FONDAZIONE ITALIANA LINFOMI

LATE EFFECTS

GUARIRE DAL LINFOMA E VIVERE BENE

Dalla terapia standard alla «target therapy» del linfoma La via verso la guarigione

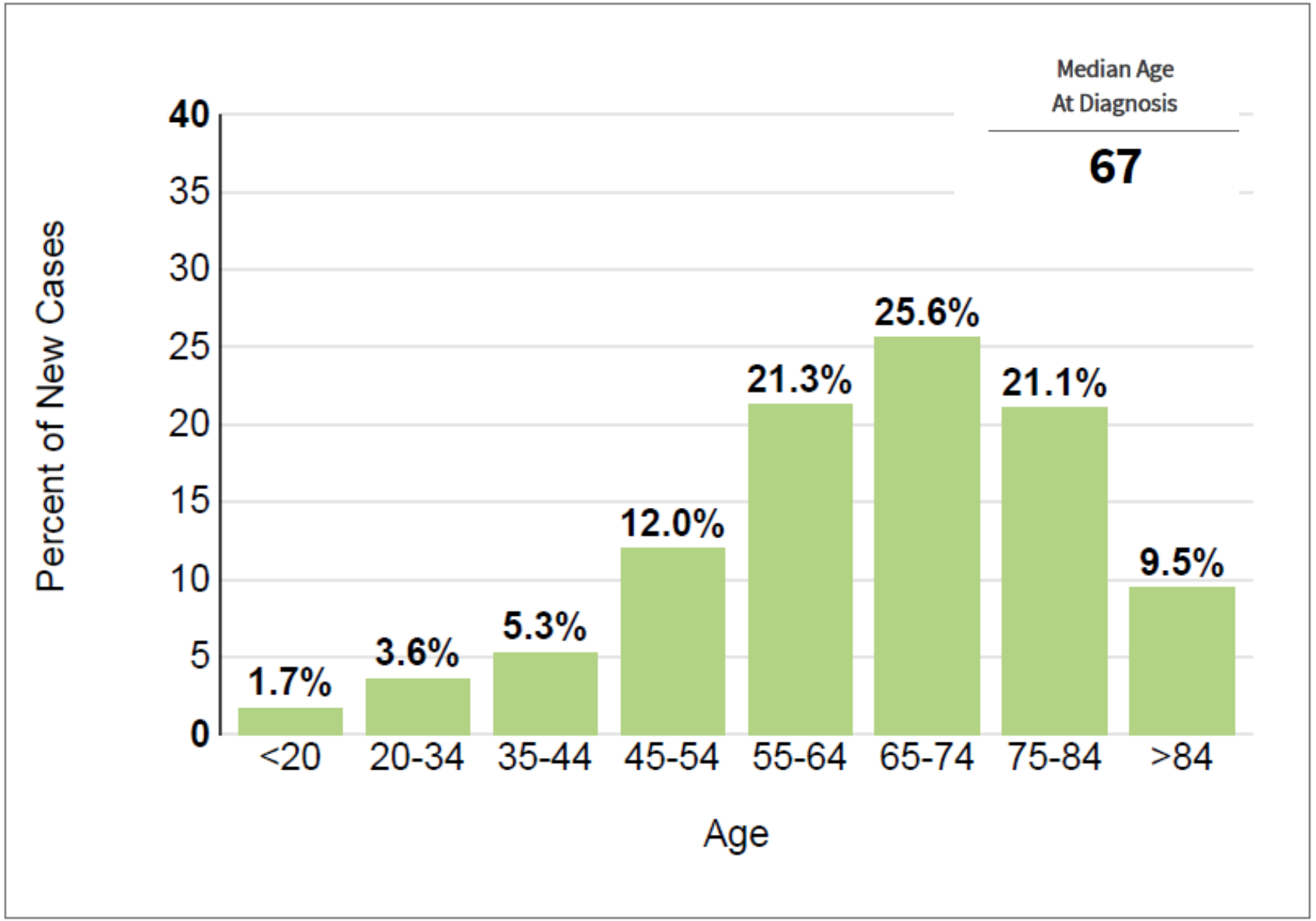
Guido Gini

LA TRISTE TOP TEN

	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1.	Breast Cancer (Female)	266,120	40,920
2.	Lung and Bronchus Cancer	234,030	154,050
3.	Prostate Cancer	164,690	29,430
4.	Colorectal Cancer	140,250	50,630
5.	Melanoma of the Skin	91,270	9,320
6.	Bladder Cancer	81,190	17,240
7.	**Non-Hodgkin Lymphoma**	**74,680**	**19,910**
8.	Kidney and Renal Pelvis Cancer	65,340	14,970
9.	Uterine Cancer	63,230	11,350
10.	Leukemia	60,300	24,370

