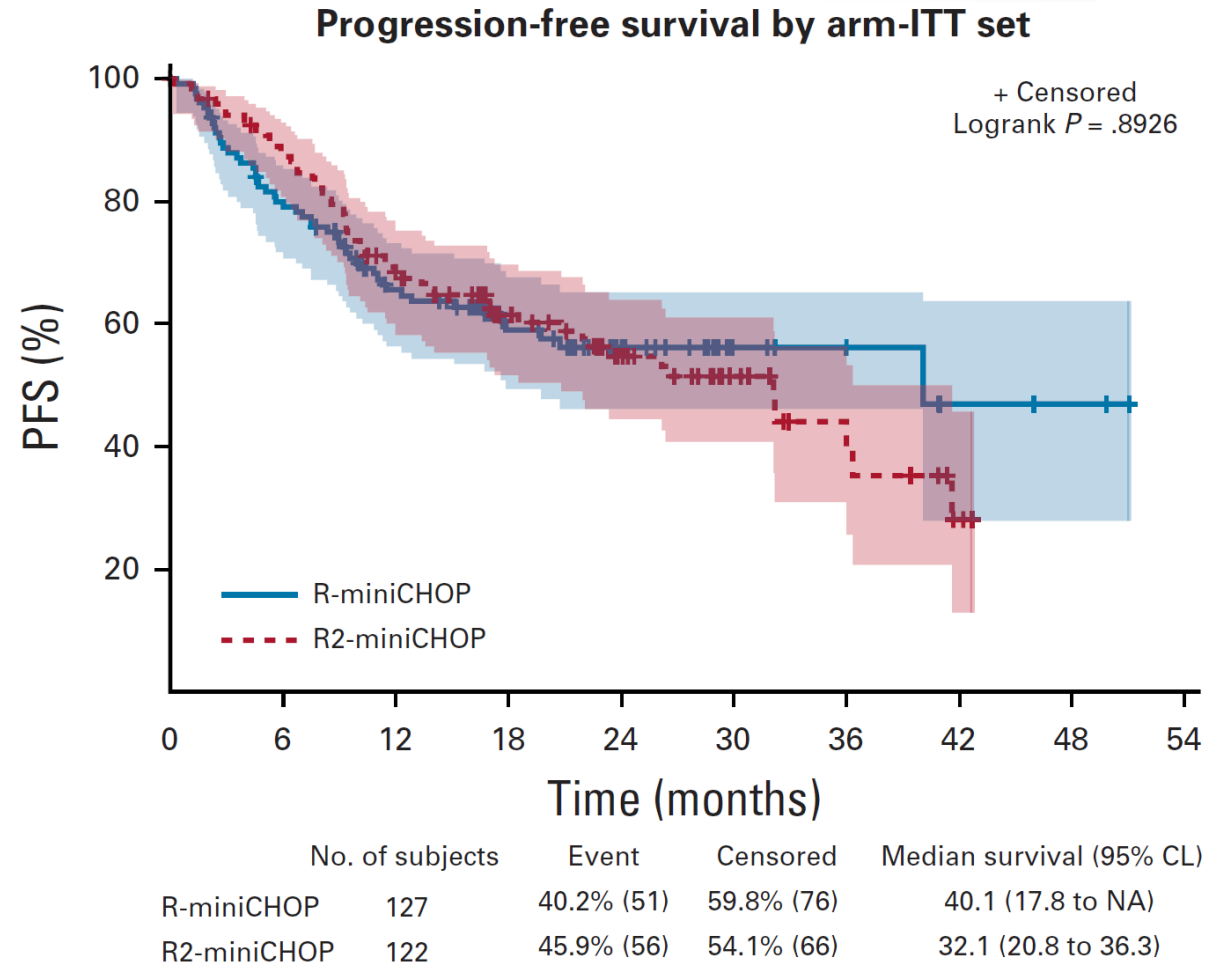
There is unmet need for older patients

- PFS from R- mini-CHOP is not adequate: 2-yr 47%
- Only 72% received the full intended 6 cycles
- 12 deaths, 8% grade 5 toxicity
- Unmet need to improve outcome
- Can we get rid of chemotherapy?



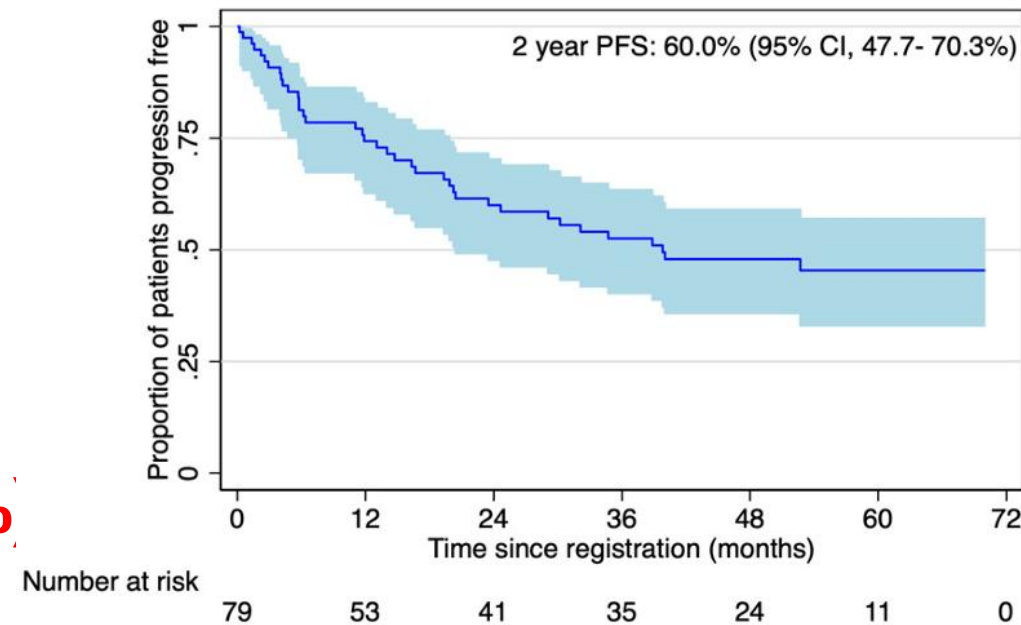
R2 + miniCHOP: LYSA study

- 249 patients
- R-miniCHOP (127) vs R2-miniCHOP (122)
- 15% patients stage I/II
- CR/uCR 53% vs 58%
- 2-year PFS
 - 56.2% in the R-miniCHOP
 - 54.8% in the R2-miniCHOP
- 15 deaths attributed to Treatment (6%)
- No improvement

