Aggressive Lymphoma Workshop

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DIPARTIMENTO DI SCIENZE MEDICHE E CHIRURGICHE

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Is It Time To Explore the Concept of "Replace R-CHOP"?

Bruce D. Cheson

Lymphoma Research Foundation

Center for Cancer and Blood Disorders

Disclosures

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZeneca						X	
Beigene					x	X	
Pharmacyclics			x				

Clinical Trial > Cancer. 1979 Feb;43(2):417-25.
doi: 10.1002/1097-0142(197902)43:2<417::aid-cncr2820430203>3.0.co;2-i.

Superiority of adriamycin-containing combination chemotherapy in the treatment of diffuse lymphoma: a Southwest Oncology Group study

S E Jones, P N Grozea, E N Metz, A Haut, R L Stephens, F S Morrison, J J Butler, G E Byrne Jr, T E Moon, R Fisher, C L Haskins, C A Coltman Jr

PMID: 84706 DOI: 10.1002/1097-0142(197902)43:2<417::aid-cncr2820430203>3.0.co;2-i

Abstract

As a part of an ongoing prospective controlled trial, the Southwest Oncology Group compared the results of treatment of advanced non-Hodgkin's lymphoma with two CHOP regimens (cyclophosphamide, adriamycin, vincristine and prednisone with either low-dose bleomycin or BCG by scarification) to a COP regimen (cyclophosphamide, vincristine and prednisone) with low-dose bleomycin (COP-Bleo). The study design emphasized histopathology review and systematic restaging to define complete remission (CR). Confirmed rates of CR for 443 evaluable patients were 59% for 286 patients receiving the CHOP regimens and 59% for 157 patients receiving COP-Bleo. Rates of CR were higher for patients with nodular lymphoma (69%) compared to those with diffuse lymphoma (54%) ($p = 0.005$). For patients with nodular lymphoma there was no difference in CR rates according to treatment. For patients with diffuse lymphomas the CR rate was higher with the CHOP programs (58%) than with COP-Bleo (44%) ($p = 0.10$). Overall duration of CR and survival was significantly longer for patients with nodular lymphoma compared to diffuse lymphoma (p less than 0.01). At this time, remission duration and survival were similar regardless of induction regimen used in patients with nodular lymphoma. However, in patients with diffuse lymphoma, the duration of CR and overall survival were improved by treatment with the CHOP regimens compared to COP-Bleo ($p = 0.02$). Thus, in this controlled study we have demonstrated that initial combination chemotherapy employing the CHOP regimen was a superior remission induction therapy for patients with diffuse lymphoma.

CHOP vs COP for Diffuse Lymphoma

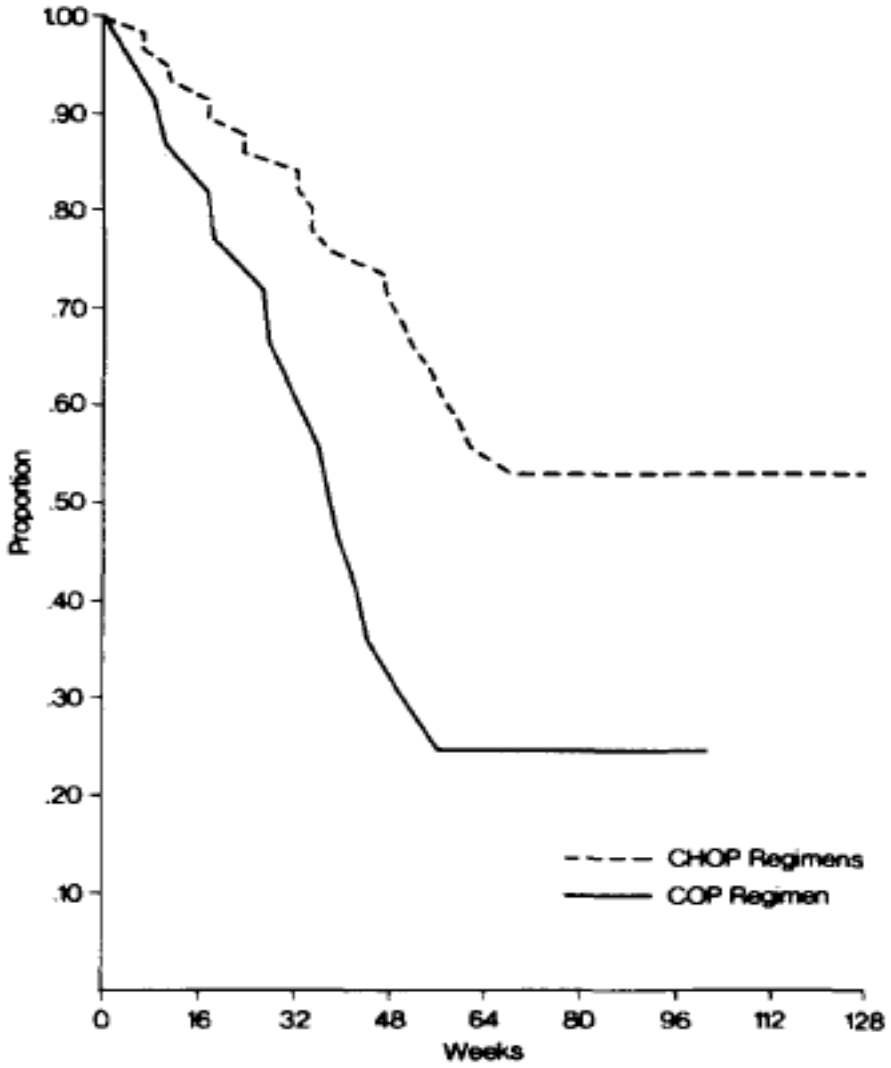


FIG. 3. Duration of CR by treatment for patients with diffuse lymphoma ($p < 0.01$).

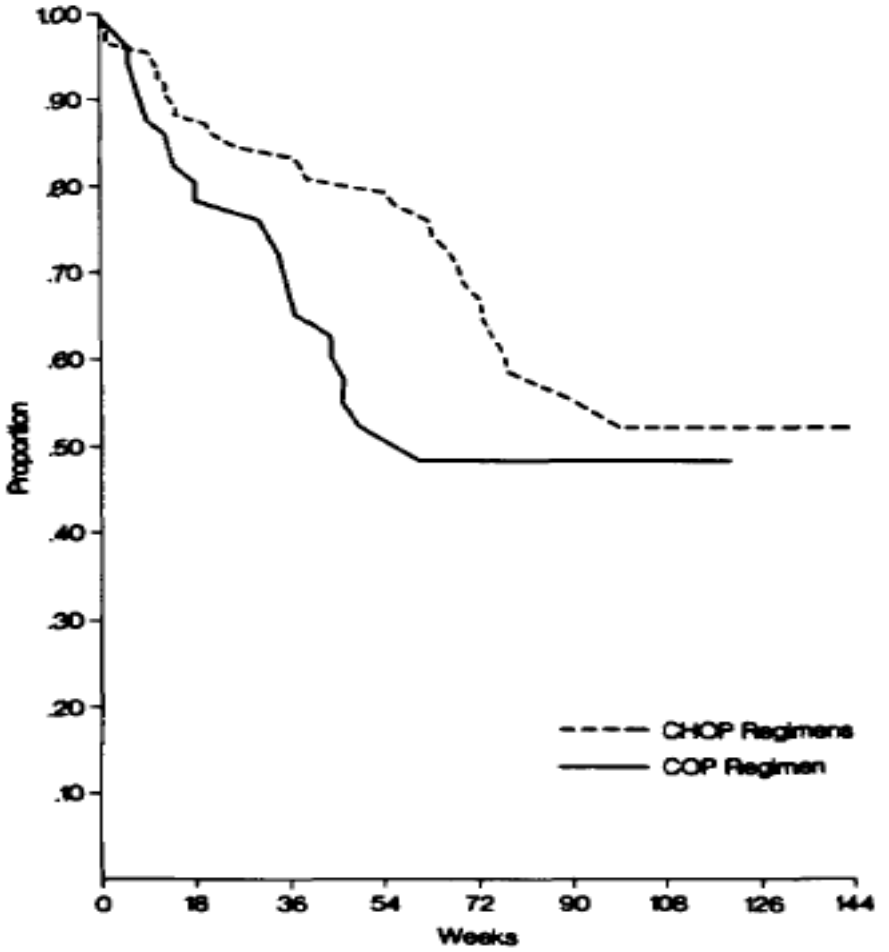
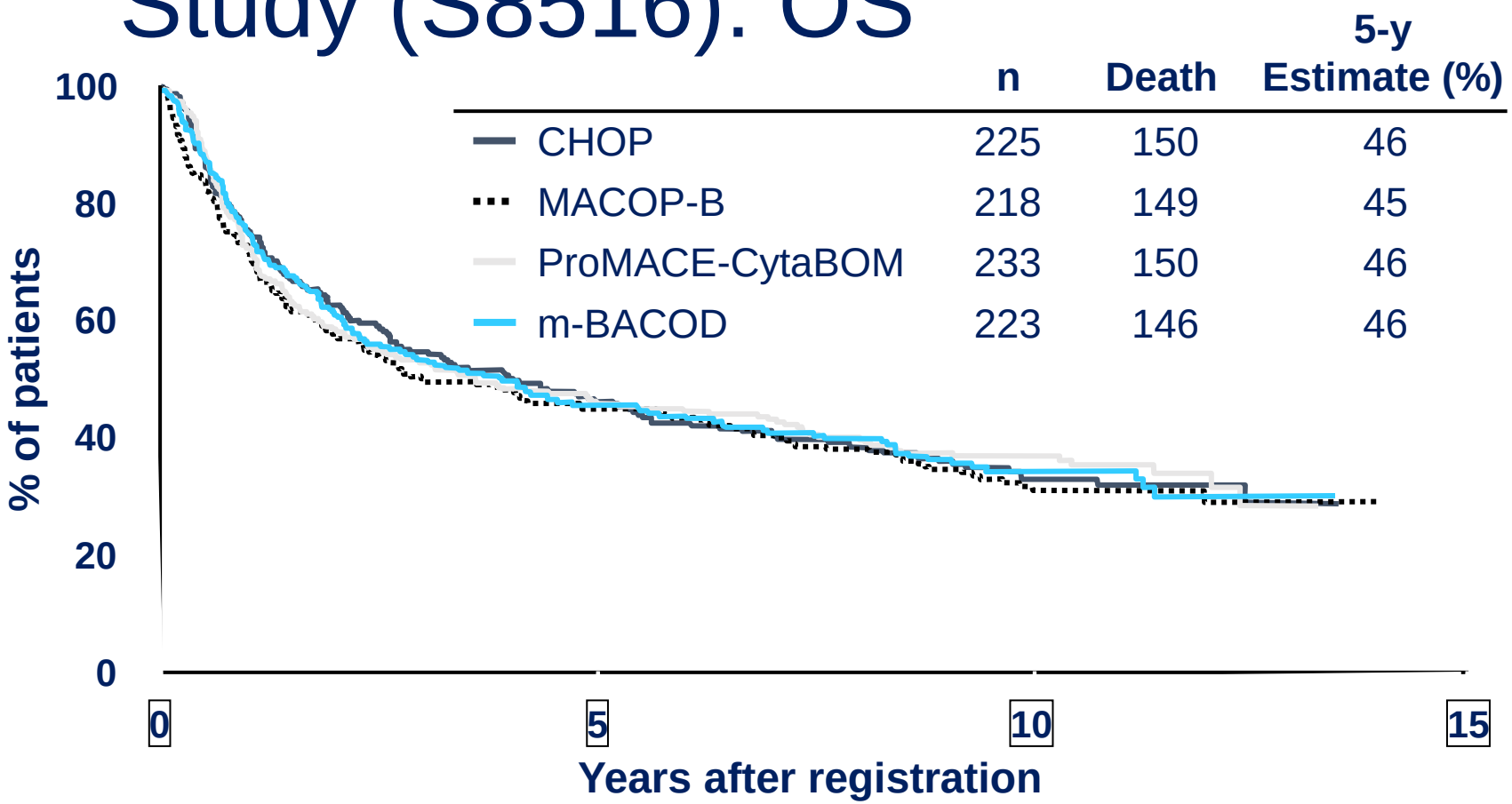


FIG. 5. Survival of patients with diffuse lymphoma according to initial treatment ($p = 0.02$).