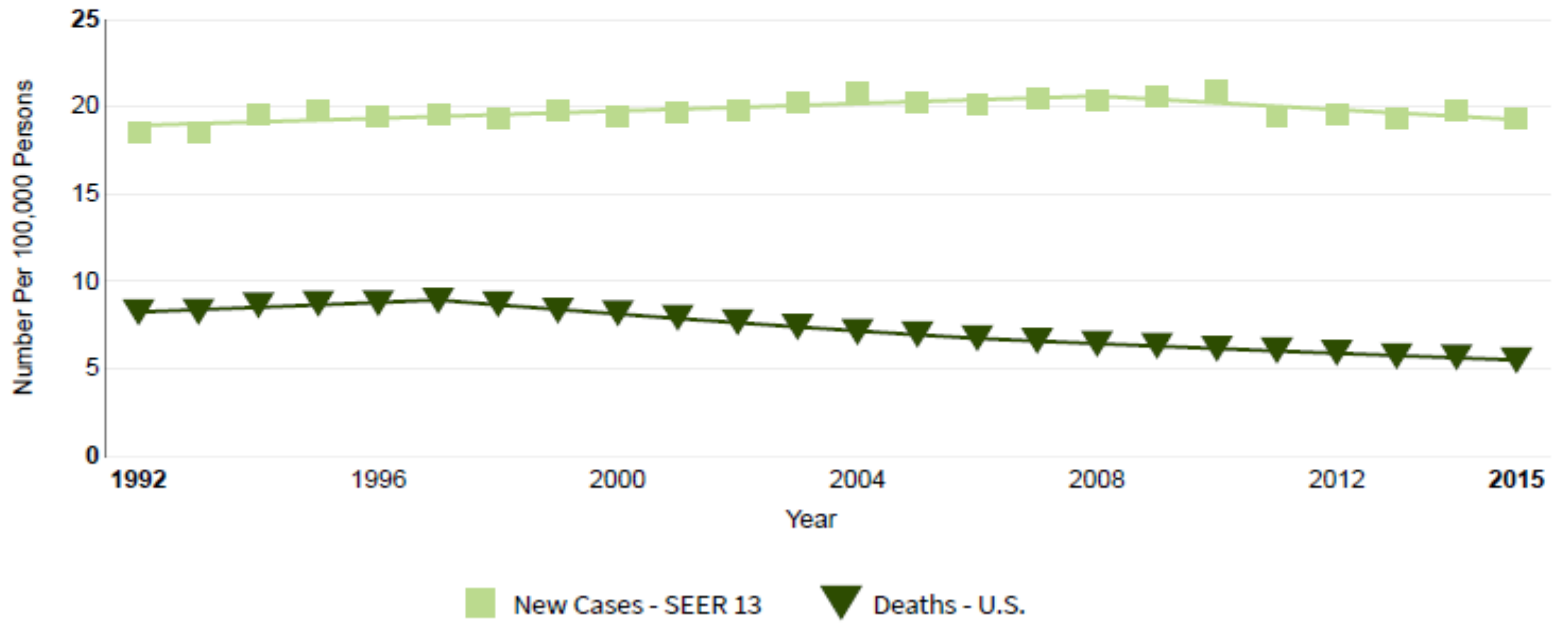
Non-Hodgkin lymphoma represents 4.3% of all new cancer cases in the U.S.