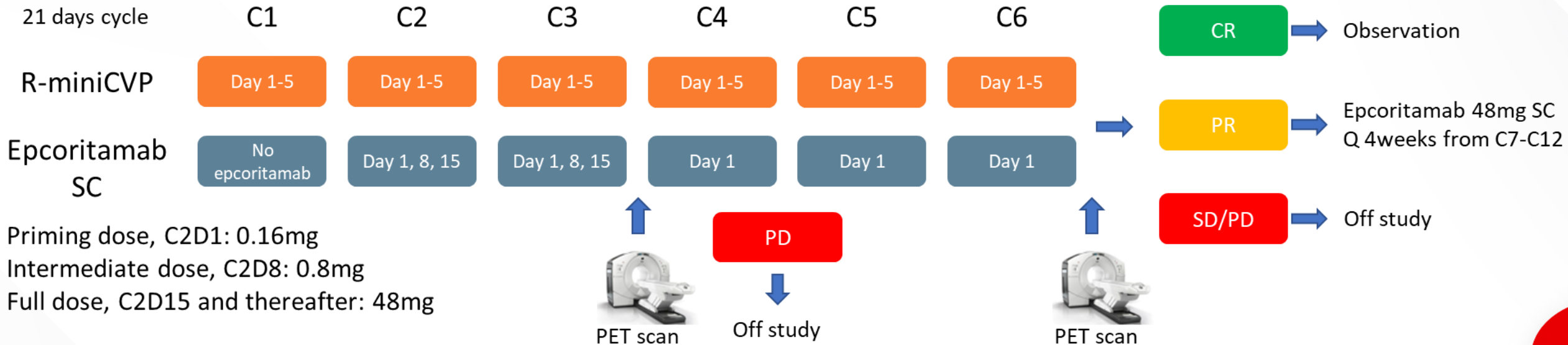


Ibrutinib + R-miniCHOP: Australian study

- Single arm 79 patients
- Age ≥ 75 are eligible, median age 82 (75-95)
- IPI high in 63%
- ORR 76%, CR rate 70%
- 2-year endpoint
 - PFS: 60% (significant from 47% ref)
 - OS: 68% (not significant from 59% ref)
- **5 deaths attributed to Treatment (7%)**
 - **12 other not reported**
- **Worked but toxic (and made trial negative)**



MDACC 1L trial for unfit/frail patients

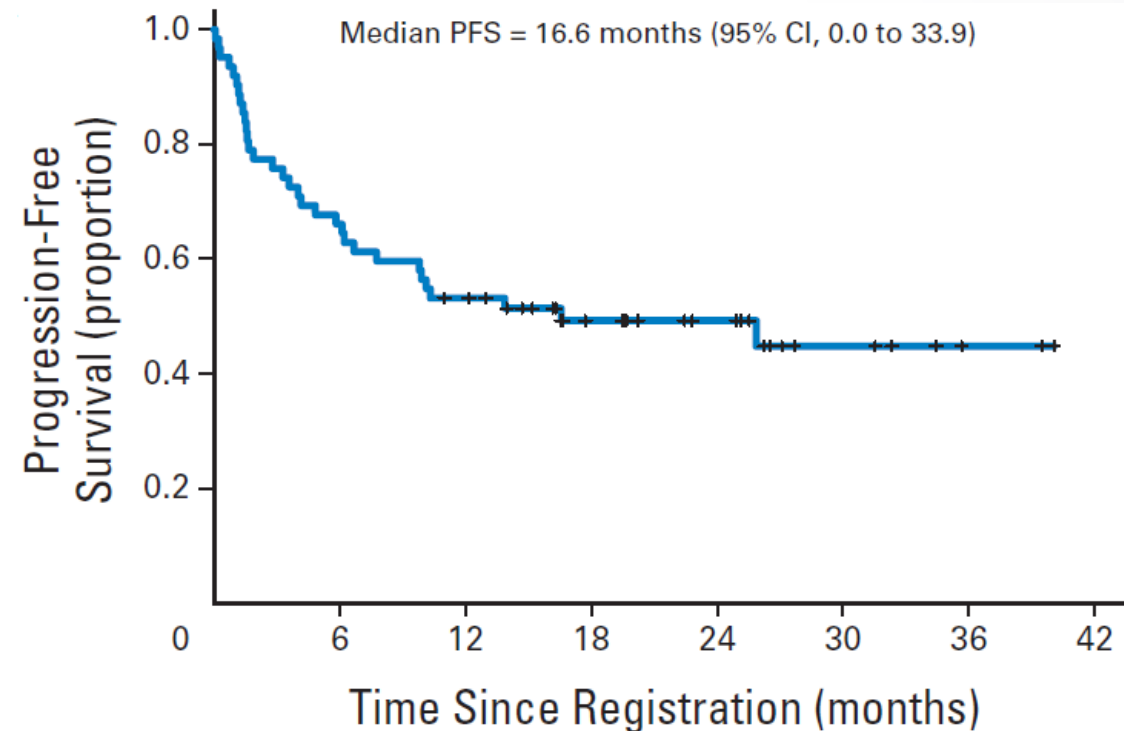


- **Hypothesis**

- **Epcoritamab in combination with R-miniCVP is tolerable and efficacious in frail patients with DLBCL**

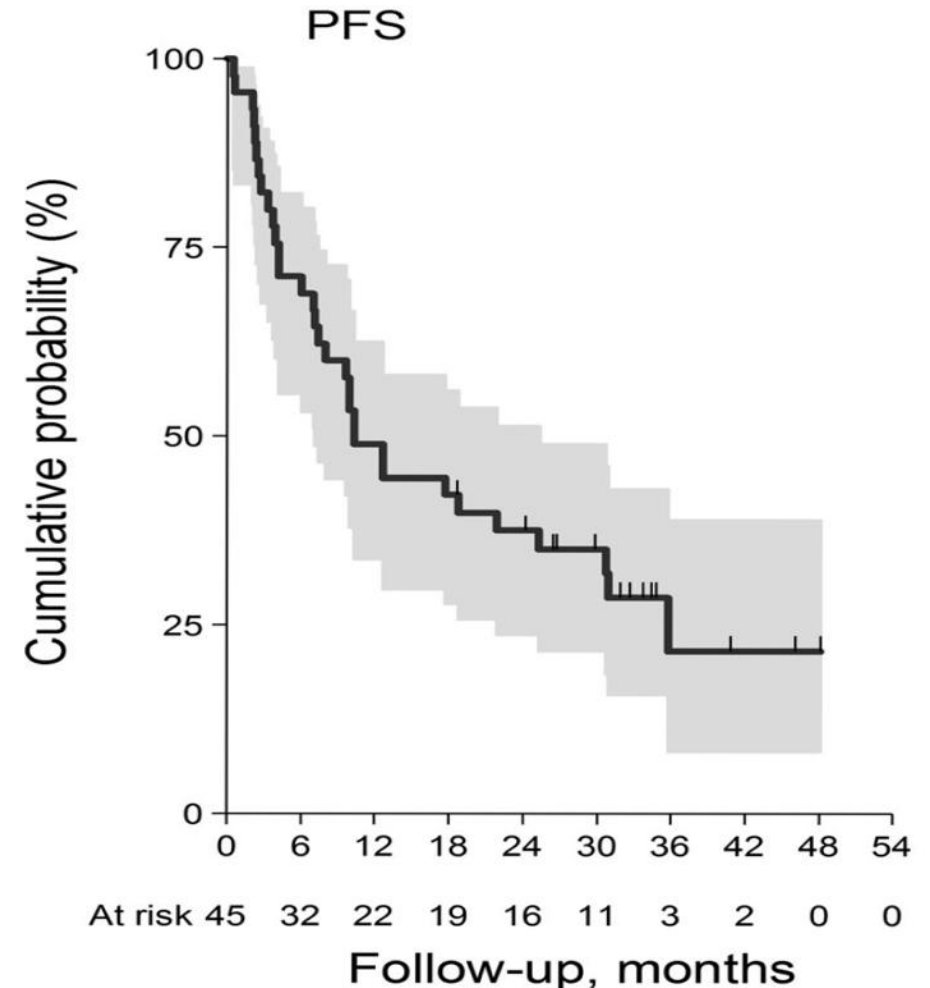
Non-anthracycline 1L treatment: R-GCVP

- 61 patients
- Median age: 76.5 (52-90)
 - Not older patients focused
 - Mainly eligible due to cardiac reason
- ORR: 61%, CR rate: 29% (non PET)
- 2-year outcomes
 - PFS: 50%
 - OS: 56%
- Only 52% received full cycles



