Non Hodgkin Lymphoma treatment in elderly

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Elderly NHL

Definition: Age > 60y in some studies or up to 80y

No clear definition of ‘elderly’ and ‘frail’ patient

Difference between biological & chronological age

Competing comorbidities

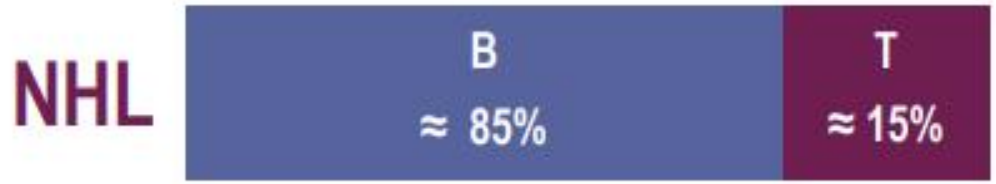
Alter the tolerability of chemotherapy

Inferior outcomes in older patients

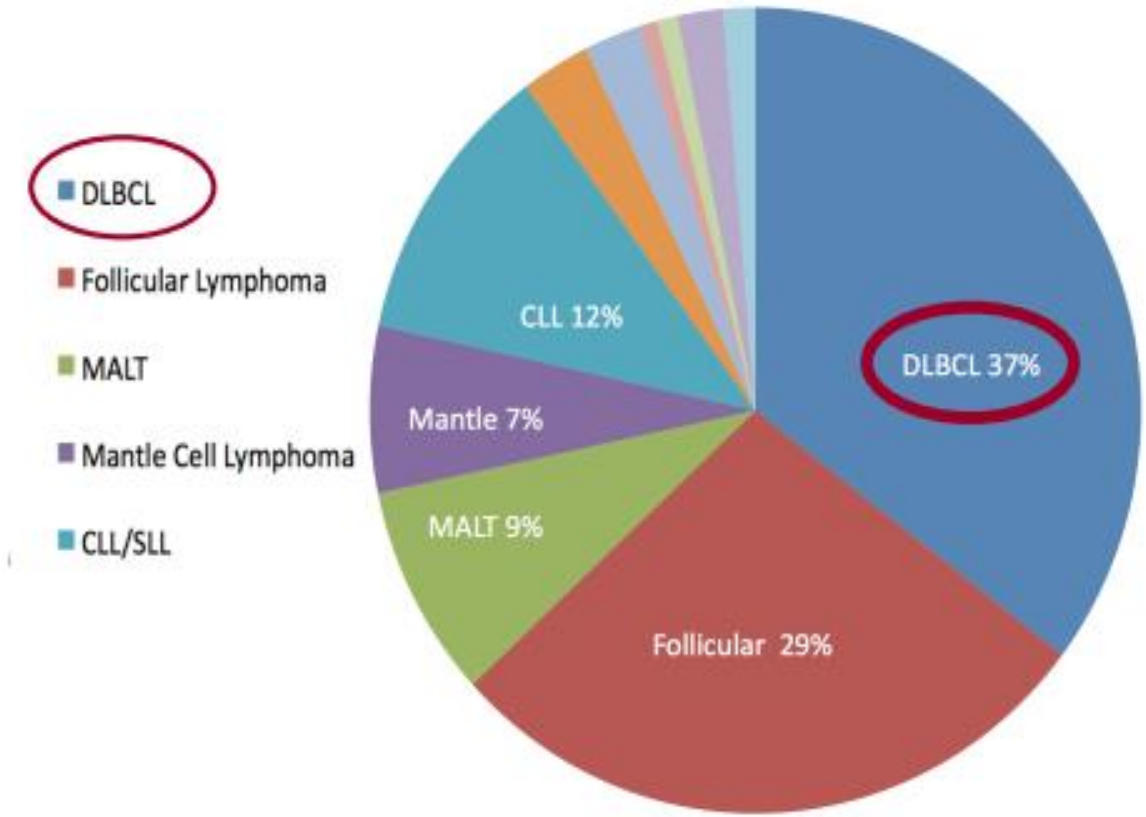
55% to 60% of NHL have a concurrent serious comorbidity

Risk of death: twice in serious comorbidities(independent to IPI)

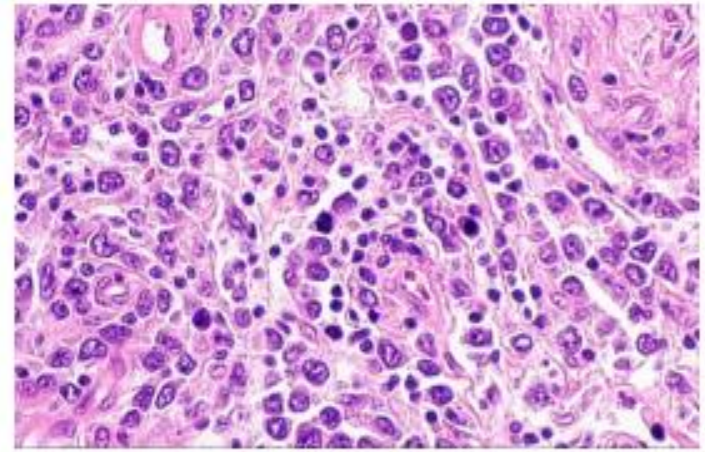
NHL OVERVIEW



Main B-cell lymphomas distribution



DLBCL:
The commonest subtype



Lymphoma Research Foundation. Understanding Non-Hodgkin Lymphoma 2012. Fourth edition;

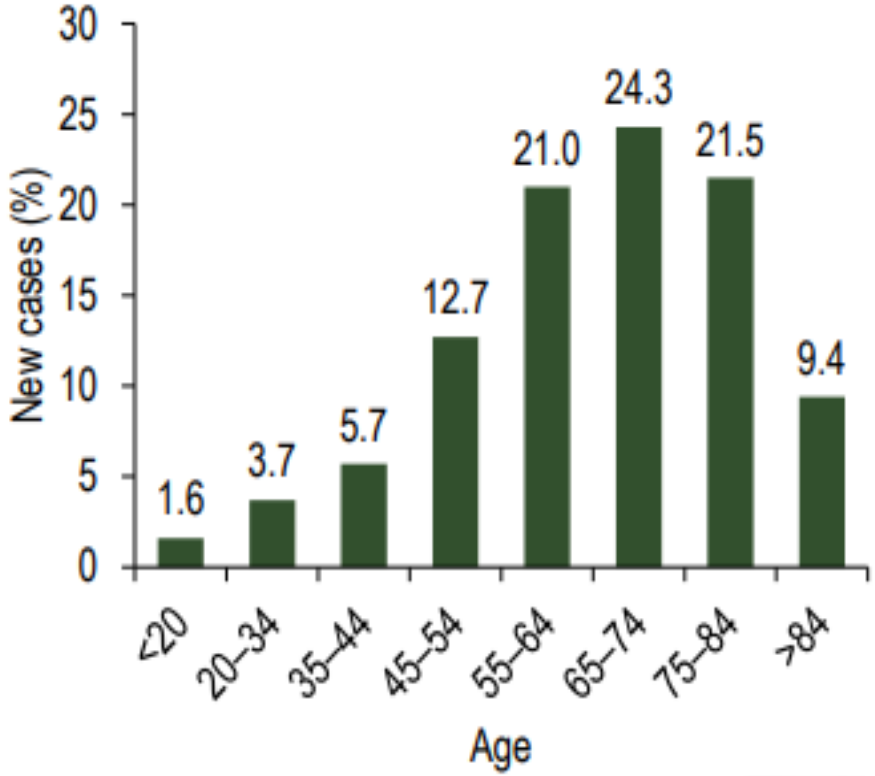
DLBCL

Presentation

De novo or after transformation: follicular lymphoma, CLL/SLL[1]

- Incidence in Europe
  - 3.8/100 000/year[2]
  - Increases with age[3]
  - Median age at diagnosis 64 years
- Risk factors[4]
  - Family history
  - Autoimmune disease
  - HIV+
  - Hepatitis C Virus+

Percent of New Cases by Age Group: NHL
SEER 18 2009-2013, All Races, Both Sexes[5]



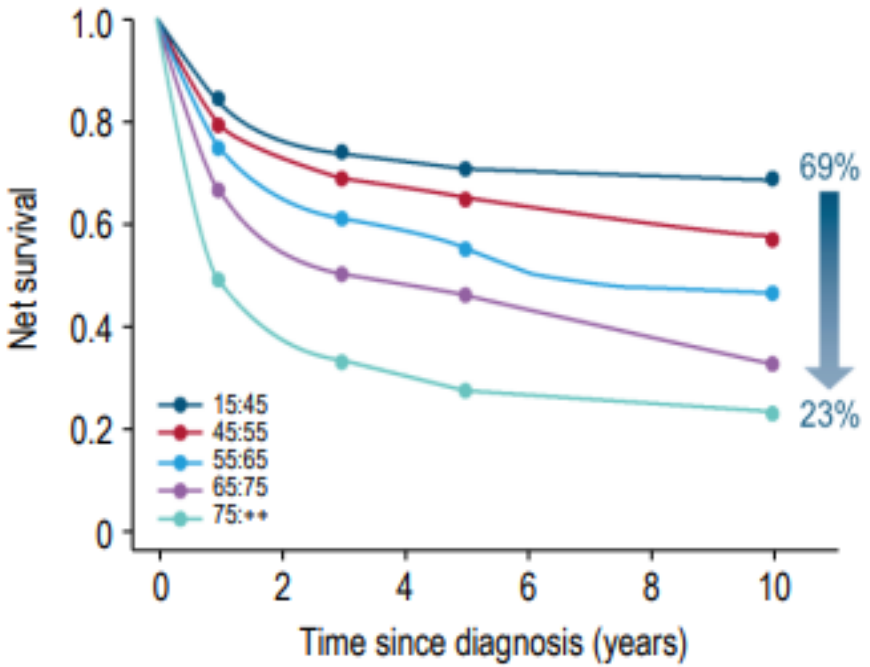
1. Raut LS, *et al.*, South Asian J Cancer 2014
2. Sant M, *et al.*, Blood 2010

DLBCL PROGNOSIS

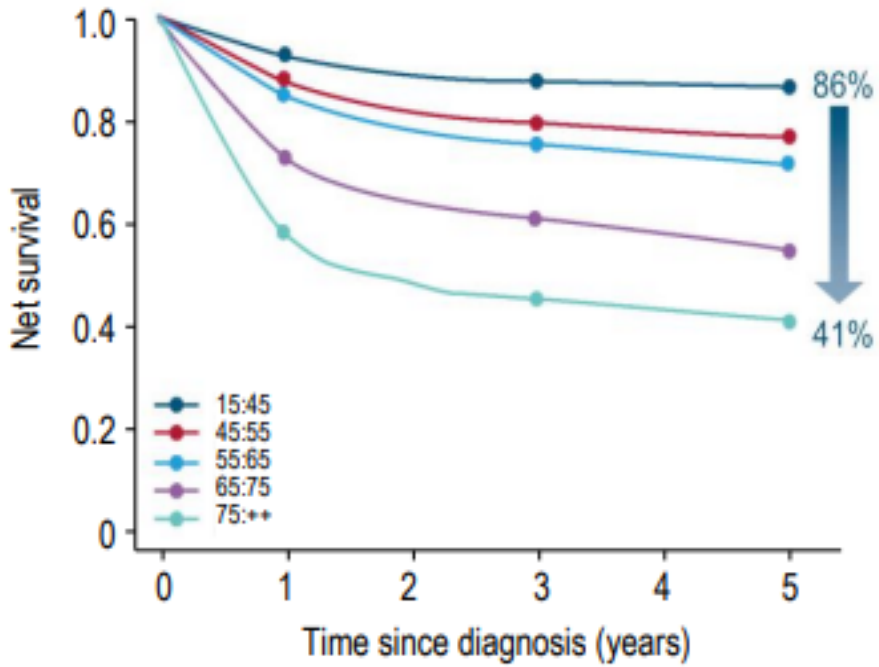
Overall Survival according to age and time period

Events occur early….