Percent of New Cases by Age Group: Non-Hodgkin Lymphoma



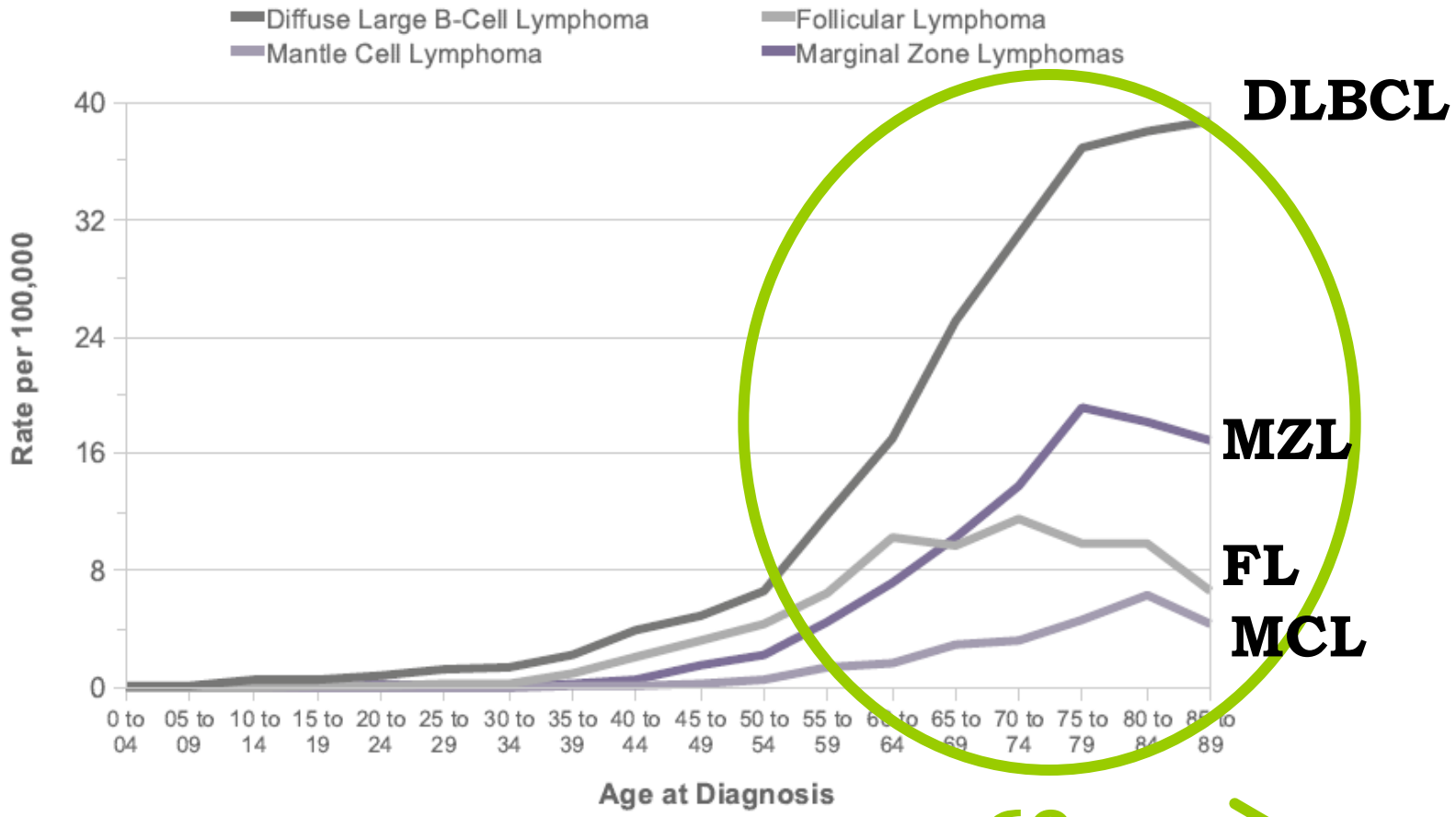
NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

Percent Surviving 5 Years
71.4%
2008-2014



Non-Hodgkin Lymphoma Subtypes: 2004-2011

Age-Specific Incidence Rates, UK (Estimates Based on HMRN data)



Please include the citation provided in our Frequently Asked Questions when reproducing this chart: http://info rg/cancerstats/faqs/#How

Prepared by Cancer Research UK

CANCER RESEARCH UK

Changes in the Survival of Older Patients With Hematologic Malignancies in the Early 21st Century

Dianne Pulte, MD[1,2]; Lina Jansen, PhD[1]; Felipe A. Castro, PhD[1]; and Hermann Brenner, MD, MPH[1,3,4]

Cancer, July 2016

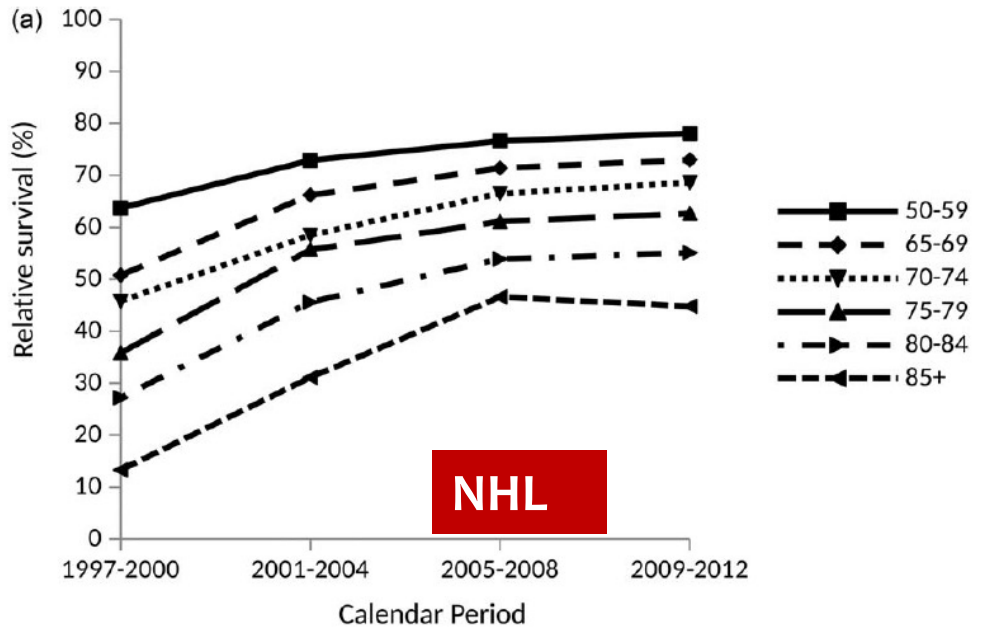
TABLE 1. Five-Year Relative Survival of Patients With Hematological Malignancies by Time Period and Age Group