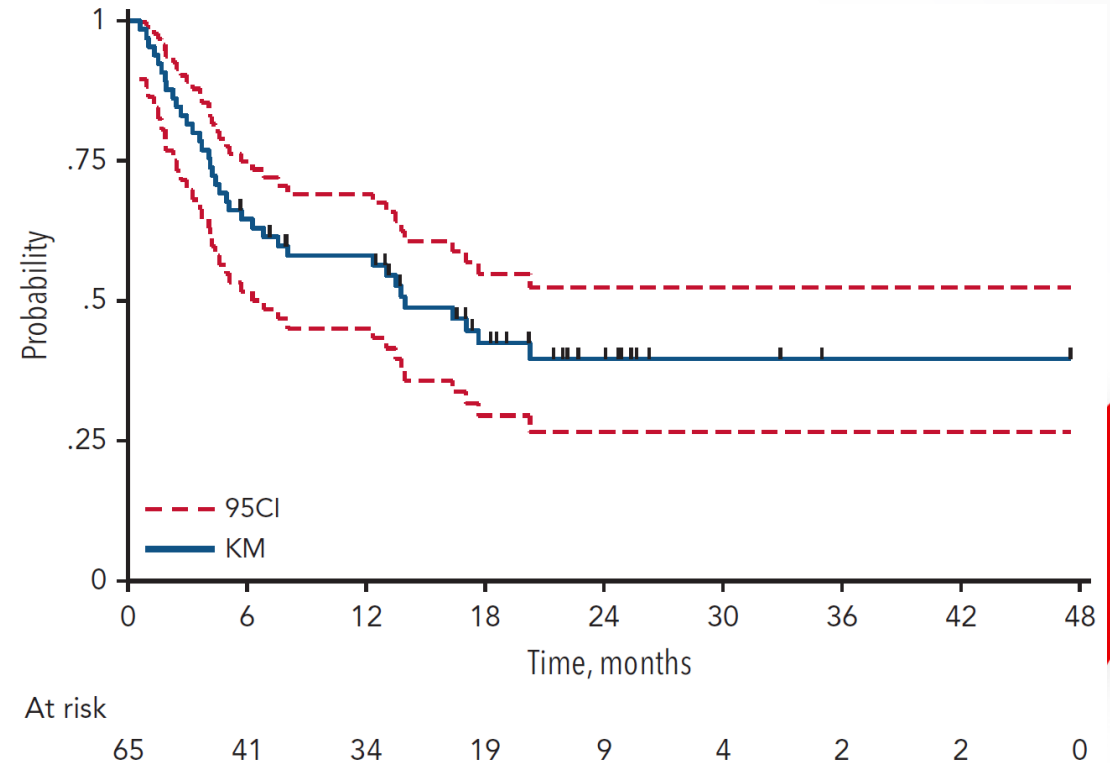
Non-anthracycline 1L treatment: BR

- 49 patients
- Dose of Bendamustine, 90mg/m²
- Median age: 81 (71-89)
- ORR: 62%, CR rate: 53% (non PET)
- 2-year outcomes
 - PFS: 38%
 - OS: 51%
- Only 52% received full cycles
- 13 (29%) primary refractory



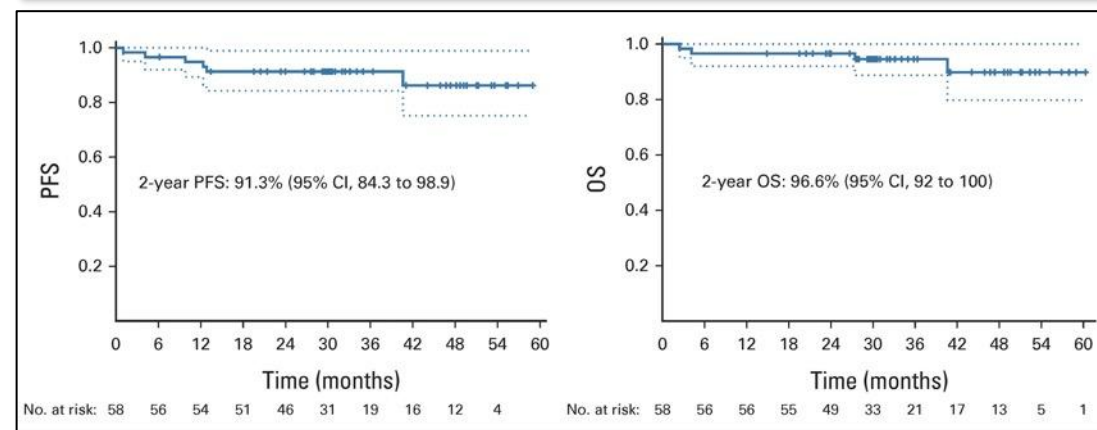
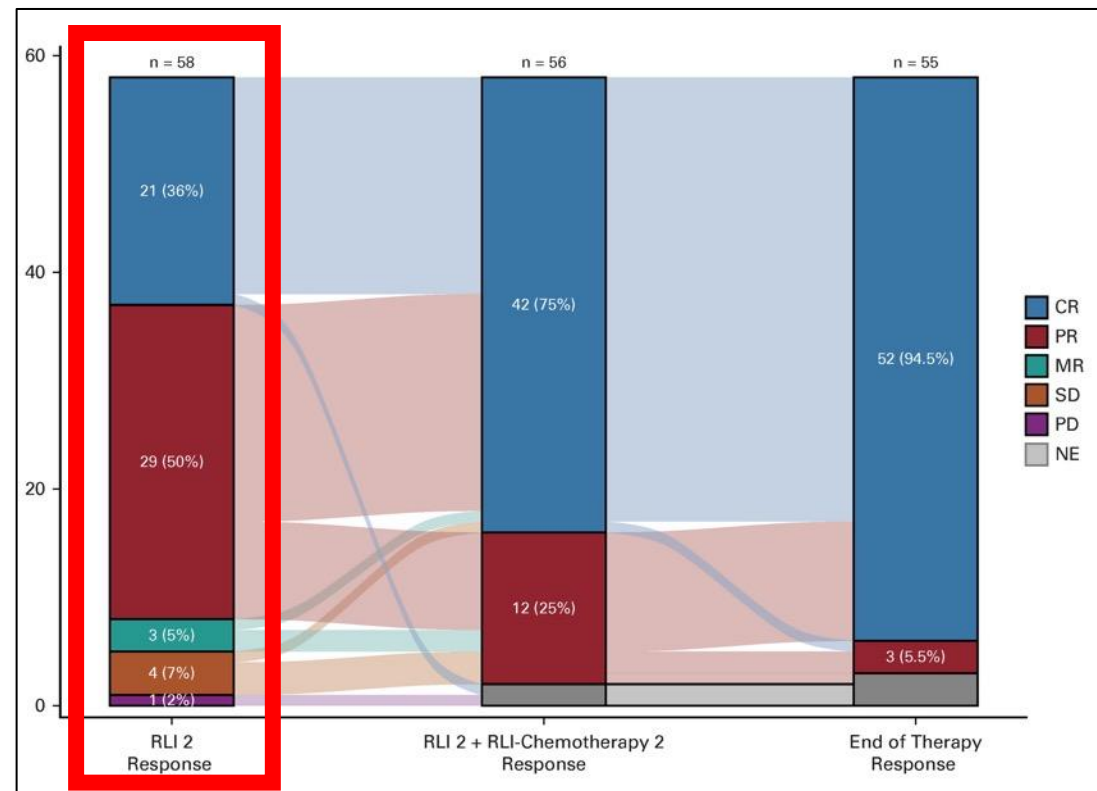
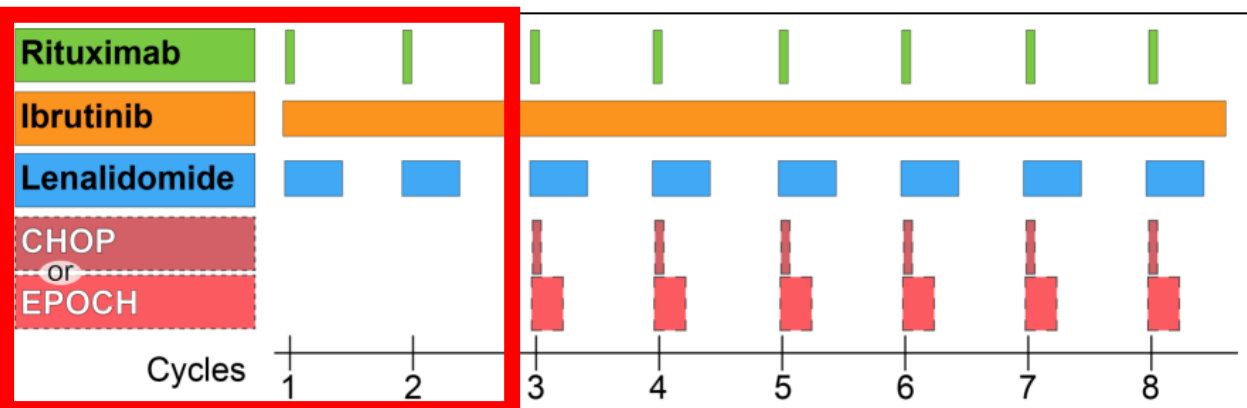
Non-anthracycline 1L treatment: R2 (or ReRi)