Jones et al, Cancer 43:417, 1979

National High-Priority Lymphoma Study (S8516): OS



Update of Fisher et al. *N Engl J Med*. 1993;328:1002. Courtesy of R. Fisher, 2005.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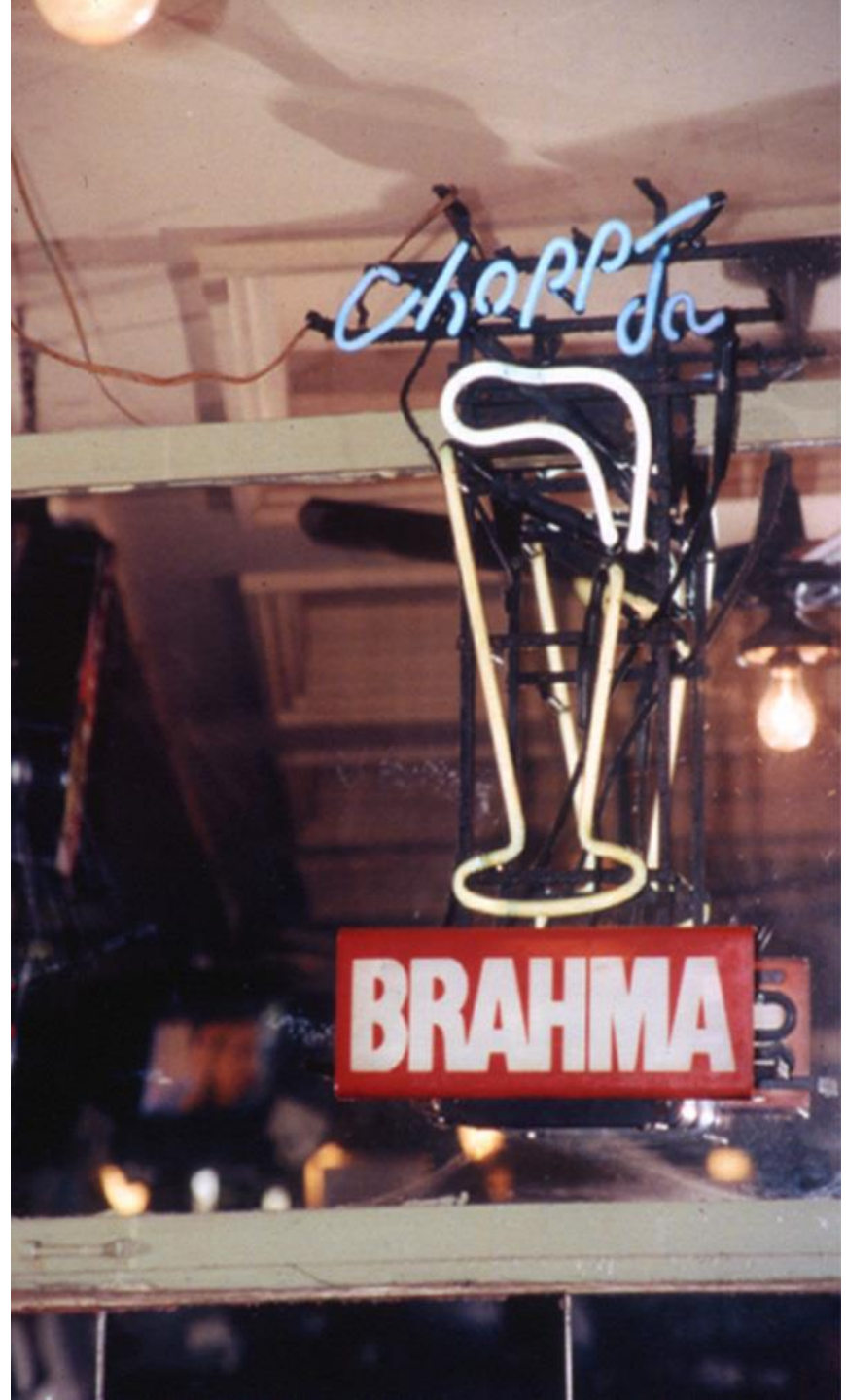
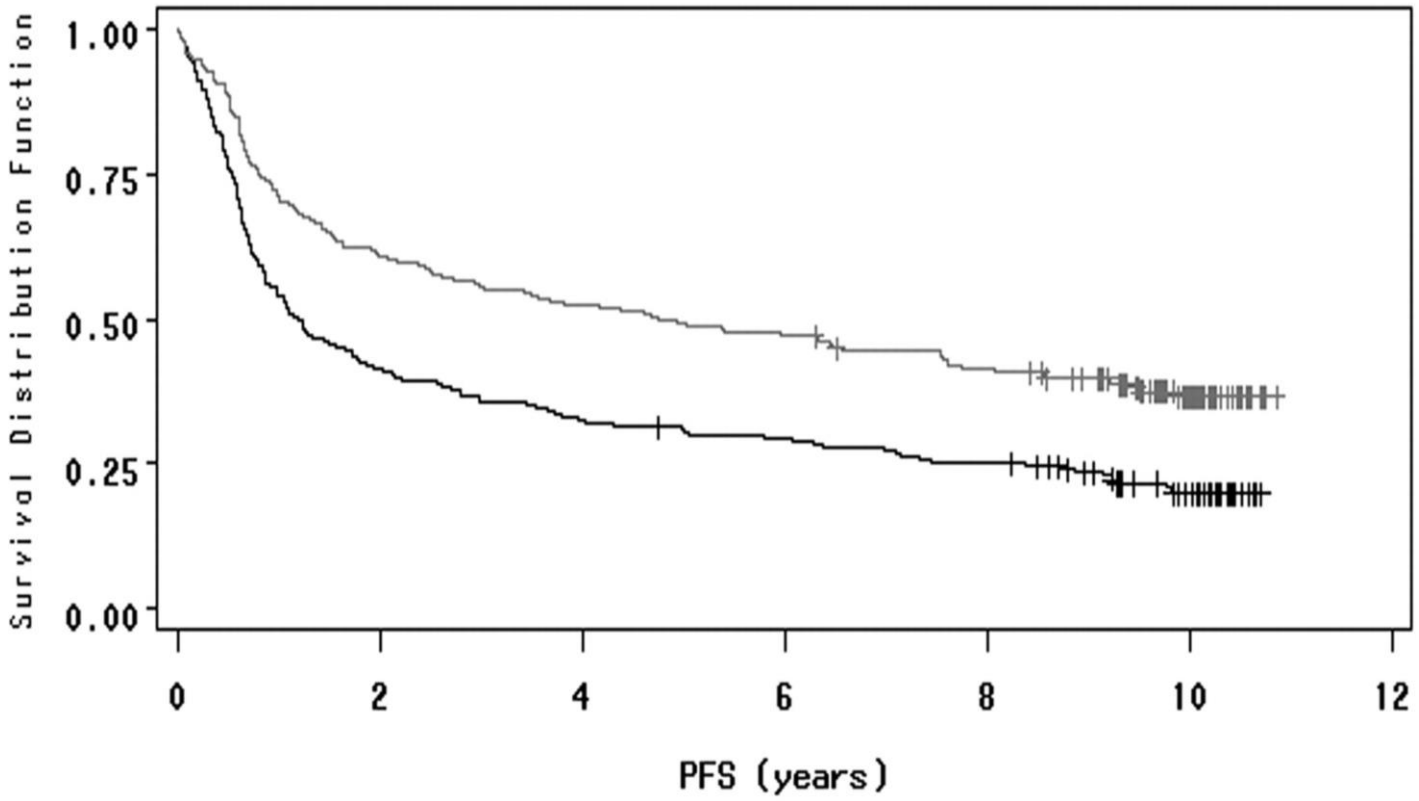