1989–2007[1]



2005–2010[2]



1. Monnereau A, *et al.*, Survie des personnes atteintes de cancer en France 1989-2007. Lymphomes diffus à grandes cellules. Études à partir des registres des cancers du réseau FRANCIM.
2. Monnereau A, *et al.*, Lymphome diffus à grandes cellules B. Available on invs.santepubliquefrance.fr

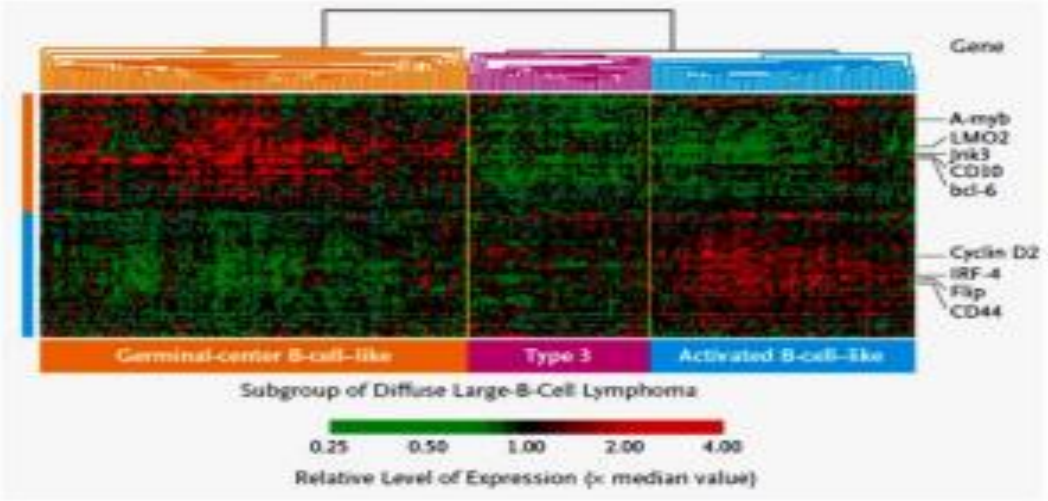
DLBCL in elderly

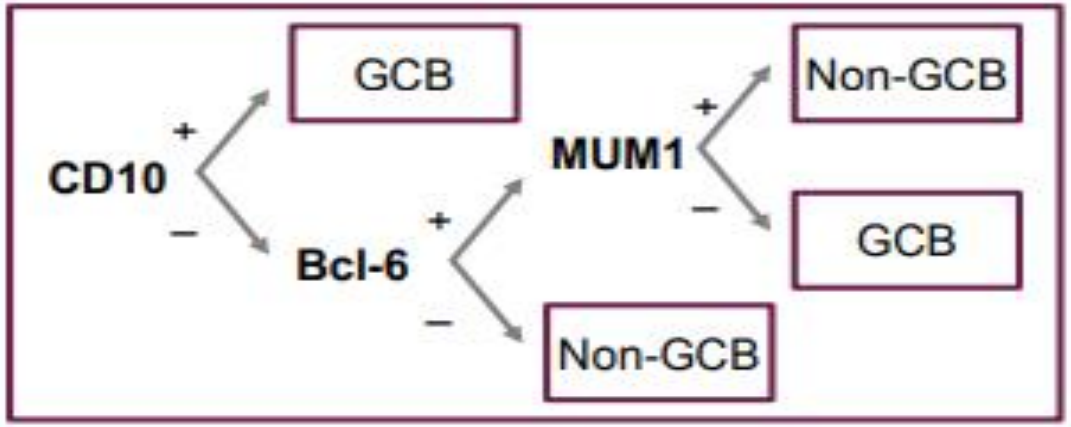
60% of all lymphoid malignancies

SEER database:

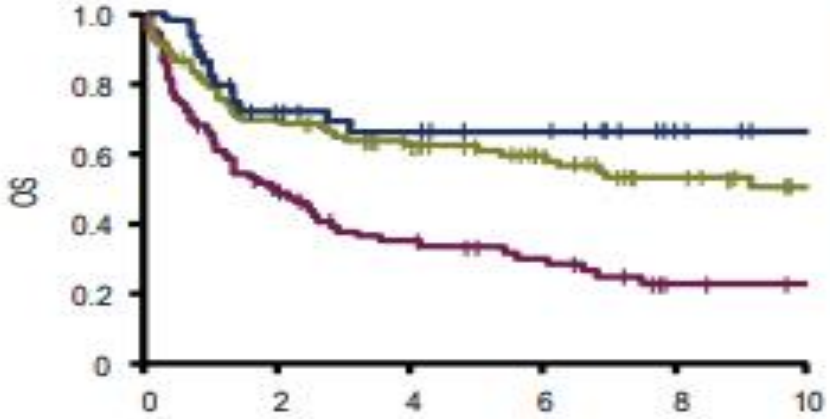
- 23% received no treatment
- Age > 80: one third of patients not receiving therapy
- Grade 3/4 toxicity occur in over 50% of higher comorbidities
- receiving< 6 cycles of therapy had a 91% higher mortality risk
- Rituximab VS No treatment: 69% decreased mortality risk in R group

IMPORTANCE OF CELL-OF-ORIGIN MOLECULAR SUBTYPES





Hans classification



DLBCL subgroup	5-Yr OS, %
PMBL	64
GCB DLBCL	59
ABC DLBCL	30

From NEJM 2002, Rosenwald A, *et al.*, The Use of Molecular Profiling to Predict Survival after Chemotherapy for Diffuse Large-B-Cell Lymphoma; 346: 1937-47.

Rosenwald A, *et al.*, J. Exp Med 2003 198,851-862.
Hans CP, *et al.*, Blood 2004;103:275-282

More common in elderly

ABC/non GCB subgroup (GEP) →→ more aggressive

MYC expression

BCL2

Double expresser phenotype

Cytogenetic Complexity

Elevated ki-67

Comprehensive Geriatric Assessment (CGA)

Validated instrument evaluating functional age

assessments of chronologic

Assessment of: age

physical function

activities of daily living (ADL)

instrumental(I)ALDs

comorbidities

Independent predictor of outcomes in patients receiving chemotherapy

Useful in identifying patients whom full-dose chemotherapy is not beneficial

ADL

Six-item scale

Assess basic self-care activities

Include: feeding

dressing

bathing

toileting

transfer

continence

IADL

Assess a patient's basic abilities to maintain an independent life

such as: preparing food laundry

using the phone shopping

ability to travel taking drugs

housekeeping handling money

CGA classifications

FIT: age < 80 with no limitations in ADL/(I)ADLs AND no serious comorbidities

Frail: limitations in (I)ADLs

serious or multiple significant comorbidities OR

are > age 80 with some limitations

Unfit: between both of them

Fit patients: ORR 87% and 5-year OS 55%

Unfit and frail patients: ORR 67% and 5-year OS 29%

Italian Lymphoma Foundation (FIL): fit survival 88%

not fit survival 56%

DLBCL treatment in elderly Trials

GELA LNH-98-5

RICOVER-60

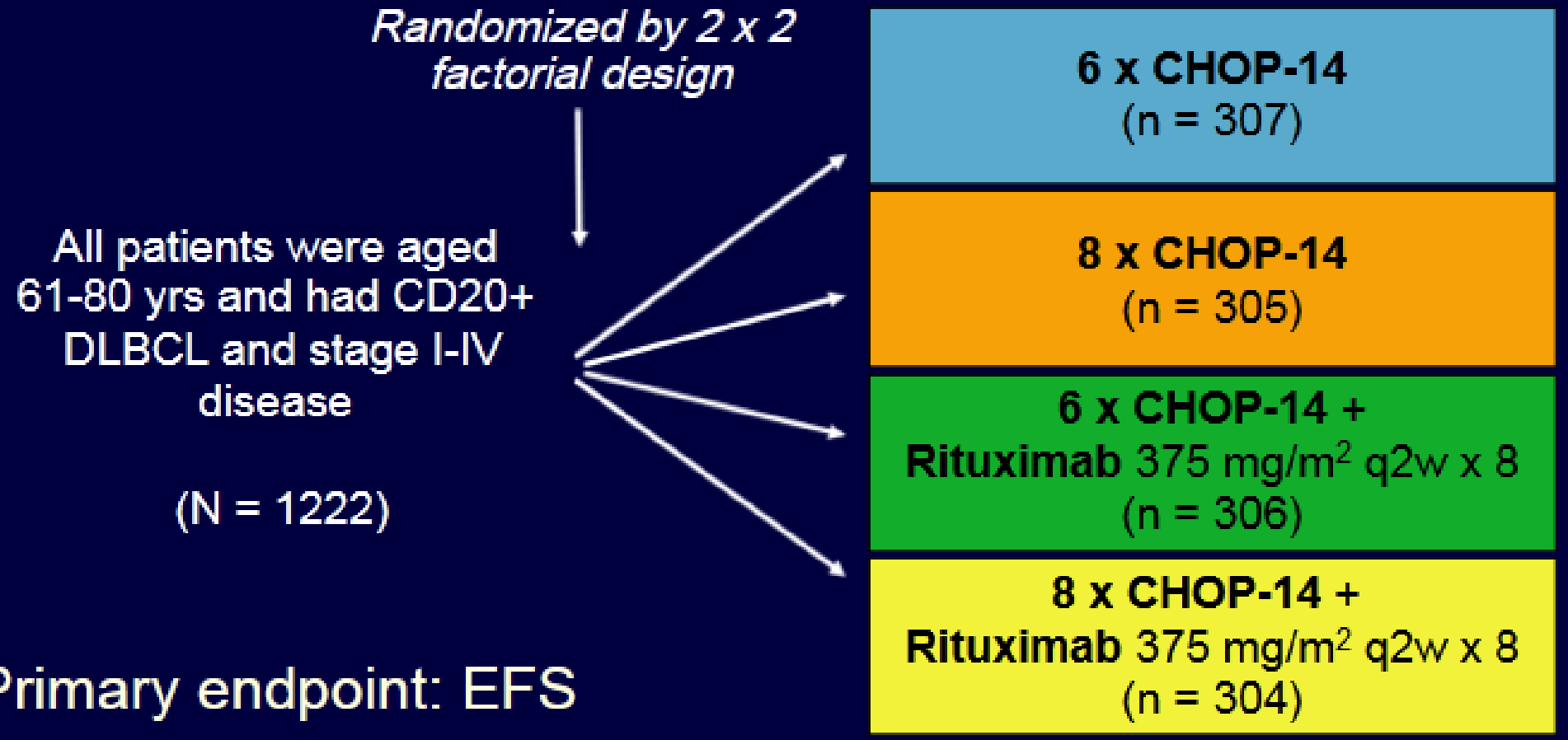
LNH03-6B

UK NCRI R-CHOP14v21

patients ages 60–80 with newly diagnosed DLBCL

Benefit of adding Rituximab to CHOP

CHOP-14 vs R-CHOP-14 RICOVER-60 Trial: Patients Aged 61-80 Yrs



- Primary endpoint: EFS

*Radiotherapy (36 Gy) was planned for patients with initial bulky disease or extranodal involvement.

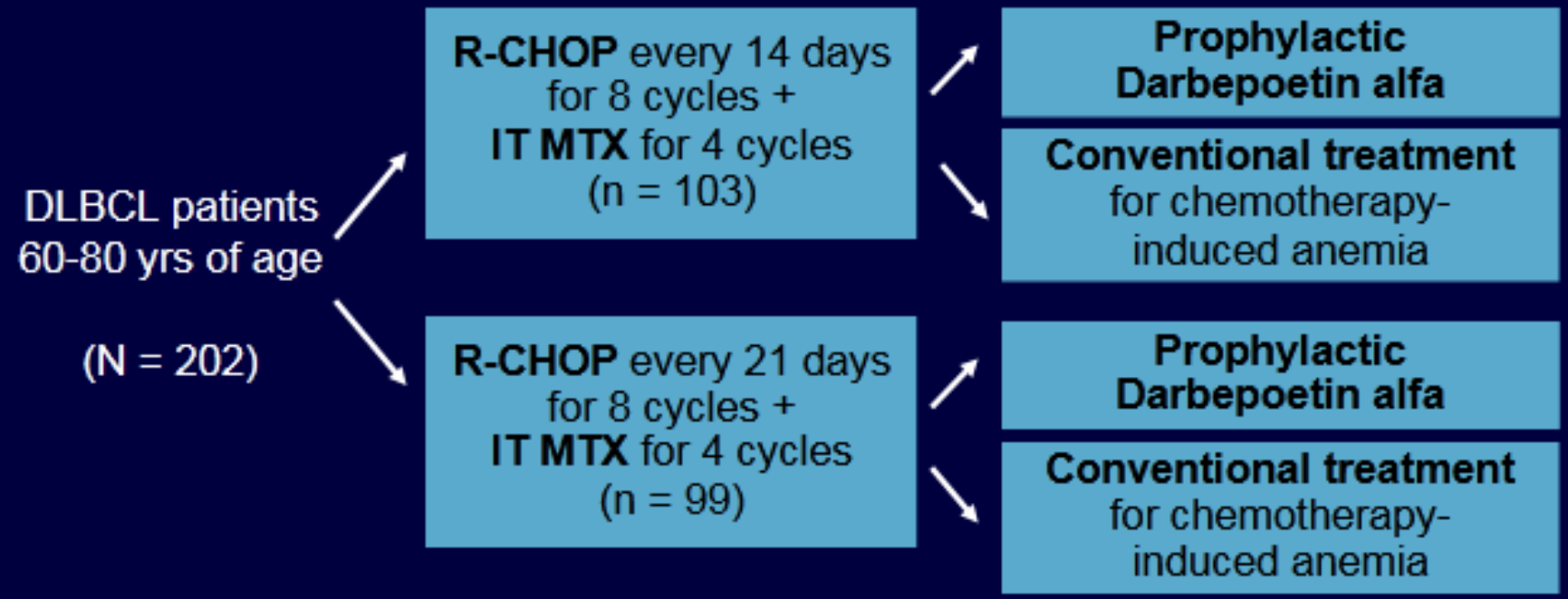
Pfreundschuh M, et al. Lancet Oncol. 2008;9:105-116.

CHOP-14 ± Rituximab in Elderly Patients With DLBCL (RICOVER-60 Trial): EFS

- EFS was significantly superior with R-CHOP-14 vs CHOP-14
  - $P < .0001$ for both 6 cycles and 8 cycles
- 8 cycles of R-CHOP-14 not superior to 6 cycles
  - 6 cycles R-CHOP-14 is preferred treatment for elderly patients

Pfreundschuh M, et al. Lancet Oncol. 2008;9:105-116.