- 65 patients
- 6 cycles induction (20mg) and 6 cycles maintenance (10mg)
- Median age: 83 (70-91)
- ORR: 51%, CR rate: 28%
- 2-year outcomes
 - PFS: 41%
 - OS: 48%
- 34% completed 1 year treatment
- Treatment delay was common, 42%



Smart Start: Rituximab, Lenalidomide, and Ibrutinib in Patients With Newly Diagnosed Large B-Cell Lymphoma

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Smart Stop dosing

Lenalidomide

Tafasitamab

Rituximab

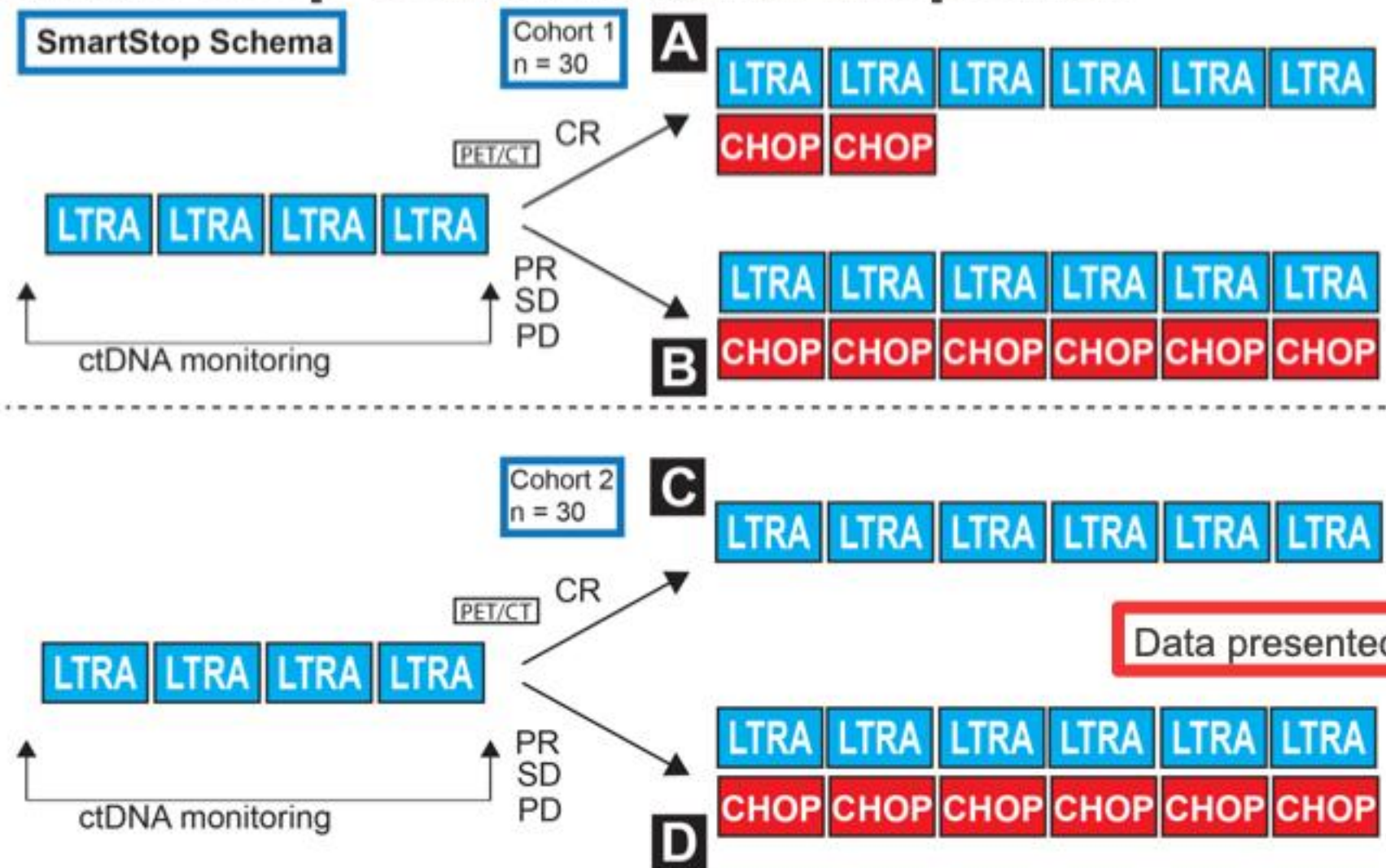
Acalabrutinib

Doses of “Smart Start” portion of the clinical trial, cycle = 21 days

Drug Name	Dose	Route	Dosing per cycle	Day of therapy
Lenalidomide (L)	25mg	PO	Daily	1-10
Tafasitamab (T)	12mg/kg	IV	Weekly	1, 8, 15
Rituximab (R)	375mg/m ²	IV	Once	1
Acalabrutinib (A)	100mg	PO	BID	1-21

