Aggressive B and T cell lymphomas: Treatment paradigms in 2019

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Disclosures

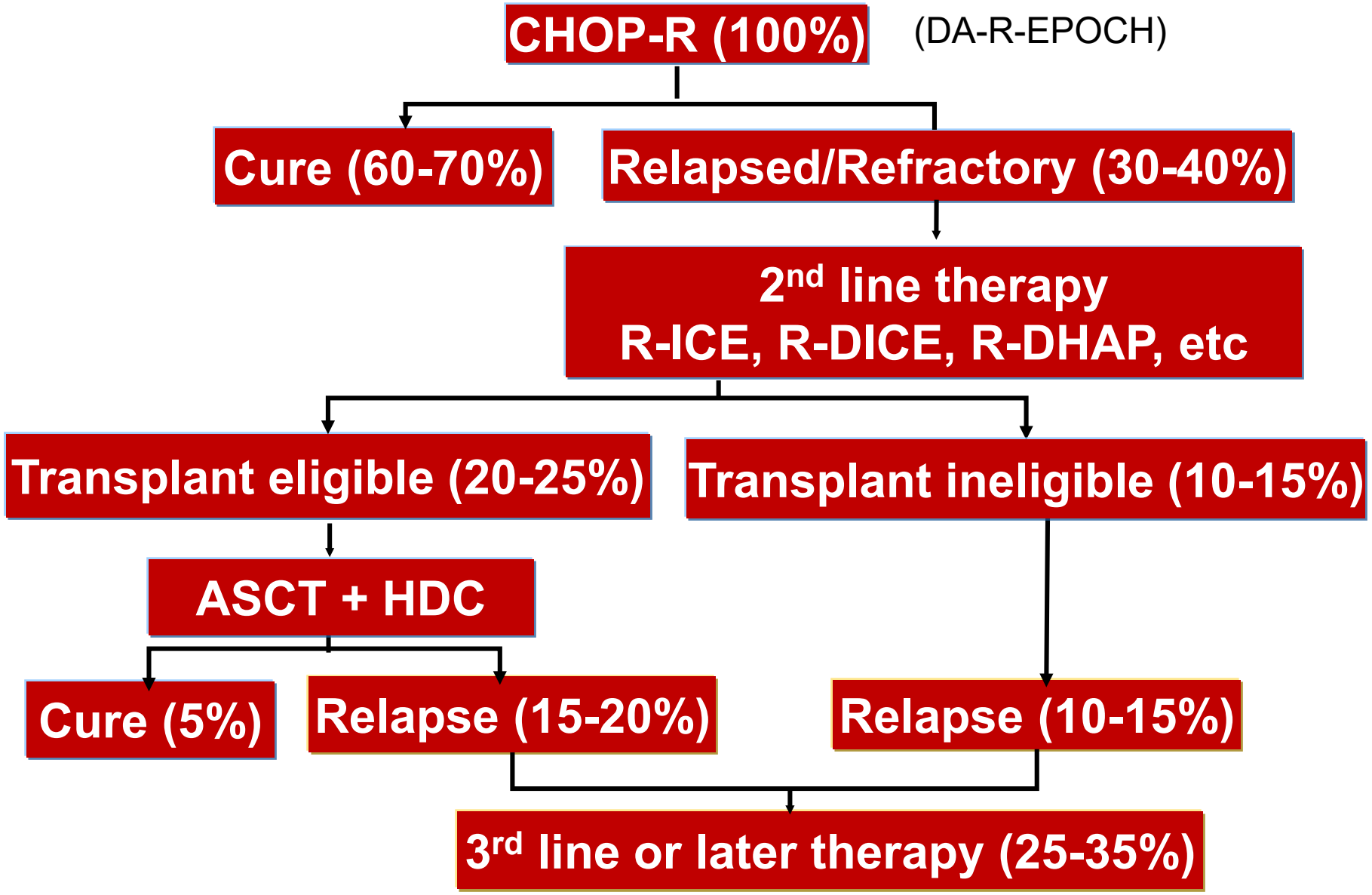
Consulting advice:

Gilead, Celgene, Sutro, BMS, Genentech/Roche, Bayer, ADC Therapeutics, AstraZeneca, Biotest, Karyopharm, MEI Pharma, Novartis, Merck, Morphosys, Beigene, Nordic Nanovector, Karyopharm

Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients treated same (R-CHOP)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis is poor

Treatment algorithm for DLBCL



When do I treat patients with DLBCL today with something other than R-CHOP x 6?

Double hit subtype

- **Data not robust in double protein subtype**

Primary mediastinal

HIV associated

Testicular

Limited stage (?)

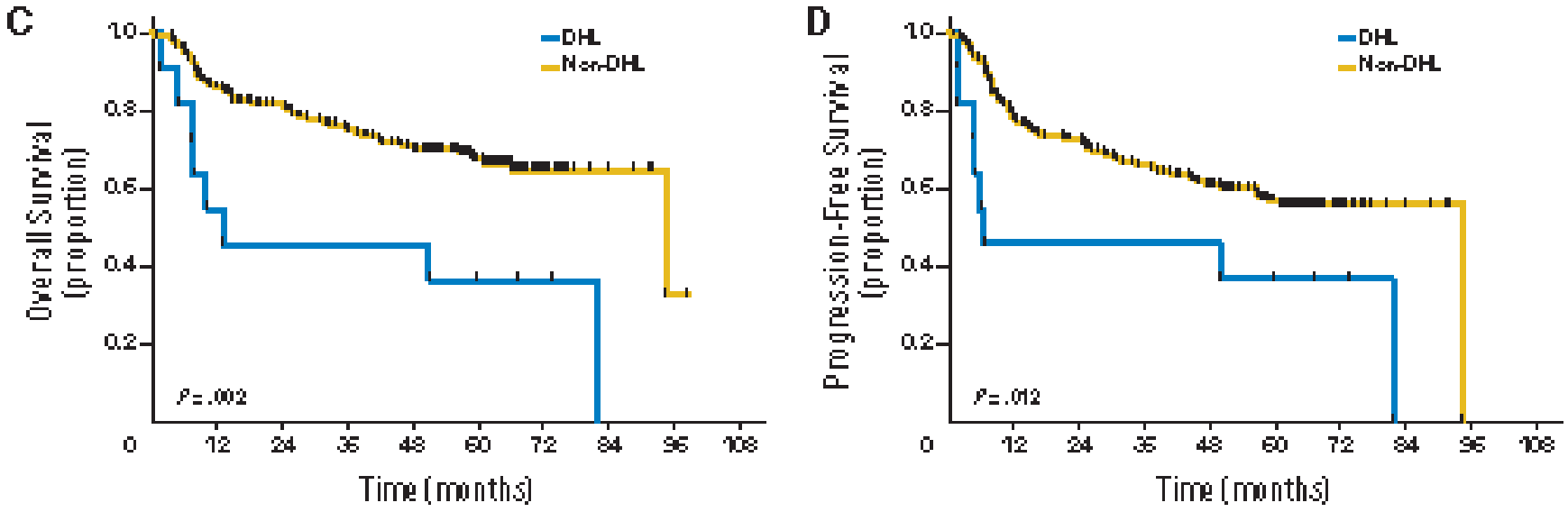
CNS

Elderly

Double hit vs Double protein DLBCL
10-25% of DLBCL

- **Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both ("triple-hit")**
  - **Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma**
  - **Cell of origin: Virtually always germinal center subtype**
  - **Outcome poor with standard therapies**
- **Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations**
  - **Cell of origin: Usually activated B cell subtype**
  - **Outcome inferior to other DLBCLs, but not as poor as DHL**

FISH DH DLBCL and treatment with R-CHOP



Green et al, JCO 2012

Prognostic Significance of *MYC* Single, Double, Triple Hit and *MYC*-Translocation Partner Status in Diffuse Large B-Cell Lymphoma

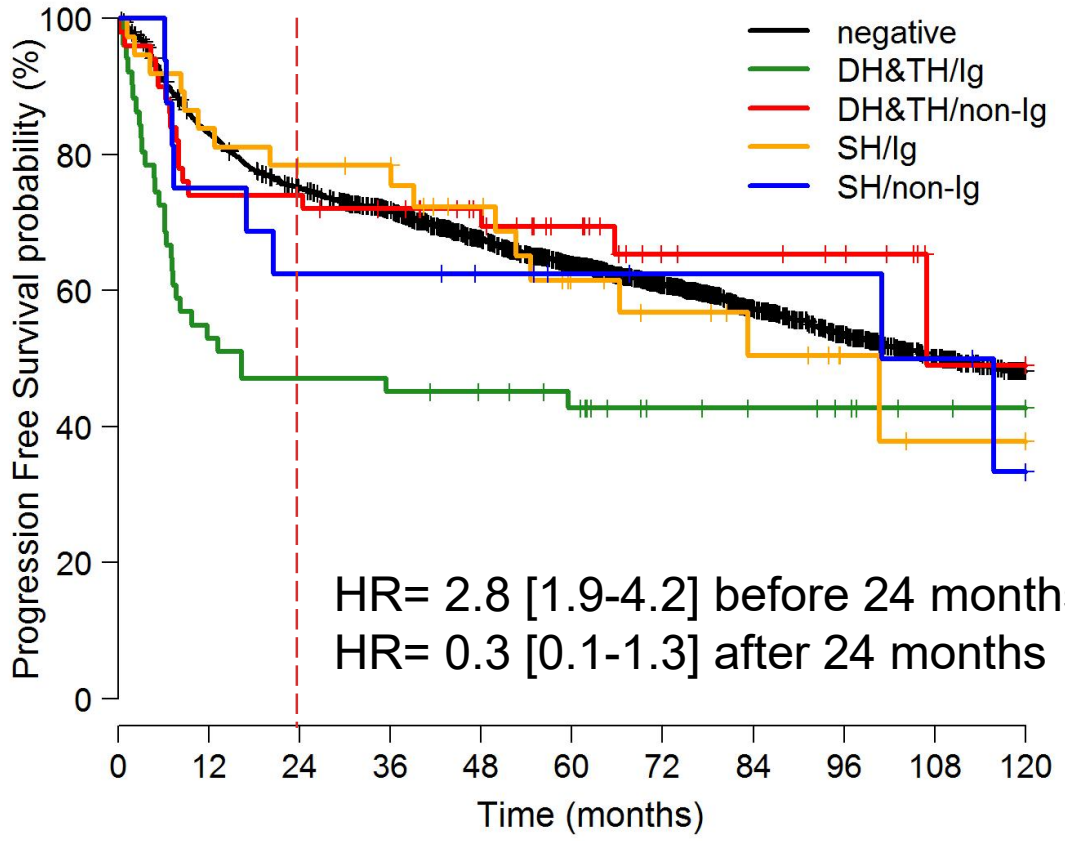
Andreas Rosenwald, Laurie H. Sehn and Delphine Maucort-Boulch on behalf of the

Lunenburg Lymphoma Biomarker Consortium (LLBC)

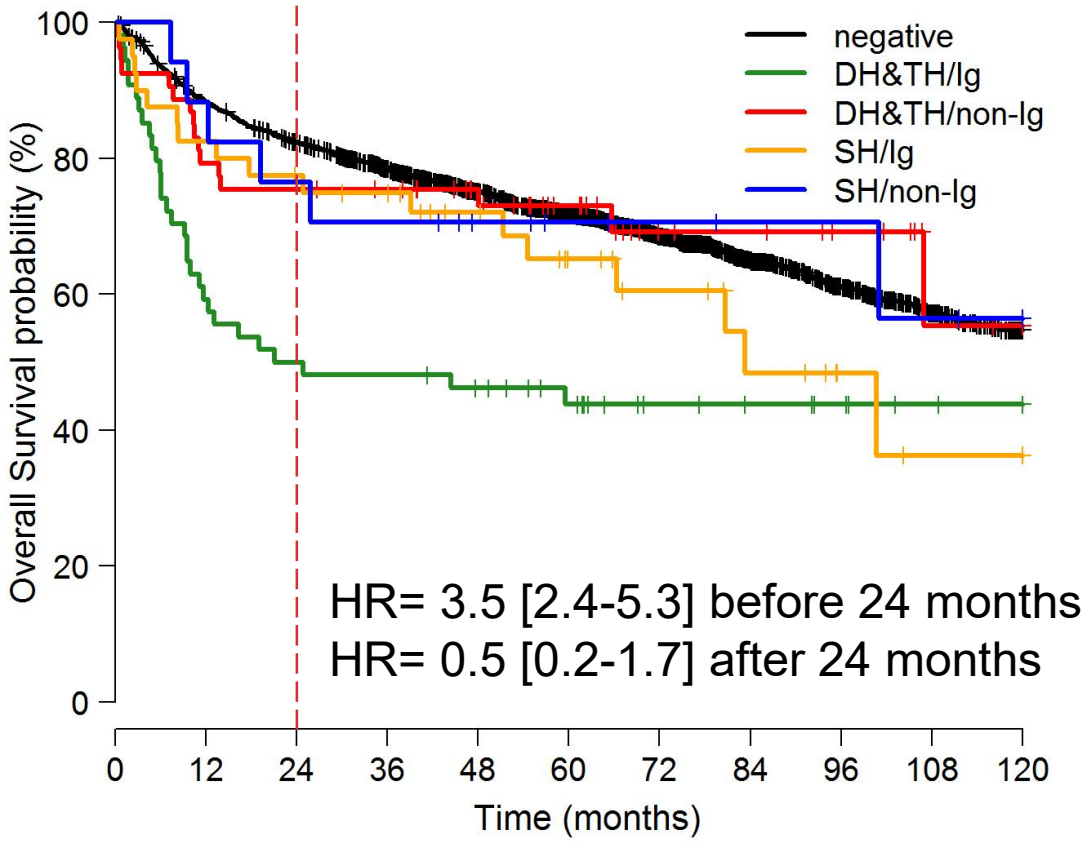
60th ASH Annual Meeting

December 2018, San Diego

MYC Translocation Partner (IG vs non-IG) is Prognostically Relevant in Double/Triple-Hit

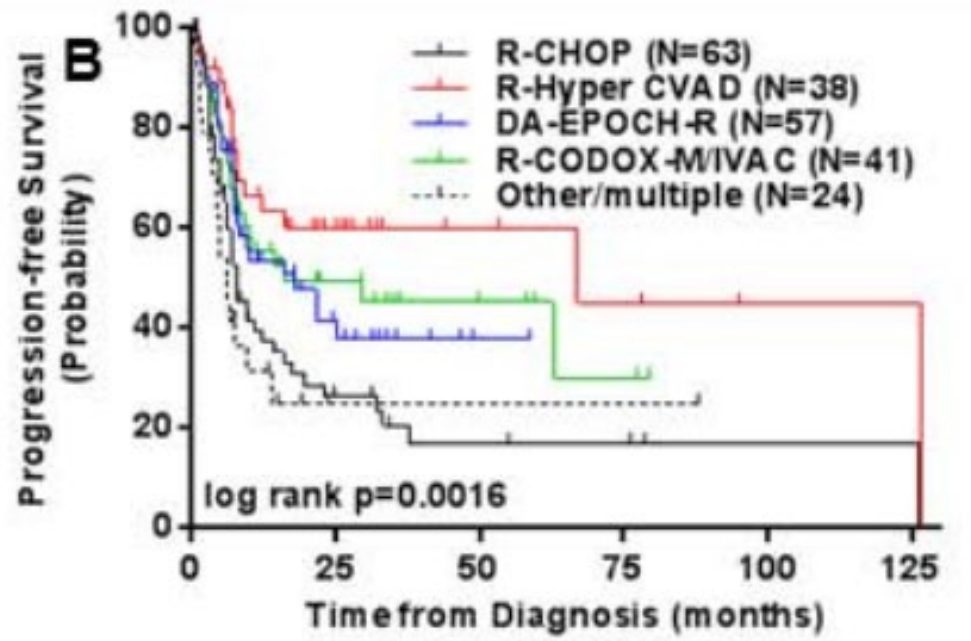


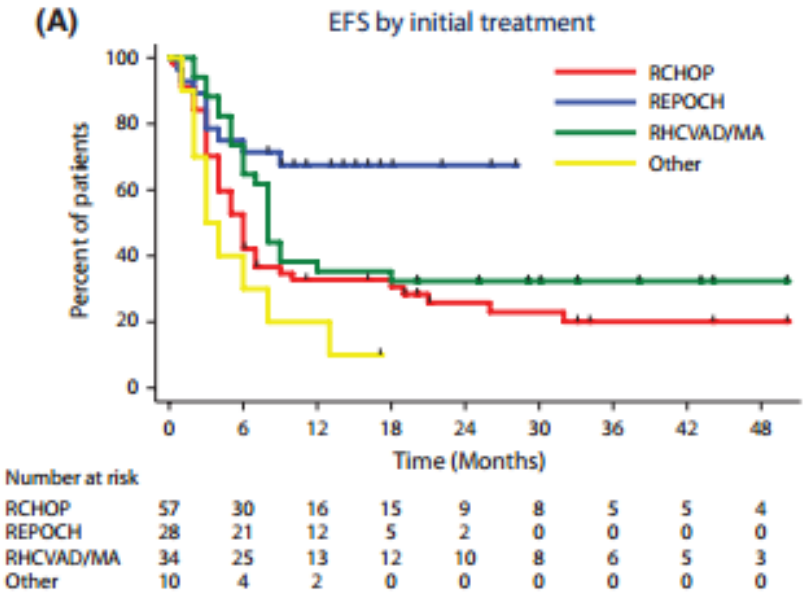
negative	2049	1687	1508	1371	1173	949	672	463	313	190	109
DH&TH/Ig	51	27	24	23	21	18	11	9	7	4	3
DH&TH/non-Ig	50	37	37	34	28	21	12	11	9	3	3
SH/Ig	37	31	28	27	21	14	11	8	4	2	2
SH/non-Ig	16	12	10	10	8	6	5	5	5	4	2



negative	2119	1858	1716	1556	1353	1106	788	544	368	218	127
DH&TH/Ig	54	32	27	26	23	18	11	9	7	4	3
DH&TH/non-Ig	53	42	40	38	31	23	13	12	9	4	3
SH/Ig	40	33	30	28	22	16	12	8	4	2	2
SH/non-Ig	17	15	13	12	9	7	6	5	5	4	3