Malignancy	Age, y	5-y Relative Survival, % (Standard Error)				Difference Between 1997-2000 and 2009-2012, %
		1997-2000	2001-2004	2005-2008	2009-2012	
NHL	50-59	63.7 (0.8)	72.9 (0.7)[a]	76.6 (0.6)[a]	78.1 (0.6)[a]	+14.4
	65-69	50.8 (0.9)	66.2 (1.0)[a]	71.4 (1.0)[a]	73.0 (0.9)[b]	+22.2
	70-74	45.8 (0.9)	58.5 (1.0)[a]	66.5 (1.0)[a]	68.6 (1.0)[b]	+22.8
	75-79	35.8 (0.9)	55.7 (1.1)[a]	61.1 (1.1)[a]	62.7 (1.1)[b]	+26.9
	80-84	27.2 (0.9)	45.6 (1.4)[a]	53.9 (1.3)[a]	55.1 (1.3)[b]	+27.9
	≥85	13.3 (0.8)	31.1 (1.7)[a]	46.6 (1.9)[a]	44.8 (1.6)	+31.5

[a] $P \leq .01$ versus the preceding period.
[b] $P \leq .05$ versus the preceding period.

For older patients with NHL survival has, in general, been increasing at least as fast as for younger patients

The age-related disparity in survival has actually been decreasing



COMPARISON OF A STANDARD REGIMEN (CHOP) WITH THREE INTENSIVE CHEMOTHERAPY REGIMENS FOR ADVANCED NON-HODGKIN'S LYMPHOMA

RICHARD I. FISHER, M.D., ELLEN R. GAYNOR, M.D., STEVE DAHLBERG, M.S., MARTIN M. OKEN, M.D., THOMAS M. GROGAN, M.D., EVONNE M. MIZE, JOHN H. GLICK, M.D., CHARLES A. COLTMAN, JR., M.D., AND THOMAS P. MILLER, M.D.

CHOP becomes the standard of care with 54% long-term survival in aggressive lymphomas

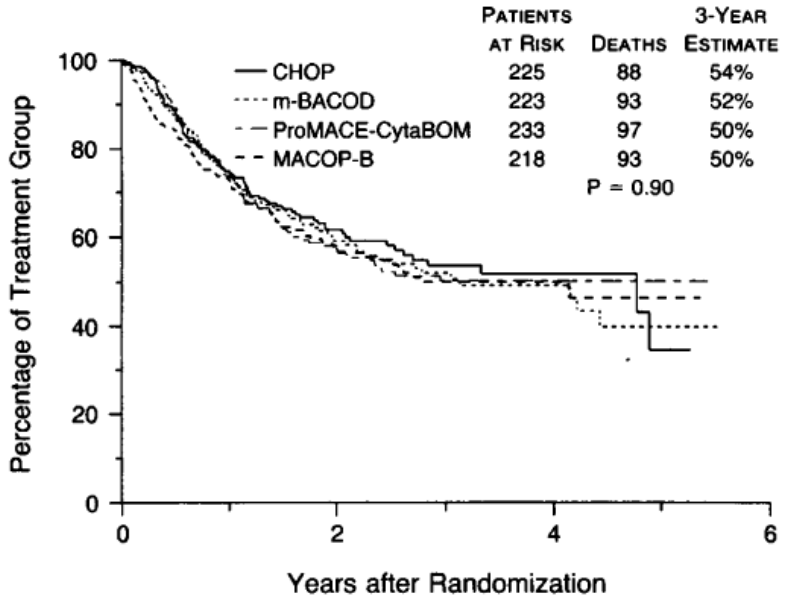
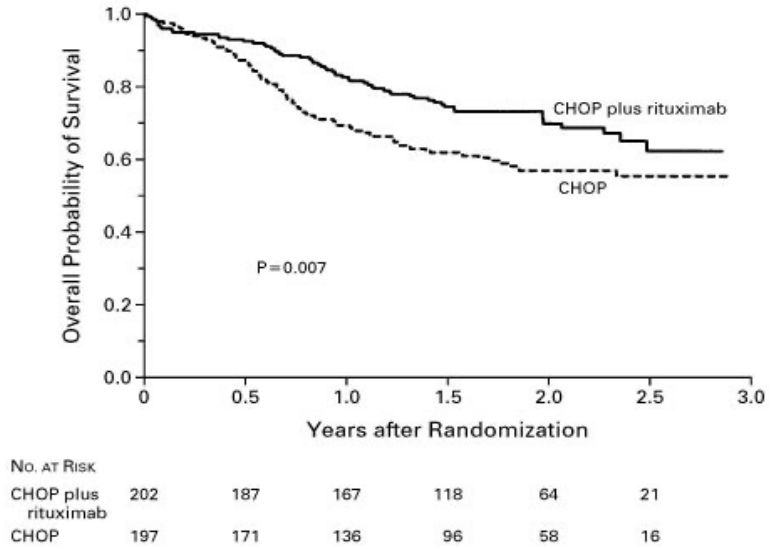
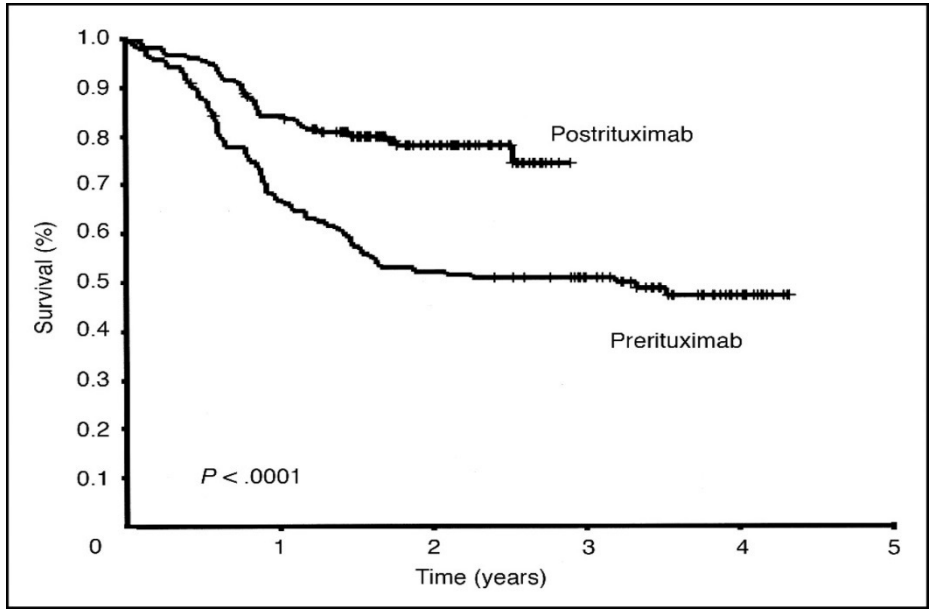