LNH03-6B GELA: R-CHOP-14 vs R-CHOP-21 in Elderly DLBCL Patients

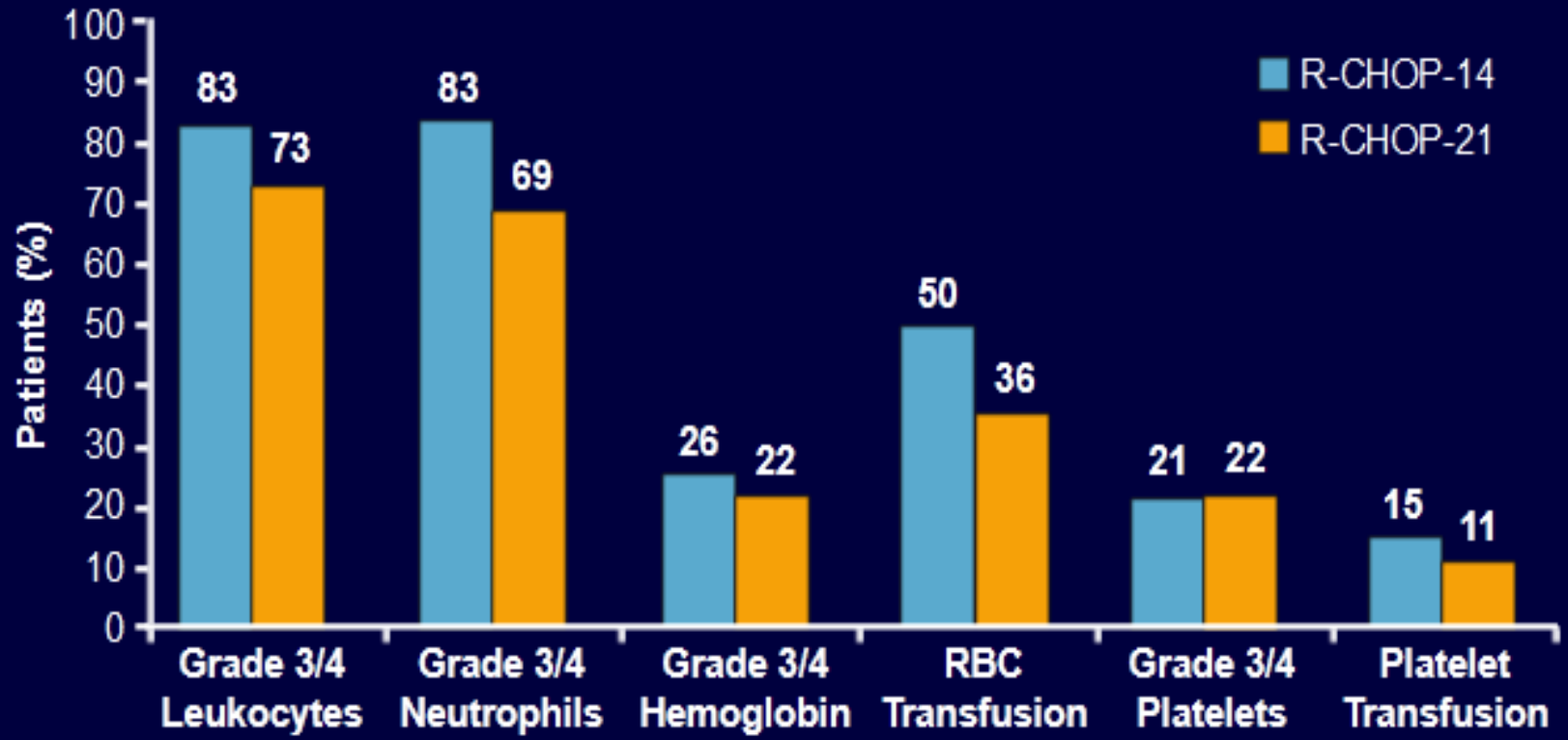


- Primary endpoint: EFS
- Secondary endpoints: CR or CRu , ORR, PFS , DFS, OS, dose intensity, toxicity

Delarue R, et al. ASH 2009. Abstract 406.

LNH03-6B GELA Trial: Toxicities

- Hematologic toxicities greater for R-CHOP-14



- Patients on R-CHOP-14 had higher rates of febrile neutropenia, hospitalization, and death due to toxicity

Delarue R, et al. ASH 2009. Abstract 406.

RCHOP problems in elderly

Not enroll patients older than 80 years

Most patients had a good performance status (ECOG-PS 0–1)

Dose dense protocol increase Hematologic and Cardiac toxicity

Consider Dose Attenuated chemotherapy protocols

Mini RCHOP in >80y/o: 2-y PFS 47% & OS 59%

R-COMP: CR 56–68% & 3–4 year survival 70% (similar outcomes to CHOP)

original article

Annals of Oncology 21: 1492–1499, 2010
doi:10.1093/annonc/mdp544
Published online 11 December 2009

Nonpegylated liposomal doxorubicin (Myocet™) combination (R-COMP) chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL): results from the phase II EUR018 trial

S. Luminari[1], A. Montanini[1], D. Caballero[2], S. Bologna[3], M. Notter[4], M. J. S. Dyer[5], A. Chiappella[6], J. Briones[7], M. Petrini[8], A. Barbato[9], L. Kayitalire[9] & M. Federico[1]*

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Received 13 May 2009; revised 14 October 2009; accepted 27 October 2009

Intergruppo Italiano Linfomi

R-miniCEOP: substituted epirubicin for doxorubicin

FIT elderly patients

phase 3 trial compared with R-CHOP

70% complete response with R-miniCEOP

Equivalent 5-y EFS with R-CHOP(46% VS 48%)

Double hit lymphoma in elderly

More common in older adults

Dose-adjusted-EPOCH-R in untreated MYC-rearranged aggressive B-cell lymphoma

50% of patients older than age 60

2-y EFS and OS were 75% and 91.7%

Dose-attenuated DA-(E)POCH in 2 studies of patients older than age 70

Results: 3-y OS of approximately 60%

no significant cardiac events

Annals of Hematology (2018) 97:1809–1816
https://doi.org/10.1007/s00277-018-3369-7

ORIGINAL ARTICLE

Reduced-dose EPOCH-R chemotherapy for elderly patients with advanced stage diffuse large B cell lymphoma

Wen-Hao Zhang[1] · Gao-Yang Li[1] · Yu-Jie Ma[1] · Zhi-Chao Li[1] · Yang Zhu[1] · Jun Chang[1] · Si-Guo Hao[1] · Rong Tao[1]

Received: 10 September 2017 / Accepted: 7 May 2018 / Published online: 12 May 2018

Abstract

The standard treatment in elderly patients with diffuse large B cell lymphoma (DLBCL) has not yet been finely established. We investigated the efficacy and safety of rituximab with a reduced-dose of EPOCH chemotherapy in elderly patients who had advanced DLBCL with high IPI scores. The dose of 70% EPOCH was given to patients aged 75 to 79 years, and dose of 50% to patients aged over 80 years. Thirty-one patients with a median age of 79 years (range 75–86 years) were enrolled. Patients received a median of 6 cycle's chemotherapy. The complete response rate was 71.0%. The 3-year overall survival (OS) and progression-free survival rates were 62.8 and 60.3%, respectively. The most frequent grade 3/4 adverse effects were neutropenia (3 patients, 7 events), febrile neutropenia (3 patients, 5 events), and pulmonary infection (3 patients, 3 events). Our study showed

Table 1 Select clinical trials in elderly patients with newly diagnosed diffuse large B-cell lymphoma

	Trial	Phase	Treatment	*n*	Age, frailty	ORR %	CR %	PFS %	OS %
Anthracycline containing									
Full-dose	LNH98-5 [25,30]	3	CHOP	399	60–80	69	63*	30, 5 years	45, 5 years
			R-CHOP			83	75	54	58
	RICOVER [51]	3	R-CHOP + Rx2	166	60–80	6	76*	72, 3 years	77, 3 years
			R-CHOP + Rx2 + RT			13	78	73	78
	UK NCRI R-CHOP14v21, subgroup [28, 29••]	3	R-CHOP14	604	> 60	91	67	64, 5 years	69, 5 years
			R-CHOP21			91	62		
	LNH03-6B [27]	3	R-CHOP14	602	60–80	87	71	60, 3 years	69, 3 years
			R-CHOP21			86	74	62	72
	Corazzelli, 2011 [34]	2	R-COMP-14	41	> 60, cardiac comorbidity	73	68	77, 4 years	67, 4 years
	EUR018 [35]	2	R-COMP	75	≥ 60	71	57	69, 3 years	72, 3 years
	HEART01 [36•]	2	R-COMP	51	≥ 18, cardiac comorbidity	72	56	30, 3 years	22, 3 years
Dose-attenuated	Peyrade, 2011 [33]	2	R-Mini-CHOP	150	> 80	73	62	47, 2 years	59, 2 years
	Musolino, 2011 [40]	2	DA-POCH-R	23	≥ 70	90	57	56, 3 years	54, 3 years
	Zhang, 2018 [39•]	2	DA-EPOCH-R, 50–70% dose reduction by age group	31	> 70	87.1	71.0	62.8, 3 years	60.3, 3 years
	ANZINTER3 [37]	3	R-miniCEOP (epirubicin)	224	≥ 65	81	68	46, 5 years†	63, 5 years
			R-CHOP			87	73	48	62†

Non anthracycline Containing Therapy

For frail patients or contraindication to anthracyclines

R-CEOP (rituximab, cyclophosphamide,etoposide, vincristine, and prednisone)

Gemcitabine based regimens

R-CVP

BR (bendamustine and rituximab)

Curable but are generally inferior to R-CHOP with long-term survival of 50%

British Columbia guidelines

81 DLBCL patients with contraindication to anthracycline

R-CEOP 3-4 cycles in limited stages and 6 cycles in advanced stages

5-y time to progression similar to RCHOP

OS was inferior in R-COEP group (49% vs. 64% p = 0.02)

US cohort: 2-y PFS in non-GCB and GCB were 26% and 85%,

Bendamustine + Rituximab

Patients ≥ 65 y

Poor candidates for R-CHOP

50% with an ECOG PS ≥ 2 (Frail)

Response rates were high

But: median OS was < 1 y

PFS was < 6 months

Similar results with R-GCVP and R-GemOX

Anthracycline-free regimens =expense of reduced efficacy

Novel approaches

REAL07 Phase II Study Eligibility and Endpoints

Eligibility (N = 49*)
- Age 60-80 y, fit - CD20+ DLBCL or Grade IIIb FL - Ann Arbor Stage II-IV - IPI: Low-intermediate/intermediate-high/high risk - No peripheral neuropathy, CNS disease or recent DVT - No prior chemotherapy or prior malignancies in past 3 years

* Includes 9 patients treated at MTD in Phase I

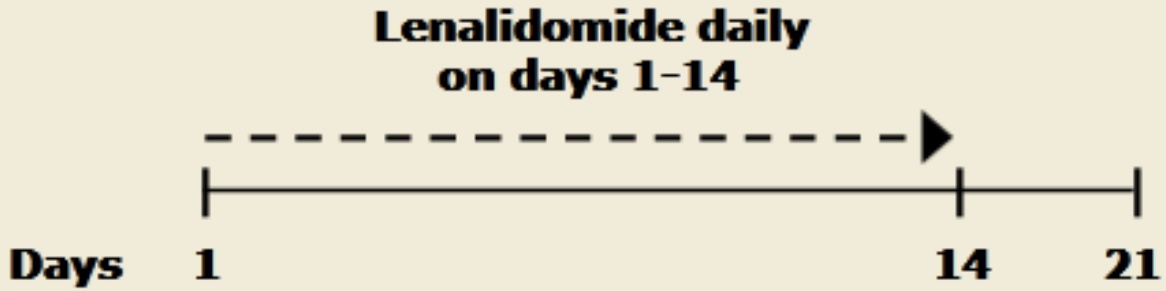
Primary endpoints: Overall response rate (ORR) and complete response (CR)

Secondary endpoints: Included 2-year overall survival (OS) and 2-year progression-free survival (PFS)

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

REAL07 Phase II Study Design

Treatment cycles

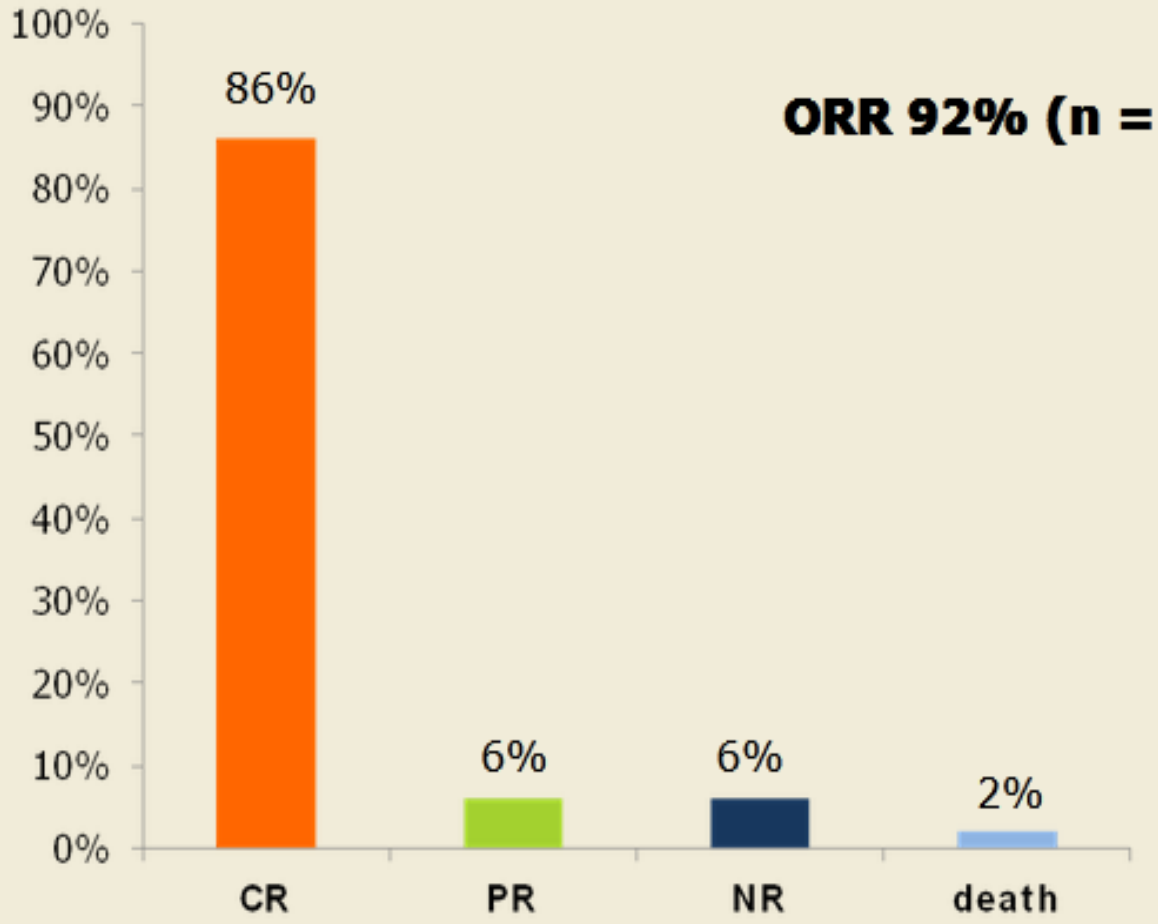


Lenalidomide at MTD:
15 mg daily on days 1-14 (Vitolo U, ASH 2010)