DA-EPOCH-R in double hit lymphoma





Petrich et al Blood 2014
Oki et al BJH 2014

Amsterdam UMC
University Medical Centers

MYC rearrangement positive large B-cell lymphoma patients can be treated successfully with R-CHOP plus lenalidomide

results of the multicenter phase II HOVON 130 trial

M.E.D. Chamuleau, C.N. Burggraaff, M. Nijland, K. Bakunina, R. Mous, P.J. Lugtenburg, D. Dierickx, G.W. van Imhoff, J.S. Vermaat, W.F.M. Marijt, O. Visser, C. Mandigers, Y.M. Bilgin, A. Diepstra, A. Arens, O.S. Hoekstra, J.M. Zijlstra, D. de Jong, M.J. Kersten

HOVON

Stichting Haemato-Oncologie voor Volwassenen Nederland • www.hovon.nl

Weill Cornell Medicine

NewYork-Presbyterian

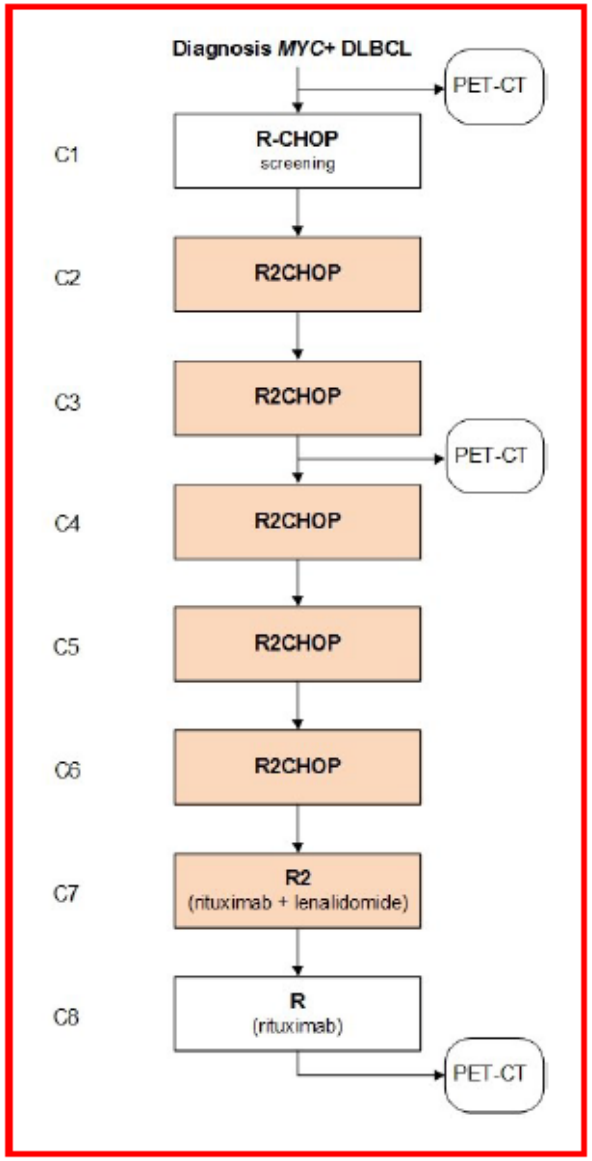
R2CHOP: Rituximab-CHOP + lenalidomide

	Agent	Dose/day	
Day 1	Cyclophosphamide	750 mg/m^2	i.v.
	Vincristine	1.4 mg/m^2 (max 2 mg)	i.v.
	Doxorubicin	50 mg/m^2	i.v.
	Rituximab	375 mg/m^2	i.v.
Day 1-5	Prednisone	100 mg	orally
Day 1-14	Lenalidomide	15 mg	orally

R2CHOP regimen, every 3 weeks

-6 cycles of R-CHOP + 2 cycles of rituximab
-6 cycles of lenalidomide (C2-C7)

Additionally:
-CNS prophylaxis, pegfilgrastim, PJP and DVT prophylaxis



HOVON

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Pathology review results

		n	%
Morphology	DLBCL	65	79 %
N=82	BCL-u	12	15 %
	Indecisive DLBCL/BCL-U	5	6 %
FISH	Single hit	20	24 %
N=82	Double hit	44	54 %
	▪*MYC+/BCL2+*	▪31	▪38 %
	▪*MYC+/BCL6+*	▪13	▪16 %
	Triple hit	9	11 %
	MYC+ (*BCL2* and *BCL6* status unknown)	9	11 %
GEP (nanostring)	GCB subtype	29	76 %
N=38	ABC subtype	7	18 %
	Intermediate	2	5 %

HOVON

Amsterdam UMC
University Medical Centers

Weill Cornell Medicine

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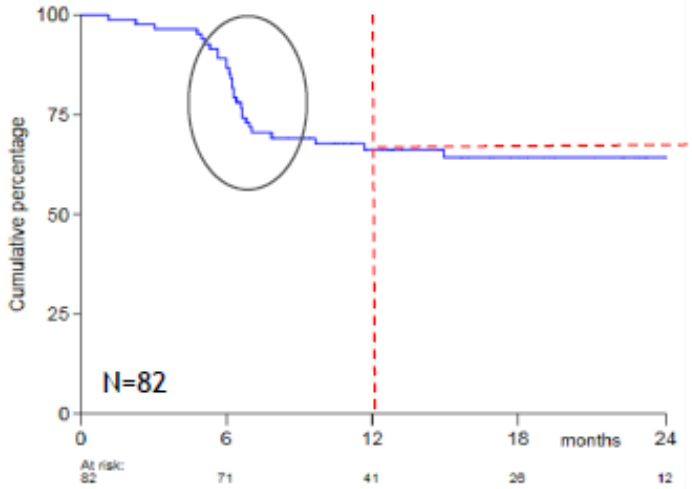
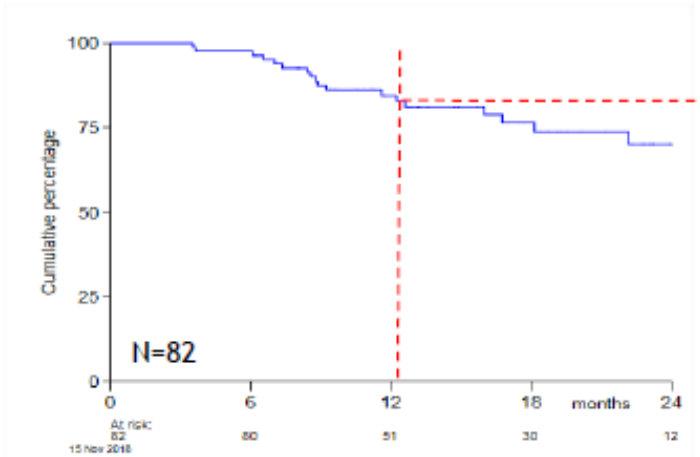
Median FU of 15·9 months, 1-year estimates

PFS

OS

R2CHOP

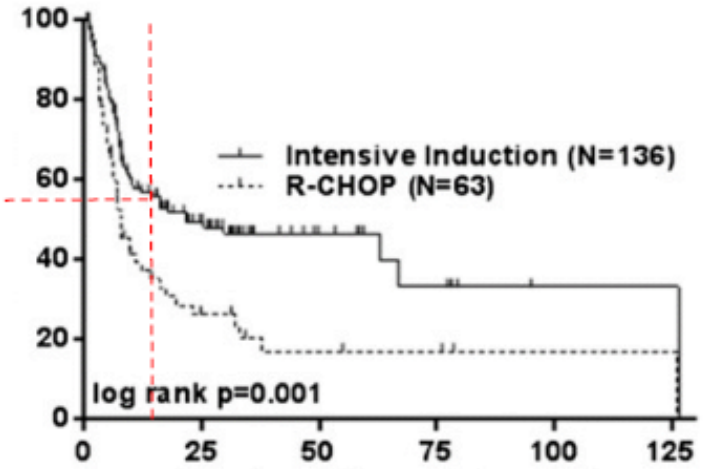


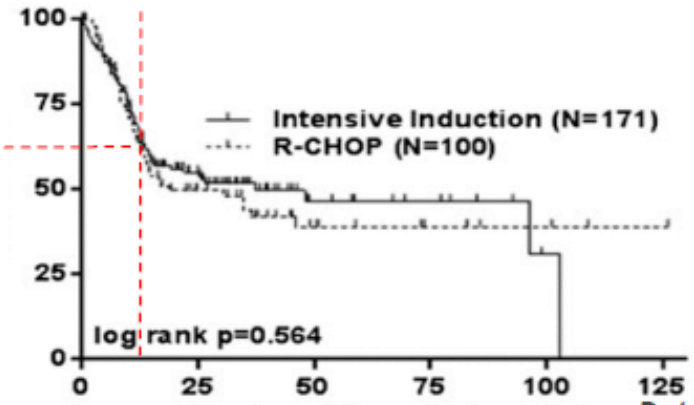


66% vs 55%

85% vs 60%

Historical R-CHOP and intensive regimens



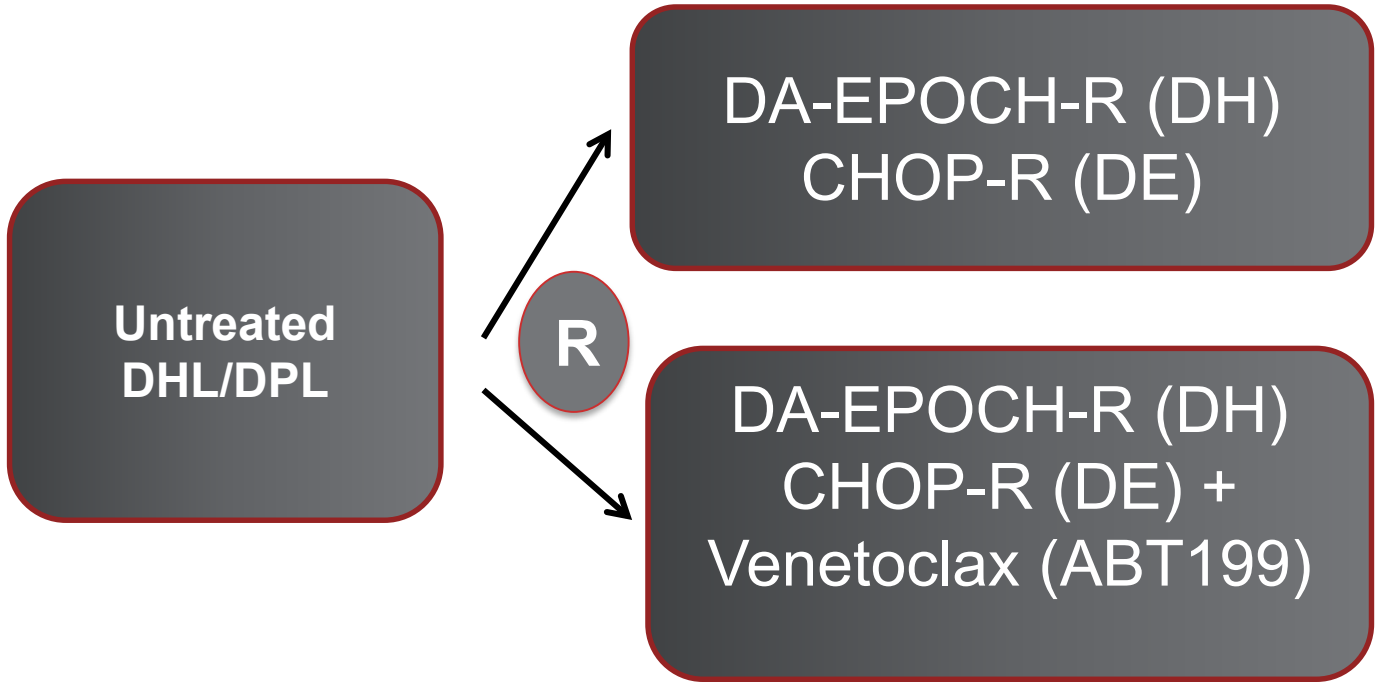


Petrich Blood 2014

Weill Cornell Medicine

NewYork-Presbyterian

Planned Intergroup Trial in DH/DE DLBCL
Phase I then Phase II-III
BCL-2 inhibitor Venetoclax

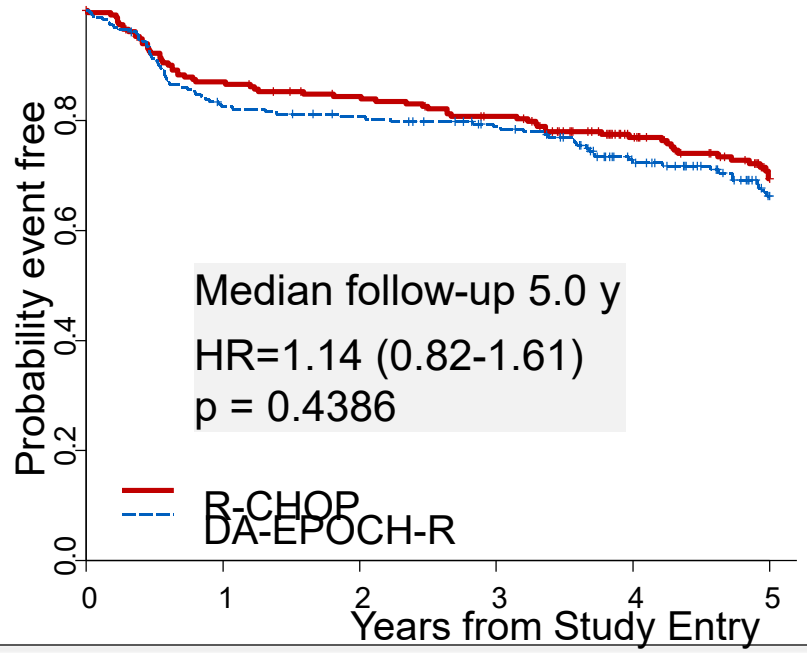


Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)

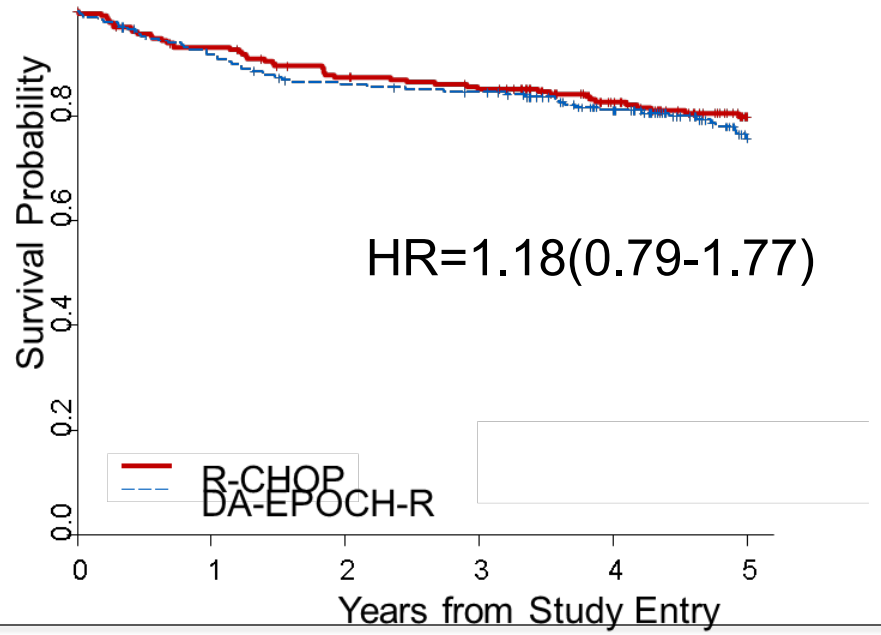
Alliance 50303: Outcomes

	R-CHOP	DA-EPOCH-R	P-value
ORR	89%	89%	0.983
CR/CRu	62%	61%	
PR	27%	27%	

Event Free Survival



Overall Survival



supported by:
Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

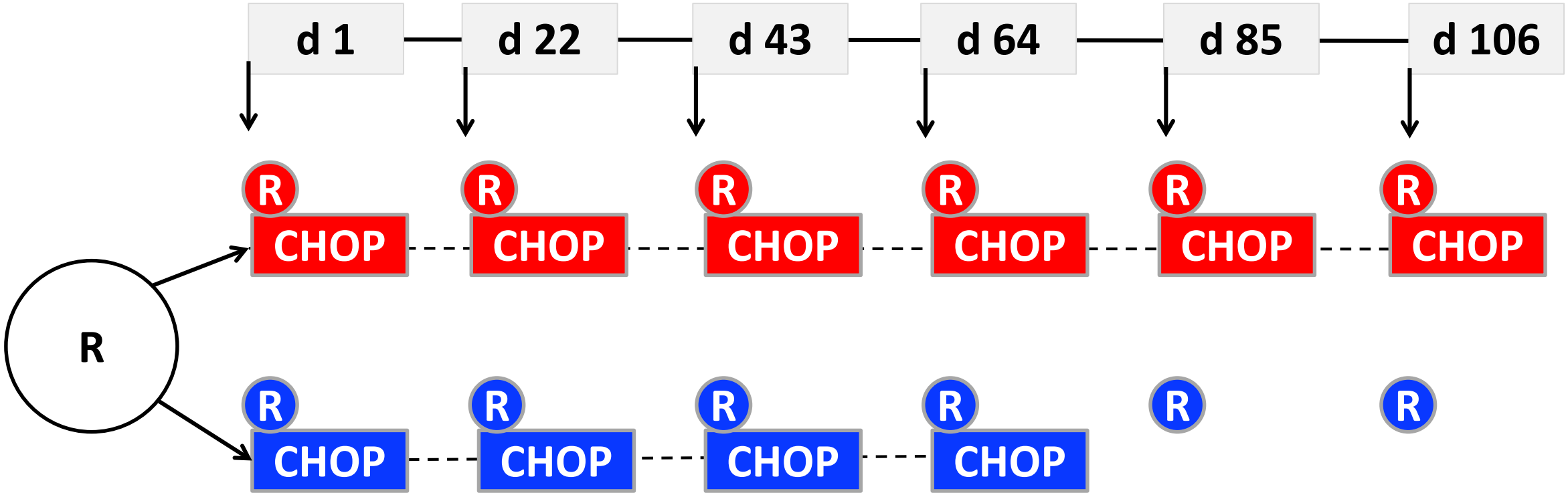
Excellent outcome of young patients (18-60 years) with favourable-prognosis diffuse large B cell lymphoma (DLBCL) treated with 4 cycles CHOP plus 6 applications of rituximab: Results of the 592 patients of the FLYER trial of the DSHNHL/GLA. (ASH 2018 Abstract 781)