LTRA

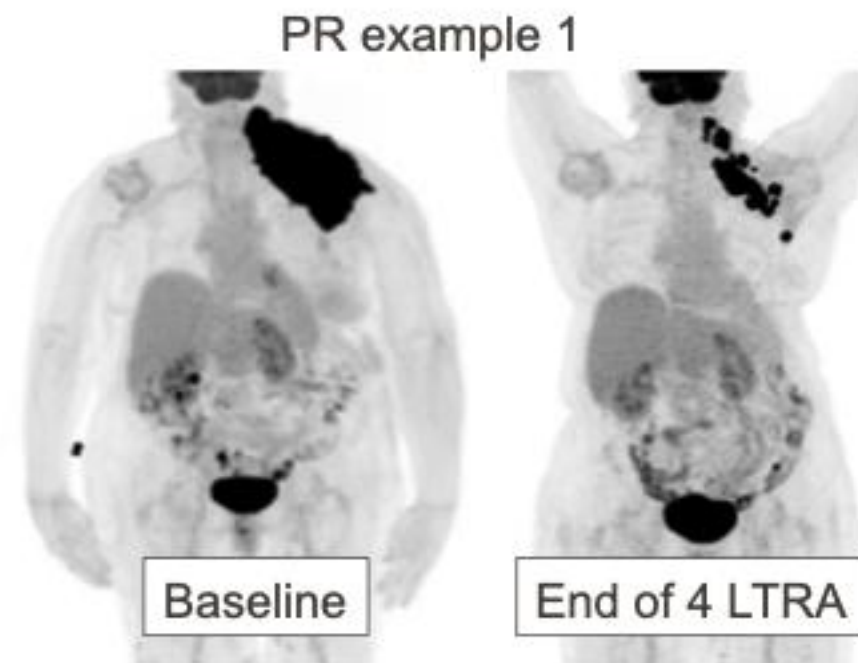
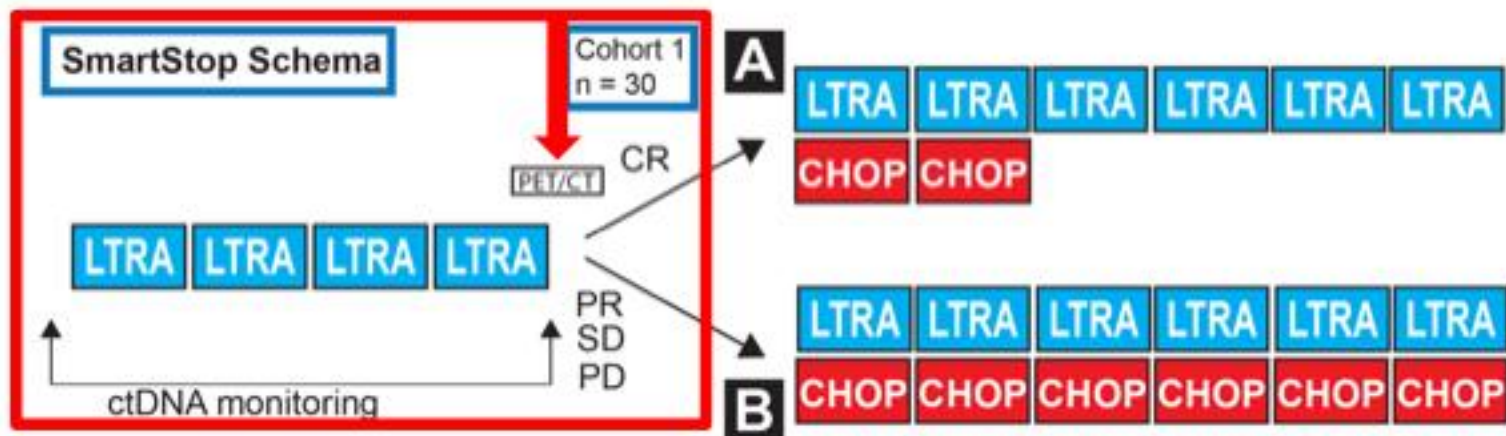
Smart Stop Schema and Endpoints



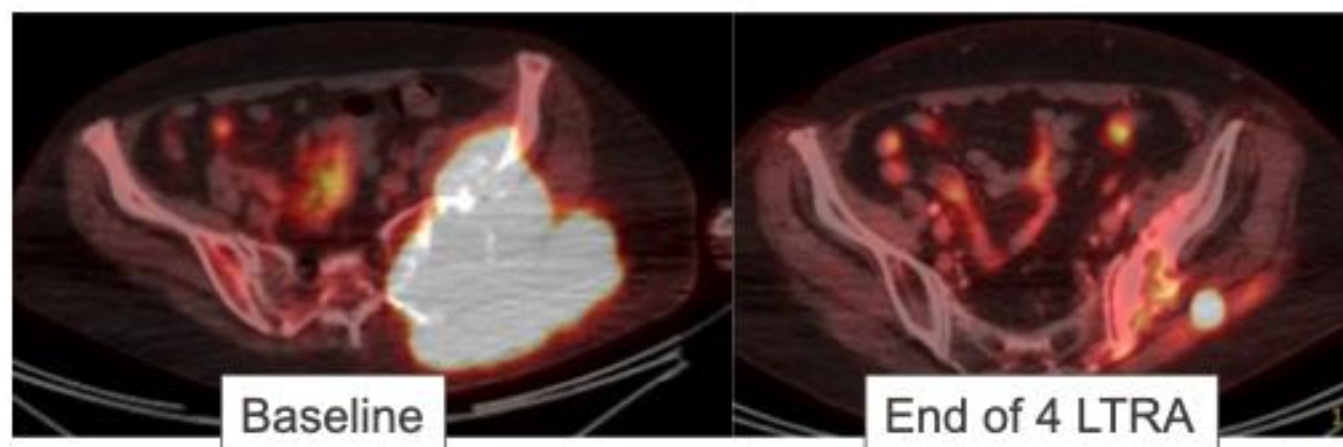
Phase II
Single center
Investigator Initiated
Open label

Primary Endpoints:
1A ORR after 4 LTRA
1B CRR at end of therapy

Results – after 4 cycles of LTRA



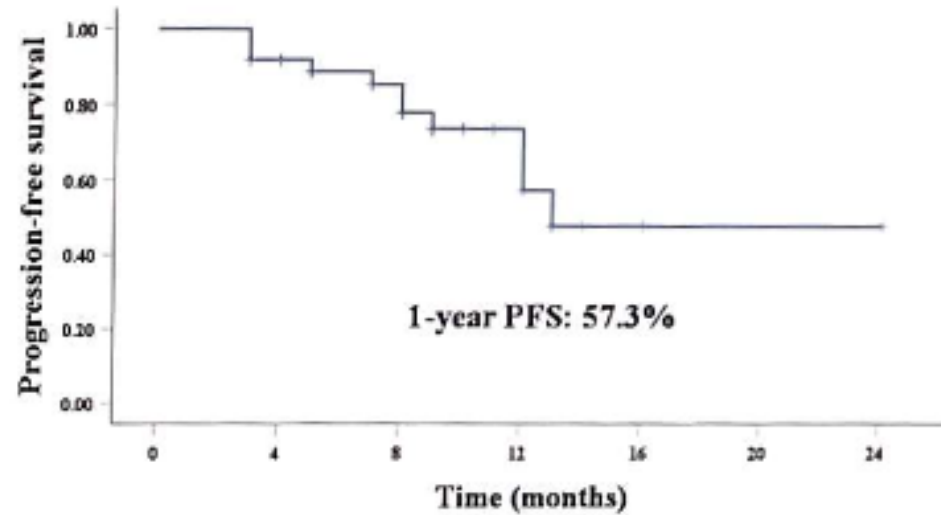
PR example 2



Primary Endpoint 1A: ORR after 4 LTRA is 100%

	All (N=30)	GCB (N=5)
CR	19 (63.3%) (95% CI: 50.0 ~ 75.2%)	4 (80%)
PR	11 (36.7%)	1 (20%)
SD	0	0
PD	0	0
ORR	30 (100%) (95% CI: 92.6 ~ 100%).	