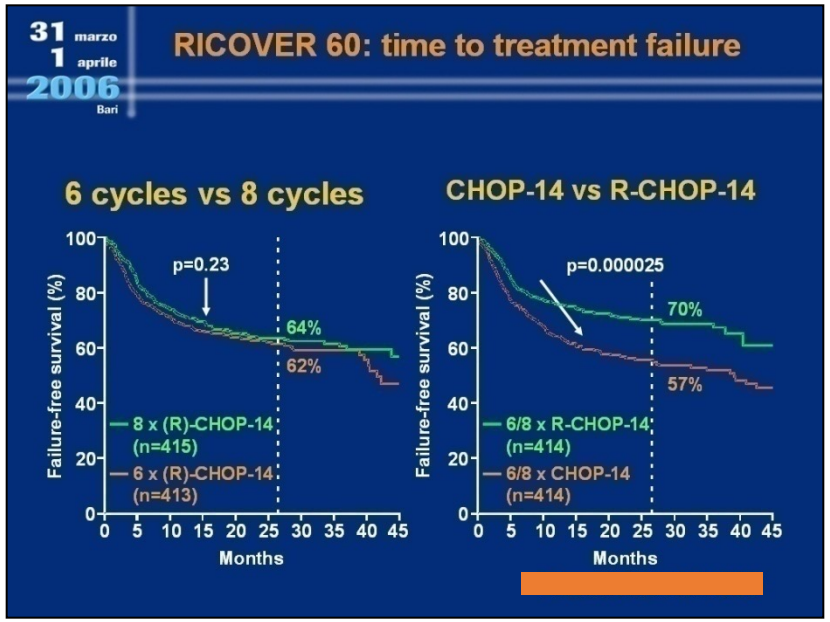
Figure 2. Overall Survival in the Treatment Groups. The three-year estimate is of overall survival.



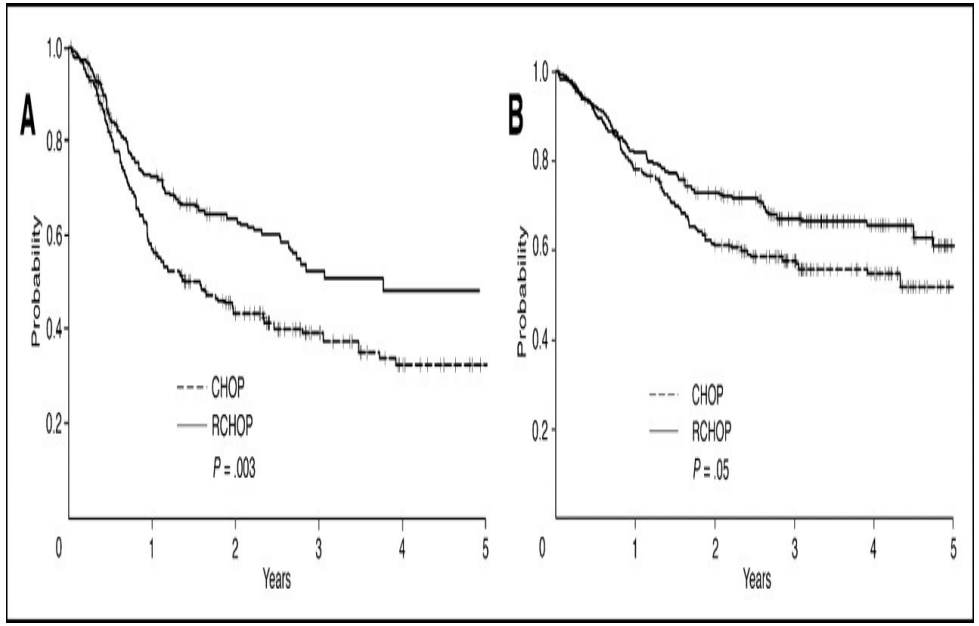
Coiffier B et al. N Engl J Med 2002;346:235-242