Viola Poeschel[1], Gerhard Held[1], Marita Ziepert[2], Bettina Altmann[2], Mathias Witzens-Harig[3], Harald Holte[4], Lorenz Thurner[1], Andreas Viardot[5], Peter Borchmann[6], Lothar Kanz[7], Ulrich Keller[8], Christian Schmidt[9], Rolf Mahlberg[10], Bernd Metzner[11], Reinhard Marks[12], Heinz-Gert Hoeffkes[13], Konstantinos Christofyllakis[1], Josif Amam[1], Christian Berdel[14], Stephan Stilgenbauer[1], Norbert Schmitz[15], Lorenz Truemper[16], Niels Murawski[1], Markus Löffler[2], Michael Pfreundschuh[1]

[1]Department of hematology, oncology and rheumatology, Saarland University Medical School, Homburg / Saar, Germany; [2]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; [3]Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; [4]Oslo University Hospital, Oslo, Norway; [5]Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany; [6]Department of Haematology and Oncology, University Hospital of Cologne, Cologne, Germany; [7]University Hospital of Tuebingen, Tuebingen, Germany; [8]Klinikum rechts der Isar der TU München, Munich, Germany; [9]Department of Medicine III, University Hospital, Munich, Germany; [10]Klinikum Mutterhaus der Borromaerinnen, Trier, Germany; [11]Klinikum Oldenburg, Oldenburg, Germany; [12]Department of Hematology and Oncology, University Medical Center, Freiburg, Germany; [13]Klinikum Fulda Tumorklinik, Fulda, Germany; [14]Department of radiooncology, Saarland University Medical School, Homburg / Saar, Germany; [15]Medizinische Klinik A, University Hospital Münster, Münster, Germany; [16]Georg August University, Goettingen, Germany

FLYER: Study Design

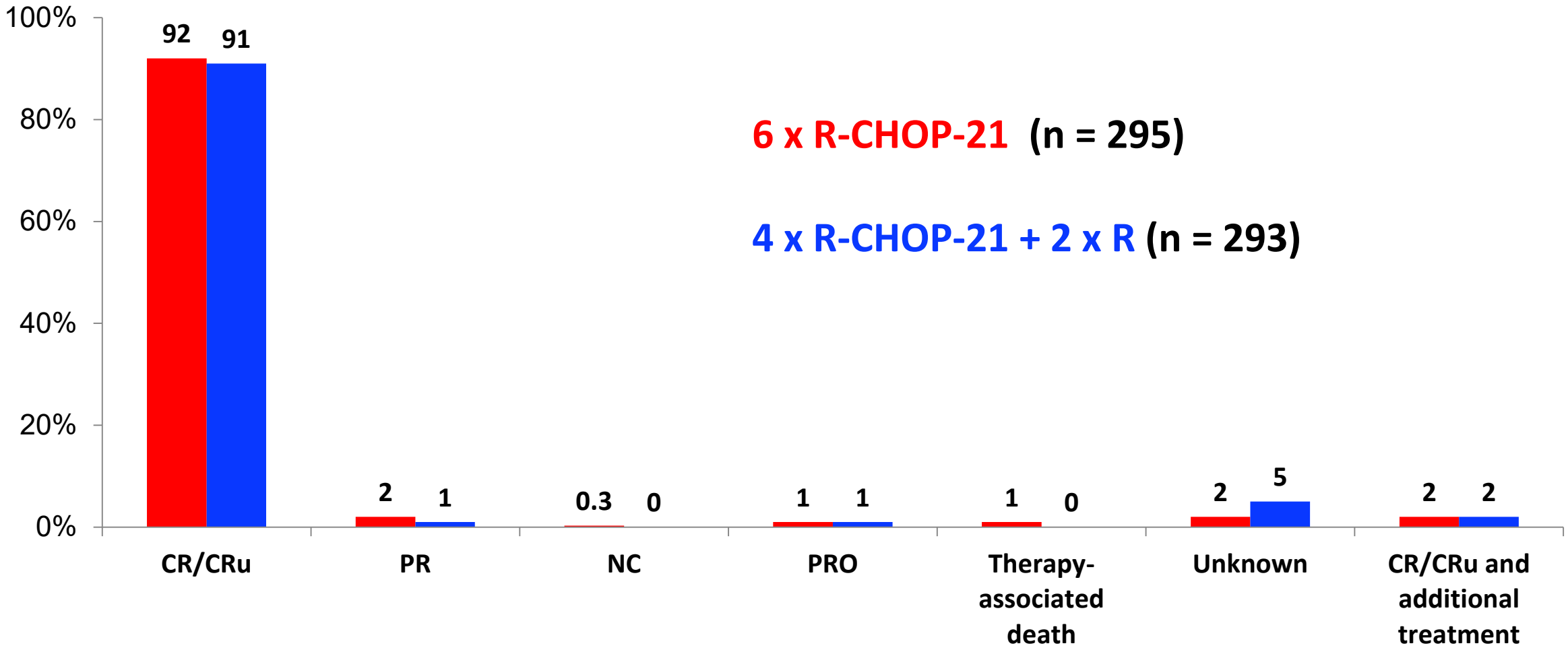
- **Front-line treatment of aggressive B-cell lymphoma**
- **18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)**



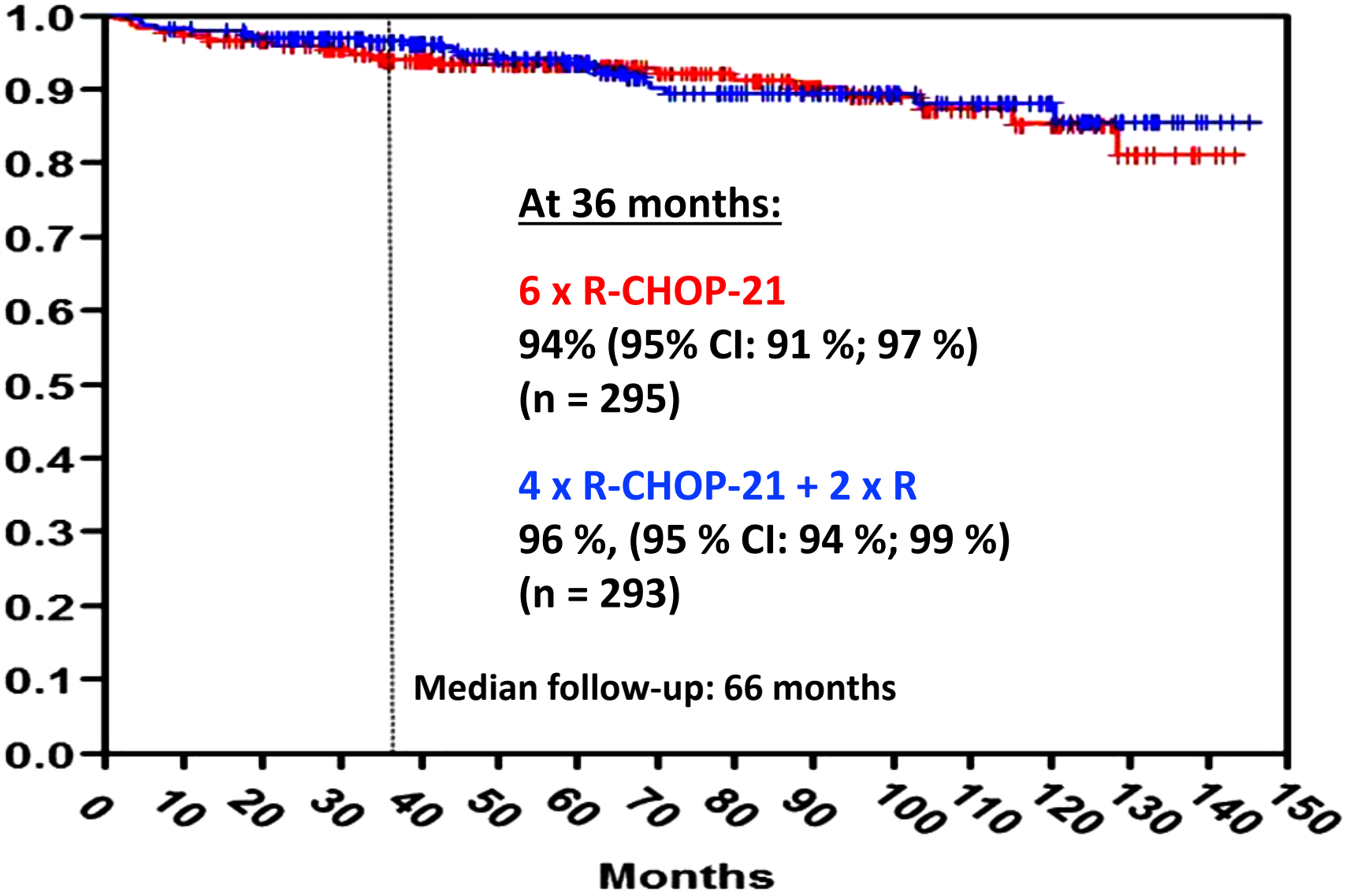
Demographics

	Total (n = 588)		6 x R-CHOP (n = 295)		4 x R-CHOP (n = 293)		p-value
Female	234	(40 %)	116	(39 %)	118	(40 %)	0.814
Age, median (range)	48	(18, 60)	47	(19, 60)	49	(18, 60)	0.438
LDH > UNV	0	(0 %)	0	(0 %)	0	(0 %)	-
ECOG > 1	0	(0 %)	0	(0 %)	0	(0 %)	-
Stage I **II** **III/IV**	346 236 6	(59 %) (40 %) (1 %)	172 119 4	(58%) (40 %) (1 %)	174 117 2	(59 %) (40 %) (1 %)	0.953
aaIPI 0 **1**	582 6	(99 %) (1 %)	291 4	(99 %) (1 %)	291 2	(99 %) (1 %)	0.686
Extralymph. involvement	191	(32 %)	96	(32 %)	95	(32 %)	0.975
Bulky disease	2	(0.3 %)	1	(0.3 %)	1	(0.3 %)	1.000
B-symptoms	36	(6 %)	9	(3 %)	27	(9 %)	0.002

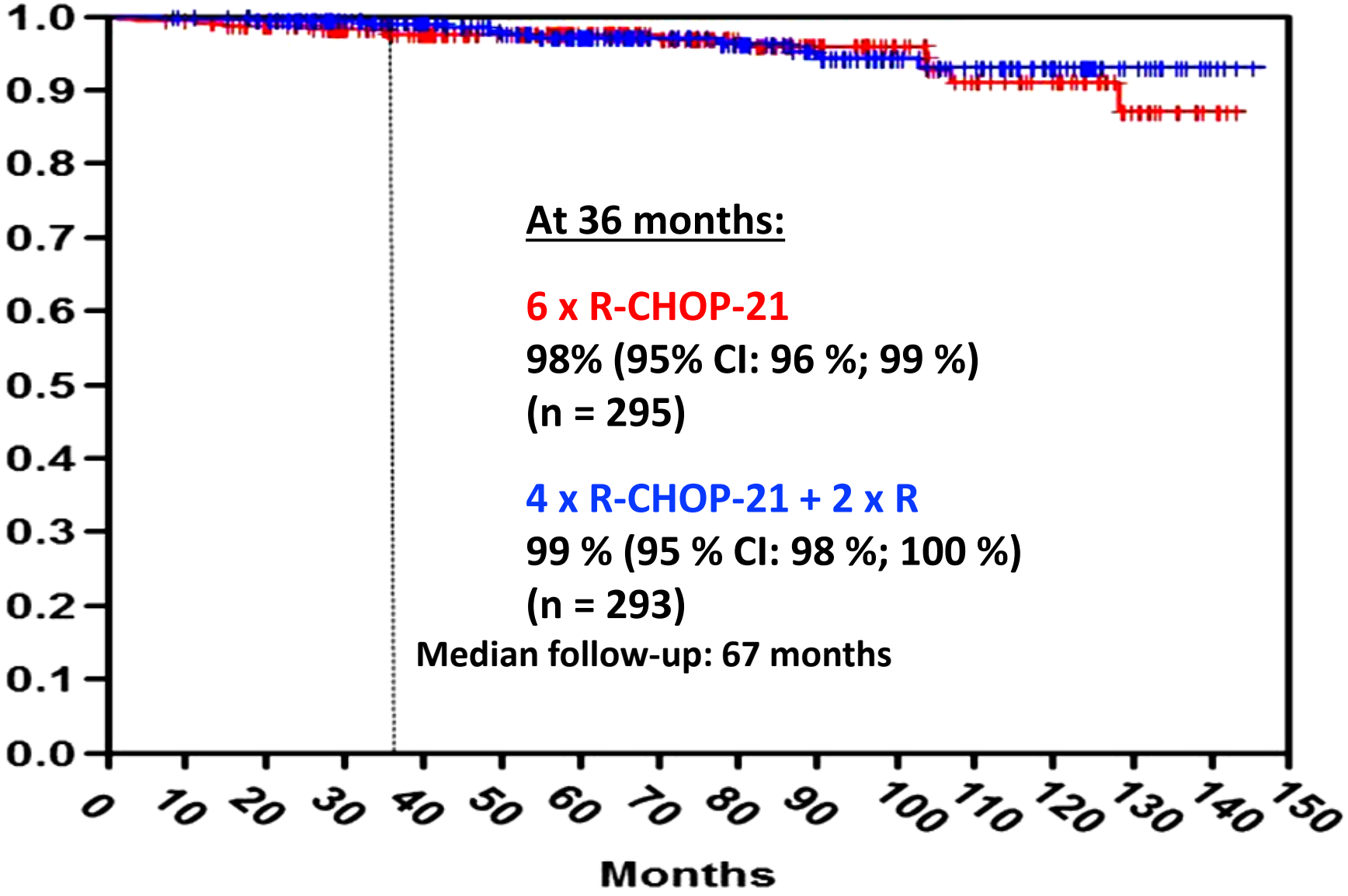
Response Rates



Primary Endpoint: PFS



Overall Survival (OS)



At 36 months:

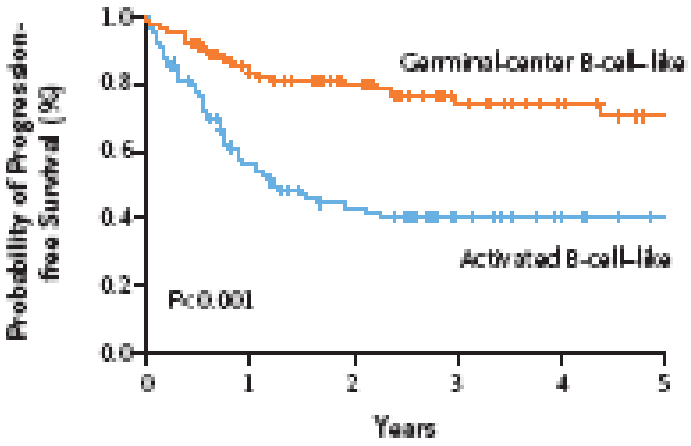
6 x R-CHOP-21
98% (95% CI: 96 %; 99 %)
(n = 295)

4 x R-CHOP-21 + 2 x R
99 % (95 % CI: 98 %; 100 %)
(n = 293)

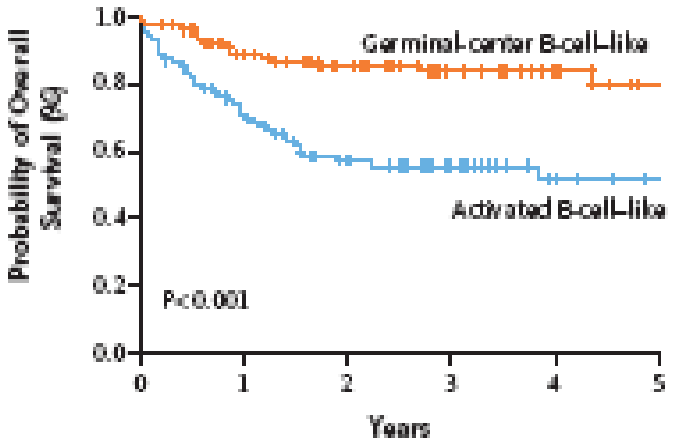
Median follow-up: 67 months

Outcome by GCB vs ABC gene signatures in DLBCL N=233 patients treated with R-CHOP