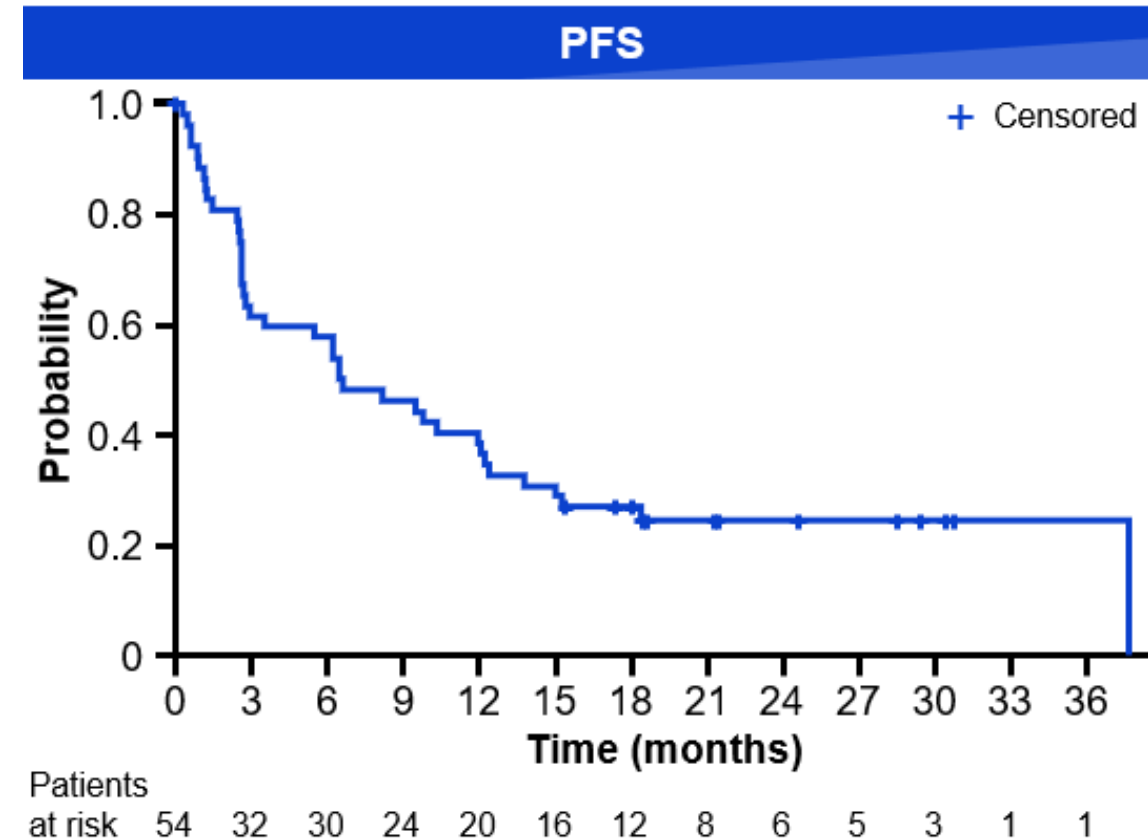
BTK + lenalidomide + rituximab



BTK was Zanubrutinib or orelabrutinib

Non-anthracycline 1L treatment: mosunetuzumab

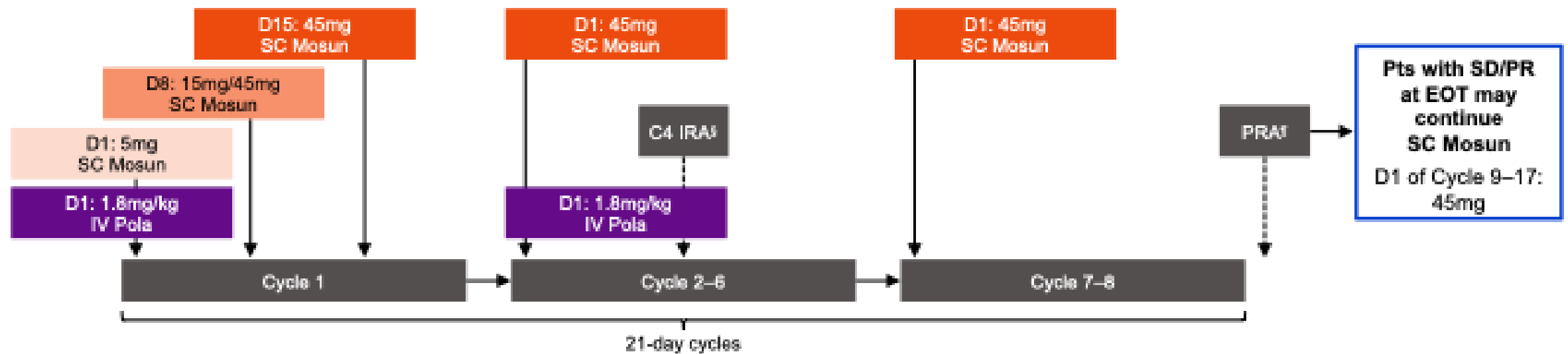
- 54 patients
- Mosun 8 cycles (17 if PR or SD)
- 30mg, not 45mg
- Median age: 83 (65-100)
- ORR: 56%, CR rate: 43%
- 1-year outcomes
 - PFS: 38%
 - OS: 75%
- No grade 3 CRS, 7% grade 2
- Does not work for DHL, bulky disease



Study overview

Key inclusion criteria	CRS mitigation strategies	Primary efficacy endpoint
<ul style="list-style-type: none"> Previously untreated DLBCL Age ≥80 years OR age 65–79 years and considered ineligible* for CIT ECOG PS 0–2 	<ul style="list-style-type: none"> Step-up SC Mosun dosing in Cycle 1 Pre-medication with dexamethasone in Cycle 1† Pre-medication with acetaminophen and diphenhydramine may also be given‡ 	<ul style="list-style-type: none"> ORR by PET-CT at the PRA as assessed by IRC according to Lugano 2014 criteria¹ Additional objectives: Evaluation of safety, immunogenicity, pharmacokinetics, and pharmacodynamics

SC Mosun-Pola administration: Cohort C1 (N=7): 5/15/45mg; Cohort C2 + C Expansion (N=101): 5/45/45mg (target dose cohort)