chopp
BRAHMA

R-CHOP vs CHOP in DLBCL

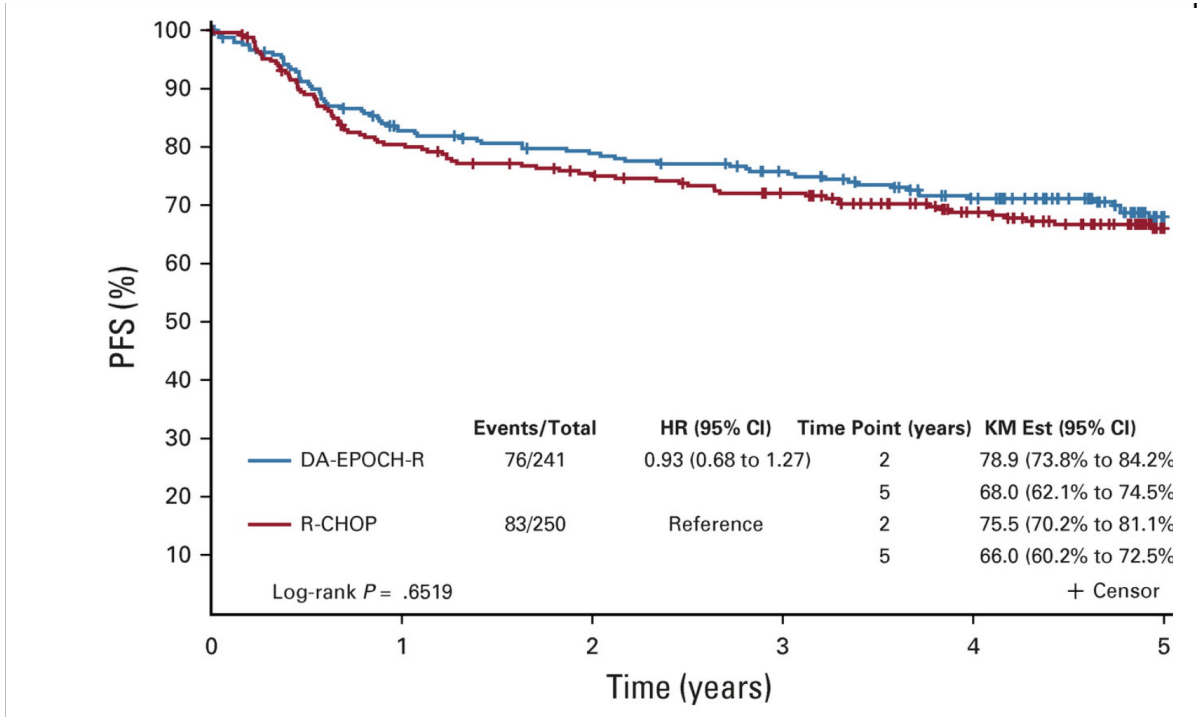


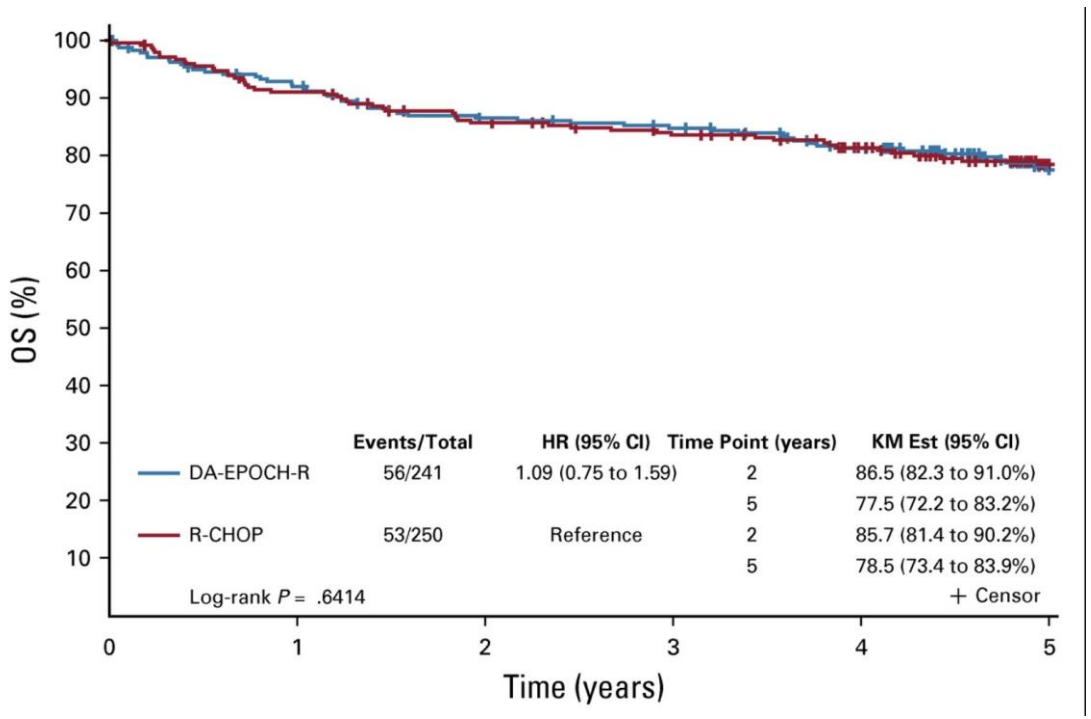
Coiffier et al, Blood 116:2020, 2010

THE EPOCH TIMES

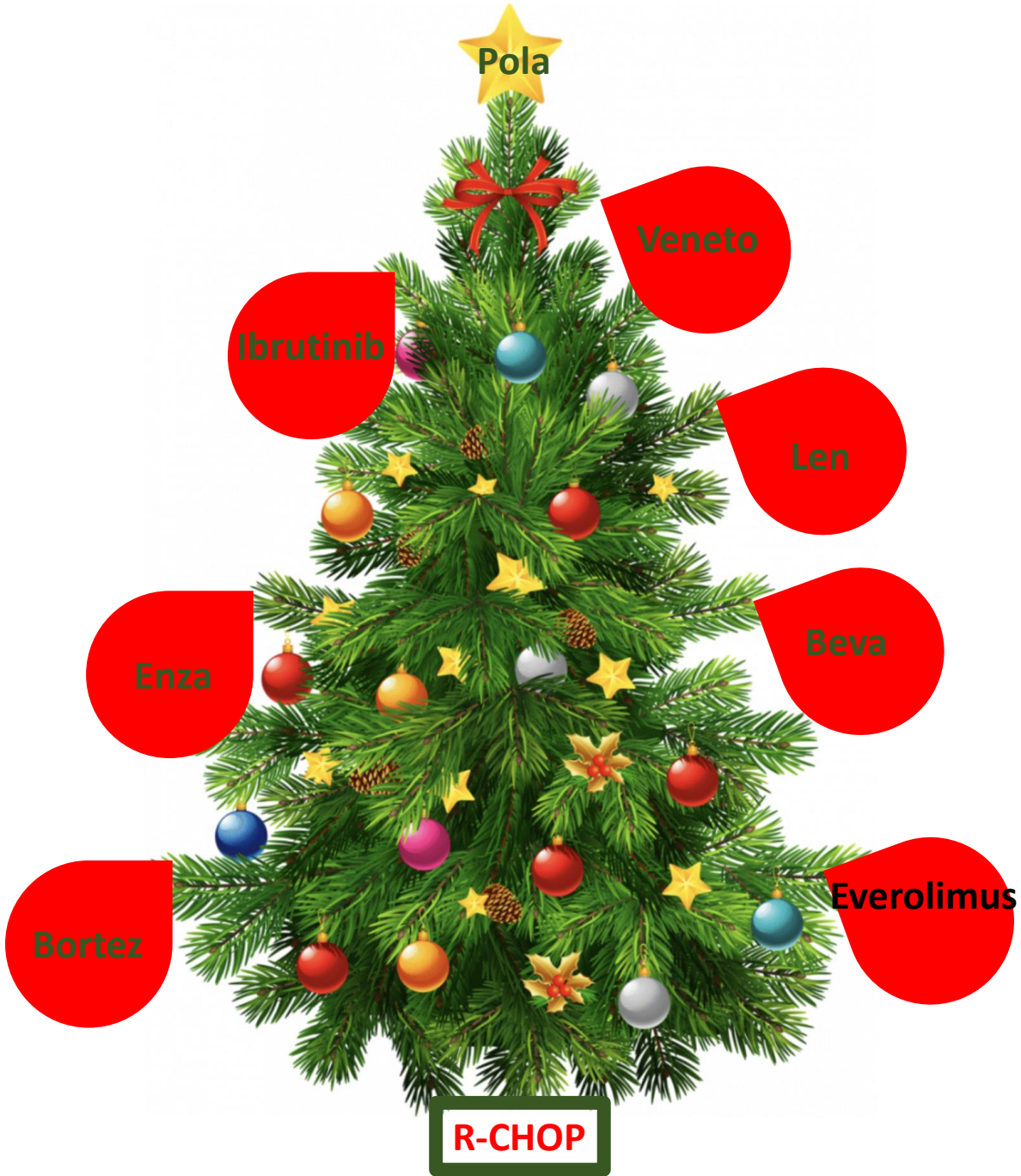
TRUTH AND TRADITION

CALGB 50303 – PFS/OS

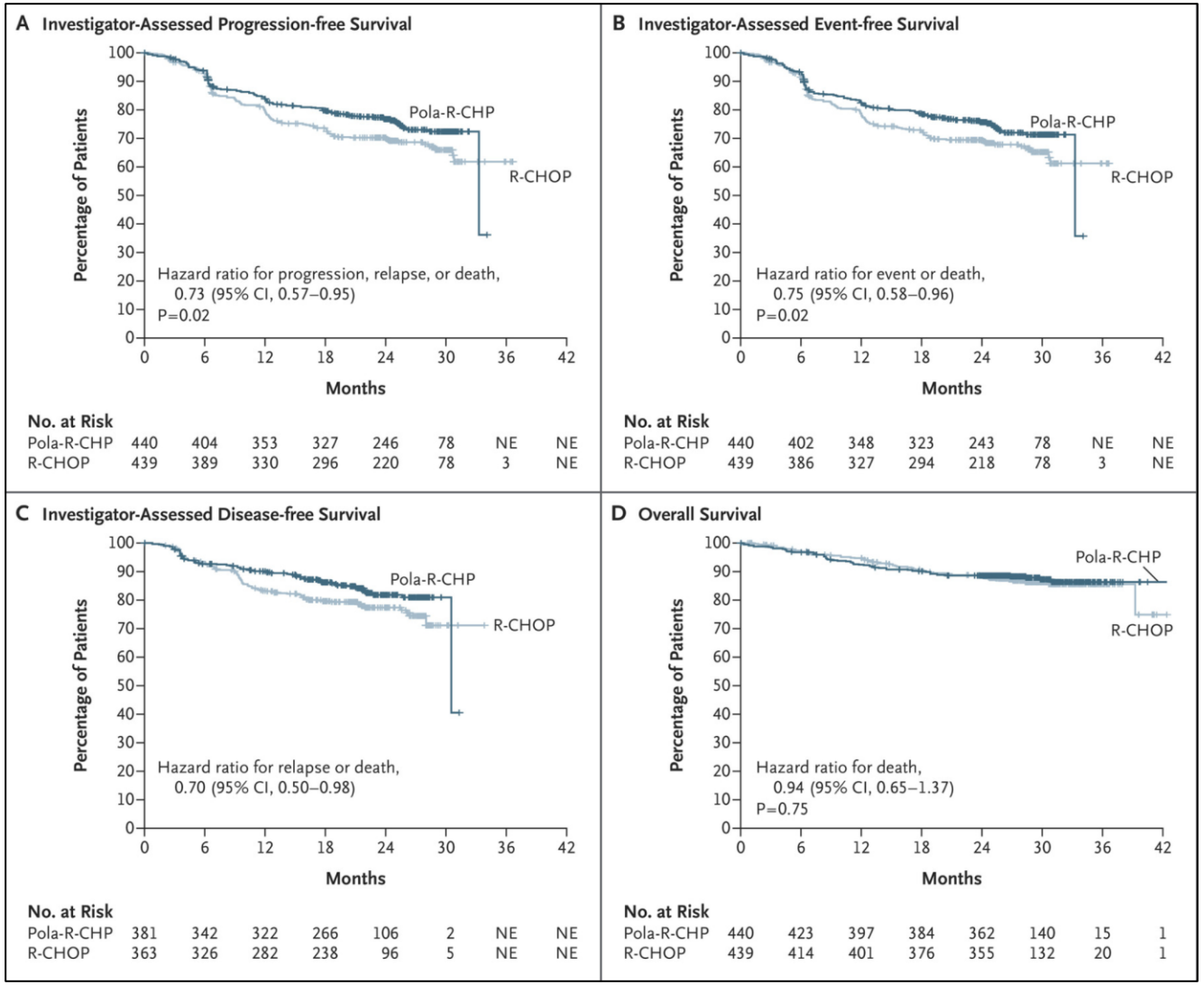




Bartlett et al JCO 37:1790, 2019

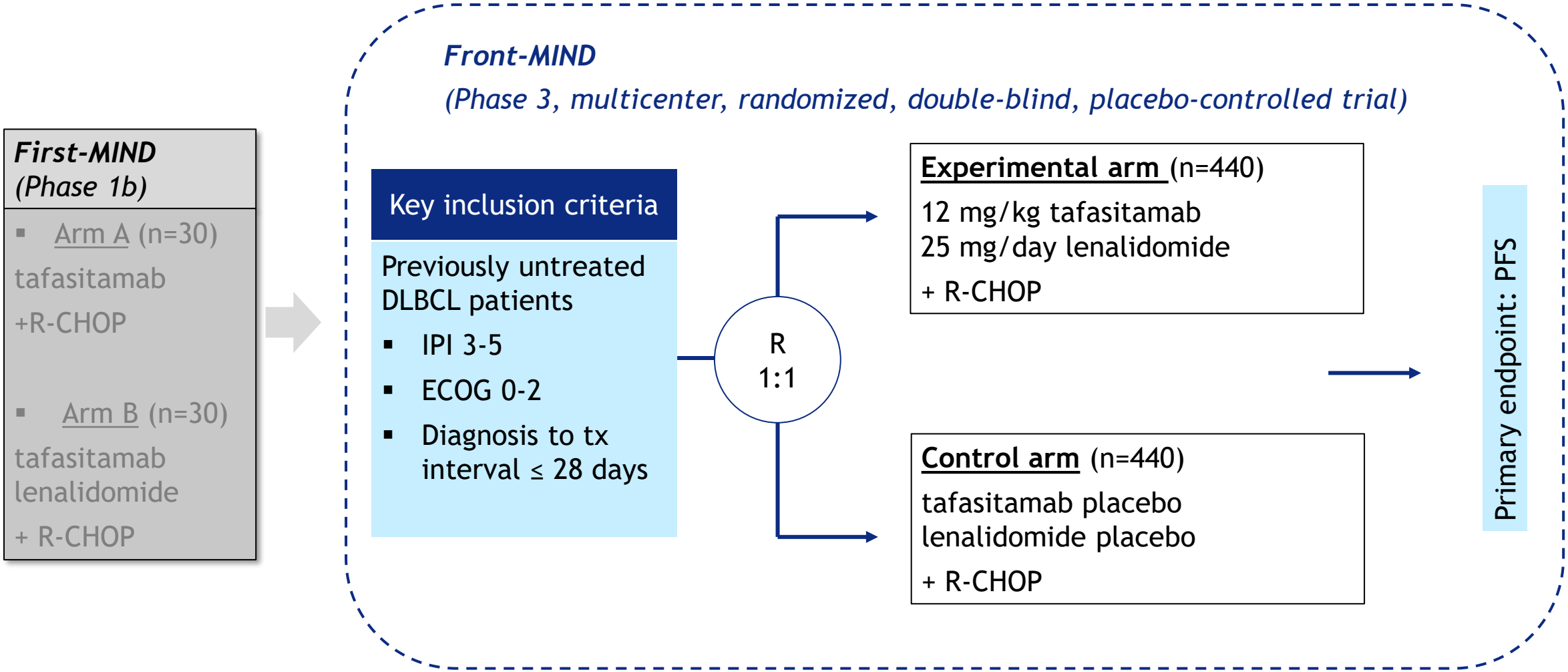

Pola
Veneto
Ibrutinib
Len
Enza
Beva
Bortez
Everolimus
R-CHOP

POLARIX Trial Results

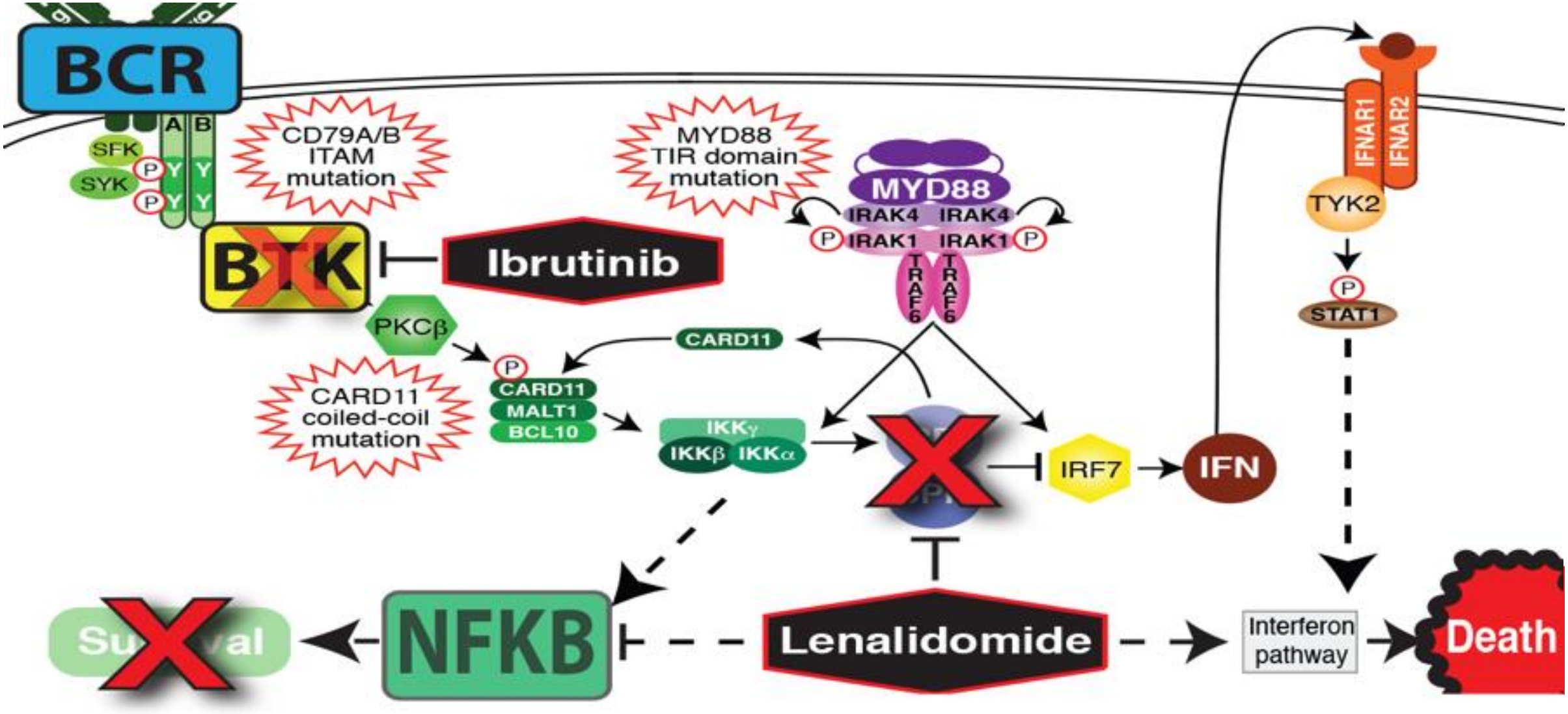


Tilly et al, NEJM 386:551, 2022

Front-MIND: A pivotal phase 3 study in front-line DLBCL



Synthetic Lethality of Lenalidomide and Ibrutinib



Yang, Staudt Cancer Cell 2012

Len: Upregulate IL2 in T-cells