PFS



OS



No. at Risk												
Germinal-center B-cell–like	107	82	61	39	27	15	101	74	56	35	24	14
Activated B-cell–like	93	60	38	23	11	6	90	45	30	17	10	5

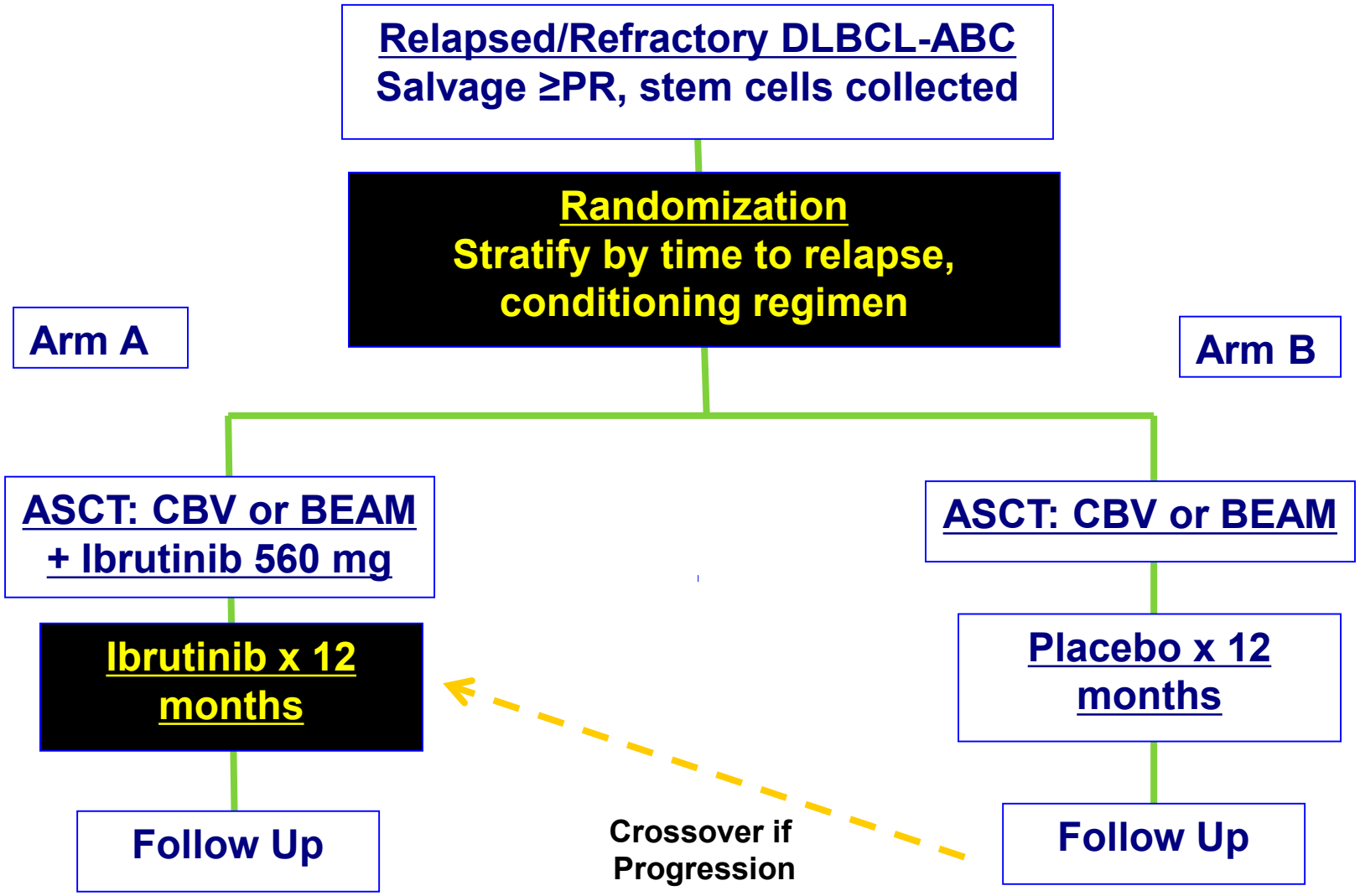
Lenz G, et al, NEJM 2008

Oncogenic mechanisms and potential therapeutic targets in GCB and ABC DLBCLs

DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	*BCL2* translocation* *EZH2* mutations‡ *PTEN* deletions§ Loss of PTEN expression	BCL6 EZH2 PI3K/Akt
ABC	Post-germinal centre B-cell	NF-κB activation‖ *CARD11* mutations *MYD88* mutations *CD79B* mutations *A20* deletions	BCR CBM complex IRAK-4 JAK–STAT

Roschewski M. et al. *Nat. Rev. Clin. 2013;*11:12-23.

Alliance 51301 Study Schema



A Global, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Patients With Previously Untreated Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

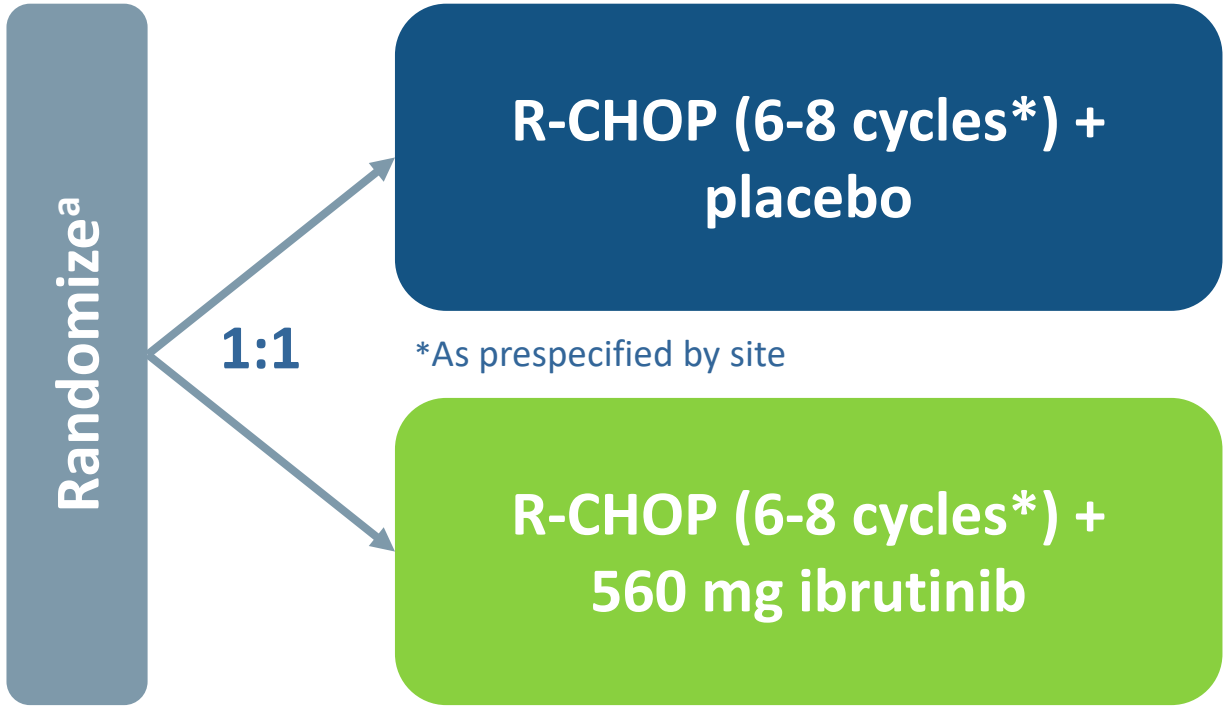
Anas Younes,[1] Laurie H Sehn,[2] Peter Johnson,[3] Pier Luigi Zinzani,[4] Xiaonan Hong,[5] Jun Zhu,[6] Olga Samoilova,[7] Cheolwon Suh,[8] Itaru Matsumura,[9] Andres Lopez-Hernandez,[10] Ulrich Dührsen,[11] Catherine Thieblemont,[12] Jodi Carey,[13] Grace Liu,[14] S. Martin Shreeve,[15] Steven Sun,[14] Jessica Vermeulen,[16] Louis Staudt,[17] and Wyndham Wilson,[18] on behalf of the PHOENIX investigators

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]BC Cancer Centre for Lymphoid Cancer, Vancouver, BC, Canada; [3]Cancer Research UK Clinical Centre, University of Southampton, Southampton, UK; [4]Institute of Hematology, "Seràgnoli" University of Bologna, Bologna, Italy; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China; [7]Regional Clinical Hospital, Nizhniy Novgorod, Russian Federation; [8]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [9]Department of Hematology and Rheumatology, Kindai University Faculty of Medicine, Osakasayama, Japan; [10]Department of Hematology, University Hospital Vall d'Hebron, Barcelona, Spain; [11]Department of Hematology, University Hospital Essen, Essen, Germany; [12]APHP, Hôpital Saint-Louis, Hemato-Oncology, Paris, France; Diderot University, Sorbonne Paris-Cité, Paris, France; [13]Janssen R&D, Spring House, PA, USA; [14]Janssen Research & Development, Raritan, NJ, USA; [15]Janssen Research & Development, San Diego, CA, USA; [16]Janssen Research & Development, LLC, Leiden, The Netherlands; [17]Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [18]National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Study Design: Double-Blind, Placebo-Controlled Study

PHOENIX PCI-32765DBL3001

N = 838



*As prespecified by site

[a]Stratified by R-IPI, region, and number of prespecified treatment cycles (6 vs 8 cycles).

- Prophylactic antibiotics and G-CSF were not mandated but were permitted at the investigator's discretion per local or other standard guidelines

[†]EFS: time from randomization to PD, relapse from CR, initiation of subsequent disease-specific therapy for PET-positive or biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death.

Key eligibility criteria

- Untreated non-GCB DLBCL
  - Determined by Hans-based IHC at a central laboratory
  - Retrospectively analyzed for ABC subtype using GEP
- Stage II to IV measureable disease
- R-IPI ≥ 1
- ECOG performance status ≤ 2

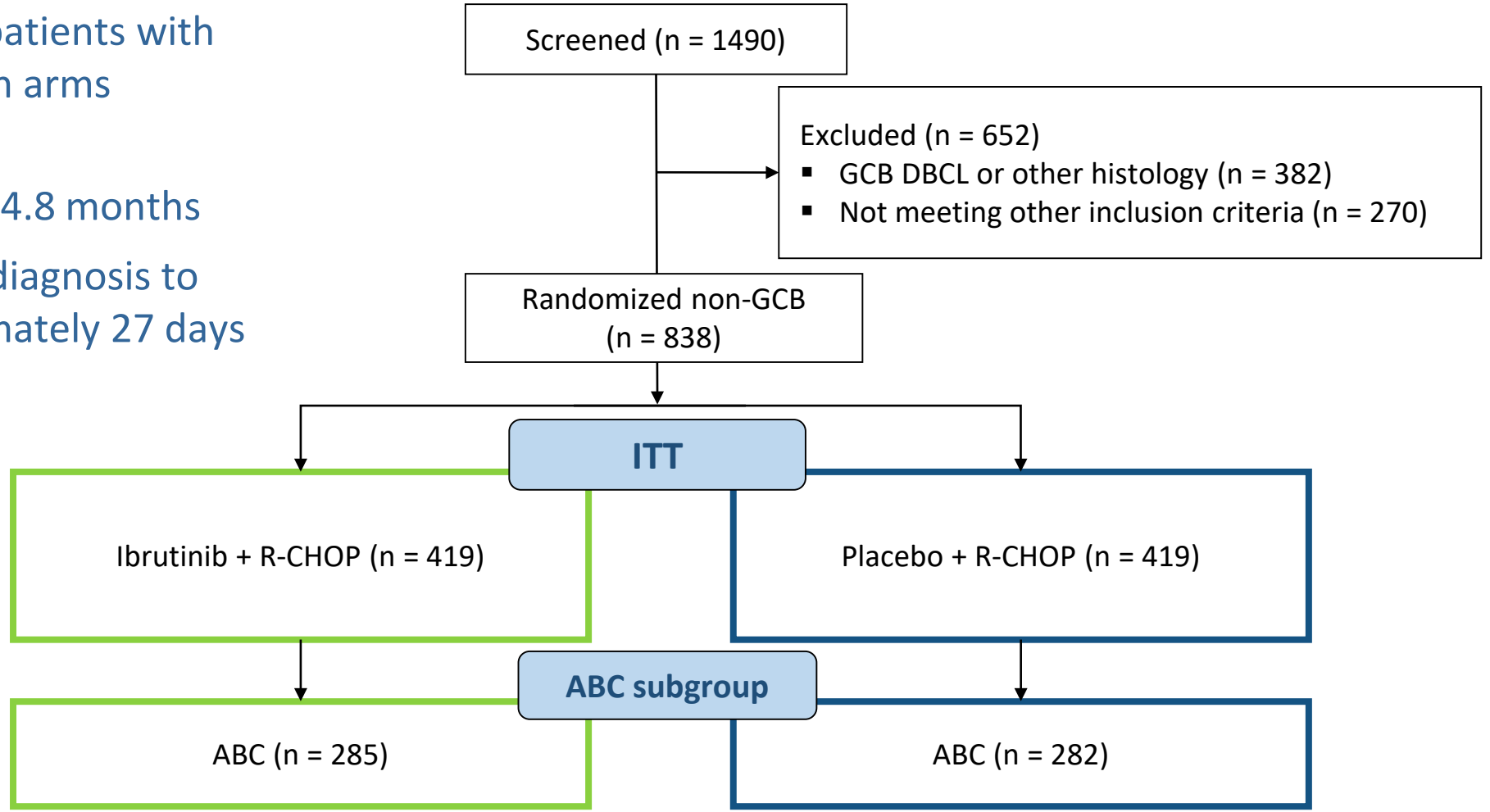
End points

- Primary end point: EFS[†] in ITT (non-GCB) and ABC subgroup
- Secondary end points: PFS, CR rate, OS, safety
  - Response assessed per Revised Response Criteria for Malignant Lymphoma[1]

1. Cheson BD, et al. *J Clin Oncol*. 2007;25:579-586.

Patient Disposition (ITT)

- Similar number of patients with ABC subtype in both arms (77.0% vs 74.8%)
- Median follow-up 34.8 months
- Median time from diagnosis to treatment approximately 27 days



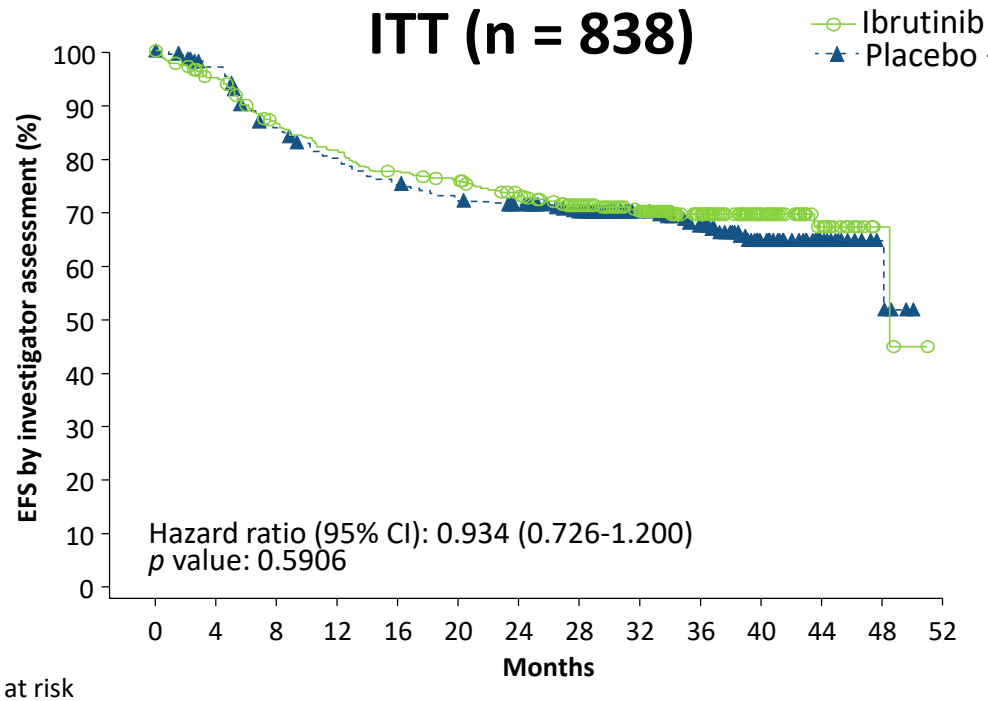
Patient Demographics and Disease Characteristics (ITT)

	Ibrutinib + R-CHOP (n = 419)	Placebo + R-CHOP (n = 419)
Age, years		
Median	63.0	61.0
> 65 years, n (%)	188 (44.9)	160 (38.2)
Sex, n (%)		
Male	221 (52.7)	226 (53.9)
Region, n (%)		
US/Western Europe	131 (31.3)	131 (31.3)
Rest of world	288 (68.7)	288 (68.7)
Baseline stage of DLBCL at entry, n (%)		
I	0	1 (0.2)
II	101 (24.1)	103 (24.6)
III	130 (31.0)	118 (28.2)
IV	188 (44.9)	197 (47.0)

	Ibrutinib + R-CHOP (n = 419)	Placebo + R-CHOP (n = 419)
ECOG performance status, n (%)		
0	190 (45.3)	187 (44.6)
1	191 (45.6)	170 (40.6)
2	38 (9.1)	62 (14.8)
Bone marrow involvement, n (%)		
Yes	50 (11.9)	43 (10.3)
No	369 (88.1)	376 (89.7)
Number of planned treatment cycles, n (%)		
6 cycles	246 (58.7)	246 (58.7)
8 cycles	173 (41.3)	173 (41.3)
R-IPI score index number, n (%)		
1-2	236 (56.3)	238 (56.8)
3-5	183 (43.7)	181 (43.2)