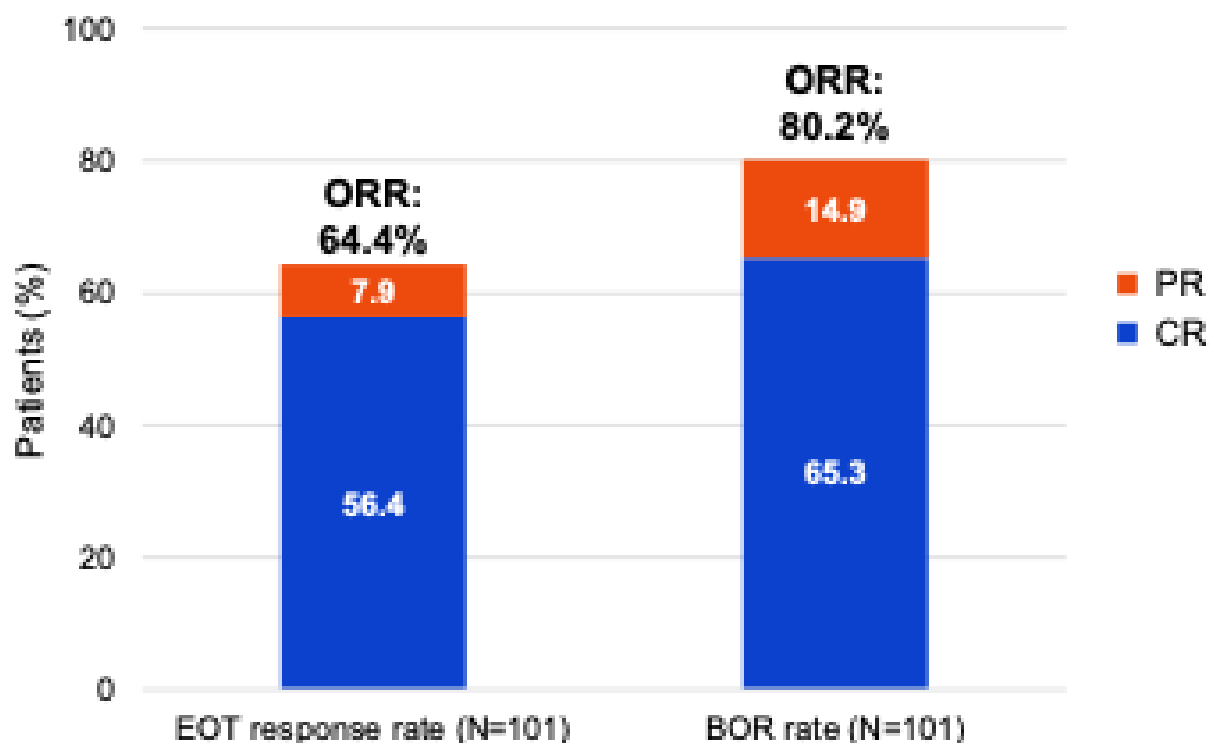


*Per simplified geriatric assessment: Impairment in ≥2 ADL components and/or impairment in IADL components and/or CIRS-G score of at least one comorbidity with a severity score of 3–4 or a score of 2 in ≥8 comorbidities. †Optional from C2+. ‡Optional from C1+. §In Cycle 4 between D14 and D21. ¶6–8 weeks after Cycle 8 D1 or the final dose of study treatment for those who discontinue prematurely. ADL, activity of daily living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CIT, chemoinmunotherapy; CRS, cytokine release syndrome; D, Day; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; IADL, instrumental activity of daily living; IRA, interim response assessment; IRC, independent review committee; IV, intravenous; ORR, objective response rate; PET-CT, positron emission tomography-computed tomography; PR, partial response; PRA, primary response assessment; SD, stable disease.

1. Cheson, et al. J Clin Oncol 2014;32:3059–68.

Investigator-assessed EOT and BOR response rates

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



Response rate, n (%)	EOT N=101	BOR N=101
ORR	65 (64.4)	81 (80.2)
CR	57 (56.4)	66 (65.3)
PR	8 (7.9)	15 (14.9)
SD	4 (4.0)	4 (4.0)
PD	10 (9.9)	4 (4.0)
ND	22 (21.8) [*]	12 (11.9) [†]

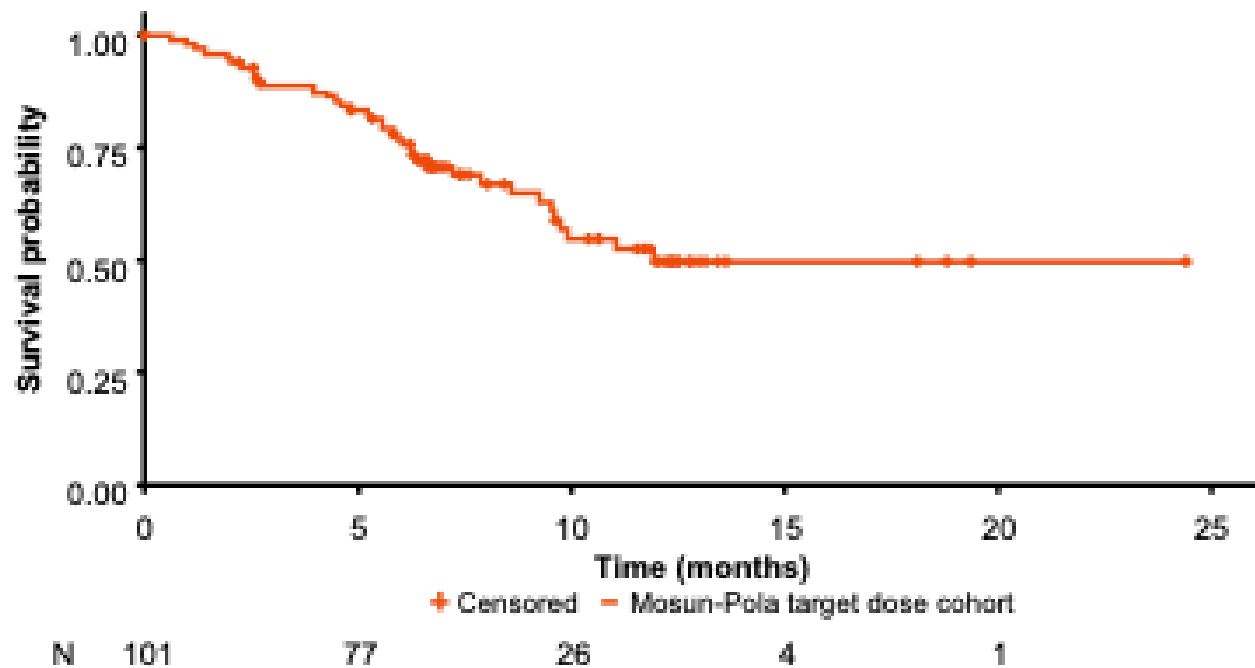
- 6/8 pts with PR at EOT continued treatment beyond Cycle 8, and 3/6 pts converted from PR to CR during continuation
- The difference between BOR and EOT is attributed to 22 patients who did not reach the EOT visit due to AEs, death, and subject withdrawal, which reflects the frailty and high co-morbidity burden of the study population

Mosun-Pola induces encouraging response rates in elderly unfit or frail pts with previously untreated DLBCL

Data cut-off: August 5, 2023; 16 pts withdrew consent, 14 discontinued early due to AEs, 1 discontinued due to investigator decision, and 1 had early PD in C1; 14 pts withdrew consent, 6 discontinued early due to AEs, 1 discontinued due to PI decision, 1 had early PD in C1; BOR, best overall response; CR, complete response; ND, not done or missing; PD, progressive disease.

PFS in Mosun-Pola target dose cohort

KM curve of PFS in Mosun-Pola target dose cohort



	Mosun-Pola target dose cohort N=101
Median PFS, months (95% CI)	11.9 (9.5, NE)
9-month PFS event-free rate, % (95% CI)	64.8 (54.2, 75.5)
12-month PFS event-free rate, % (95% CI)	49.7 (36.8, 62.5)
Patient disposition	
Censored/no event at CCOD	64 (63.4)
Event	37 (36.6)
Disease progression	12 (12)
Death	25 (25)

Early data show encouraging PFS with Mosun-Pola in elderly unfit or frail pts with previously untreated DLBCL