(↑) Rituximab	375 mg/m²
Cyclophosphamide	750 mg/m²
Doxorubicin	50 mg/m²
Vincristine	1.4 mg/m² (capped at 2.0 mg)
Prednisone	40 mg/m² on days 1-5

Prophylaxis included: GCSF or PEG-GCSF, low-molecular-weight heparin or low-dose aspirin, co-trimoxazole

Final Response After 6 Cycles of LR-CHOP21



ORR 92% (n = 49)

PR = partial response; NR = no response

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

REAL 07 trial results

Add lenalidomide seemed to diminish the negative prognostic impact of COO

Cell Of Origin

GCB: 5y-PFS was 52.8% 5y-OS was 68.6%

Non GCB: 5y-PFS was 64.5% 5y-OS was 74.1%

REMARC study

Maintenance lenalidomide in elderly patients responding to R-CHOP

Lenalidomide 25 mg/day or placebo for 21/28 days for 24 months

Statistically significant improvement in PFS in maintenance group

BUT

Absolute difference was small (75% vs. 80% PFS at 2 years)

No difference in OS

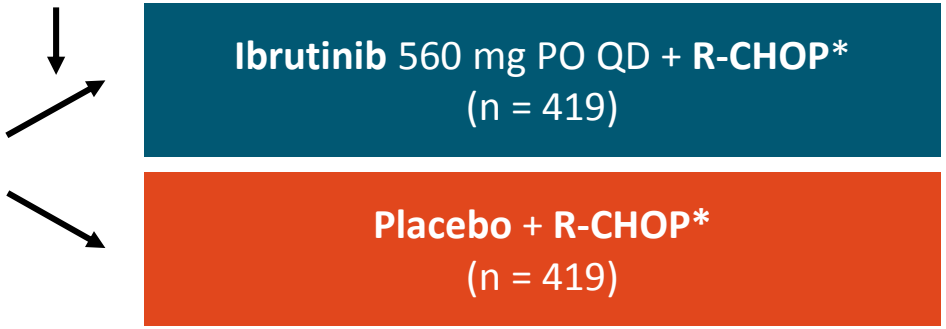
Associated with increased toxicity

PHOENIX: Study Design

- International, randomized, double-blind phase III trial[1]

Stratified by R-IPI, region (US/Western Europe vs rest of world), no. prespecified R-CHOP cycles (6 vs 8)

Patients with untreated non-GCB DLBCL determined centrally by Hans-based IHC; stage II-IV measurable disease; R-IPI ≥ 1; ECOG PS 0-2 (N = 838)



*Rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1, prednisone or equivalent 100 mg PO QD on Days 1-5. G-CSF and antibiotics permitted.[1,2]

- Primary endpoint: EFS in ITT population and ABC subgroup (determined retrospectively by gene expression profiling)
  - EFS events defined as PD, relapse from CR, starting subsequent disease-specific tx for PET-positive/biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death
- Secondary endpoints: CR rate, OS, PFS, safety
  - Response evaluated with Revised Response Criteria for Malignant Lymphoma[3]
- Exploratory stepwise analyses of potential interactions between treatment and prespecified BL characteristics for EFS and, if significant, PFS and OS

1. Younes. ASH 2018. Abstr 784. 2. NCT01855750. 3. Cheson. J Clin Oncol. 2007;25:579.

Slide credit: clinicaloptions.com

PHOENIX: EFS by Age

EFS Outcome in ITT Population, Event/N	Ibrutinib + R-CHOP	Placebo + R-CHOP	HR (95% CI)
Age < 65 yrs	54/231	81/259	0.71 (0.51-1.01)
Age ≥ 65 yrs	64/188	48/160	1.24 (0.85-1.80)

- In preplanned exploratory stepwise analyses, age was the only BL characteristic that significantly interacted with treatment for EFS, PFS, and OS
- Age met significance criteria both as a continuous and a categorical variable
  - HR for OS favored ibrutinib + R-CHOP in age categories of < 50 yrs, 50-55 yrs, and 55-60 yrs

Younes. ASH 2018. Abstr 784.

Slide credit: clinicaloptions.com

PHOENIX: AEs and Treatment Exposure by Age

- Among patients aged < 60 yrs and ≥ 60 yrs, AEs were similar between treatment arms
- Higher rates of both serious AEs and AEs leading to treatment discontinuation were observed in older patients receiving ibrutinib + R-CHOP vs placebo + R-CHOP
  - Primary TEAEs leading to dose reduction/discontinuation were febrile neutropenia and peripheral neuropathy
- In the safety population, drug exposure was lower with ibrutinib + R-CHOP vs placebo + R-CHOP, particularly among older patients

Patients Receiving ≥ 6 Cycles of Treatment, n (%)	Age < 60 Yrs		Age ≥ 60 Yrs	
	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
With R-CHOP	143 (92.9)	172 (93.0)	193 (73.7)	207 (88.8)
With ibrutinib or placebo	138 (89.6)	170 (91.9)	178 (67.9)	202 (86.7)

Younes. ASH 2018. Abstr 784.

Slide credit: clinicaloptions.com

PHOENIX: Conclusions

In patients with non-GCB DLBCL, first-line ibrutinib + R-CHOP did not prolong EFS in the ITT population or in those with ABC DLBCL vs placebo + R-CHOP

Ibrutinib + R-CHOP benefit and safety profiles varied by age

- Among those aged < 60 yrs, ibrutinib + R-CHOP improved EFS, PFS, and OS vs placebo + R-CHOP
  - HR: for EFS, 0.579 (95% CI: 0.380-0.881); for OS, 0.330 (95% CI: 0.162-0.673)
- Among those aged ≥ 60 yrs, ibrutinib + R-CHOP showed higher rates of serious AEs and AEs leading to discontinuation of R-CHOP, along with decreased drug exposure

Investigators concluded that risk outweighs benefit of adding ibrutinib to R-CHOP in older patients; observed benefit in younger patients requires confirmation in prospective trial

Younes. ASH 2018. Abstr 784.

original report

Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non–Germinal Center B-Cell Diffuse Large B-Cell Lymphoma

Anas Younes, MD[1]; Laurie H. Sehn, MD[2]; Peter Johnson, MD[3]; Pier Luigi Zinzani, MD, PhD[4]; Xiaonan Hong, MD[5]; Jun Zhu, MD[6]; Caterina Patti, MD[7]; David Belada, MD, PhD[8,9]; Olga Samoilova, PhD[10]; Cheolwon Suh, MD, PhD[11]; Sirpa Leppä, MD[12,13]; Shinya Rai, MD, PhD[14]; Mehmet Turgut, MD, PhD[15]; Wojciech Jurczak, MD, PhD[16]; Matthew C. Cheung, MD[17]; Ronit Gurion, MD[18,19]; Su-Peng Yeh, MD[20]; Andres Lopez-Hernandez, MD[21]; Ulrich Dührsen, MD[22]; Catherine Thieblemont, MD, PhD[23,24]; Carlos Sergio Chiattone, MD, PhD[25]; Sriram Balasubramanian, PhD[26]; Jodi Carey, RN[27]; Grace Liu, PhD[28]; S. Martin Shreeve, MD, PhD[26]; Steven Sun, PhD[28]; Sen Hong Zhuang, MD, PhD[28]; Jessica Vermeulen, MD, PhD[29]; Louis M. Staudt, MD, PhD[30]; and Wyndham Wilson, MD, PhD[30]; on behalf of the PHOENIX investigators

OBINUTUZUMAB

Novel CD20 antibody

Combination with mini-CHOP

phase 2 study

patients with age ≥ 65 and unfit

Compared with R-mini CHOP

OUTCOME: similar to R-mini CHOP

CR:42% 2-y PFS:49%

OS:68%

ELSEVIER

Journal of Geriatric Oncology

Volume 11, Issue 1, January 2020, Pages 37-40

Obinutuzumab and miniCHOP for unfit patients with diffuse large B-cell lymphoma. A phase II study by Fondazione Italiana Linfomi

Francesco Merli [a], Federica Cavallo [b], Flavia Salvi [c], Alessandra Tucci [d], Gerardo Musuraca [e], Luca Nassi [f], Michele Merli [g], Monica Tani [h], Guido Gini [i], Angela Ferrari [a], Anna Lia Molinari [j], Anna Marina Liberati [k], Annarita Conconi [l], Paola Matteucci [m], Alessia Bari [n], Renato Scalone [o], Simone Ferrero [b], Manuela Zanni [c]

Hypomethylating agents

Azacitidine has been used in older patients with AML and MDS

Oral azacitidine : FDA-approved for maintenance therapy in AML

who are unable to receive additional intensive chemotherapy

SWOG S1918 trial: compare R-miniCHOP to R-miniCHOP with oral azacitidine

442 Patients ≥ age 75

New diagnosed aggressive B-cell NHLs

stage II bulky, stage III, or stage

Use ctDNA as prognostic marker and response evaluation

Journal of Geriatric Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Clinical Trial Protocol

SWOG 1918: A phase II/III randomized study of R-miniCHOP with or without oral azacitidine (CC-486) in participants age 75 years or older with newly diagnosed aggressive non-Hodgkin lymphomas – Aiming to improve therapy, outcomes, and validate a prospective frailty tool

Elizabeth A. Brem [a,*], Hongli Li [b,c], Anne W. Beaven [d], Paolo F. Caimi [e], Leandro Cerchietti [f], Ash A. Alizadeh [g], Rebecca Olin [h], N. Lynn Henry [i], Hildy Dillon [j], Richard F. Little [k], Cara Laubach [l], Michael LeBlanc [b,c], Jonathan W. Friedberg [m], Sonali M. Smith [n]

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[b] *SWOG Statistics and Data Management Center, Seattle, WA, USA*

Non-anthracycline containing									
	Merli, 2007 [47]	3	Mini-CEOP (etoposide) P-VEBEC	232	> 65	90 54	78 66	48, 5 years‡ 57	32, 5 years
	Rashidi, 2015 [44•]	2	R-miniCEOP (etoposide)	26	> 60	75	68	49, 2 years	59, 2 years
	Storti, 2018 [16]	2	BR	49	> 70, Frail by CGA	62	53	38, 2 years	51, 2 years
	Park, 2016 [49]	2	BR	23	≥ 65, Unfit for anthracycline	78	52	5.4 months (median)	10.2 months (median)
	Fields, 2014 [50]	2	R-GCVP	62	≥ 18, Unfit for anthracycline	61.3	29	50, 2 years	56, 2 years
	Qui-Dan, 2018 [46]	2	R-GemOx	60	> 70	49	47	49, 3 years	65, 3 years
Novel agent combinations									
Lenalidomide	REAL07 [54•]	2	Lenalidomide + RCHOP	14	60–80, fit by CGA	90	86	80, 2 years	92, 2 years
	REMARC [58•]	3	RCHOP + R maintenance RCHOP + placebo	650	60–80	n/a	n/a	80, 2 years 75	87, 2 years 89
Novel anti-CD20	Flinn, 2019 [60]	2	Bendamustine Ofatumumab	21	> 70, unfit for anthracycline	90.5	33.3	8.6 months (median)	12 months (median)
	Merli, 2020 [15••]	2	Obinutuzumab + miniCHOP	34	≥ 65, unfit by CGA	66	42	49, 2 years	68, 2 years
	Peyrade, 2017 [59•]	2	Ofatumumab + miniCHOP	120	> 80	68	56	68, 2 years	64.7, 2 years

*†‡ complete response and complete response uncertain; event-free survival; relapse-free survival