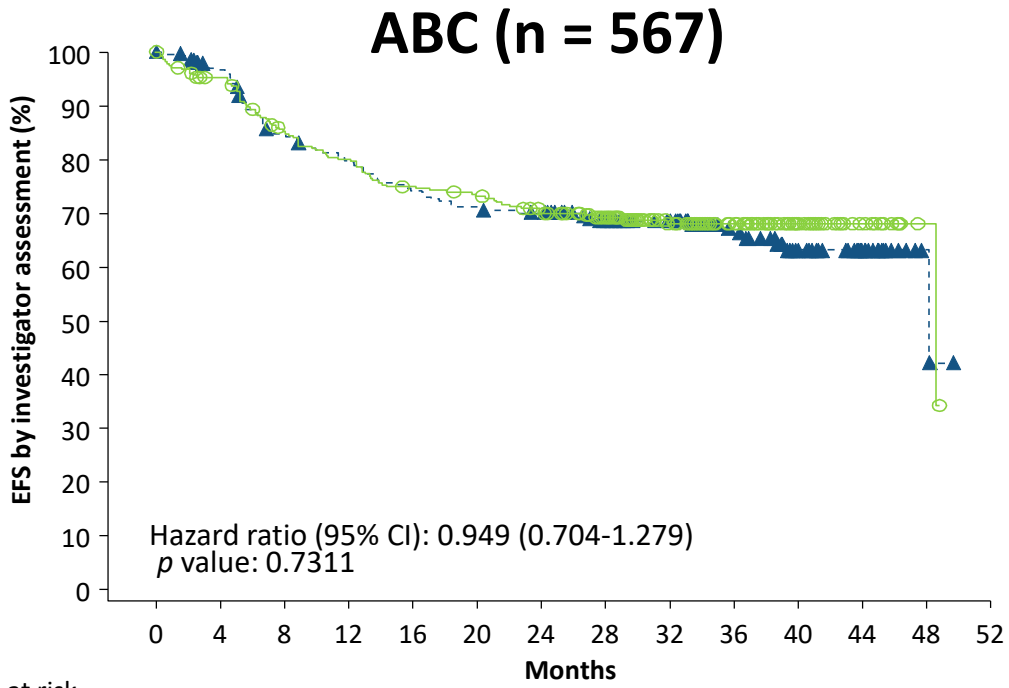
American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

Primary End Point EFS in the ITT and ABC Population



Patients at risk

Ibrutinib + R-CHOP	419	374	336	316	300	291	276	233	179	120	63	25	3	0
Placebo + R-CHOP	419	390	341	316	297	286	277	244	184	118	60	33	5	0



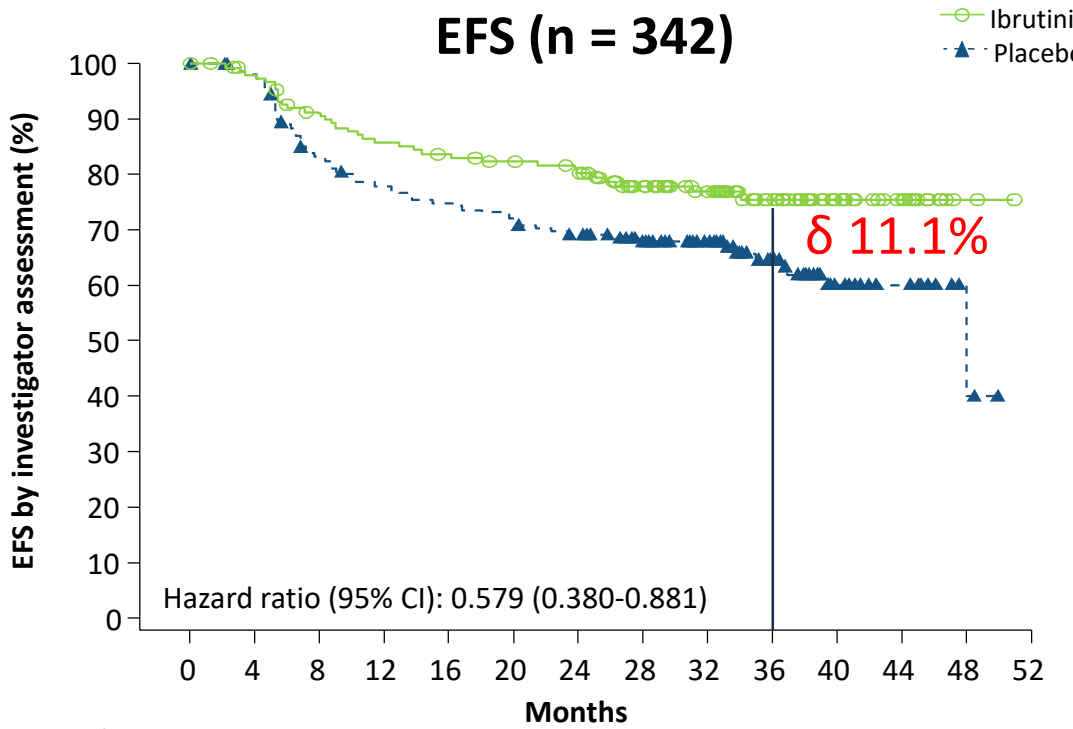
Patients at risk

Ibrutinib + R-CHOP	285	256	225	211	197	191	181	149	111	77	39	15	2	0
Placebo + R-CHOP	282	260	225	212	196	188	183	160	125	78	41	25	3	0

- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ITT population**
- **CNS progression was observed: 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms**

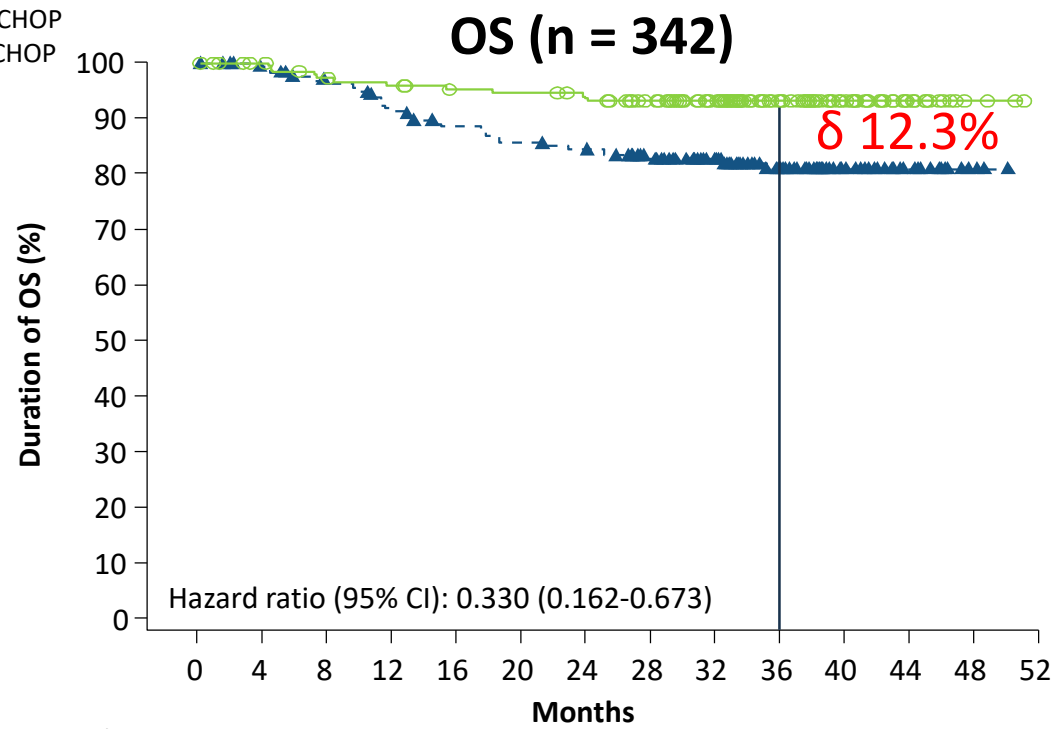
American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

EFS and OS in Patients < 60 Years



Patients at risk

Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0

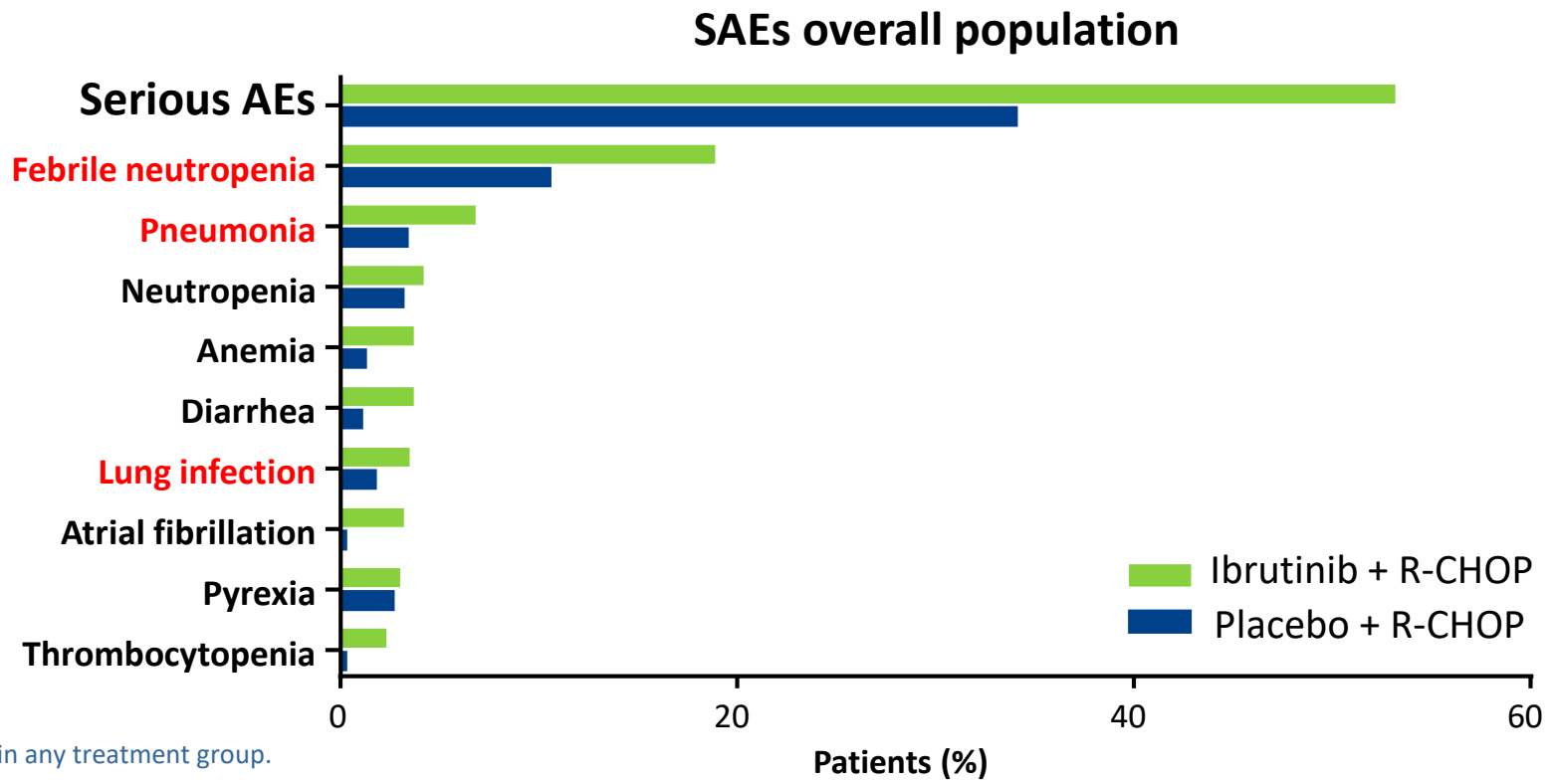


Patients at risk

Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

- **Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients < 60 years of age**
- **Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors**
- **A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922] for EFS; HR [95% CI]: 0.345 [0.138-0.862] for OS)**
- **More patients on the placebo + R-CHOP arm received subsequent antilymphoma therapy (25.2% vs 33.5%)**

Treatment-Emergent SAEs,* Overall Population



*Occurring in ≥ 2% patients in any treatment group.

- TEAE types were consistent with those expected for ibrutinib and R-CHOP
- Prophylactic G-CSF was used in 66.1% vs 63.9% patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms
  - 56.5% vs 56.2% in patients < 60 years
  - 71.8% vs 70.0% in patients ≥ 60 years

Treatment Received by Age < and ≥ 60 Years

n (%)	Age < 60 Years		Age ≥ 60 Years	
	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
R-CHOP* cycles received ≥ 6 cycles	143 (92.9)	172 (93.0)	193 (73.7)	207 (88.8)
Ibrutinib/placebo cycles received ≥ 6 cycles	138 (89.6)	170 (91.9)	178 (67.9)	202 (86.7)

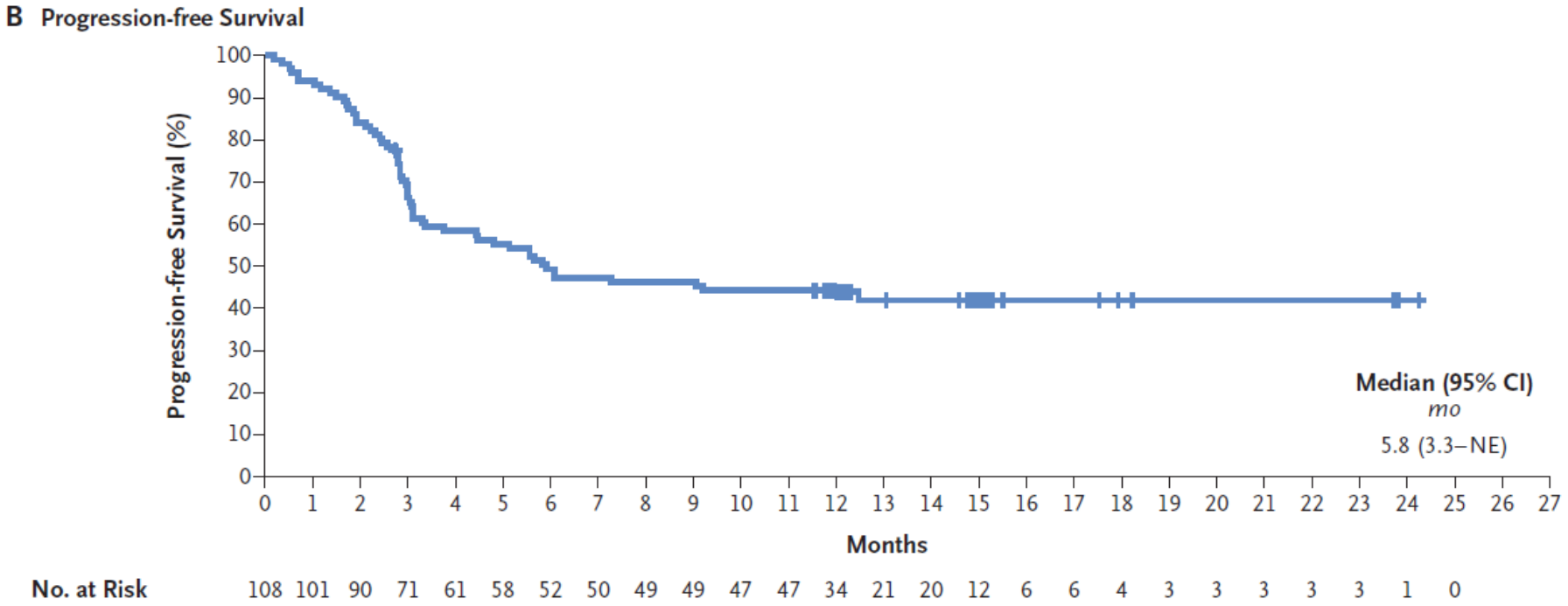
*Any component.