Ibr: ITK inhibition shift Th2 to Th1

Trial record **10 of 16** for: acalabrutinib | dlbcl

Previous Study | Return to List | Next Study

Acalabrutinib With DA-EPOCH-R or R-CHOP for People With Untreated Diffuse Large B-cell Lymphoma

Arms and Interventions

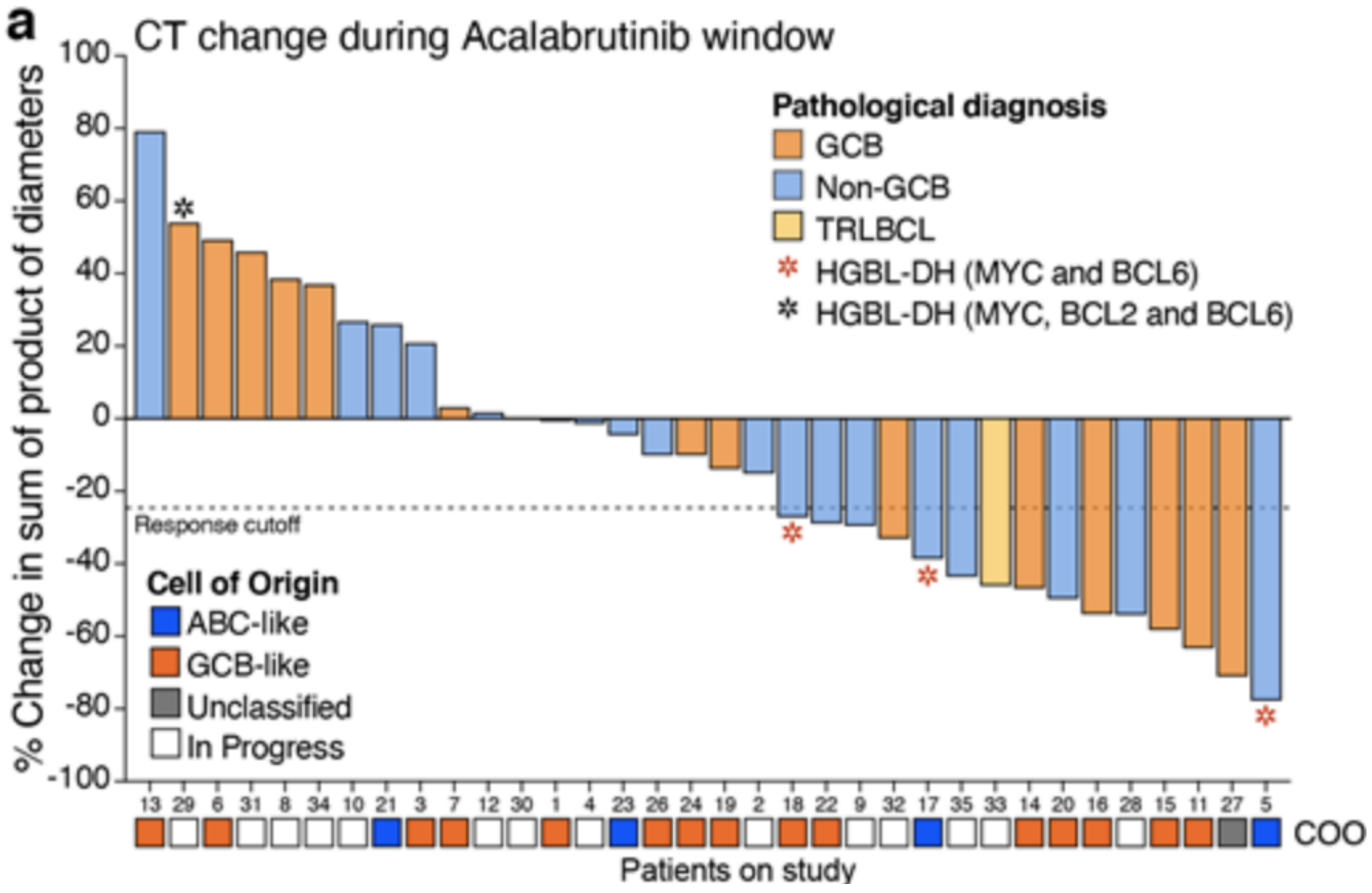
ClinicalTrials.gov Identifier: NCT04002947

Arm

Experimental: 1

Acalabrutinib 100 mg orally twice a day for 14 days; Following window: patients with > or = to 25% tumor reduction, treat with DA-EPOCH-R or R-CHOP + **acalabrutinib** 100mg orally twice a day for the first 10 days, for 6 cycles; whereas, patients with <25% tumor reduction, treat with DA-EPOCH-R or R-CHOP alone for 6 cycles