Sehn, L. H. et al. J Clin Oncol; 23:5027-5033 2005

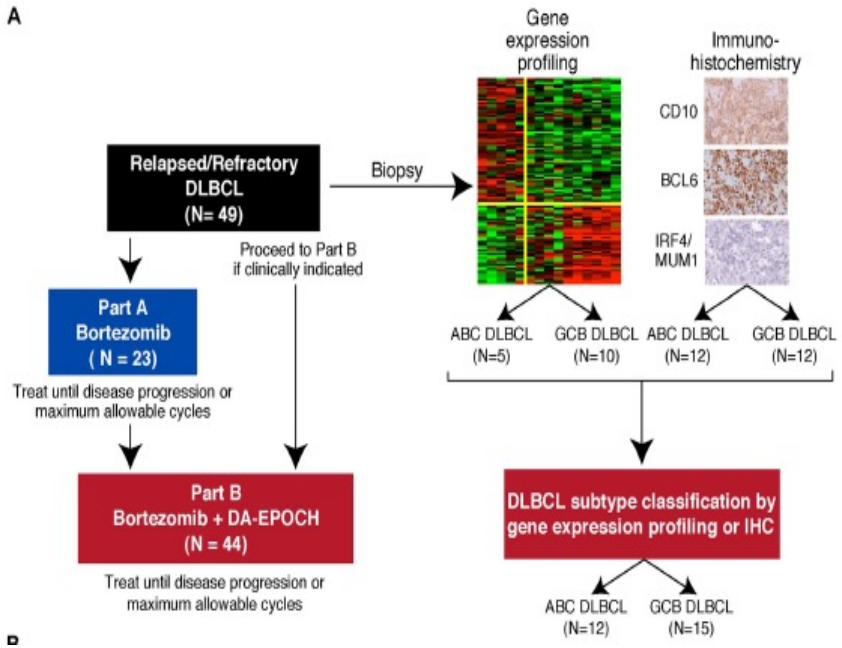


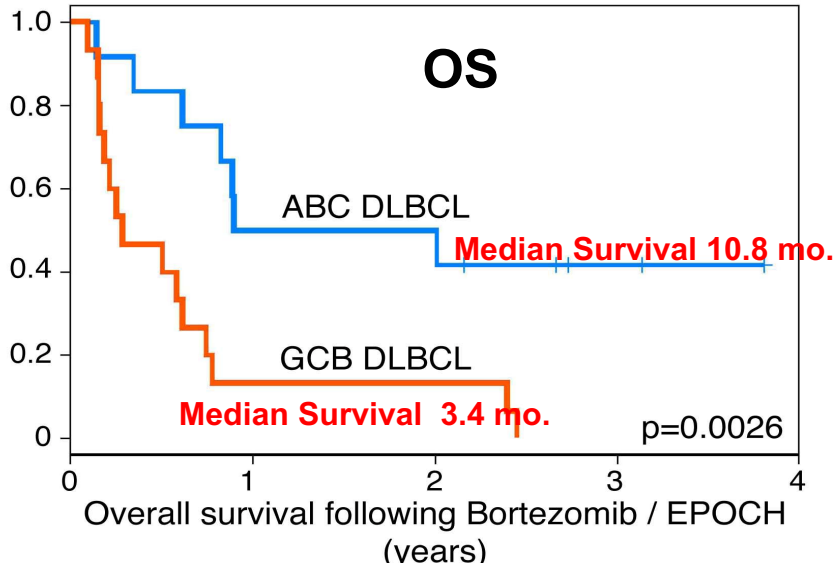
Pfreundschuh M et al. Lancet Oncology 2008;9(2):105-116



Habermann TM et al. J Clin Oncol; 24:3121-3127 2006

“Old” new drugs in DLBCL: BORTEZOMIB





Subtype	Total	Complete response	Partial response	No response	p-value
ABC DLBCL	12	5 (41.7%)	5 (41.7%)	2 (17%)	0.0004
GCB DLBCL	15	1 (6.5%)	1 (6.5%)	13 (87%)	