- In the safety population, ibrutinib/placebo and R-CHOP exposure was reduced in the ibrutinib + R-CHOP arm compared with the placebo + R-CHOP arm
- The reduced ibrutinib/placebo and R-CHOP exposure was primarily seen in older patients

American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

111 enrolled, 101 received drug



Neelapu et al; NEJM 377;26:2531-44, 2017

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

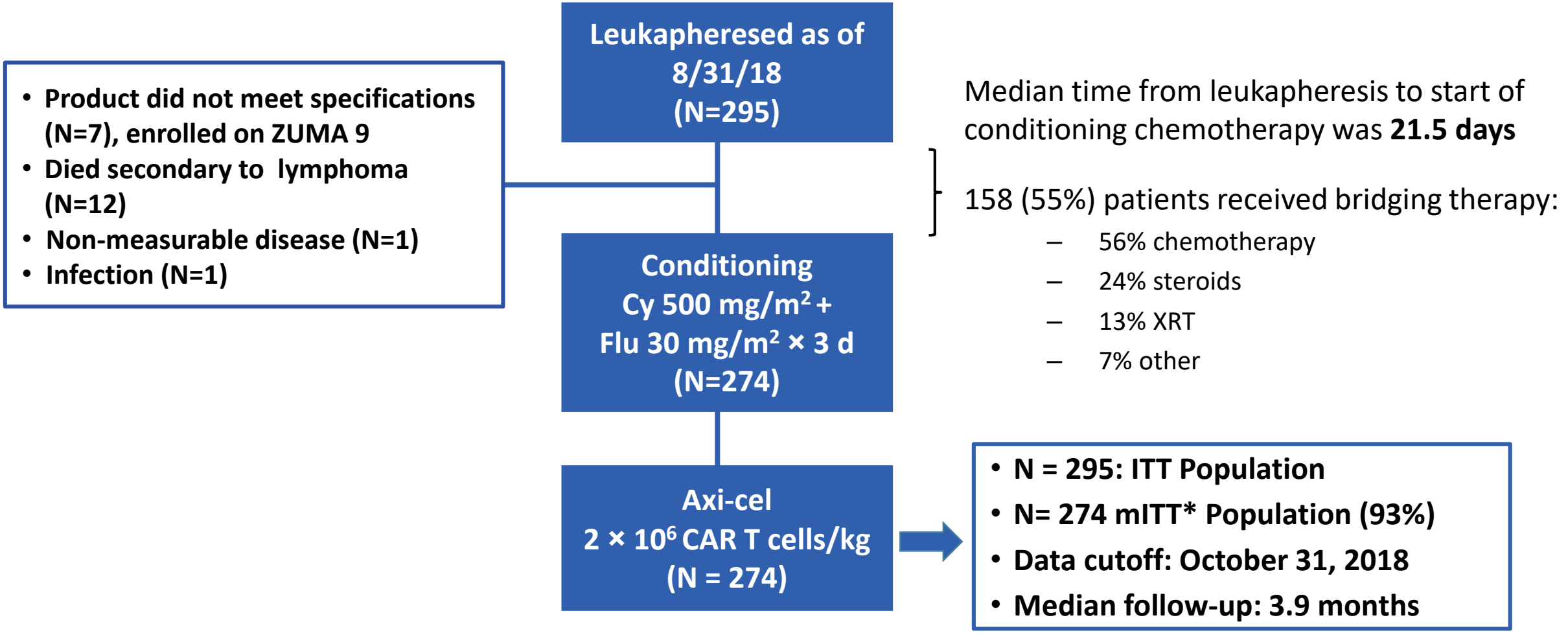
Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma: Real World Experience

Loretta J. Nastoupil*, Michael D. Jain*, Jay Yaakov Spiegel, Armin Ghobadi, Yi Lin, Saurabh Dahiya, Matthew Lunning, Lazaros Lekakis, Patrick Reagan, Olalekan Oluwole, Joseph McGuirk, Abhinav Deol, Alison R. Sehgal, Andre Goy, Brian T. Hill, Andreadis Charalambos, Javier Munoz, Jason Westin, Julio C. Chavez, Amanda Cashen, Nabil N. Bennani, Aaron Rapoport, Julie M. Vose, Lei Feng
David B. Miklos, Sattva S. Neelapu**, Frederick L. Locke****

*LJN and MDJ are co-first authors
**DBM, SSN, and FLL are co-senior authors

ASH 2018 Abstract 91

Axi-Cel SOC Consort Diagram



*includes 3 patients treated on ZUMA9 with product that was out of spec

Characteristics Differentiating Patients in the Real World from ZUMA-1

- 124 of 286* (43%) patients would not have met eligibility for ZUMA-1 at the time of leukapheresis.

Criteria Excluded from ZUMA-1	N=124 N (%)
Platelets < 75	37 (13)
Active DVT/PE	27 (9)
Prior CD19 or CAR T cell therapy	24 (8)
GFR < 60	22 (8)
History of CNS lymphoma	22 (8)
Symptomatic pleural effusion	11 (4)
LVEF < 50%	10 (4)
Prior allogeneic SCT	7 (2)

ASH 2018 Abstract 91

* Missing data on 7 subjects enrolled on ZUMA 9

Hospitalization Period and Grade 5 AEs

	SOC Axi-cel N = 274	ZUMA-1[1] N = 108
Tocilizumab usage	63%	45%
Corticosteroid usage	55%	29%
Median hospital stay	14 days	N/A
ICU stay, N (%)	85 (32%)	N/A
Grade 5 AEs, N (%)	7 (3%)	4 (4%)
Treatment-related deaths	2 (1%)	2 (2%)

- 7 deaths due to non-relapse mortality after SOC axi-cel
  - Infection (N=5; infection, sepsis, fungemia, candidemia, pneumonia)
  - HLH (N=1)
  - Cerebral Edema (N=1)

[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

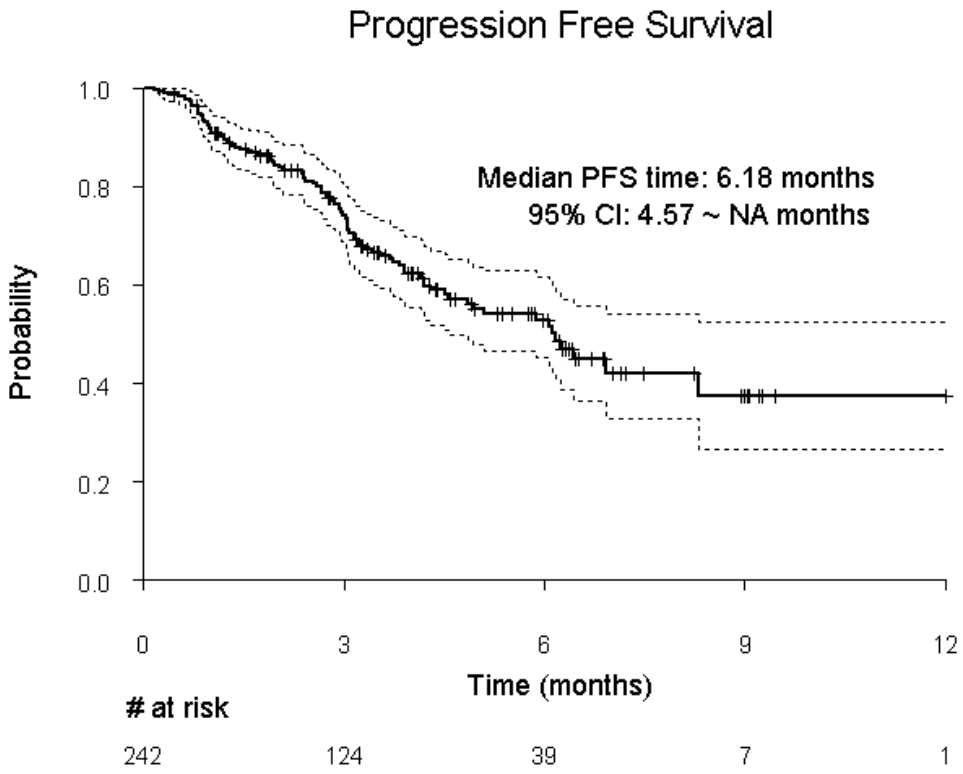
Efficacy of Axi-Cel in the Real World

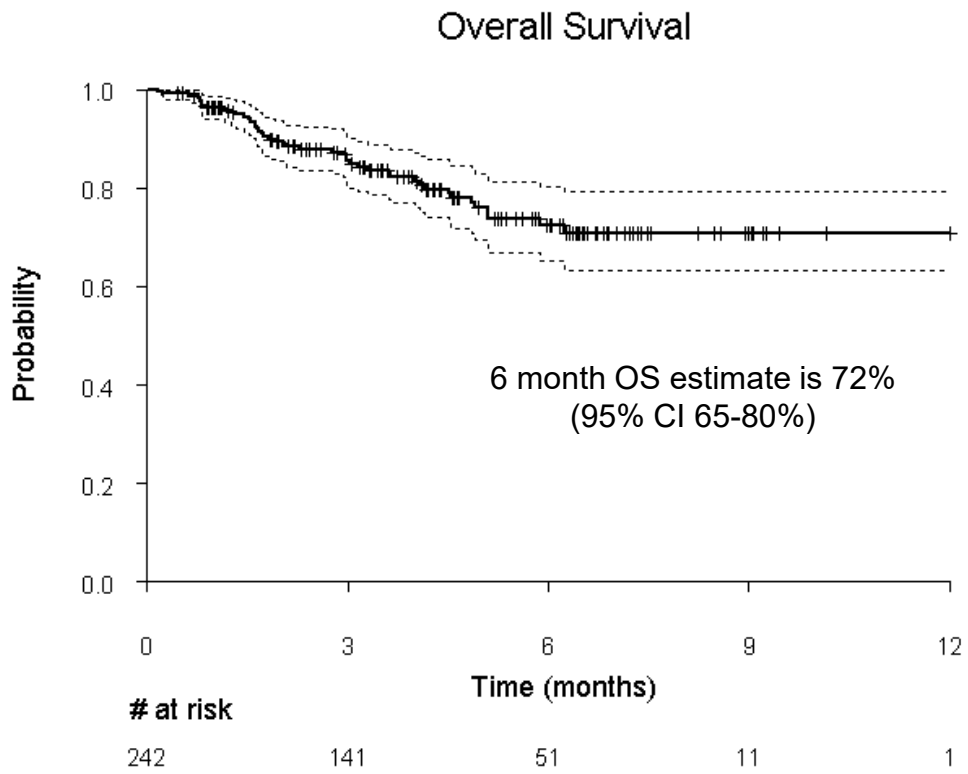
	SOC Axi-cel Evaluable	SOC Axi-Cel	ZUMA-1[1] N=108
Median follow up, months		3.9	15.4
Day 30 ORR, N (%)	238	191 (80)	N/A
Day 30 CR, N (%)		113 (47)	N/A
Best ORR at Day 90, N (%)	248[a]	201 (81)	89 (82)
Best CR at Day 90, N (%)		142 (57)	63 (58)

[a] Evaluable patients as of data cut-off date of October 31, 2018

[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

PFS and OS at Median F/U of 3.9 Months in the Real World





mITT population, OS calculated from time of CAR T infusion until death or last contact.

Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance & Toxicity (ASH 2018 Abstract 92)

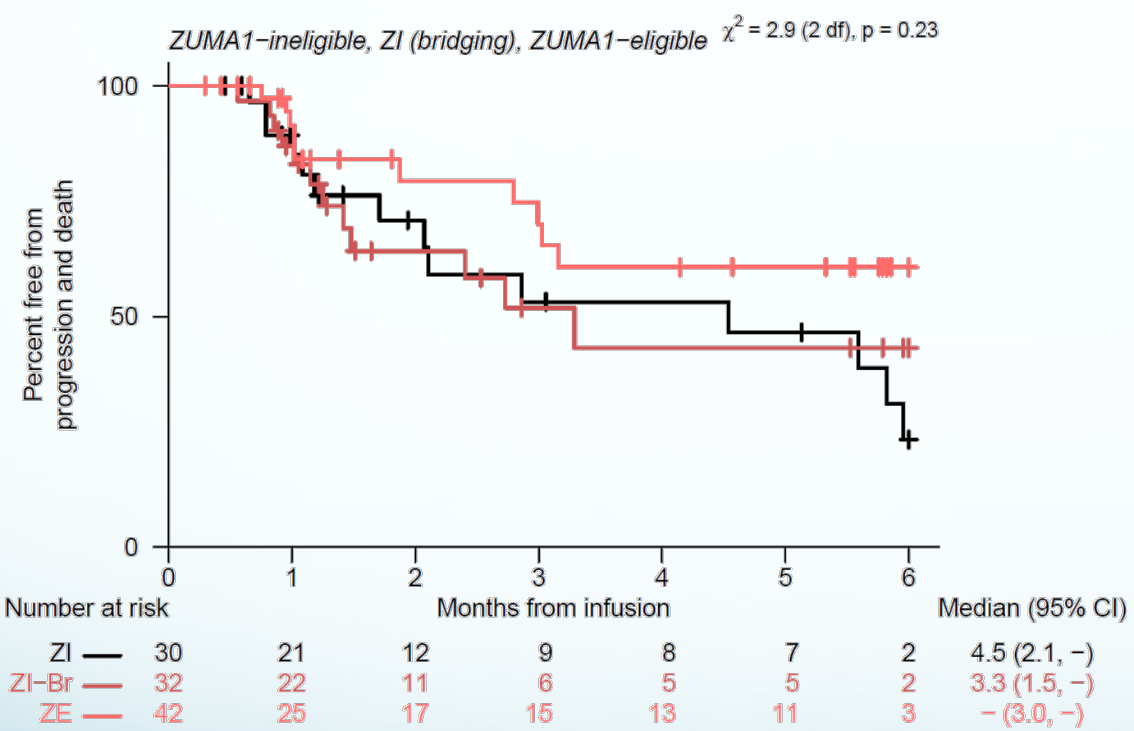
Caron A. Jacobson, MD [1], *Bradley Hunter, MD, MPH[1], Philippe Armand, MD, PhD[1], Yusuke Kamihara, MD, PhD[1], Jerome Ritz, MD, PhD[1], Scott J Rodig, MD[2], Kyle Wright, M.D., Ph.D.[2], Mikel Lipschitz, M.S.[2], Robert A. Redd, MS[1], Joseph Maakaron, MD[3], Samantha Jaglowski, MD, MPH[3], Marcela V. Maus, MD, PhD[4], Yi-Bin Chen, MD[4], Jeremy S. Abramson, MD, MMSc[4], Justin Kline, MD[5], Jonathon B. Cohen, MD, MS[6], Stephen D. Smith, MD[7], David G. Maloney, MD, PhD[8], Ajay K. Gopal, MD[8], Matthew J. Frigault, MD[4]* and Utkarsh H. Acharya, DO[7,8]**

[1]*Dana Faber Cancer Institute, Boston, MA,* [2]*Brigham and Women's Hospital, Boston, MA,* [3]*Ohio State University, Columbus, OH,* [4]*Massachusetts General Hospital Cancer Center, Boston, MA,* [5]*University of Chicago, Chicago, IL,* [6]*Emory University, Atlanta, GA,* [7]*Seattle Cancer Care Alliance, University of Washington, Seattle, WA,* [8]*University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

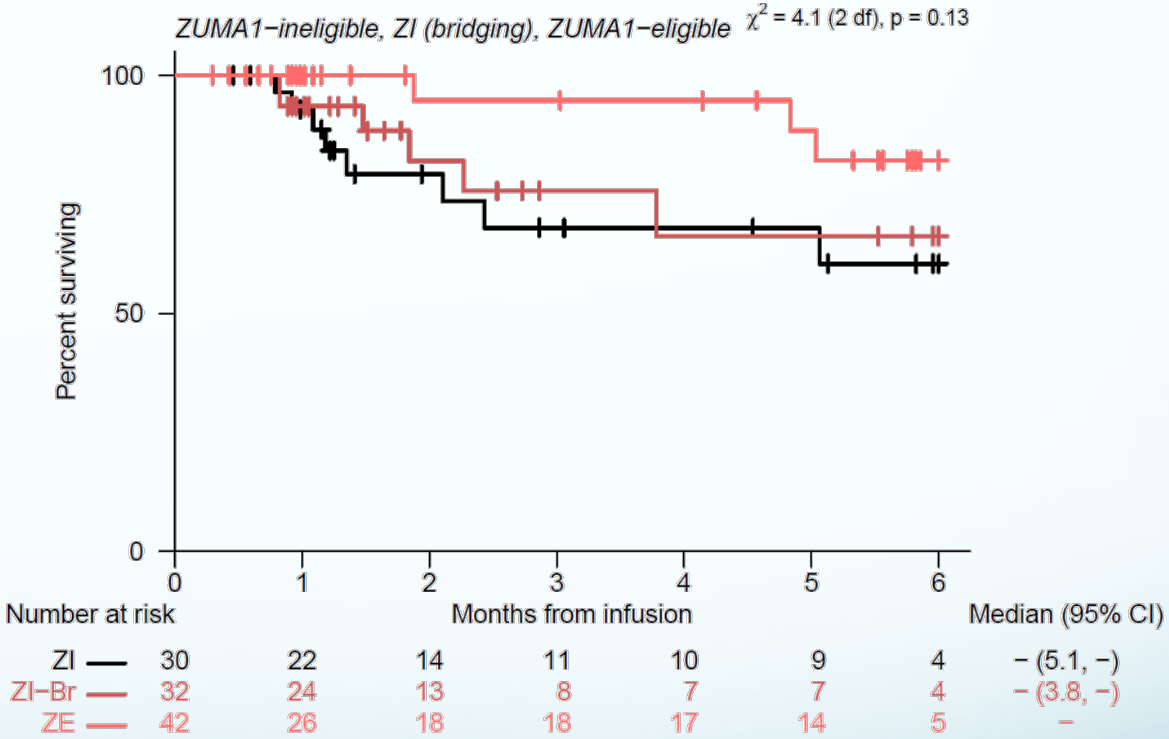
**Contributed equally to this work*

ZUMA-1 Eligibility and Bridging Therapy: Outcomes

Progression-free Survival



Overall Survival



ZUMA-1 Ineligible: Other (+/- Bridging)