Acalabrutinib Window Study in DLBCL



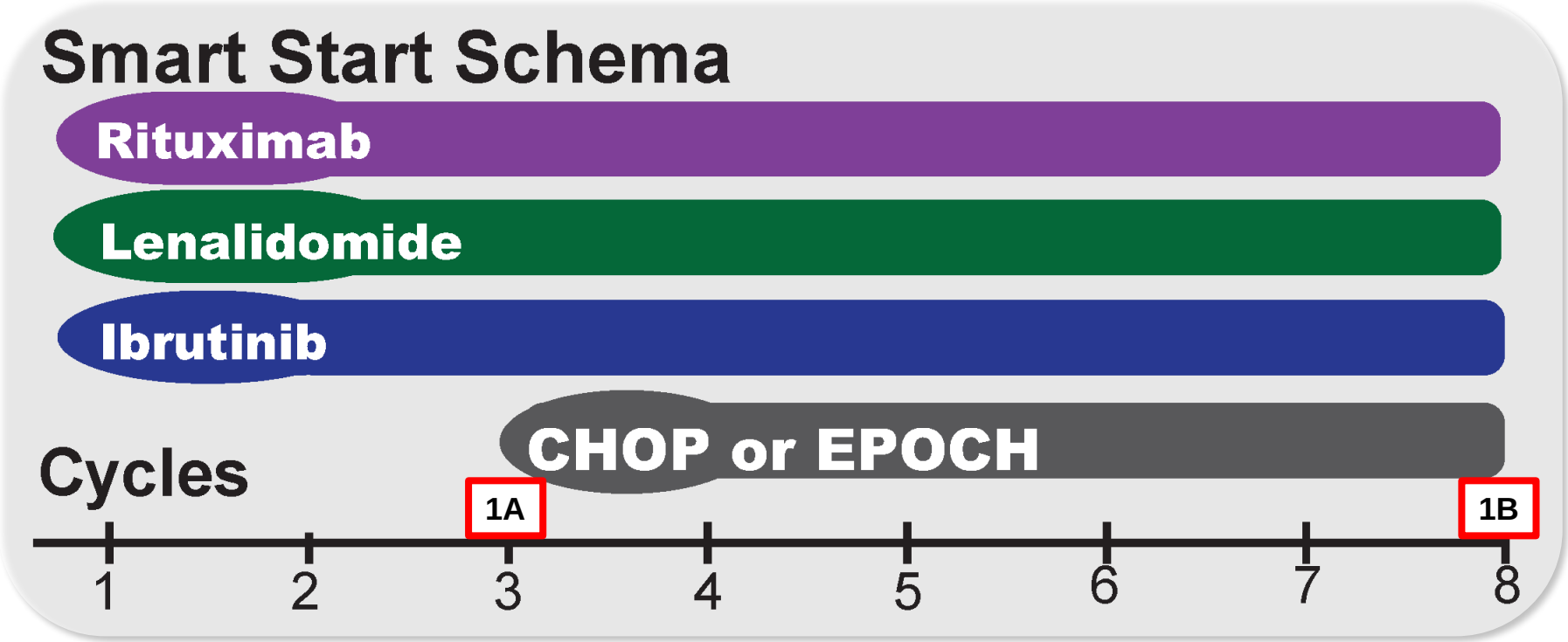
Roschewski et al, Blood 138 (suppl 1): abstr#626, 2021

AZ - ACRUE Phase II Trial

- Treatment naïve or elderly patients
- Previously untreated DLBCL
- Ineligible for R-CHOP-like regimens
- Treatment with acalabrutinib+rituximab
- Expected accrual from October, 2023-April, 2025

Smart Start Study Design

- Phase II, single arm, single center, investigator-initiated trial



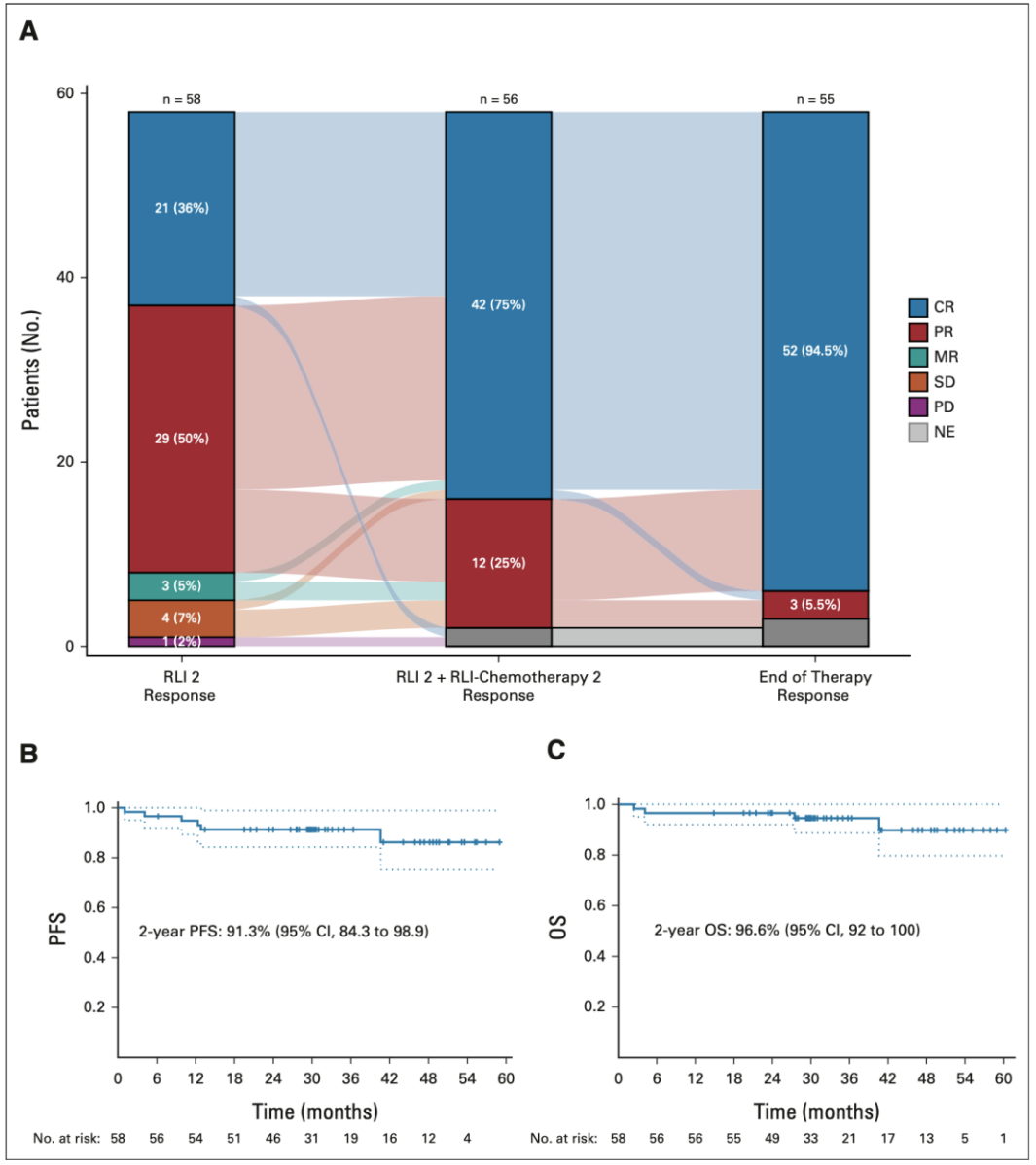
- Primary Objectives
  - 1A: To determine the ORR at the end of 2 cycles of RLI alone
  - 1B: To determine the CR rate at the end of RLI x 2 + RLI combined with chemotherapy x 6

Westin et al, JCO 41:745, 2023

Characteristic	Value
Median age (range), years	63.5 (29-83)
≥ 60, No. (%)	43 (72)
≥ 70, No. (%)	17 (28)
≥ 80, No. (%)	4 (7)
Sex, No. (%)	
Female	28 (47)
Male	32 (53)
Revised IPI, No. (%)	
0-1	19 (32)
2	16 (27)
3-5	25 (42)
ECOG PS score, No. (%)	
0	27 (45)
1	32 (53)
2	1 (2)
LDH, No. (%)	
Normal	27 (45)
Elevated	33 (55)
Extranodal site, No. (%)	
0-1	45 (75)
> 1	15 (25)
Stage, No. (%)	
I-II	22 (37)
III-IV	38 (63)
Bulky tumor (≥ 10 cm), No. (%)	
Yes	13 (22)
No	47 (78)
Ki-67 ≥ 90%, n = 51, No. (%)	23 (45)
Median time from diagnosis to treatment (range), days	28 (9-138)
Double expressor of MYC and BCL2 on IHC, n = 39, No. (%)	24 (62)
DLBCL90 cell of origin classification, n = 25, No. (%)	
ABC	13 (52)
GCB	5 (20)
Unclassified	4 (16)
Insufficient	3 (12)