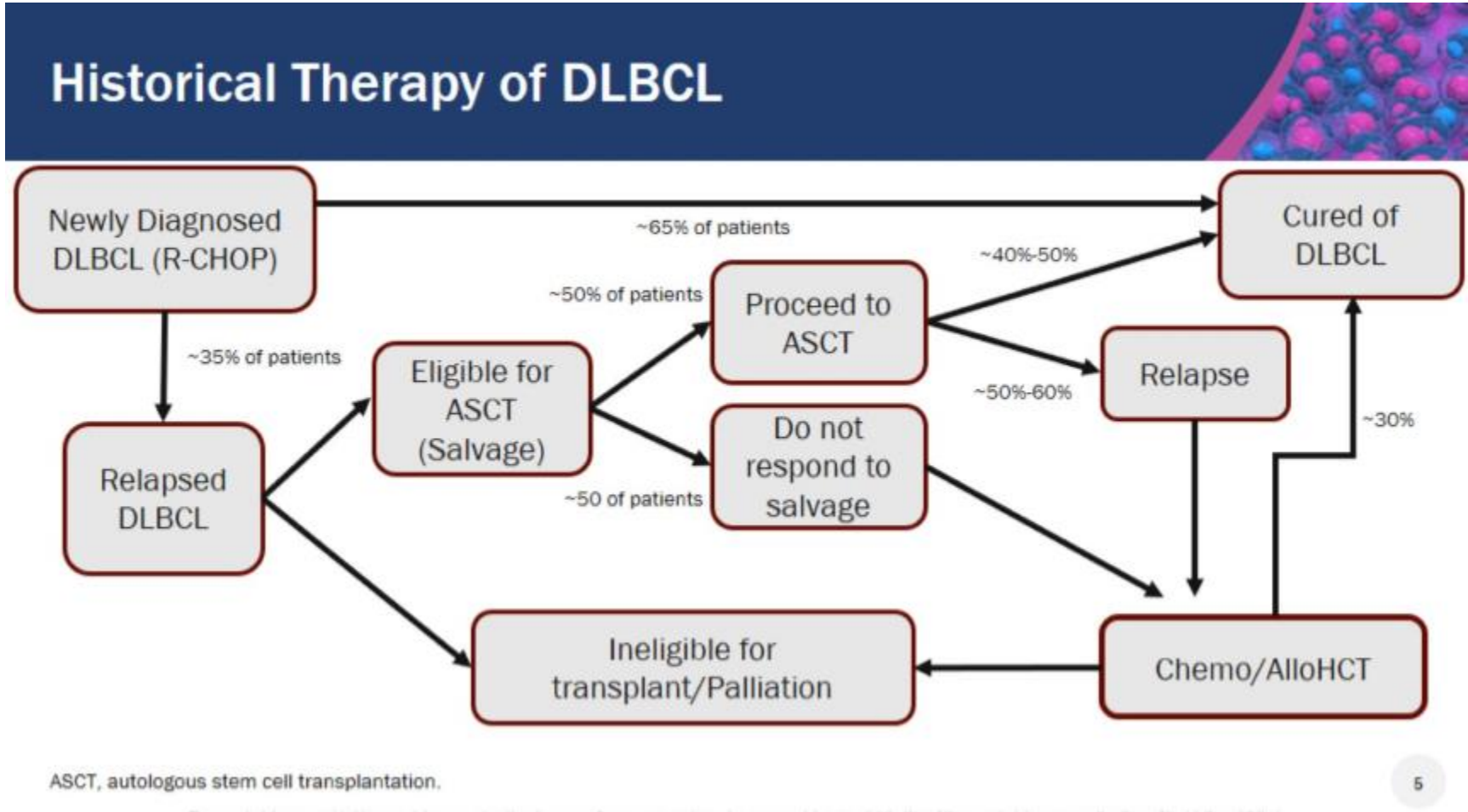
Relapsed DLBCL treatment in elderly

Poor prognosis

ASCT for younger

Increase toxicity

Consider palliative care



ESMO CLINICAL PRACTICE GUIDELINES: RECOMMENDED TREATMENT STRATEGIES IN DLBCL

First relapse/progress

Eligible for transplant	Not eligible for transplant
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, RGDP) as salvage treatment	Platinum- and/or gemcitabine-based regimens
For chemosensitive patients: R-HDCT with ASCT as remission consolidation	Clinical trials with novel drugs
Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT	
or in patients with poor-risk factors at relapse	

R, rituximab; HDCT, high-dose chemotherapy; ASCT, autologous stem-cell transplantation; DHAP, cisplatin, cytarabine, dexamethasone; ICE, ifosfamide, carboplatin, etoposide; GDP, cisplatin, gemcitabine, dexamethasone

ESMO

Tilly H, *et al.*, Annals of Oncology 2015

Additional Therapies For Relapsed DLBCL

Agent	Response Rate (ORR)	Median PFS	Toxicities
Ibrutinib (phase I/II)[1]	ABC = 37% (CR 16%) GCB = 5% (CR = 0%)	2 .02 mo 1.31 mo	Cytopenias, arthralgias
Lenalidomide (phase II)[2]	ORR = 28% (CR = 22%)	2.8 mo	Cytopenias
Selinexor (phase II)[3]	ORR = 28% (CR = 12%)	2.6 mo	Cytopenias, GI

1. Wilson. Nat Med. 2015;21:922. 2. Wang. Leukemia. 2013;27:1902. 3. Kalakonda. Lancet Haematol. 2020;7:e511.

Slide credit: clinicaloptions.com

Lenalidomide in relapsed DLBCL

102 patients of DLBCL

Received at least 2 prior treatments

Randomized 1:1 to lenalidomide or other treatments

ORR of 27.5% in lenalidomide versus 11.8% in others

Median PFS:13.6w vs 7.9 w

Greater improvements in non-GCB compared with GCB (15.1 vs 7.1w)

Conclusions: benefit of Lenalidomide

more evident in the non-GCB

more pronounced in the GEP-defined ABC

Lenalidomide in relapsed DLBCL

Published OnlineFirst April 5, 2017; DOI: 10.1158/1078-0432.CCR-16-2818

Cancer Therapy: Clinical

Clinical Cancer Research

A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Myron S. Czuczman[1], Marek Trněný[2], Andrew Davies[3], Simon Rule[4], Kim M. Linton[5], Nina Wagner-Johnston[6], Randy D. Gascoyne[7], Graham W. Slack[7], Pierre Brousset[8], David A. Eberhard[9], Francisco J. Hernandez-Ilizaliturri[1], Gilles Salles[10], Thomas E. Witzig[11], Pier Luigi Zinzani[12], George W. Wright[13], Louis M. Staudt[14], Yandan Yang[14],

Novel agents in development for DLBCL

Class	Target	Agent	Overall response rate (%)	Complete response rate (%)	Reference
Monoclonal antibody	CD19	tafasitamab + lenalidomide	60	43	Salles et al
Antibody drug conjugates	CD19	loncastuximab tesirine	59	41	Kahl et al
	CD79b	polatuzumab vedotin	52	13	Palanca-Wessels et al
		polatuzumab vedotin + BR versus BR	45 17.5	40 17.5	Sehn et al
Bispecific antibodies	CD19/CD3	blinatumomab	43	19	Viardot et al
	CD20/CD3	mosunetuzumab	35	19	Schuster et al
		glofitamab	38	31	Dickinson et al
Other target inhibitors	BCL2	venetoclax	18	12	Davids et al
	XPO1	selinexor	28	12	Kalakonda et al
Checkpoint inhibitors	PD-1	nivolumab	≤ 10	≤ 3	Ansell et al
	CD47	magrolimab	40	33	Advani et al

Salles et al., Lancet Oncol. 2020; Kahl et al., Clin Cancer Res. 2019; Palanca-Wessels et al., Lancet Oncol. 2015; Sehn et al., JCO 2020; Viardot et al., Blood 2016; Schuster el al., ASH 2019; Dickinson et al., EHA 2020; Davids et al., JCO 2017; Kalakonda et al., Lancet Haematol. 2020; Ansell et al., JCO 2019; Advani et al., N Engl J Med., 2018

DLBCL Treatment Options for Second- and Later Lines, Continued

Consolidation After Alternate Second-Line Therapy

Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative) for patients in CR/PR after alternative second-line therapy

Third-Line and Subsequent Therapy Options

Anti-CD19 CAR T-cell therapy (only after ≥2 previous lines of therapy):
Axicabtagene ciloleucel
Lisocabtagene maraleucel
Tisagenlecleucel

Loncastuximab tesirine (only after ≥2 previous lines of therapy)

Selinexor (only after ≥2 previous lines of therapy, including patients with PD after transplantation or CAR T-cell therapy)

NCCN. Clinical practice guidelines in oncology: NSCLC. v5.2021.

CAR-T cell

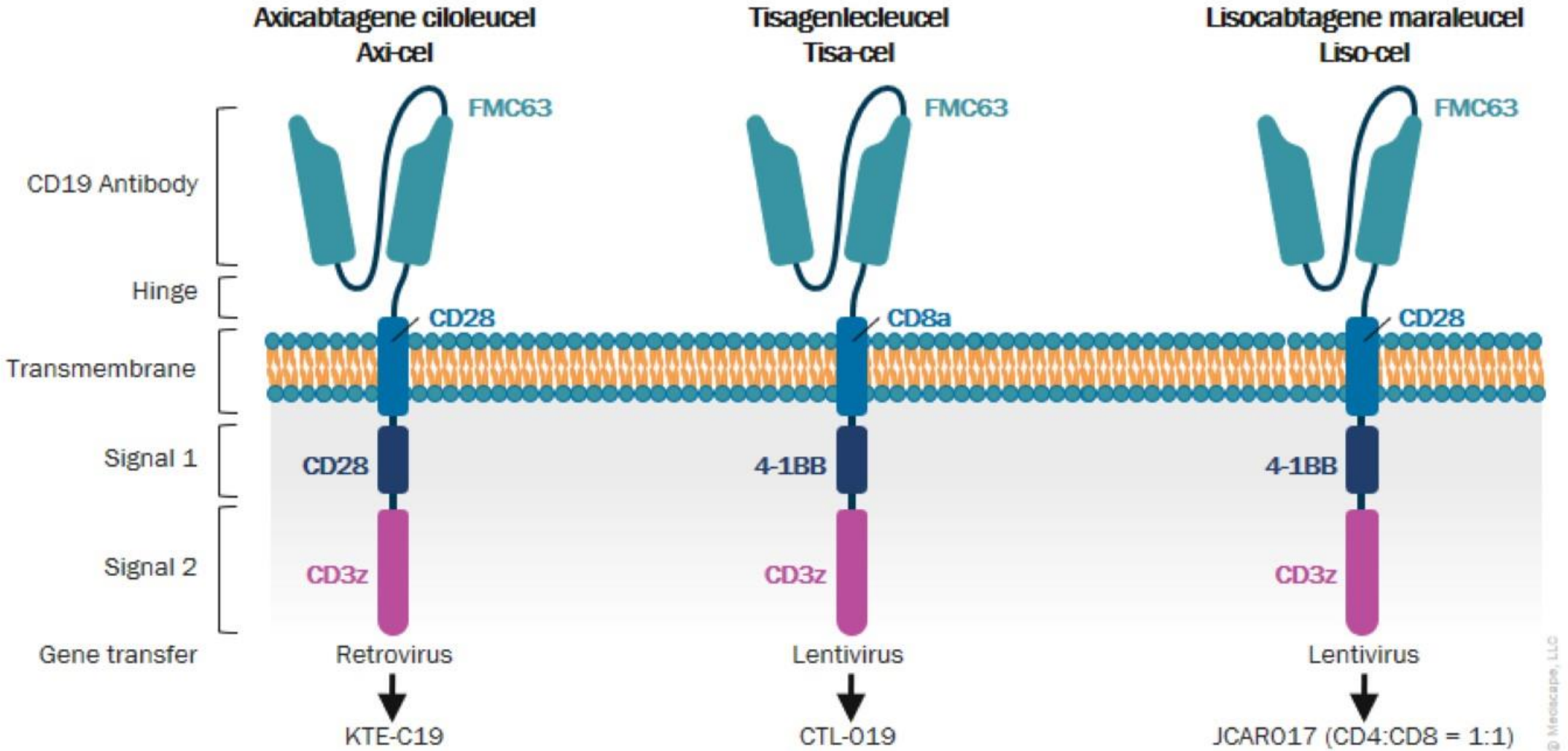
Curable options in older patients with relapsed DLBCL

Either relapsed or ineligible for autologous transplantation

Approved for relapsed or refractory DLBCL patients including older adults

ZOMA1 trial

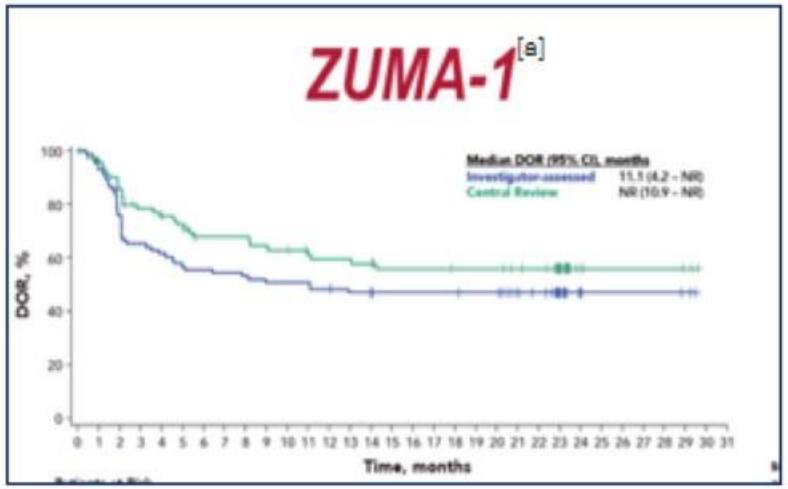
Chimeric Antigen Receptor Modified T cells (CAR T cells)



Adapted from van der Steegen SJC, et al. Nat Rev Drug Discov. 2015;14:499-509.