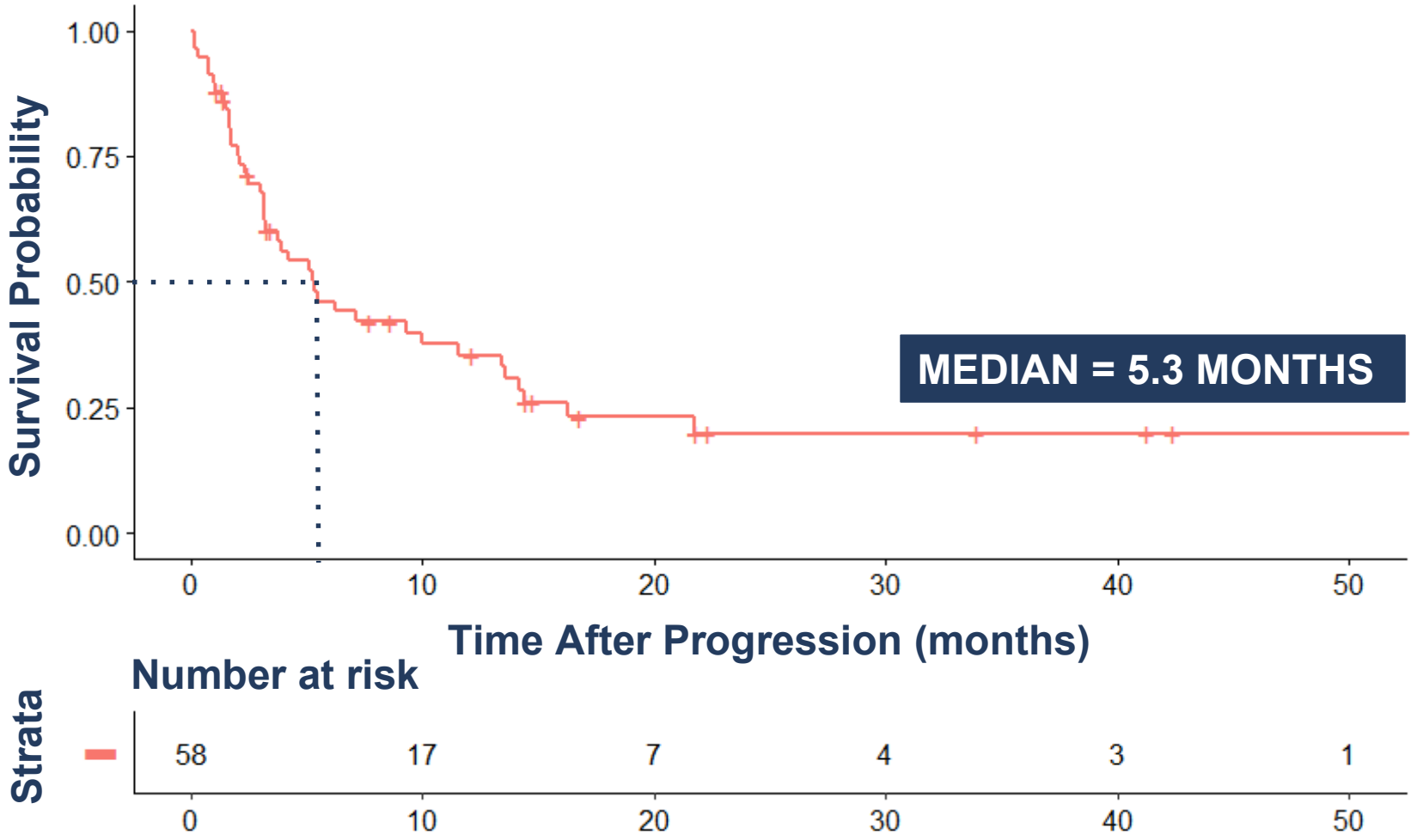
ZUMA-1 Ineligible: Bridging only

ZUMA-1 Eligible

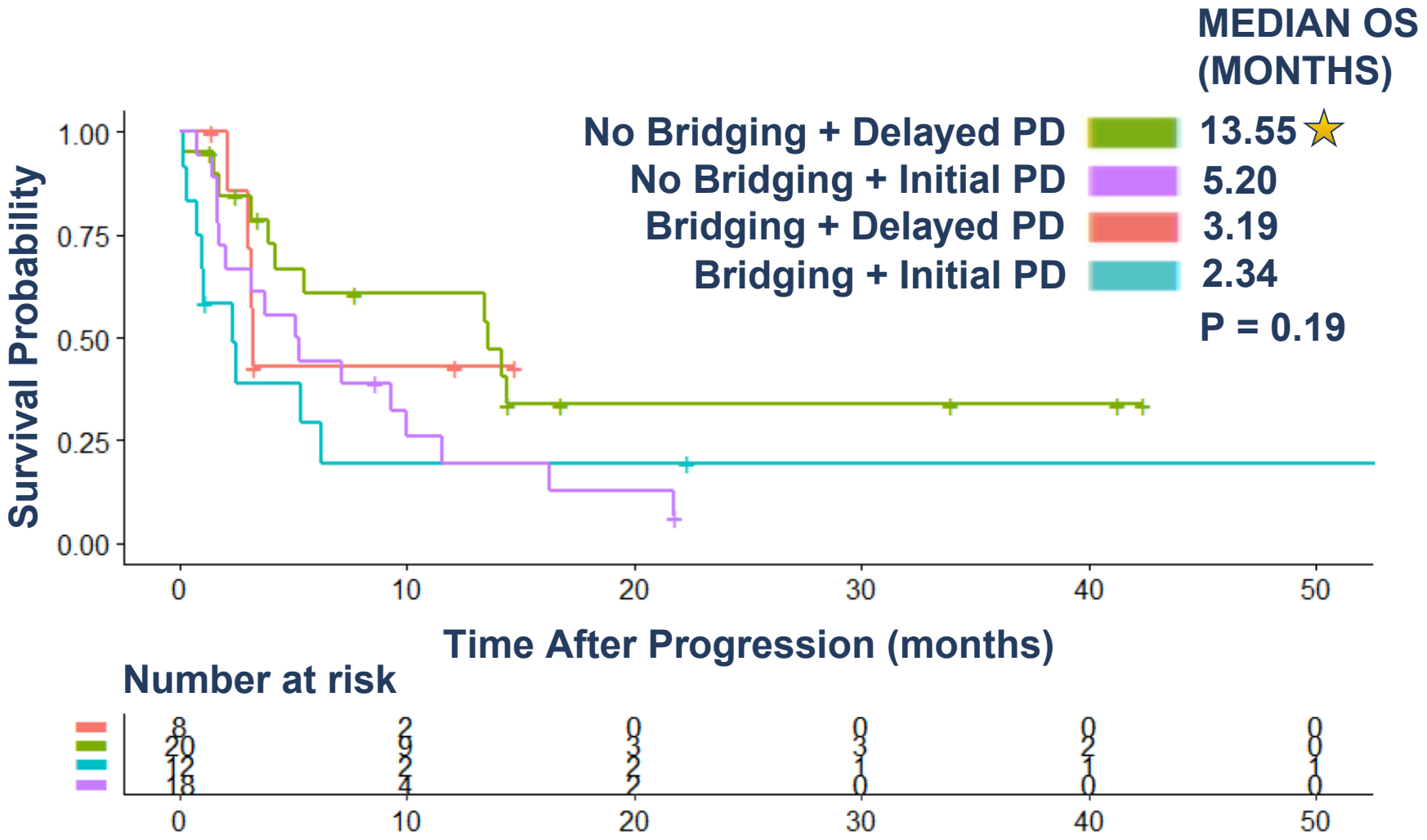
Outcomes of Patients with Large B-Cell Lymphomas and Progressive Disease Following CD19-Specific CAR T-cell Therapy (ASH 2018 Abst 94)

Victor A. Chow, Ajay K. Gopal, David G. Maloney, Cameron J. Turtle, Stephen D. Smith, Mazyar Shadman, Ryan D. Cassaday, Brian G. Till, Yolanda D. Tseng, Edus H. Warren, Andrei R. Shustov, Manoj P. Menon, Sandra Kanan, Utkarsh H. Acharya, Erin Mullane, Lindsay M. Hannan, Jenna M. Voutsinas, Ted Gooley, and Ryan C. Lynch

Poor OS after progressive disease



Impact of bridging therapy and type of progression on survival

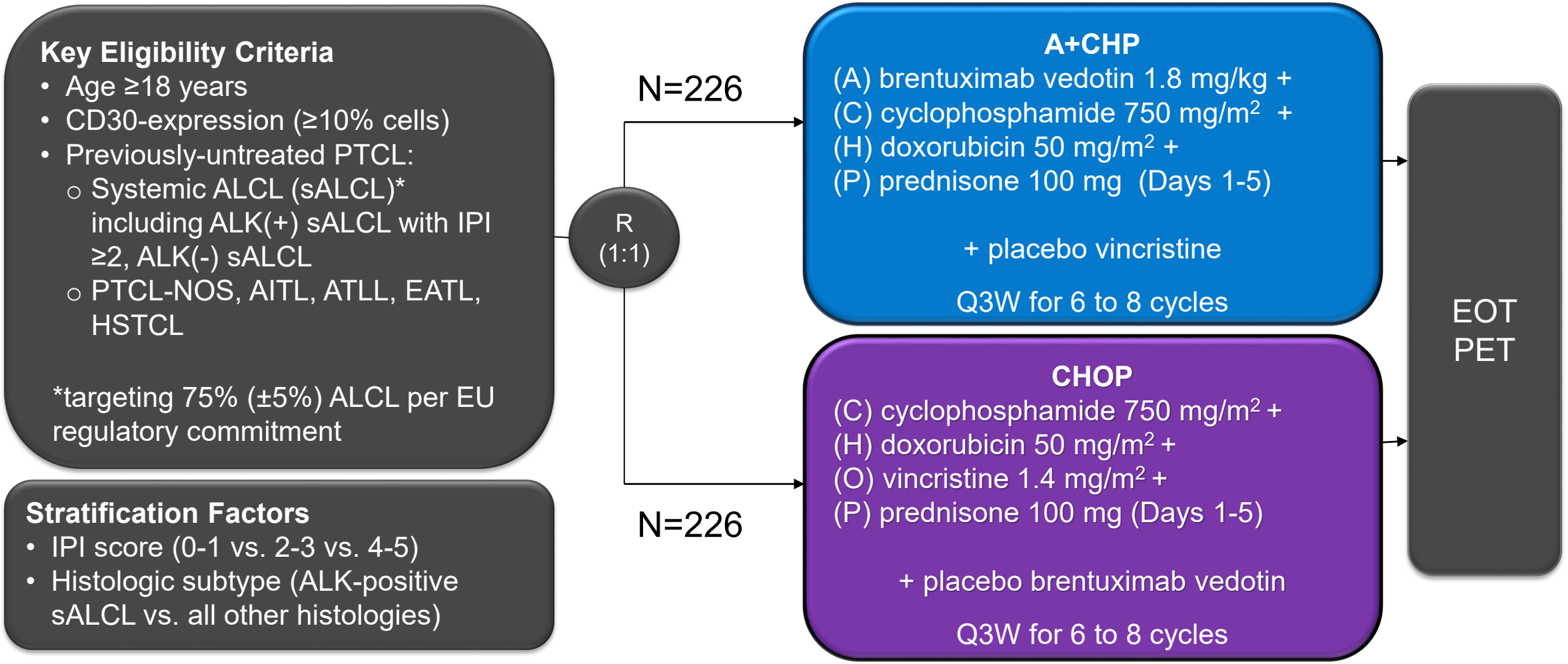


The Phase 3 ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Steven Horwitz, Owen A O'Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper

American Society of Hematology Annual Meeting; San Diego, California, December 1-4, 2018, Abstract #997

ECHELON-2 Study Design (NCT01777152)



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukaemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

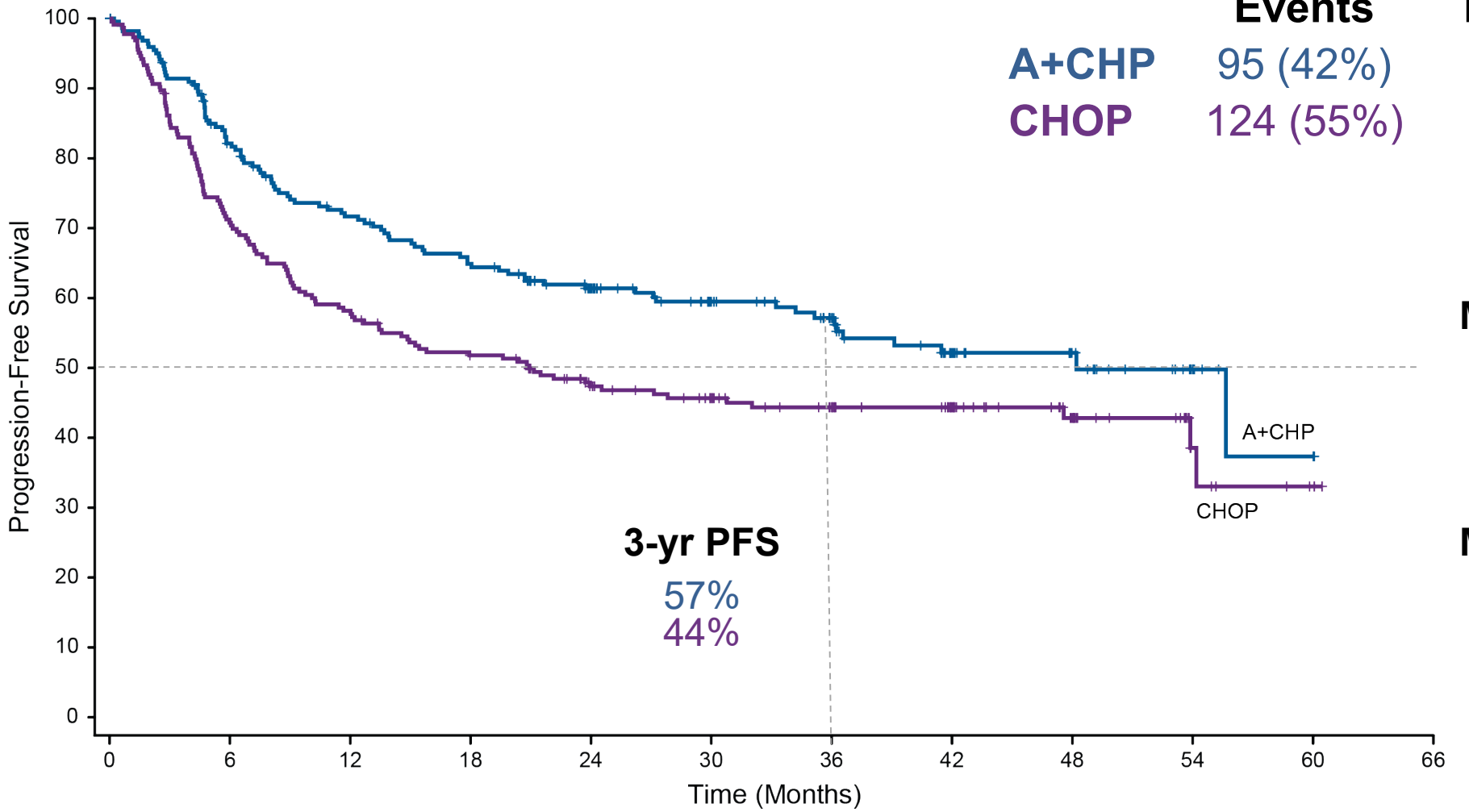
Per investigator discretion:
GCSF primary prophylaxis, consolidative RT and SCT

Baseline Characteristics

	A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)
Age in years, median (range)	58 (18-85)	58 (18-83)
IPI score, n (%)		
0-1	53 (23)	48 (21)
2-3	140 (62)	144 (64)
4-5	33 (15)	34 (15)
Stage III/IV, n (%)	184 (81)	180 (80)

	A+CHP (N=226)	CHOP (N=226)
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

Progression-free Survival



	Events	HR (95% CI)	*P*
A+CHP	95 (42%)	0.71 (0.54, 0.93)	0.011
CHOP	124 (55%)		

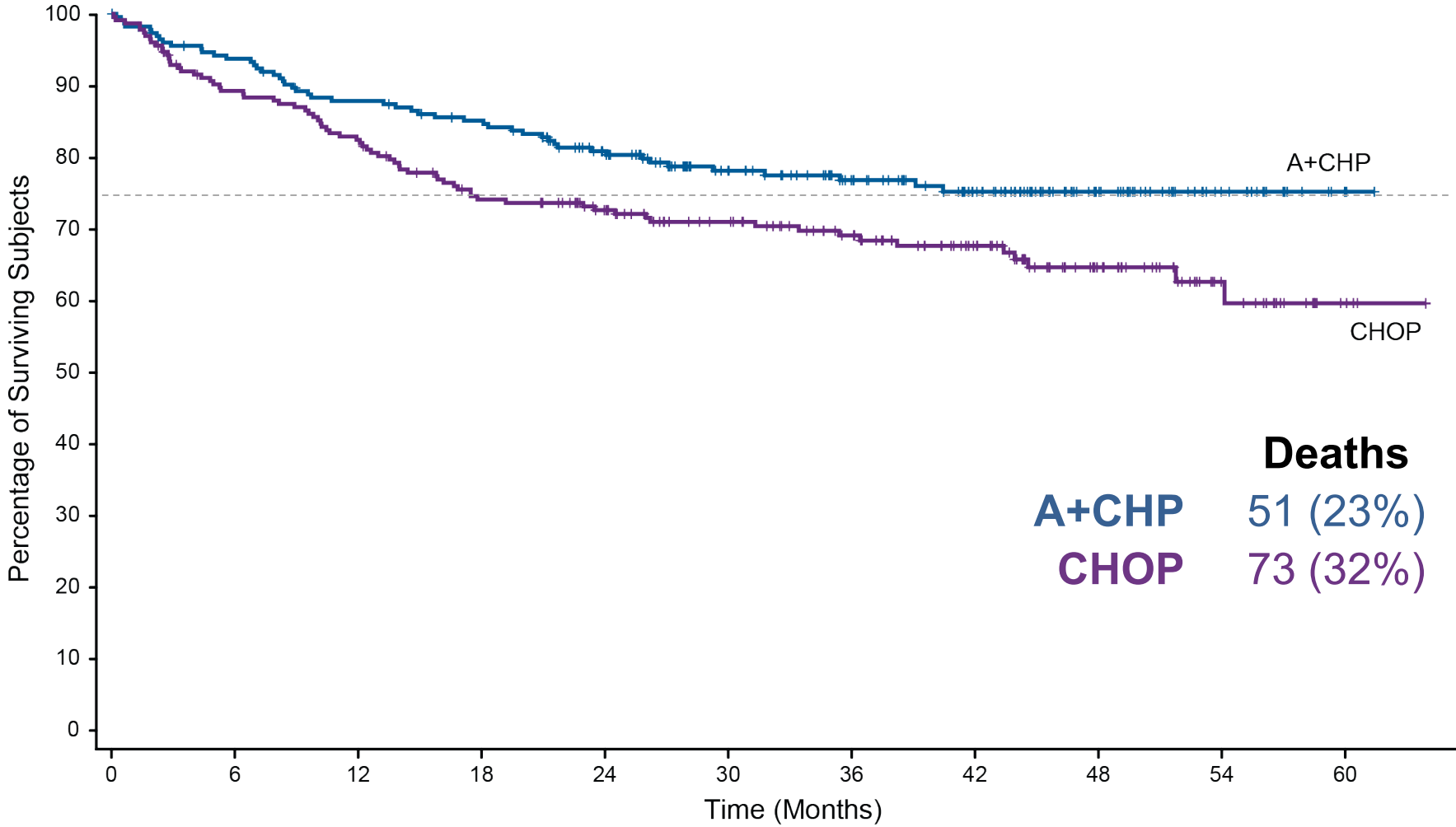
Median PFS (95% CI)