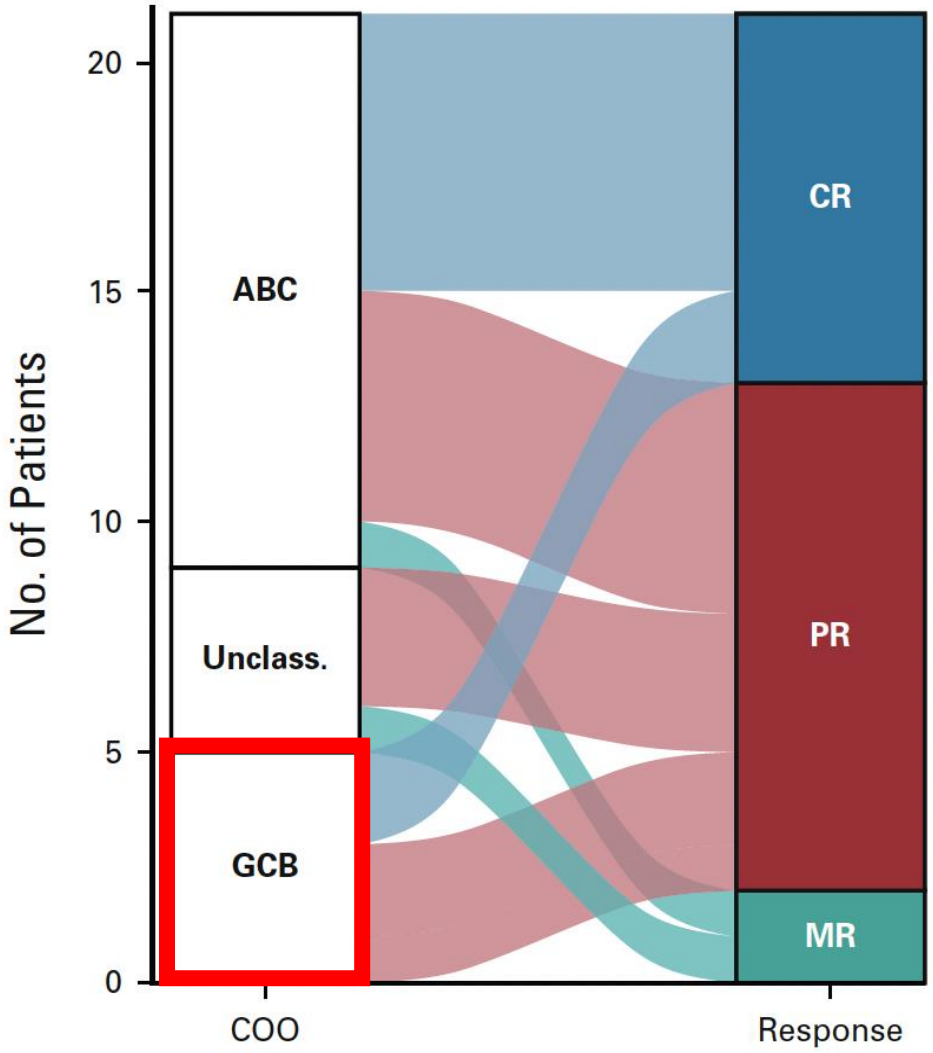
Westin et al, JCO 41:745, 2023

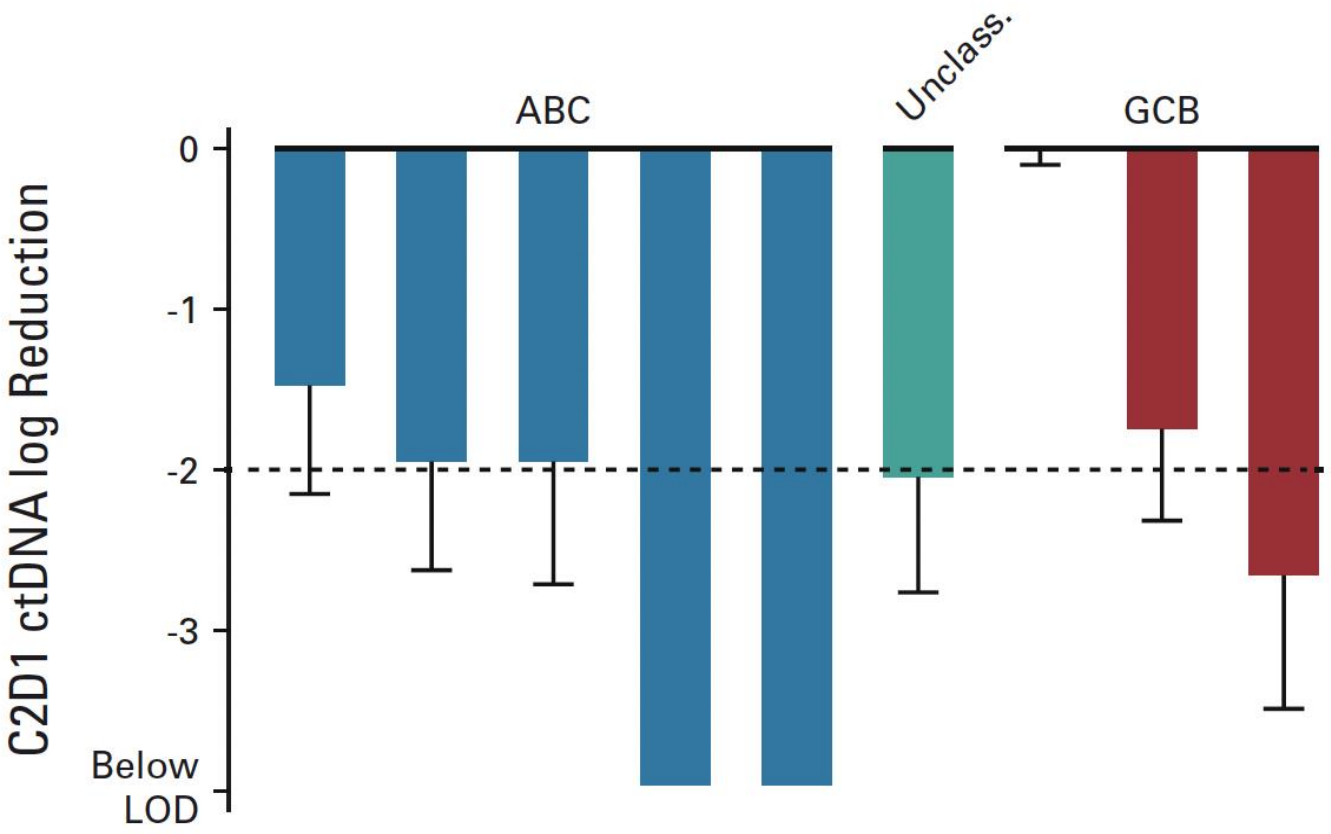
Smart Start Trial: Results



Westin et al, JCO 41:745, 2023

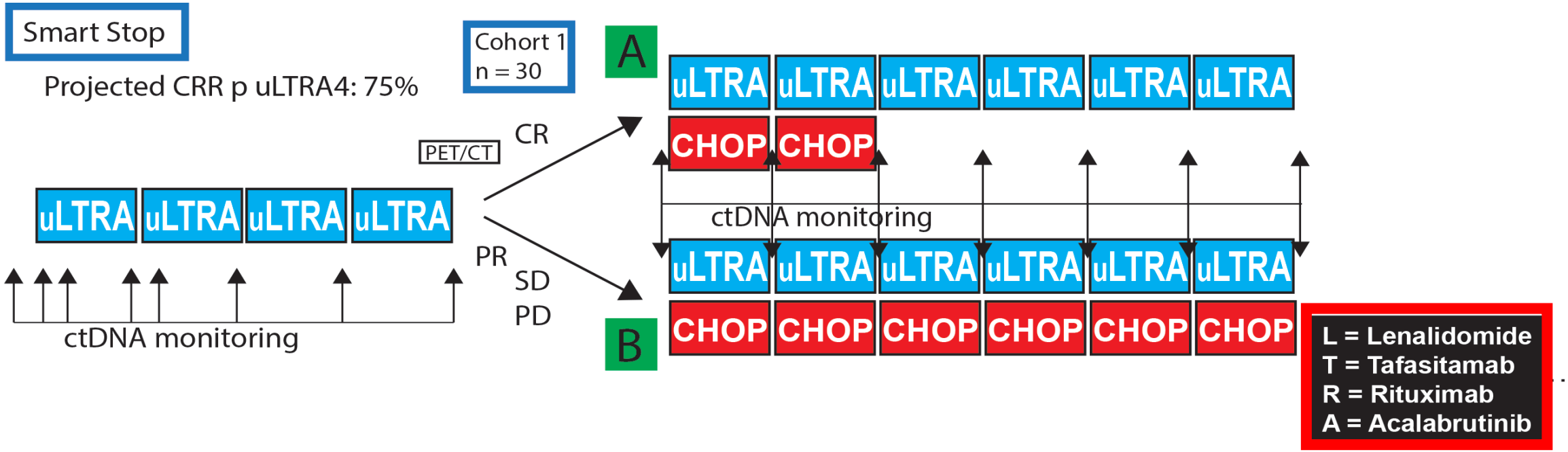
Smart Start Results by COO





Westin, JCO 2023

Smart Stop Schema (J. Westin, ongoing)



ZUMA-12 Eligibility

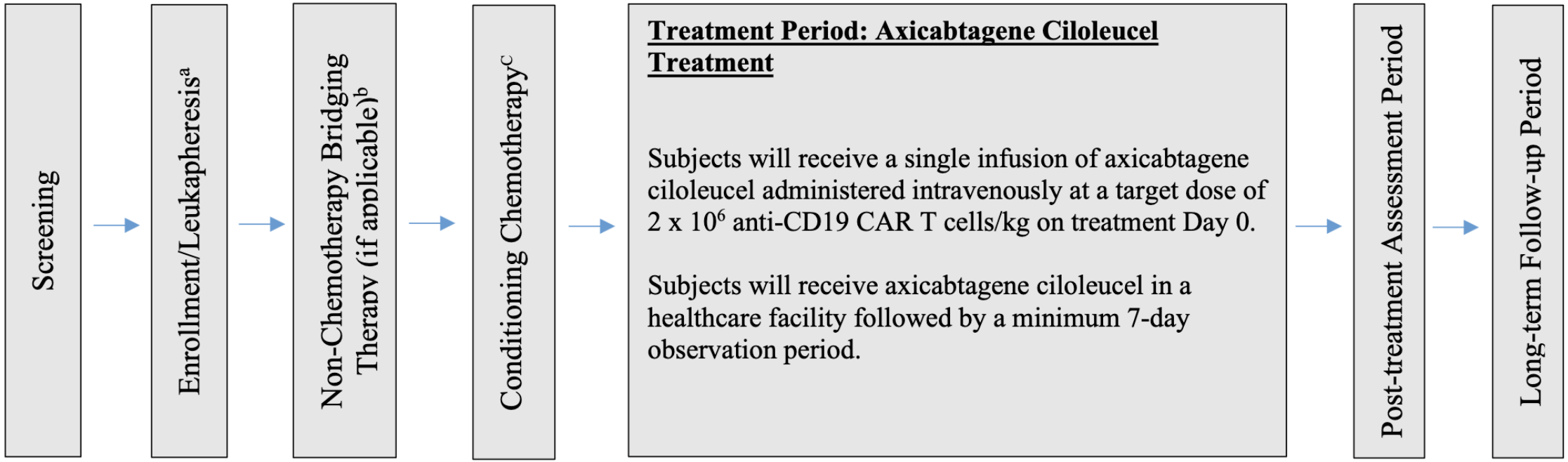
Approximately 40 subjects who are either double hit/triple hit or have IPI ≥ 3 will be enrolled and treated.

[a] **Enrollment/Leukapheresis:** Subjects who have a positive interim PET per the Lugano Classification {Cheson 2014} (Deauville PET score of 4 or 5) after 2 cycles (PET2+) of an anti-CD20 monoclonal antibody and anthracycline-containing regimen per local standard of care (eg, DA-EPOCH-R) if double hit/triple hit, or an anti-CD20 monoclonal antibody and anthracycline-containing regimen per local standard of care (eg, R-CHOP) if large B-cell lymphoma with IPI score ≥ 3.

[b] **Non-Chemotherapy Bridging Therapy:** At the discretion of the investigator, corticosteroid or HDMP + rituximab bridging therapy may be considered for subjects with high disease burden at screening or baseline assessments. Localized radiation therapy for symptom control may also be allowed, provided that the radiation field does not include a target lesion. Refer to Section 6.1.2 for details.

[c] **Conditioning Chemotherapy:** Subjects will receive a 3-day conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day (Day –5 to Day –3) followed by 2 rest days (Day –2 and Day –1).