Polatuzumab + Zanubrutinib + Rituximab

Figure 1. Study design.*

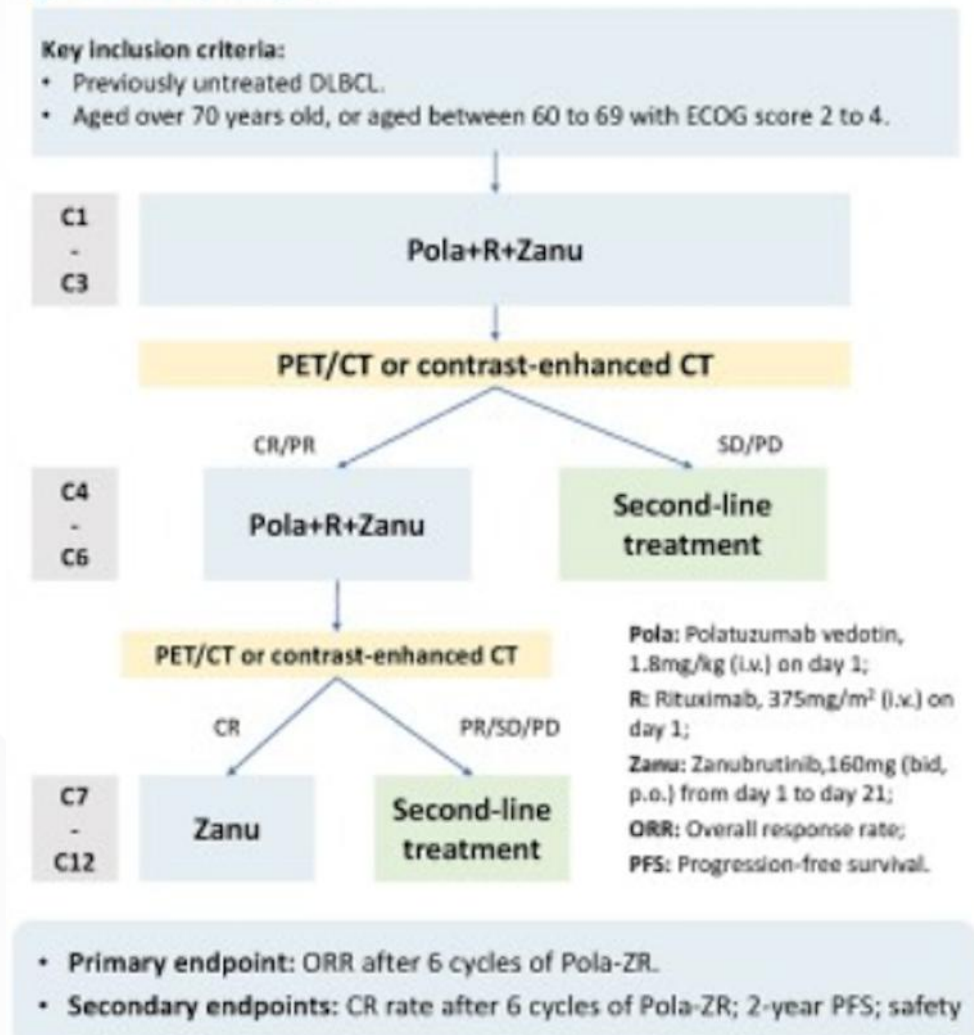
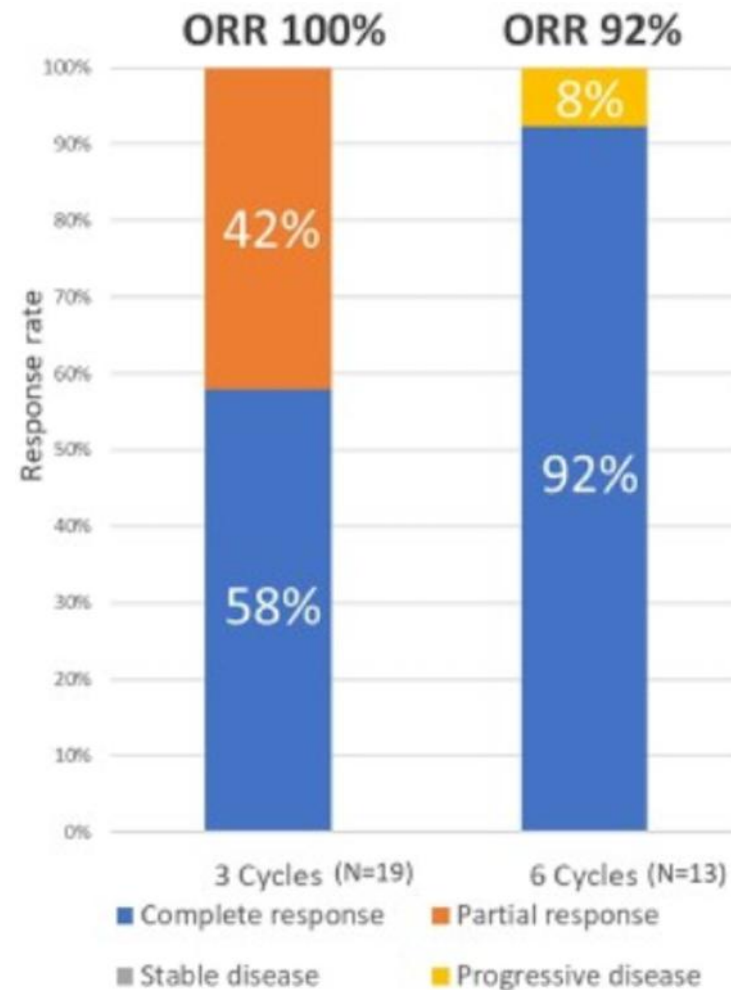
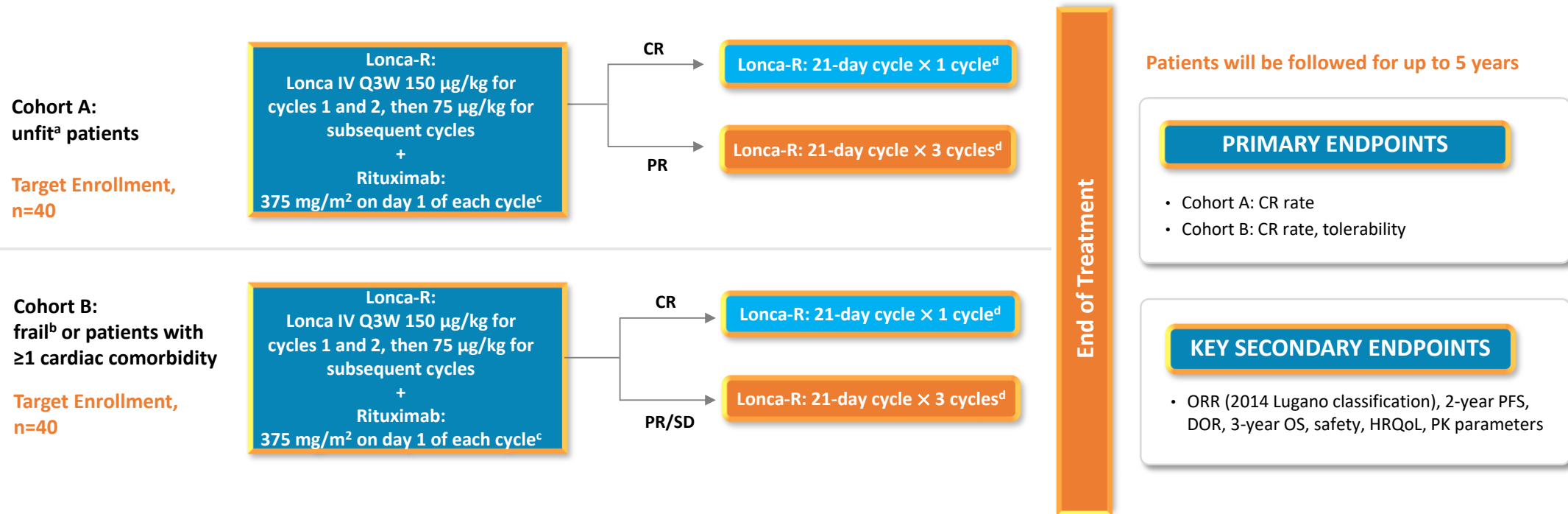


Figure 2. Efficacy of Pola-ZR regimen.



LOTIS-9 Design



^aDefined by the sGA as ≥80 years of age, an ADL score of 6, an IADL score of 8, and for CIRS-G; no score of 3-4 and <5 scores of 2 based on the FIL tool. ^bDefined by the sGA as ≥80 years of age, an ADL score of <6, an IADL score of <8, and for CIRS-G: ≥1 score of 3-4 and ≥5 scores of 2 based on the FIL tool. ^cA subcutaneous formulation of rituximab may be used at a flat dose of 1400 mg, starting from cycle 2. ^dDoses as per cycle 3.

Conclusion

- Elderly patients are a challenging population to manage a potentially fatal but treatable disease
- Dose reduced chemotherapy may help some, but is not optimal especially with high IPI
- Adding targeted therapy to RCHOP continues to underwhelm
- Novel Novel combinations are promising but not approved
- Toxicities are difficult to attribute – to drug or to age



Thank you!
Obrigado!

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