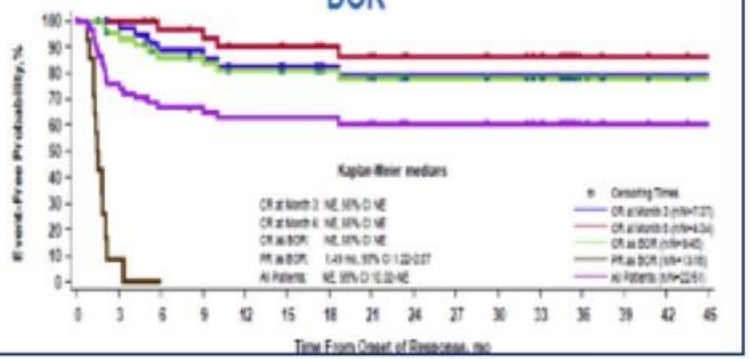
Long-Term Follow-Up of Pivotal CART Studies

ZUMA-1[a]

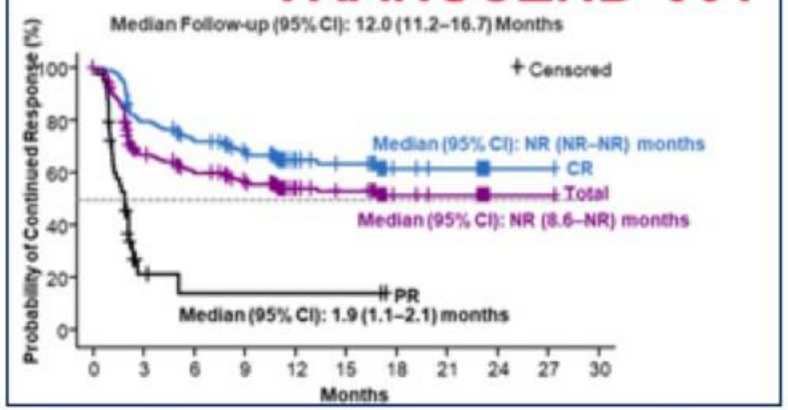


JULIET[b]

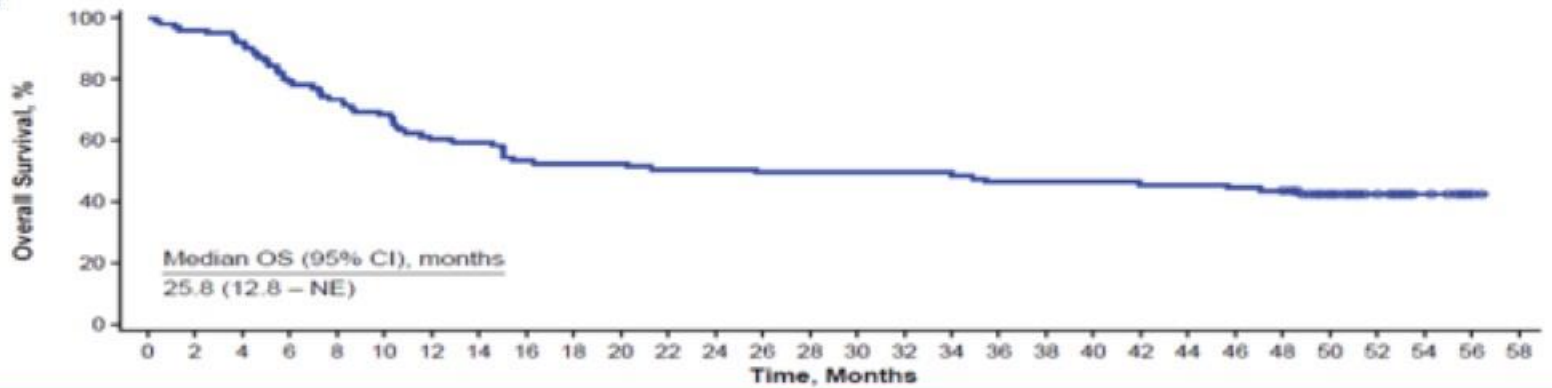
DOR



TRANSCEND-001[c]



[d]



4-year update ZUMA-1

Median f/u 51.1 mos, median OS 25.8 mos
4-year OS rate was 44%

a. Locke FL, et al. Lancet Oncol. 2019;20:31-42; b. Schuster SJ, et al. N Engl J Med. 2019;380:45-56; c. Abramson JS, et al. Lancet. 2020;396(10254):839-852; Jacobson et al. ASH 2020. Abstract 1187.

Other Possible Treatment Options: Relapsed DLBCL

- Other monoclonal antibodies for relapsed DLBCL
  - Tafasitamab + Lenalidomide

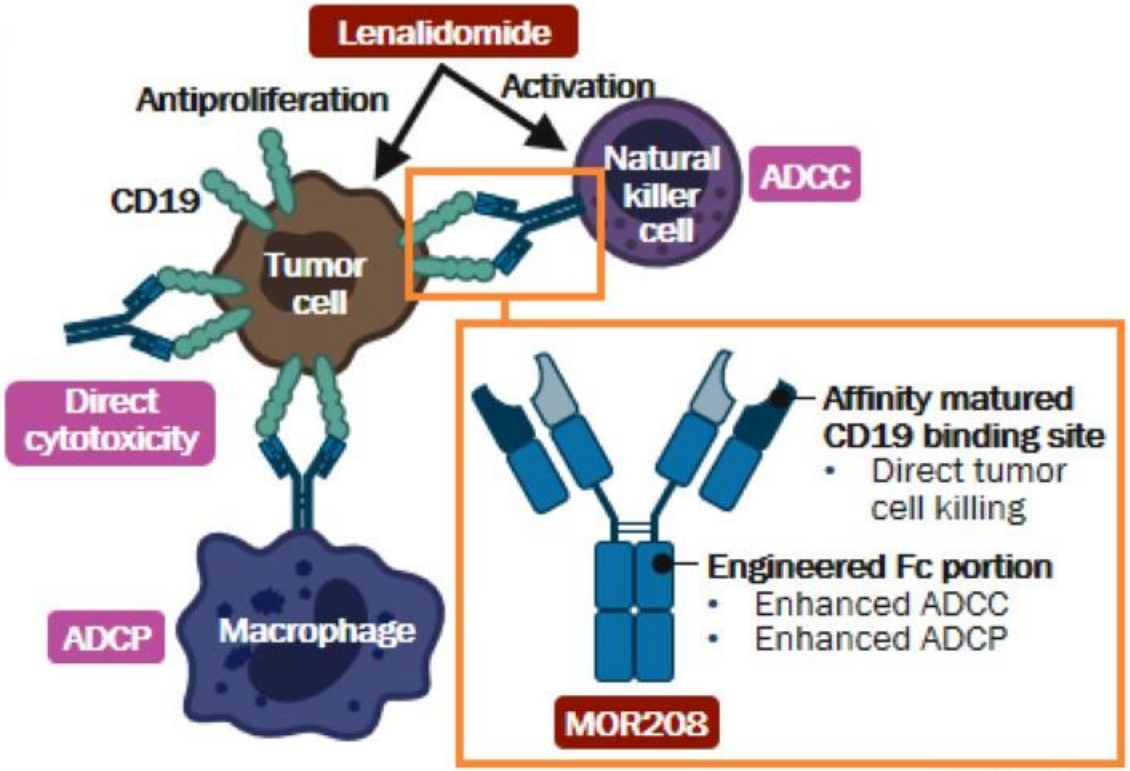
Salles. Lancet Oncol. 2020;21:978.

Slide credit: clinicaloptions.com

Tafasitamab
CD19 Monoclonal Antibody

Tafasitamab (MOR208), Fc-engineered, anti-CD19 mAb[a-d]

- ADCC
- ADCP
- Direct cell death
- Encouraging activity in patients with NHL, with long DOR in R/R DLBCL



Lenalidomide (LEN)[c,e-k]

- T cell and NK cell activation/expression
- Direct cell death
- Demonstrated activity as an antilymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

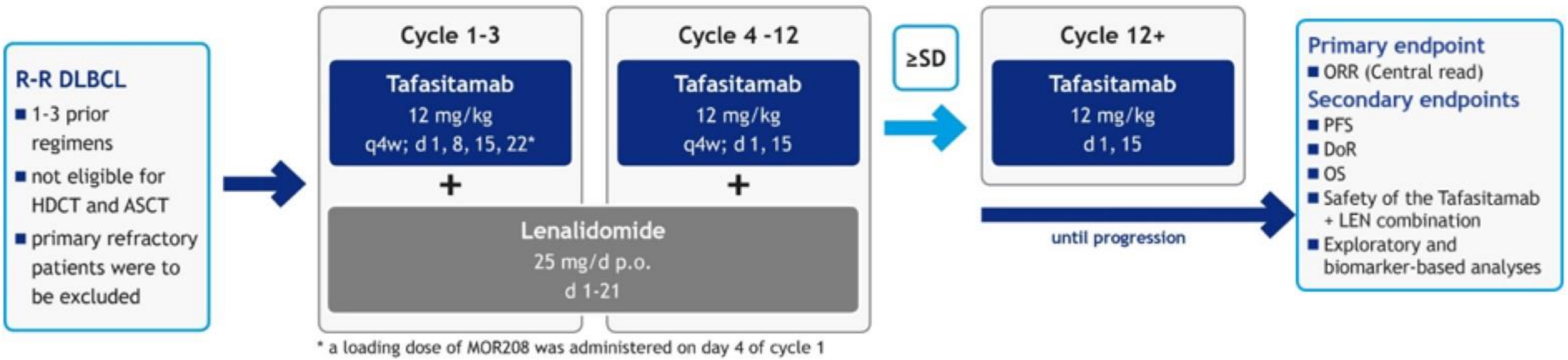
Potentiation of activity by combining tafasitamab and lenalidomide in vivo and in vitro with lenalidomide enhancing tafasitamab-medicated NK activation and ADCC[b]

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; DOR, duration of remission; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NK, natural killer; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory.

a. Horton HM, et al. Cancer Res. 2008;68:8049-8057; b. Awan FT, et al. Blood. 2010;115:1204-1213; c. Jurczak W, et al. Ann Oncol. 2018;29:1266-1272; d. Data on file. CSR. MorphoSys. Boston, MA; e. Richter J, et al. Blood. 2013;121:423-430; f. Wu L, et al. Clin Cancer Res. 2008;14:4650-4657; g. Lapalombella R, et al. Blood. 2008;112:5180-5189; h. Wiernik PH, et al. J Clin Oncol. 2008;26:4952-4957; i. Witzig TE, et al. Ann Oncol. 2011;22:1622-1627; j. Czuczman MS, et al. Clin Cancer Res. 2017;23:4127-4137; k. Lenalidomide [PI]. Approved 2005. Revised 2019.

L-MIND Study Design

- **Sample size suitable** to detect ≥ 15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- **Mature Data**: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months



* a loading dose of MOR208 was administered on day 4 of cycle 1

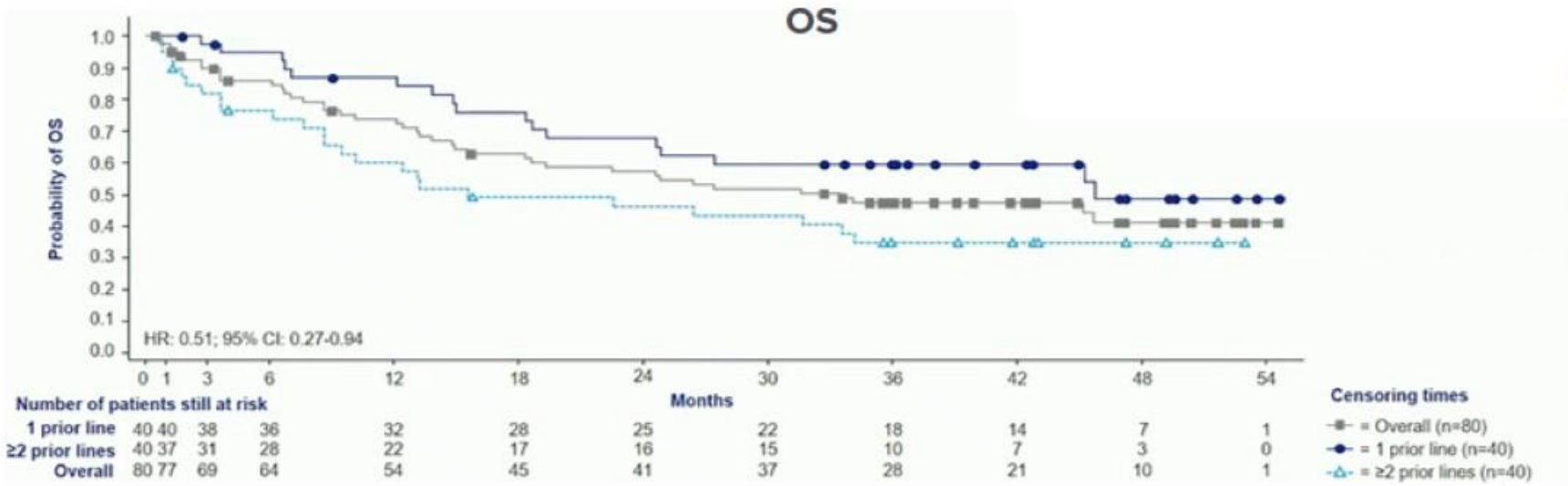
Salles G, et al. Lancet Oncol. 2020;21:978-988.