ZUMA-12 Schema



ZUMA-12 Patient Characteristics

Baseline characteristic	Patients ($n=40$)
Age, median (range), years	61 (23–86)
≥65 years, *n* (%)	15 (38)
Male sex, *n* (%)	27 (68)
Histological disease type per investigator, *n* (%)	
DLBCL not otherwise specified	22 (55)
HGBL-NOS	2 (5)
Double- or triple-hit lymphoma	16 (40)
ECOG performance status score of 1[a], *n* (%)	25 (63)
Disease stage, *n* (%)	
I or II	2 (5)
III or IV	38 (95)
IPI total score[b], *n* (%)	
1 or 2	9 (23)
3 or 4	31 (78)

Neelapu et al, Nature Med 28:735, 2022

ZUMA-12 Patient Characteristics

Previous systemic therapy regimen (two cycles)[e], *n* (%)	
R-CHOP	19 (48)
DA-EPOCH-R	18 (45)
Neither R-CHOP nor DA-EPOCH-R	6 (15)
Best response to two cycles of previous systemic therapy, *n* (%)	
PR	21 (53)
SD	2 (5)
PD	16 (40)
NE	1 (3)
Previous radiotherapy, *n* (%)	2 (5)
Received bridging therapy, *n* (%)	7 (17.5)

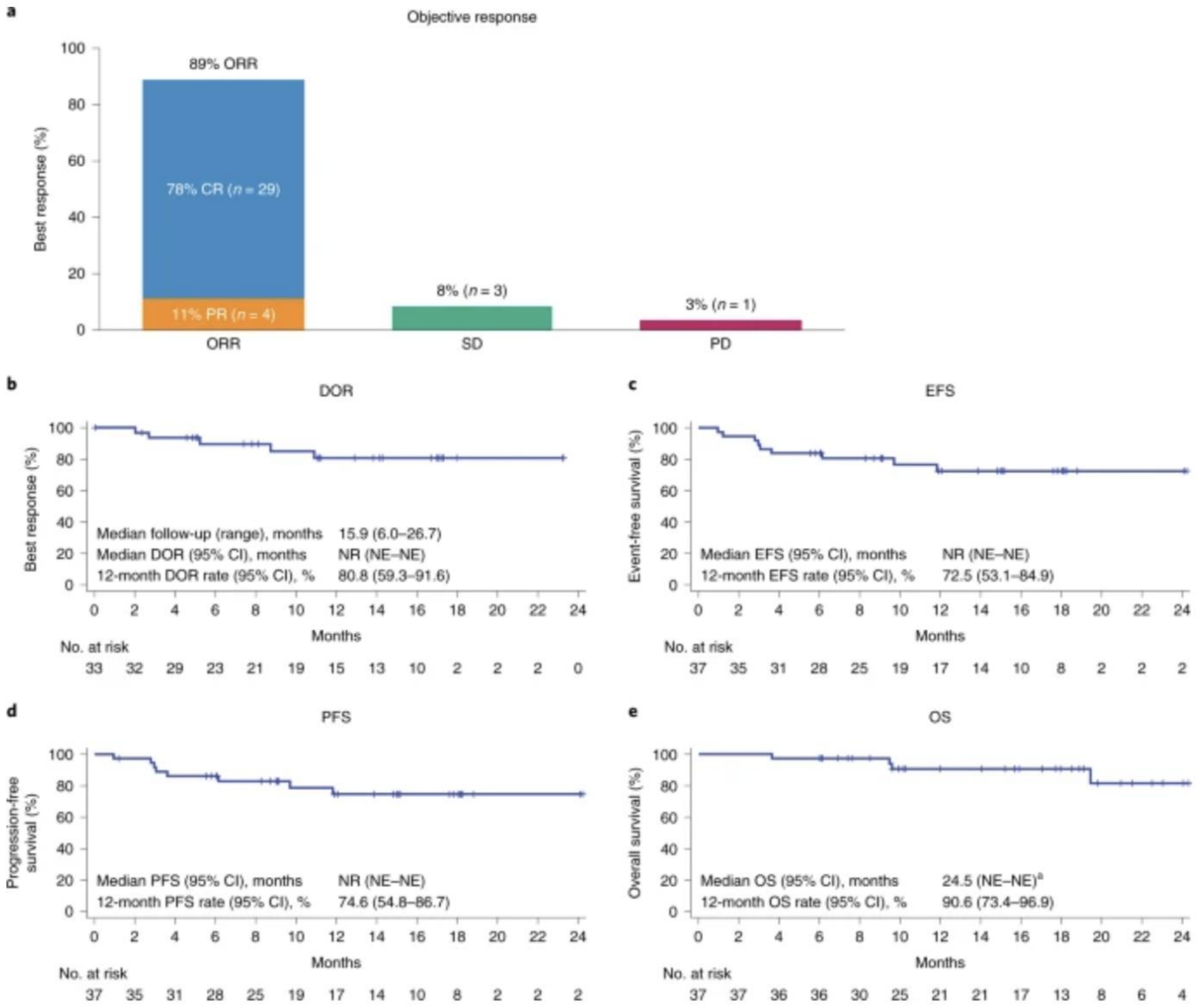
Neelapu et al, Nature Med 28:735, 2022

ZUMA-12 Patient Characteristics

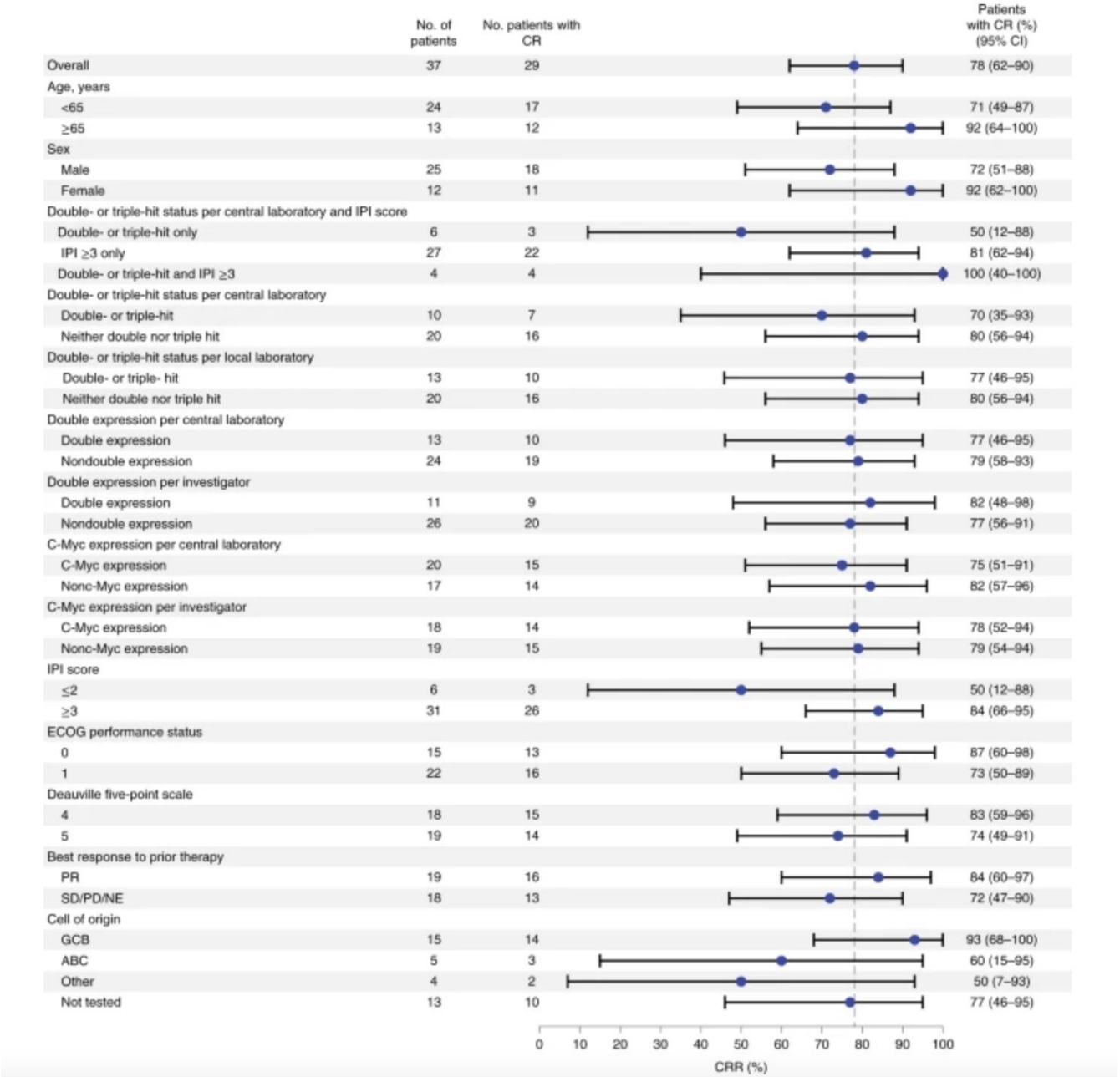
Deauville five-point scale, *n* (%)	
4	19 (48)
5	21 (53)
Bone marrow assessment at enrollment[c], *n* (%)	
Lymphoma present	10 (25)
Double- or triple-hit status by FISH per central laboratory and IPI total score, *n* (%)[d]	
Double- or triple-hit and IPI ≥3	4 (10)
Double- or triple-hit only	6 (15)
IPI ≥3 only	20 (50)
Neither double- or triple-hit nor IPI ≥3	2 (5)
Double- or triple-hit not done and IPI ≥3	7 (18)
Double- or triple-hit not done and non-IPI ≥3	1 (3)
Double expression per central laboratory, *n* (%)	13 (33)
c-Myc expression per central laboratory, *n* (%)	21 (53)

Neelapu et al, Nature Med 28:735, 2022

ZUMA-12: Outcomes



Neelapu et al, Nature Med 28:735, 2022



Neelapu et al, Nature Med 28:735, 2022

Trial record **11 of 21** for: tafasitamab | Lymphoma, B-Cell

Previous Study | Return to List | Next Study

Study of Tafasitamab and Lenalinomide Associated to Rituximab in Frontline Diffuse Large B-Cell Lymphoma Patients of 80 y/o or Older

Ages Eligible for Study:	80 Years and older (Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

ClinicalTrials.gov Identifier: NCT04974216

Criteria

Inclusion Criteria:

2.Patient with histologically proven CD20+ diffuse large B-cell lymphoma (DLBCL) (WHO classification 2017) including all clinical subtypes (primary mediastinal, intravascular, etc…), with all International Prognostic Index (IPI). May also be enrolled the following malignancies:

- De Novo transformed DLBCL from low grade lymphoma (Follicular, other...) and DLBCL associated with some small cell infiltration in bone marrow or lymph node.
- High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
- High-grade B-cell lymphoma, Not Otherwise Specified (NOS)
- Follicular lymphoma grade 3B 3.Positron-Emission Tomography (PET)-positive disease 4.Previously untreated high-grade B-cell lymphoma 5.Aged ≥ 80 years old at the time of signing the informed consent form (ICF) 6.Ann Arbor stage I, II, III or IV 7.Eastern Cooperative Oncology Group (ECO)G performance status ≤ 2 8.With a minimum life expectancy of 3 months 9.Male patients must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 4 months following study drug discontinuation, even if they have undergone a successful vasectomy 10. Patients should be able to receive R-miniCHOP regimen (left ventricular ejection fraction > 50% and good general condition, according to investigator's judgment) 11. Patients should be able to receive adequate prophylaxis and/or therapy for thromboembolic events (aspirin or low molecular weight heparin) 12. Patient covered by any social security system (France)

Trial record **18 of 18** for: mosunetuzumab | Lymphoma, B-Cell

Previous Study | Return to List | Next Study

A Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Mosunetuzumab Monotherapy in Participants With Select B-Cell Malignancies (MorningSun)

ClinicalTrials.gov Identifier: NCT05207670

Recruitment Status : Recruiting
First Posted : January 26, 2022
Last Update Posted : March 13, 2023