48.2 mo (35.2, NE)
20.8 mo (12.7, 47.6)

Median Follow-up

36.2 months

Overall Survival



75th Percentile

Not reached
17.5 mo

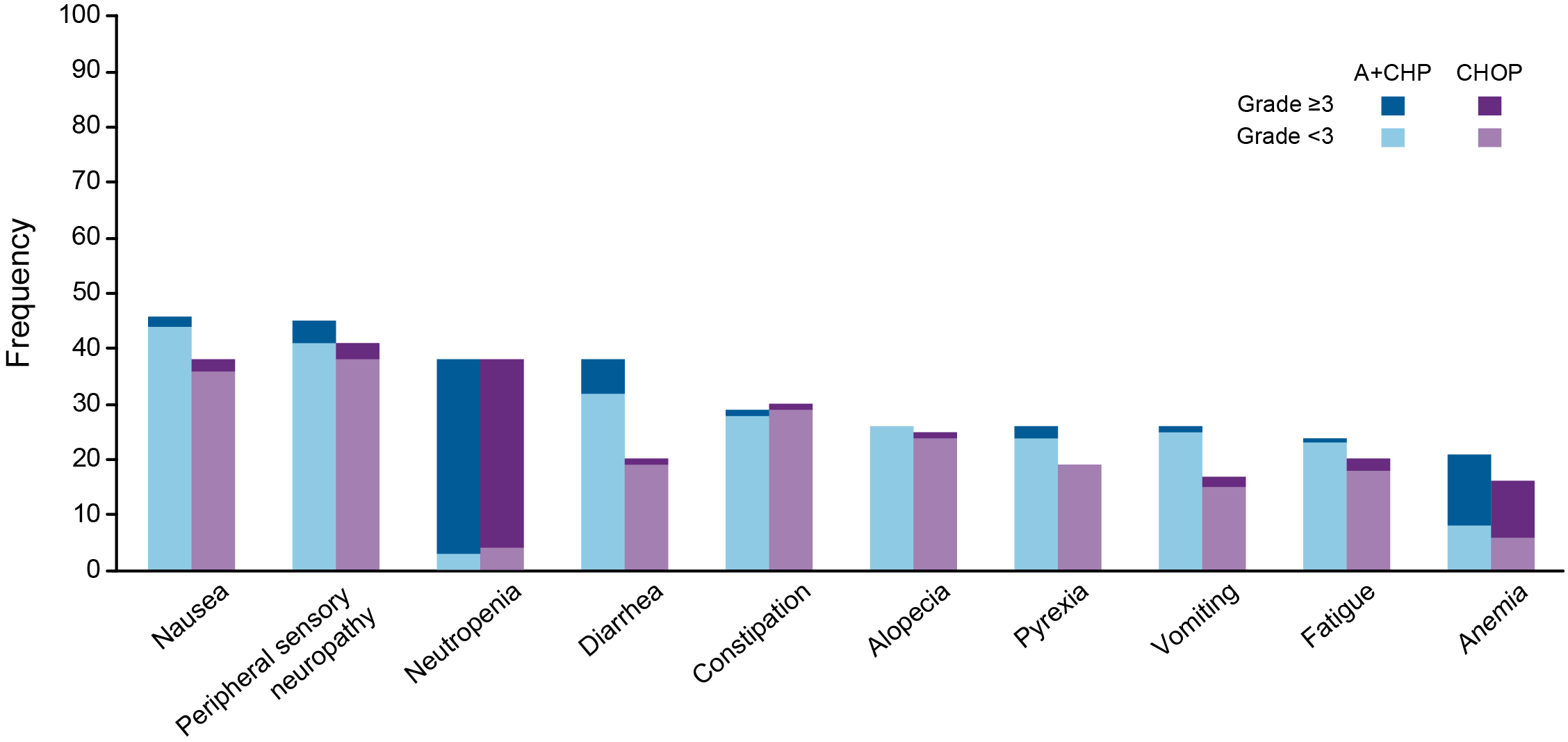
	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

Median Follow-up
42.1 months

N at Risk (Events)

A+CHP	226(0)	208(14)	193(27)	184(33)	159(42)	128(47)	108(49)	83(51)	45(51)	20(51)	4(51)	0(51)
CHOP	226(0)	196(24)	181(39)	158(57)	140(60)	121(63)	103(66)	79(68)	46(71)	22(72)	4(73)	0(73)

Adverse Events in ≥20% of Subjects



Mantle cell lymphoma (10%)

Incurable, median survival 5-10 years

Key focus:

- **More vs less intensive initial therapies**
  - **Bendamustine based rx in older pts standard**
  - **Does SCT improve survival in younger patients?**
  - **Role of MRD?**
- **Development of novel agents and translational studies to understand resistance and advance rational combinations**

MCL “standard” initial treatment options

Observation

R-CHOP

Modified R-HyperCVAD

Bortezomib-R-CAP

R-Bendamustine

Less intensive

vs

R-CHOP/DHAP/ASCT

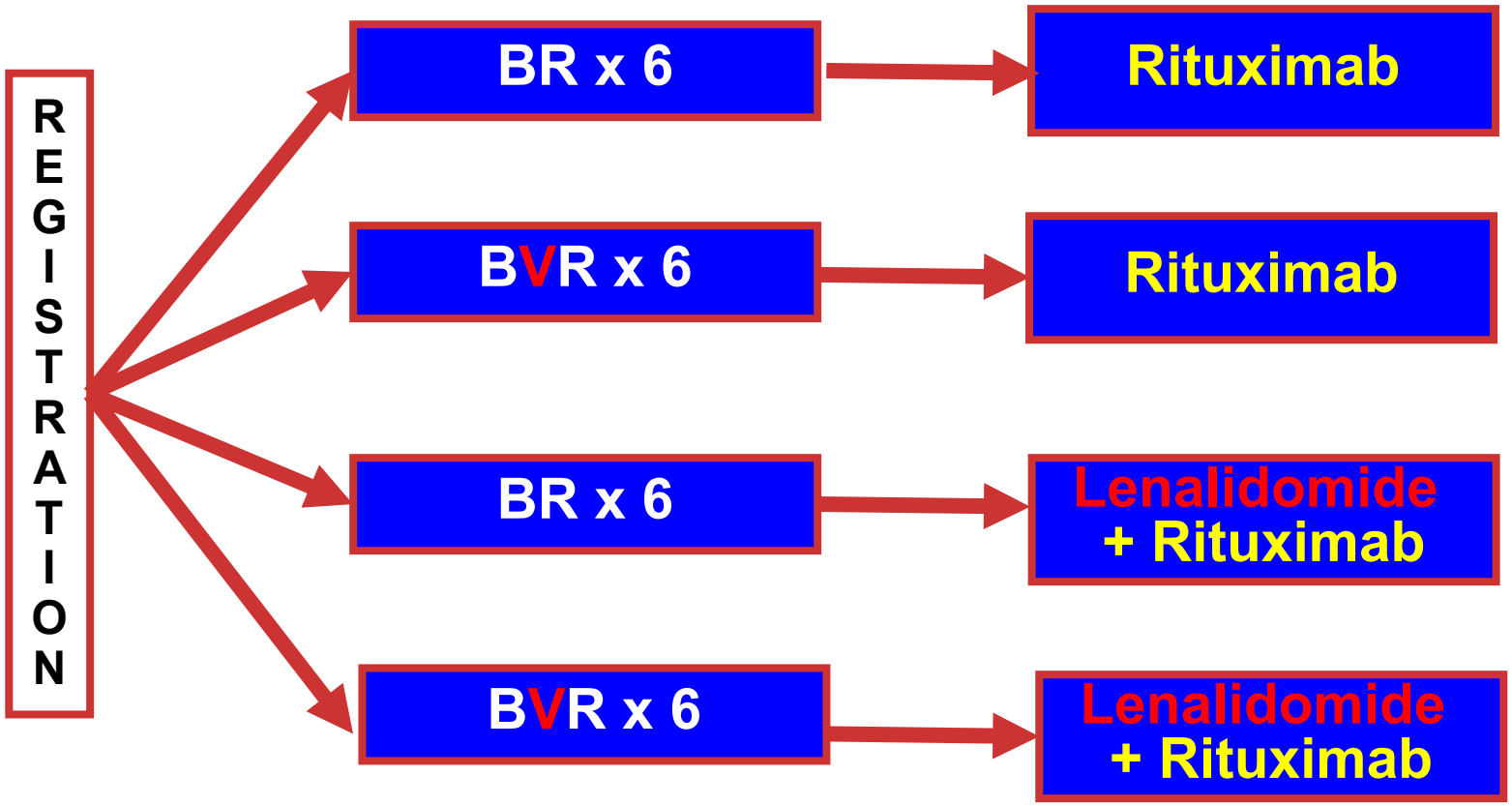
R-HyperCVAD/MTX/Ara-C

R-HyperCVAD/MTX/Ara-C/ASCT

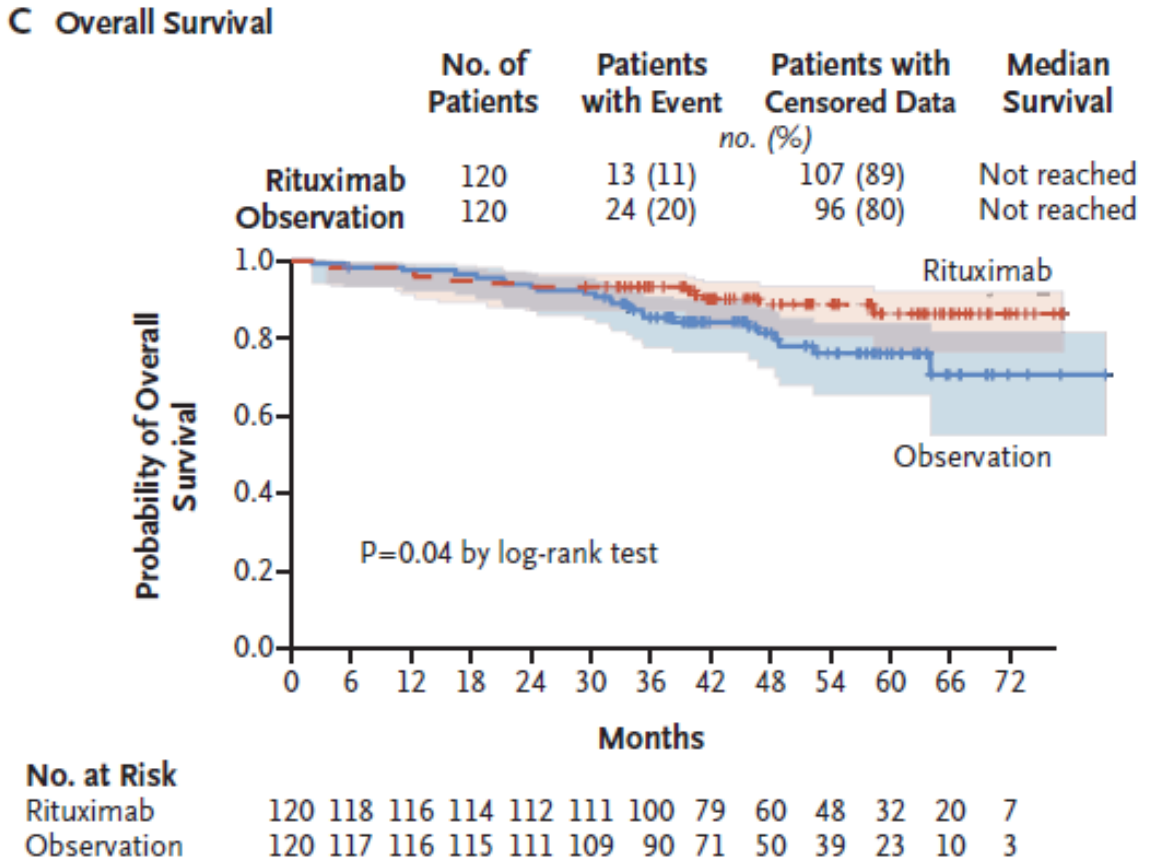
Nordic

More intensive

E1411: Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma

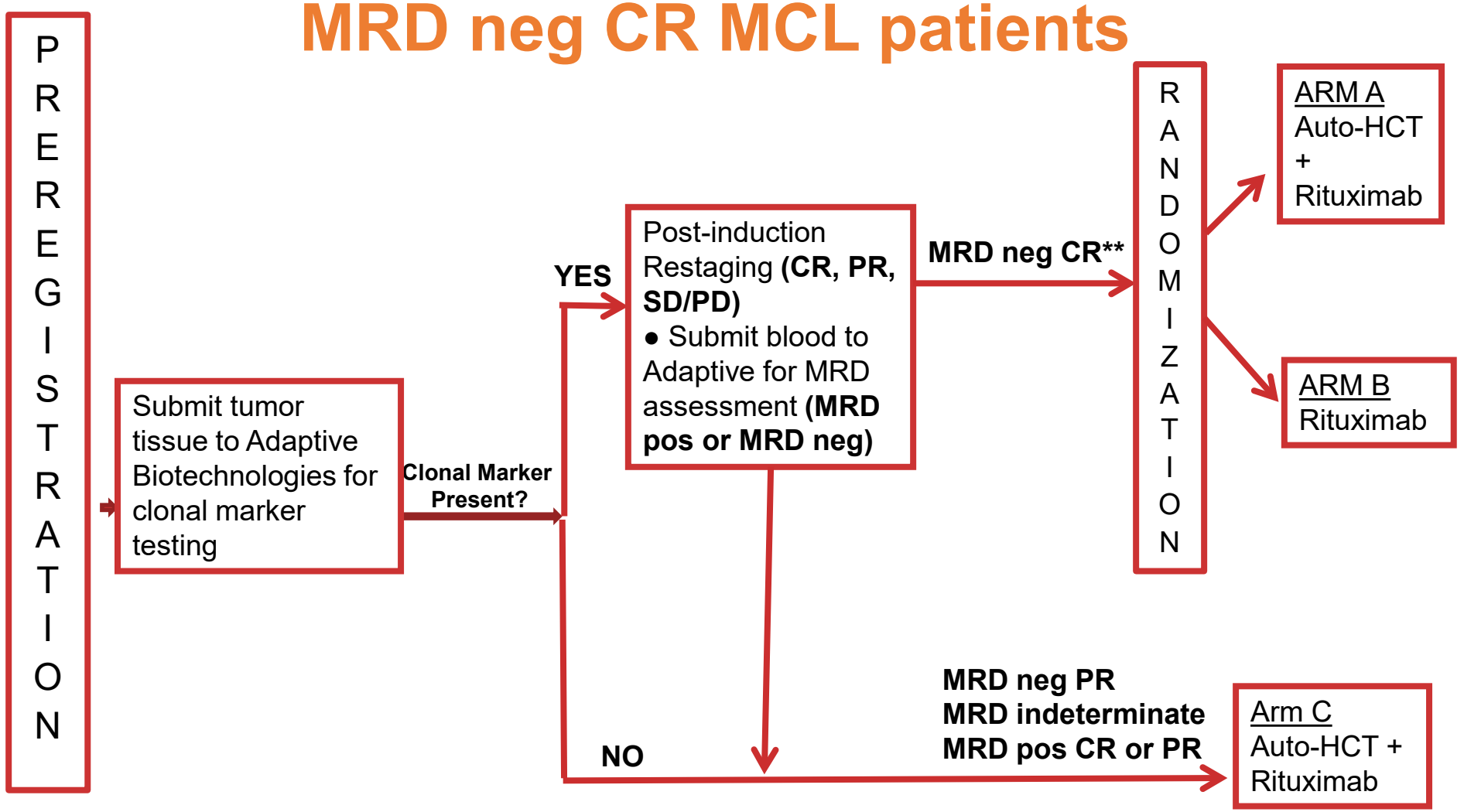


Maintenance Rituximab after AuSCT in Mantle Cell Lymphoma



Le Gouill et al; NEJM 377;13:1250-60, 2017

E4151: Randomized trial of SCT/R vs R in MRD neg CR MCL patients



Key take home points for aggressive lymphoma

- DLBCL
  - Modifications to R-CHOP currently based on clinical and pathologic features (not COO)
  - CAR-T cell rx available, undergoing further optimization
- T cell
  - CD30-directed therapy of value upfront and relapse
- MCL
  - Maintenance rituximab, ? role of MRD-directed therapy
  - BTK inhibitors in relapse