Outcomes by Prior Lines of Therapy

Tafasitamab plus LEN	1 Prior Treatment (N = 40)	≥ 2 Prior Treatments (N = 40)	Overall (N = 80)
Best objective response, n (%)			
CR	19 (47.5)	13 (32.5)	32 (40.0)
PR	8 (20.0)	6 (15.0)	14 (17.5)
SD	7 (17.5)	6 (15)	13 (16.3)
PD	5 (12.5)	8 (20.0)	13 (16.3)
NE	1 (2.5)	7 (17.5)	8 (10.0)
ORR (CR + PR), n (%) [95% CI]	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]	46 (57.5) [45.9–68.5]
Median DoR, months (95% CI)	43.9 (9.1–NR)	NR (15.0–NR)	43.9 (26.1–NR)
Median PFS, months (95% CI)	23.5 (7.4–NR)	7.6 (2.7–NR)	11.6 (6.3–45.7)
Median OS, months (95% CI)	45.7 (24.6–NR)	15.5 (8.6–NR)	33.5 (18.3–NR)

Duell J et al. ASCO 2021. Abstract 7513

L-MIND Trial
Key Efficacy Data: OS and AEs



Median OS after ≥ 35 months:

- Overall: 33.5 mos
- 1 prior line: 47.5 mos
- ≥ 2 prior lines: 15.5 mos

Study suggests this is an effective and well-tolerated non-chemotherapeutic approach for R/R DLBCL

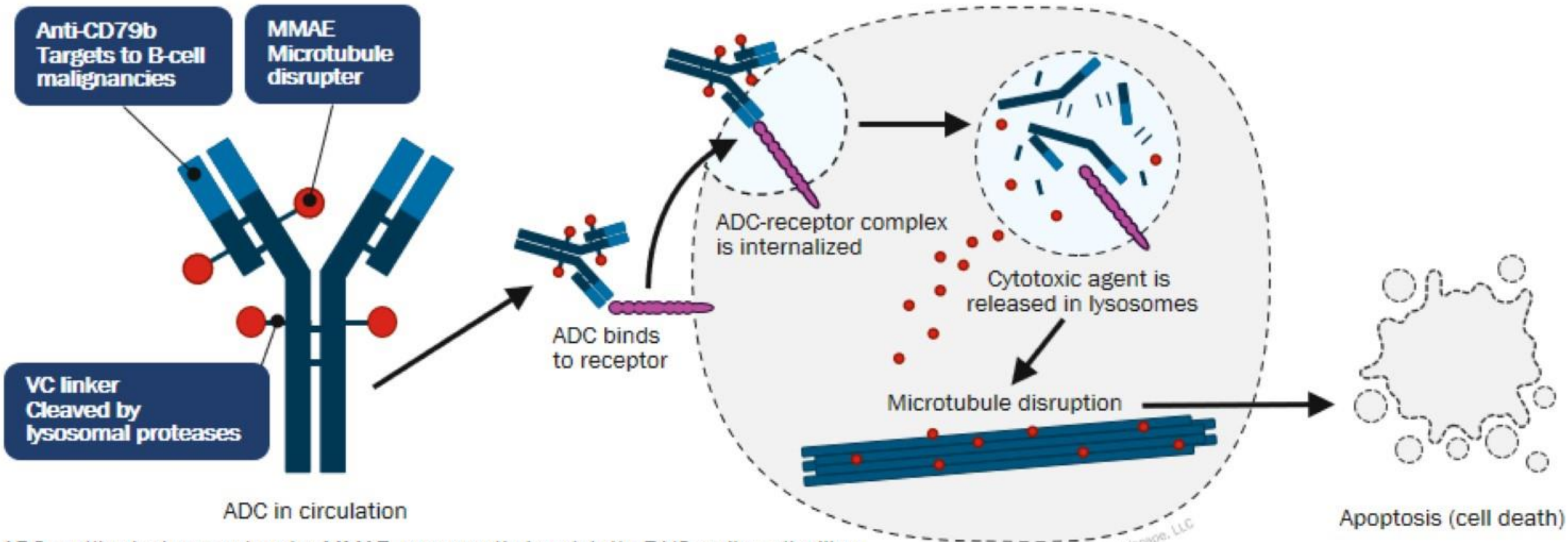
TEAEs, n (%)	All Grades (≥ 10%) All patients (N = 81)	Grade ≥ 3 (> 1 patient) All patients (N = 81)
Neutropenia	41 (50.6)	40 (49.4)
Anemia	30 (37.0)	6 (7.4)
Thrombocytopenia	25 (30.9)	14 (17.3)
Diarrhea	29 (35.8)	1 (1.2)
Asthenia	20 (24.7)	2 (2.5)
Cough	22 (27.2)	1 (1.2)

TEAE, treatment-emergent adverse event.

Düll J, et al. Presented at: ICML, Virtual Edition, June 18-22, 2021. Abstract 028.

Polatuzumab Vedotin: CD79b ADC

- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E VC, valine-citrulline.

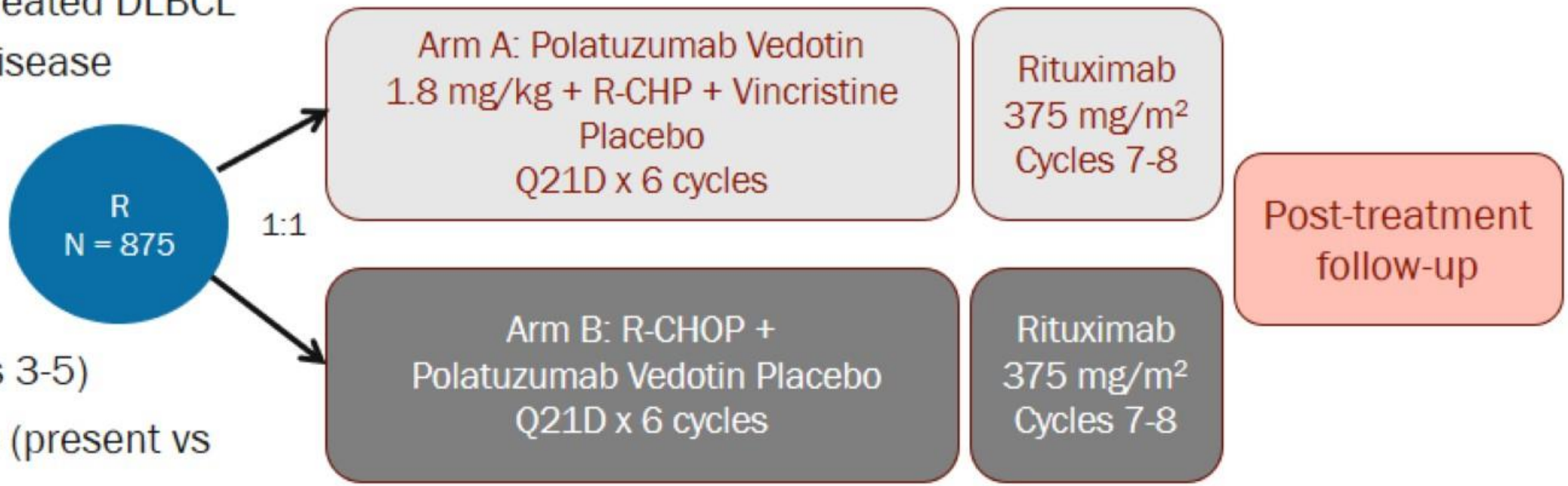
Camus V, et al. Future Oncol. 2021;17:127-135.

POLARIX
R-CHOP vs R-CHP + Polatuzumab

- Key eligibility criteria
- Previously untreated DLBCL
- Stage II to IV disease
- IPI ≥ 2
- ECOG PS ≤ 2

Stratified

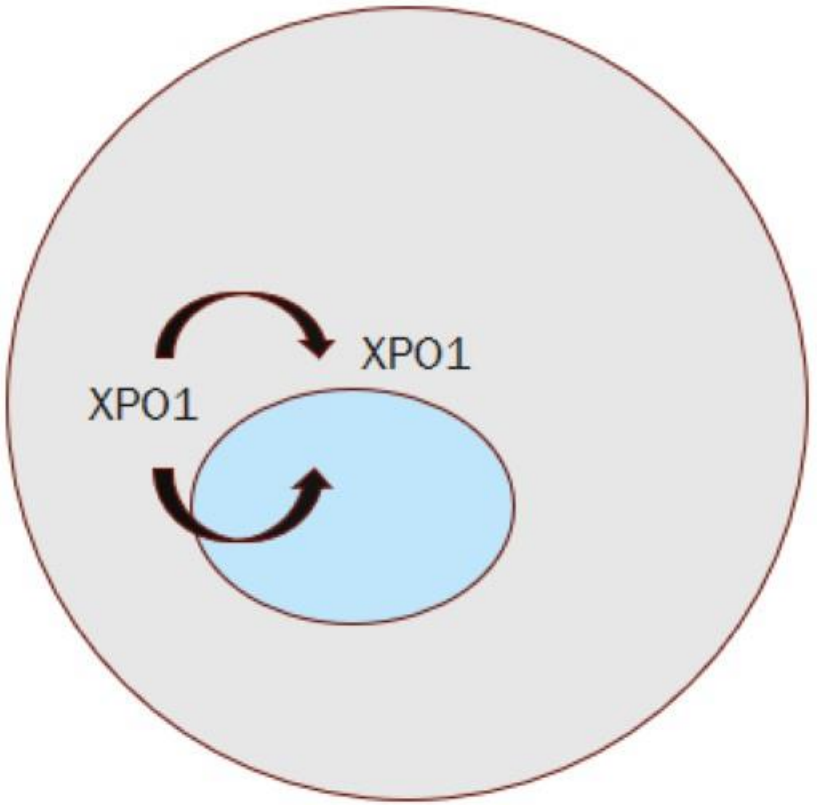
- IPI Score (2 vs 3-5)
- Bulky Disease (present vs absent)
- Region



ClinicalTrial.gov NCT03274492

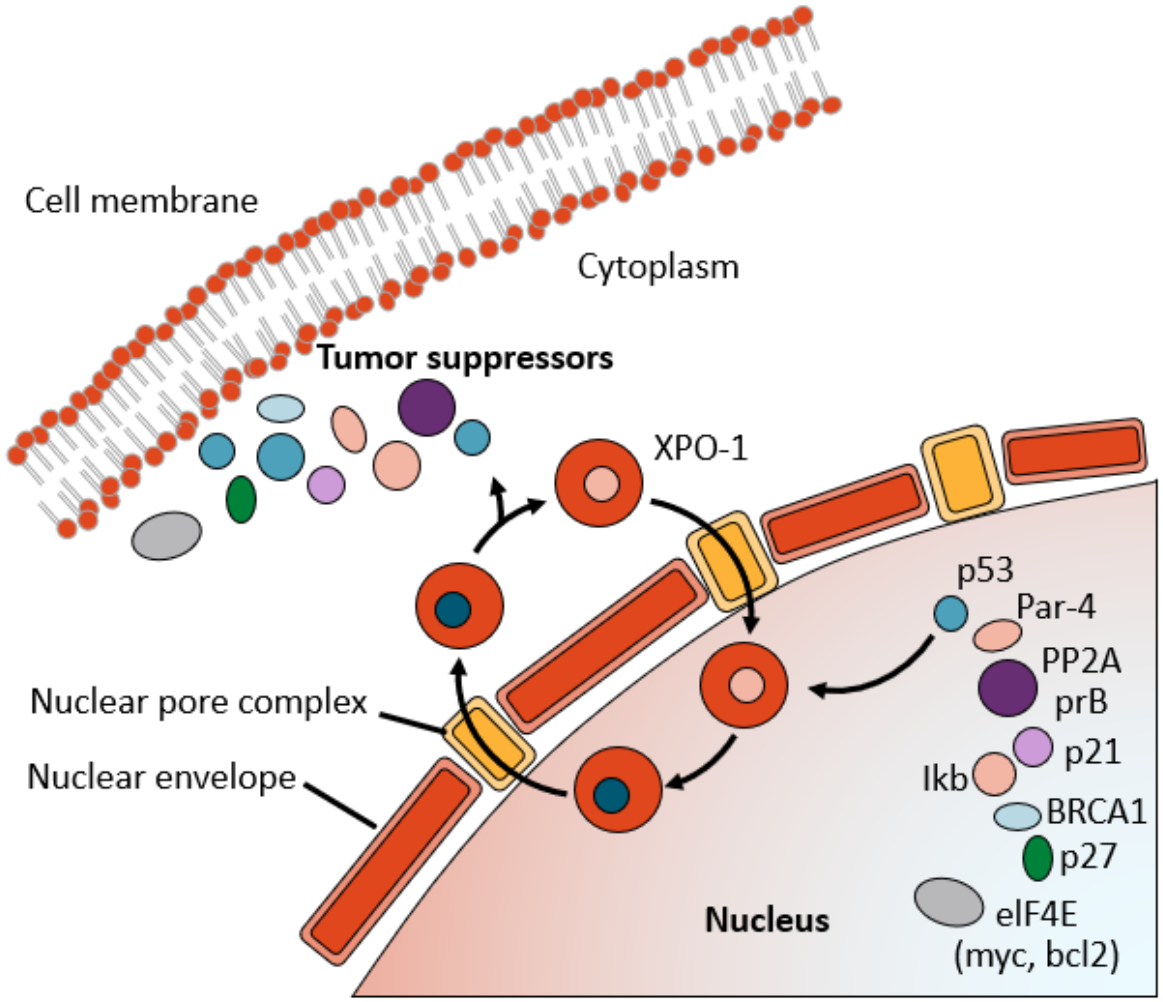
Selinexor
SINE Inhibitor

- **Selinexor**: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE) compound[a]
- XPO1 (part of the Nuclear Pore Complex) is highly expressed in DLBCL
- Responsible for protein traffic between cell nucleus and cytoplasm
- Inhibition leads to nuclear accumulation and reactivation of tumor suppressor proteins and reduction in oncoproteins[b]



a. Marullo R, et al. AACR. 2015; b. Kalakonda N, et al. Lancet Haematol. 2020;7:e511-e522.