See Contacts and Locations

Activities of Daily Living (IADL); or Cumulative Illness Rating Scale-Geriatric (CIRS-G) score of ≥ 1 comorbidity with a severity of 3-4 or a score of 2 in ≥ 8 comorbidities

- Histologically confirmed DLBCL according to WHO 2016 classification expected to express the CD20 antigen (Swerdlow et al. 2016)
- Previously untreated DLBCL with indication to start systemic therapy and are not eligible for curative therapy
- High-grade B-cell lymphomas, not otherwise specified (HGBL NOS) and HGBL with MYC and B-cell lymphoma (BCL)-2 and/or BCL-6 rearrangements
- Adequate end-organ function

Trial record **1 of 12** for: epcoritamab | Lymphoma, B-Cell

Previous Study | Return to List | Next Study

Subcutaneous Epcoritamab With or Without Lenalidomide as First Line Therapy for Diffuse Large B-Cell Lymphoma (EPCORE™DLBCL-3)

ClinicalTrials.gov Identifier: NCT05660967

Recruitment Status : Recruiting
First Posted : December 21, 2022
Last Update Posted : March 16, 2023

See Contacts and Locations

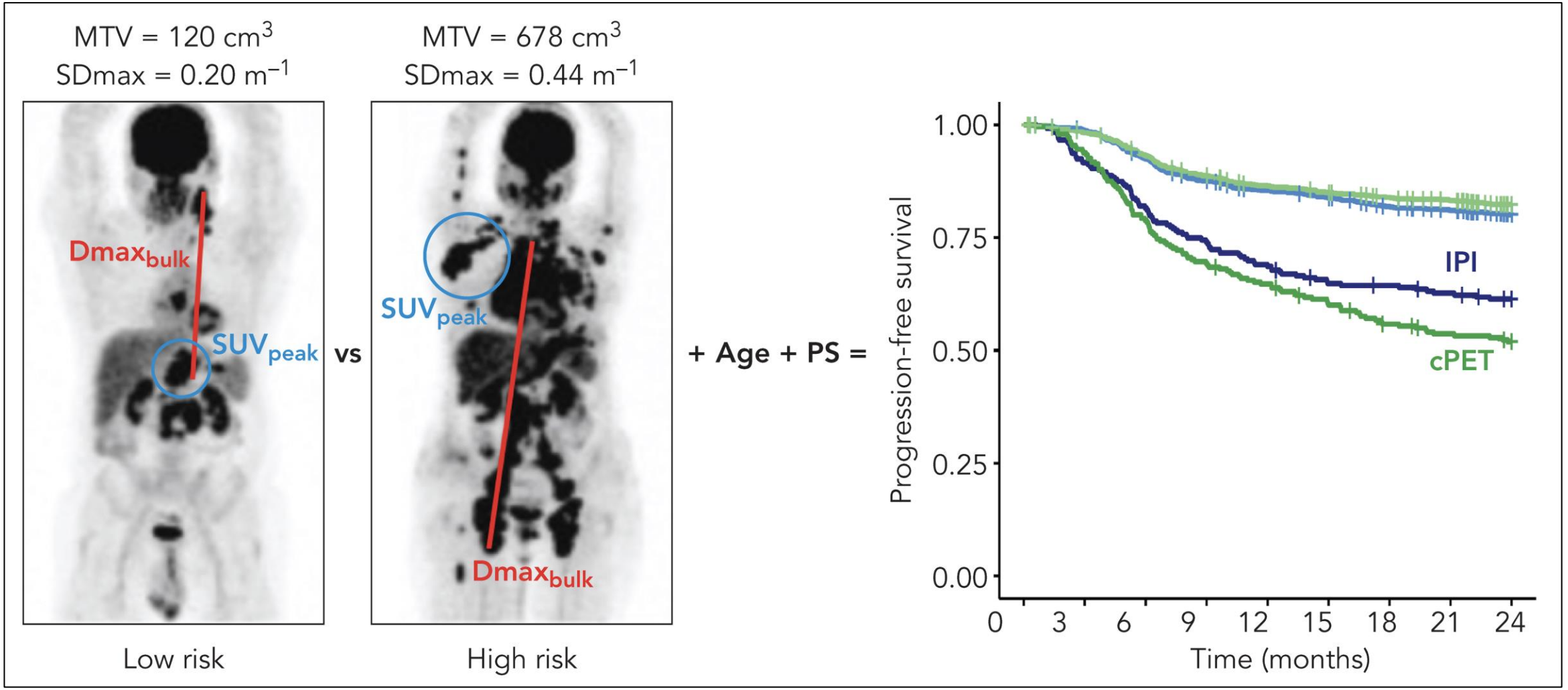
Ages Eligible for Study:	75 Years and older (Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Must have newly diagnosed CD20+ large cell lymphoma.
- Is ineligible for anthracycline-based therapy/cytotoxic chemotherapy due to:
  - Being age ≥80 years; AND/OR
  - Being age ≥75 years and having important comorbid condition(s), which are likely to have a negative impact on tolerability of anthracycline-based therapy/cytotoxic chemotherapy.
- Have Immune Effector Cell-Associated Encephalopathy (ICE) score of at least 8 out of 10.
- Have Ann Arbor Stage II-IV disease.
- Have ECOG PS of 0, 1, or 2; (ECOG PS of 3 may be considered if impairment is attributed to current lymphoma/DLBCL and if pre-phase treatment during the screening phase results in an improvement of ECOG PS to ≤2 prior to enrollment).
- Have measurable disease as per Lugano criteria.
- Have acceptable organ function based on baseline bloodwork.
- Must have fresh (preferred) or archival biopsy material at screening.

clinicalPET System for DLBCL Prognosis



Cheson commenting on Eertlink et al, Blood (in press), 2023

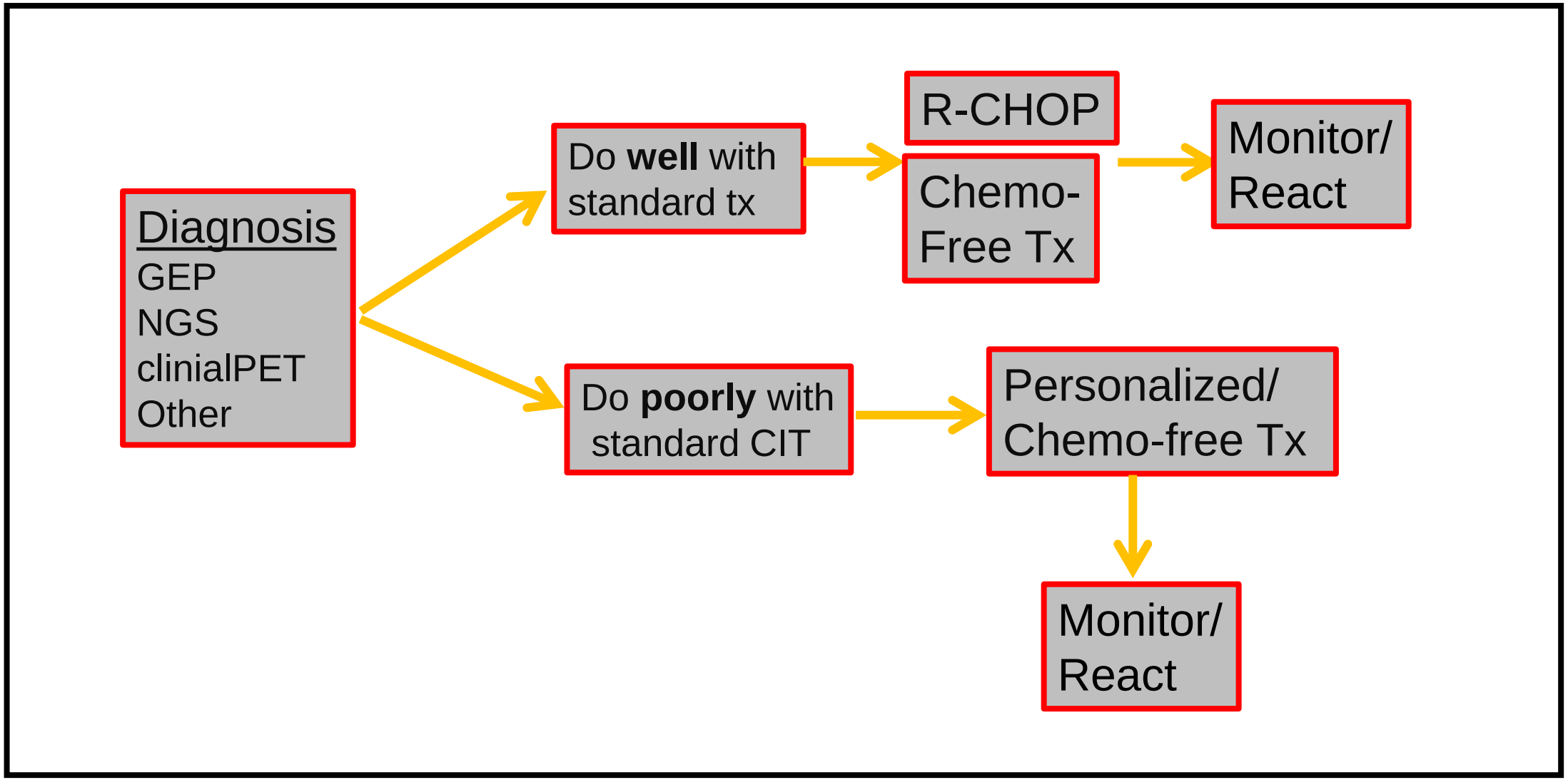
NGS Analysis of DLBCL

Cell-of-Origin Classifications of Diffuse Large B-cell Lymphoma Genomic Subtypes				
COO Classification	Subgenomic Classification		Recurrent Genetic Alterations	10-Year PFS (%)
ABC	Chapuy/Shipp	Cluster 1	BCL6, NOTCH2	70
		Cluster 5	MYD88, CD79B, BCL2, MALT1	40
	Schmitz/Staudt	MCD	MYD88, CD79B	10
		N1	NOTCH1	0
GCB	Chapuy/Shipp	Cluster 3	EZH2, BCL2, CREBBP	40
		Cluster 4	Core histone genes, immune evasion molecules, JAK/STAT members, BCR/PI3K intermediates, NFKB signaling	70
	Schmitz/Staudt	EZB	EZH2, BCL2	60
ABC+GCB	Chapuy/Shipp	Cluster 2	TP53, del17p	40
	Schmitz/Staudt	BN2	BCL6, NOTCH2	60

Abbreviations: GCB, germinal center B cell-like lymphomas; ABC, activated B cell-like lymphomas

Jacobsen C, Hematologist 2018

Anticipatory Risk -Adapted Strategy



Conclusions

- R-CHOP is archaic (CHOP 45+yrs; R-CHOP 21 yrs)
- It is effective for 50-70% of patients, but toxic (5% deaths)
- Attempts to substantially improve on it have thus far been futile
- New cellular and immunotherapeutic agents are extremely active in R/R patients
- Thus, should potentially be more effective pre-resistance
- Current non-chemo studies mostly in the elderly
- Need to base tx on prognostic/predictive markers in all patients
- Strategies replacing R-CHOP in 1L are ***inevitable***