Selinexor – Third Line Relapsed DLBCL: Mechanism of Action



- XPO1 is the major nuclear export protein for:
  - TSPs (e.g., p53, IkB and FOXO)
  - eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl- xL, cyclins)
- Selinexor is an oral selective XPO1 inhibitor; preclinical data supports that XPO1 inhibition:
  - Reactivates multiple TSPs relevant to NHL, including p53, p21, IkB and FOXO
  - Promotes nuclear localization of eIF4e, which is overexpressed in most B-cell lymphomas
  - Reduces c-Myc, Bcl-2, and Bcl-6 levels
  - Toxicities: GI toxicities may be prohibitive

Theodoropoulos. Target Oncol. 2020;15:697.

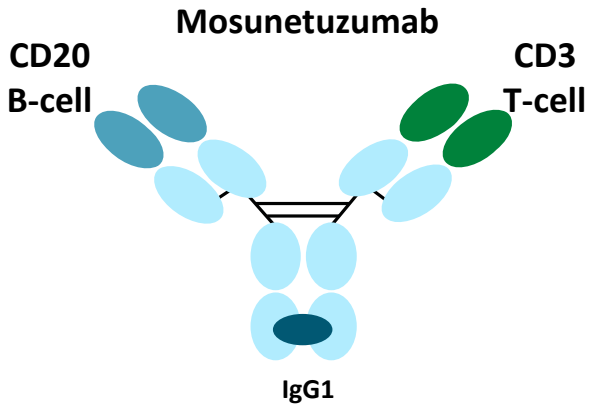
Slide credit: clinicaloptions.com

ASH 2021 Key Abstracts: Relapsed DLBCL

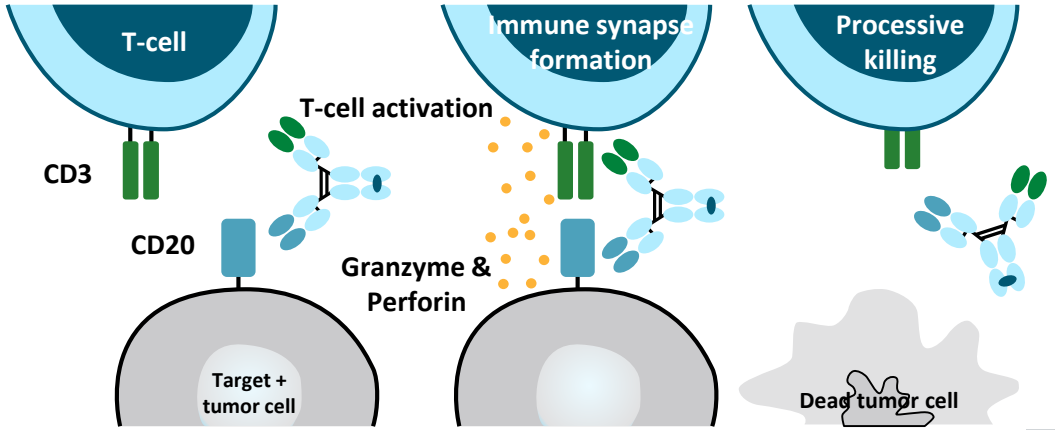
- LBA-1: POLARIX Study: Pola-R-CHP vs R-CHOP for DLBCL
- Abstract 91: Liso-cel vs ASCT as second line therapy – (Transform Study)
- Abstract 2: Axi-Cel vs ASCT as second line therapy – (ZUMA-7)
- LBA-6: Tisagenlecleucel vs ASCT as second line therapy – (Belinda Study)
- Abstract 739: Axi-Cel for front-line high risk DLBCL – (ZUMA-12)
- Abstract 6: Circulating Tumor DNA in patients with CNS Lymphoma

Mosunetuzumab: A Bispecific Antibody Targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - PK properties enable once weekly to q3w dosing
  - Does not require ex-vivo T-cell manipulation
  - Off the shelf, readily available treatment



- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells

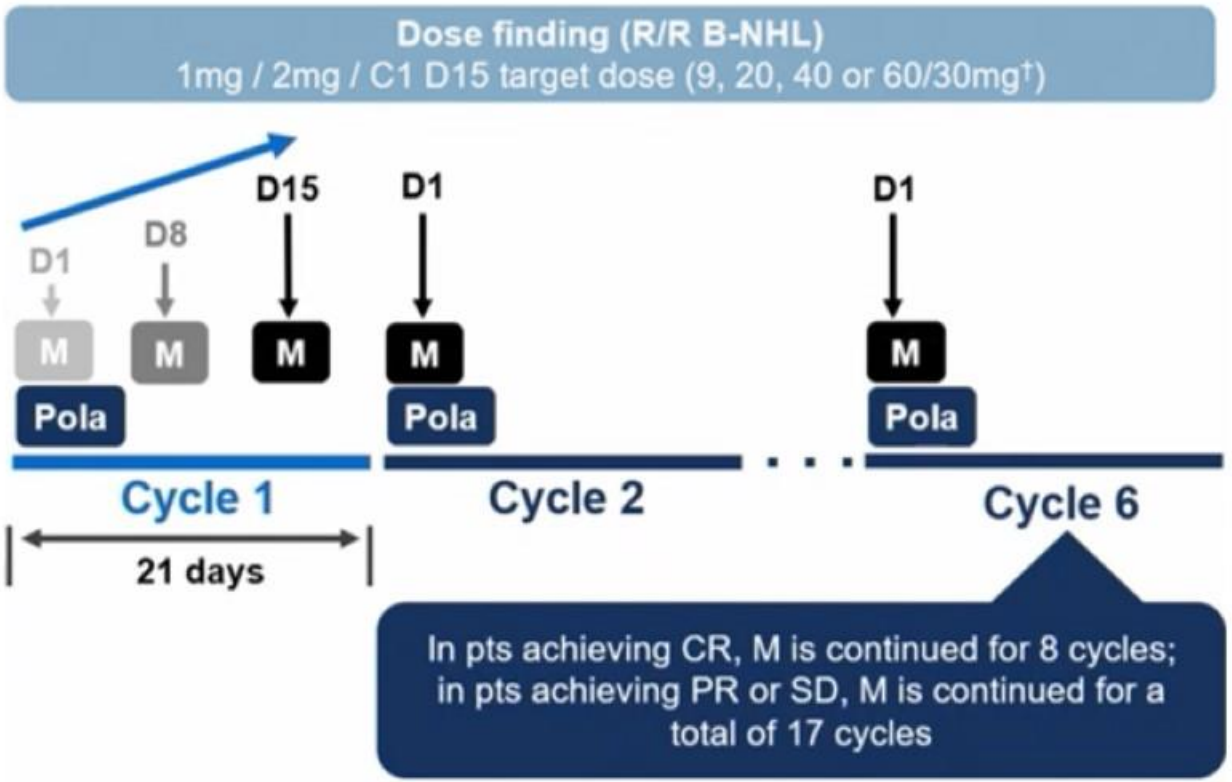


Sun. Sci Transl Med. 2015;7:287ra70. Schuster. ASH 2019. Abstr 6.

Slide credit: clinicaloptions.com

Mosunetuzumab + Polatuzumab Vedotin in R/R B-NHL
Study Design and AEs

M-Pola Dosing Schedule



Summary of AEs, *n* (%)	R/R B-NHL All cohorts (N=22)
Any AE	22 (100.0)
Treatment-related	19 (86.4)
Serious AE	8 (36.4)
Treatment-related	5 (22.7)
Gr 3–4 AE	11 (50.0)
Treatment-related	11 (50.0)
Gr 5 (fatal) AE	2 (9.1)
Treatment-related	0
AE leading to dose modification	8 (36.4)
AE leading to treatment discontinuation	3 (13.6)

Most frequent TRAEs: neutropenia and nausea (40.9%), followed by fatigue and diarrhea (36.4%)

AE, adverse event; B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; Gr, grade; PR, partial response; R/R, relapsed/refractory; SD, stable disease.

Ghosh N, et al. Presented at: EHA2021 Virtual Congress; June 9-17, 2021. Abstract S222.

Therapy of DLBCL
2021

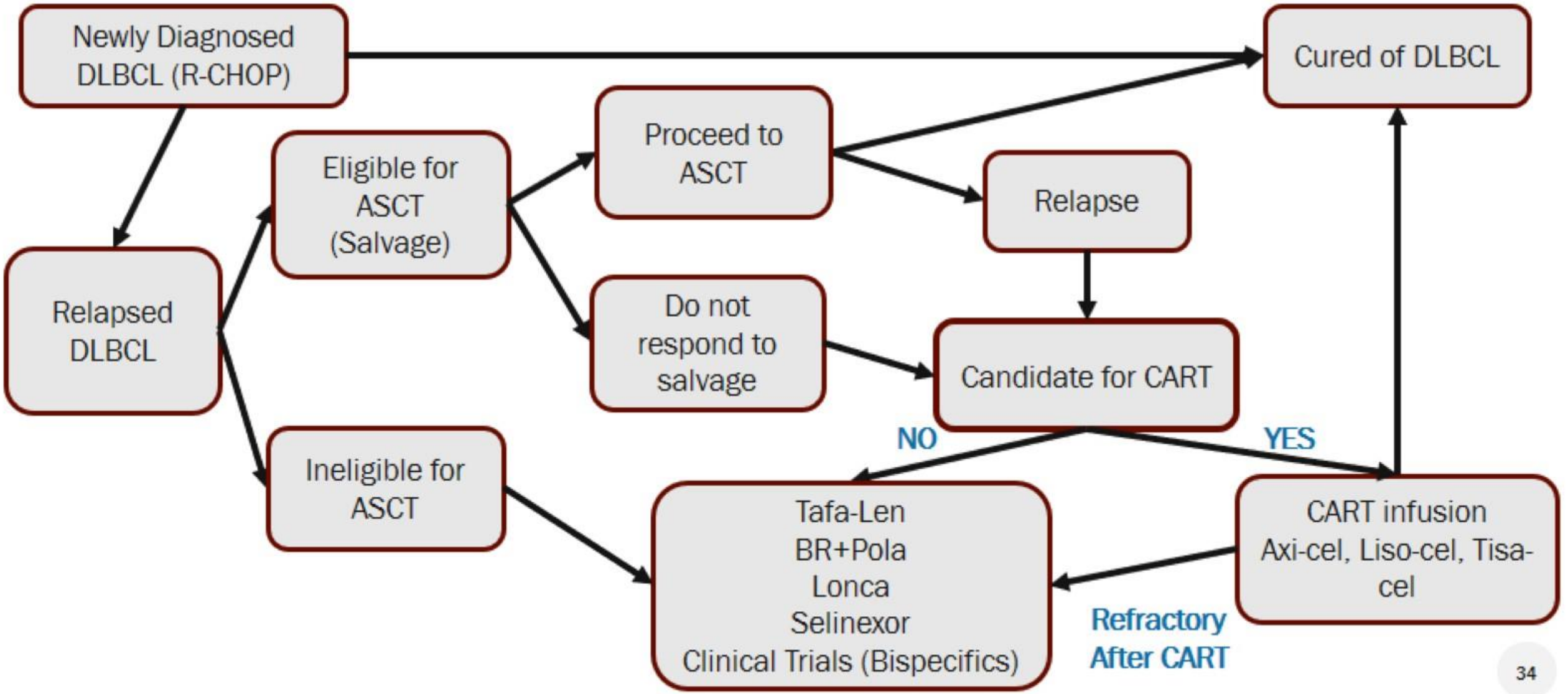


Table 1
Prospective studies in newly diagnosed diffuse large B cell lymphoma (DLBCL) focused on older patients and/or those with comorbidities.

Regimen (reference)	Key inclusion criteria	Median age (years)	Arms	2 year OS	Pre-phase?	Geriatric assessment?
R-miniCHOP [3]	≥ 80 years	83	R-miniCHOP	59%	No	None
R-70%CHOP [25]	≥ 70 years	76	R-70%CHOP	~65%	No	None
SENIOR Study [17]	≥ 80 years	83	1) R-miniCHOP 2) R-miniCHOP with lenalidomide 10 mg	1) 66% 2) 65.7%	Yes	None
Ofatumumab-miniCHOP [26]	≥ 80 years	83	1000 mg ofatumumab + miniCHOP	64.7%	Yes	None
Obinatuzumab-miniCHOP [27]	Age > 65, unfit via FIL tool	82	100 mg obinutuzumab + miniCHOP	49%	No	FIL tool for entry
R-CGVP [28]	EF ≤ 50% or EF > 50% with cardiac co-morbidities	76	rituximab, cyclophosphamide, gemcitabine, vincristine and prednisone	55.8%	No	None
R-miniCEOP [21]	"Fit," age > 65 years	72	1) R-CHOP 2) R-miniCEOP	1) ~65% 2) ~70%	No	ADLs and CIRS-G. "Fit" was defined at ADL score of or better, fewer than grade 3 CIRS-G co-morbidities and no grade 4 co-morbidities.
Mosuntuzumab [29,30]	≥ 80 years OR 60–79 years and impairment in 1 or more ADL or IADL or impairment of renal, cardiac, or haptic function precluding use of chemoimmunotherapy	84	CD20-CD3 bi-specific antibody	Not yet reported; ORR 67.7% (41.9% CR)	No	ADL or IADL assessment for inclusion for those <80

THANK YOU