Dunleavy et al. Blood 2009

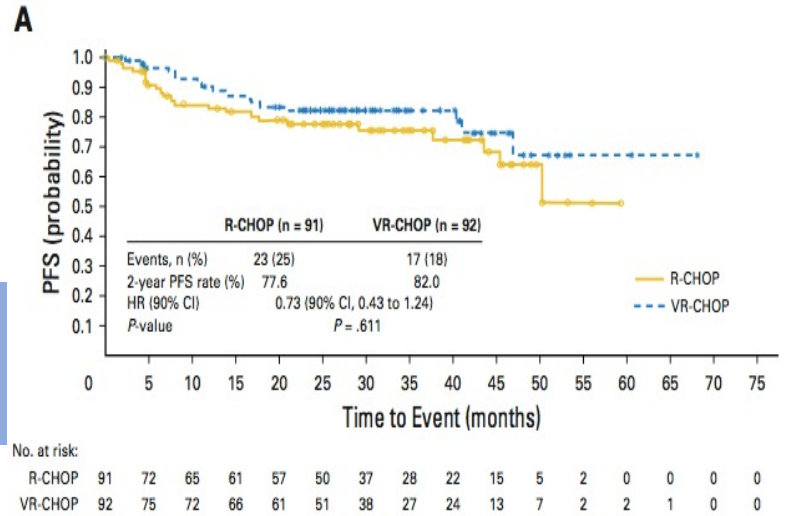
RCHOP +/- BORTEZOMIB

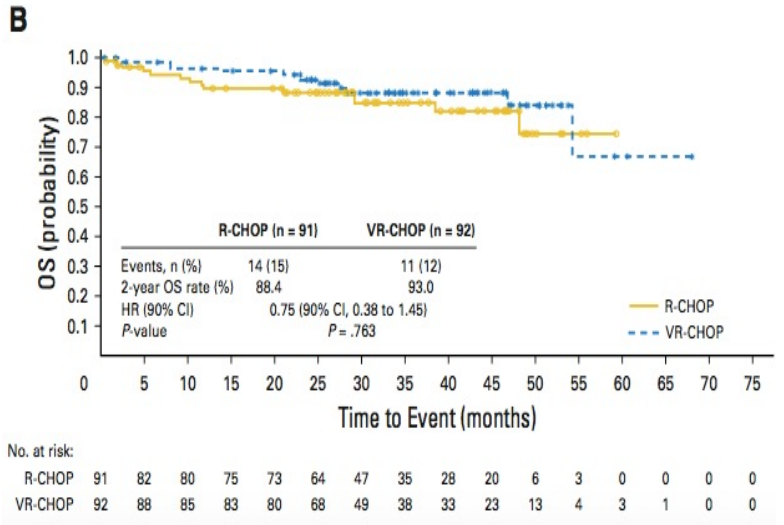
PYRAMID: Prospective randomized, open-label phase II study, non-GCB DLBCL

Treatment-naive, **non-GCB DLBCL by Hans IHC** with measurable disease, ECOG PS 0-2 (N = 183)

→ **R-CHOP* 21 days x 6 cycles (n = 91)**

→ **Bortezomib 1.3 mg/m² IV Days 1, 4 + R-CHOP* 21 days x 6 cycles (n = 92)**



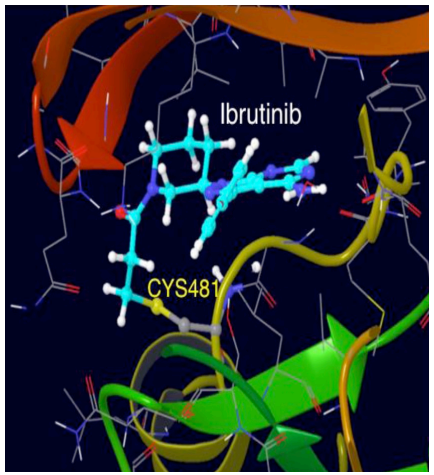


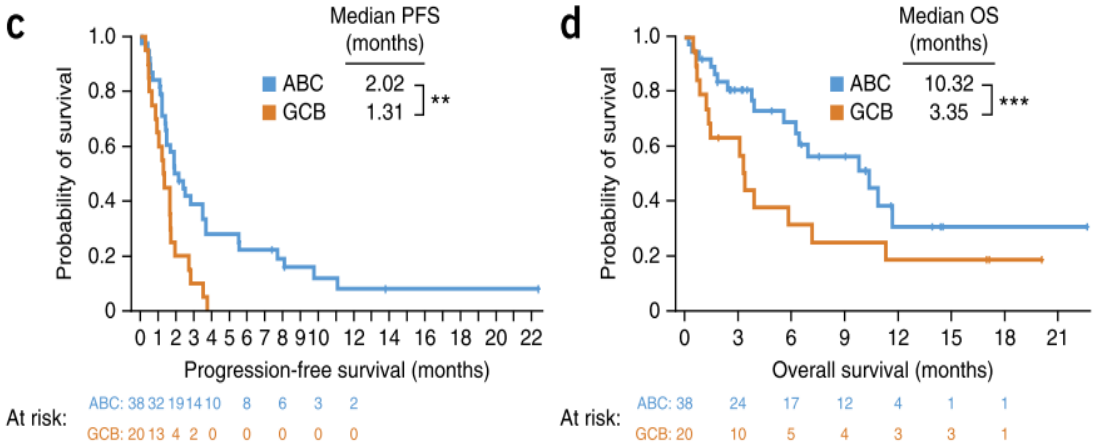
Limits:

- a probable patient selection in the PYRAMID trial → R-CHOP alone better outcomes than expected
- IHC based on Hans algorithm

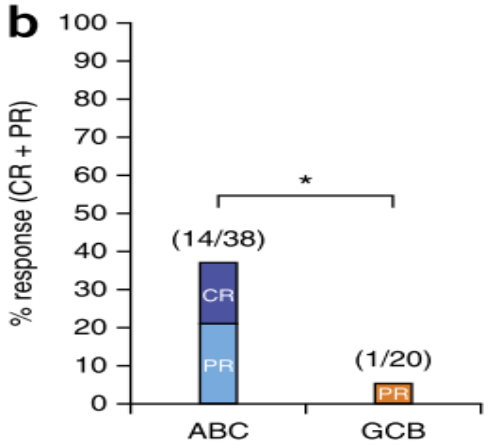
Leonard JCO 2017

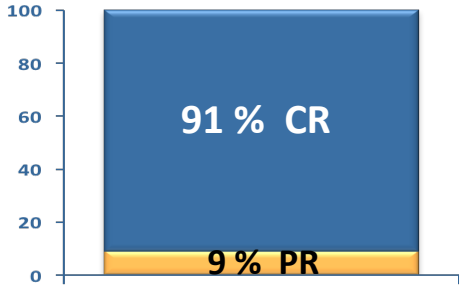
“Old” new drugs in DLBCL: **IBRUTINIB**



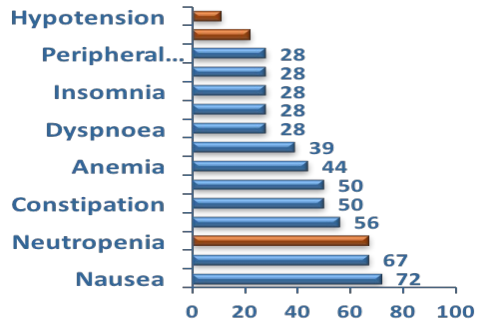


Wilson WH, et al. Nat Med. 2015;21:922-6.



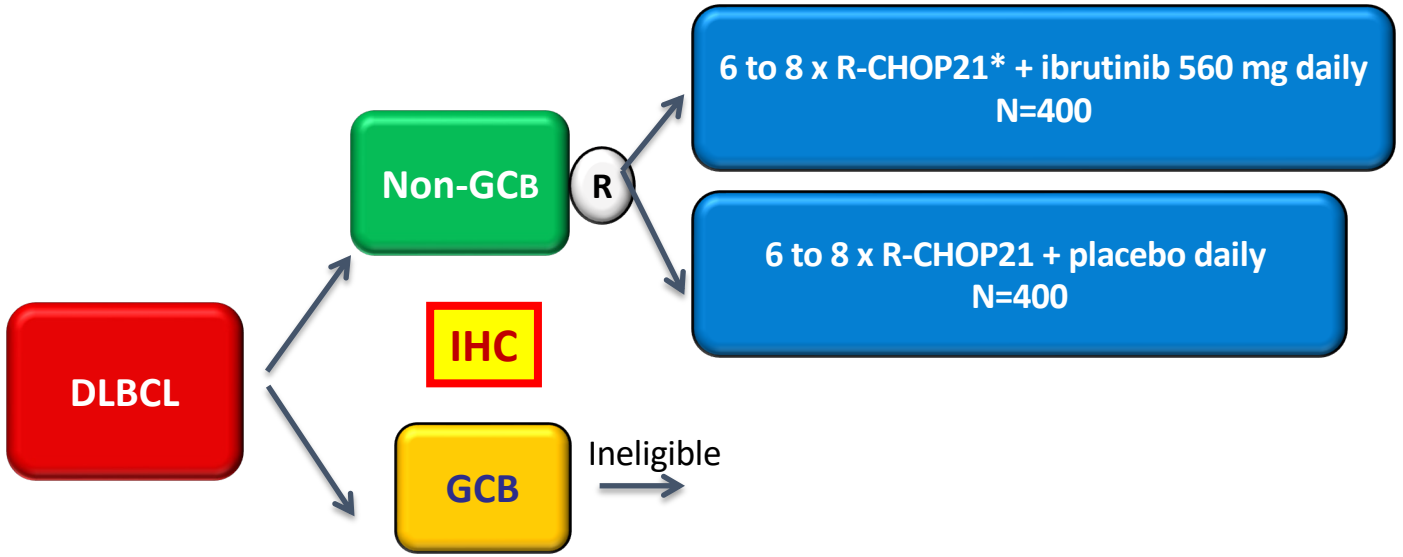


Efficacy Evaluable Patients(N=22)



Younes A, Lancet Oncol 2014

RCHOP +/- IBRUTINIB



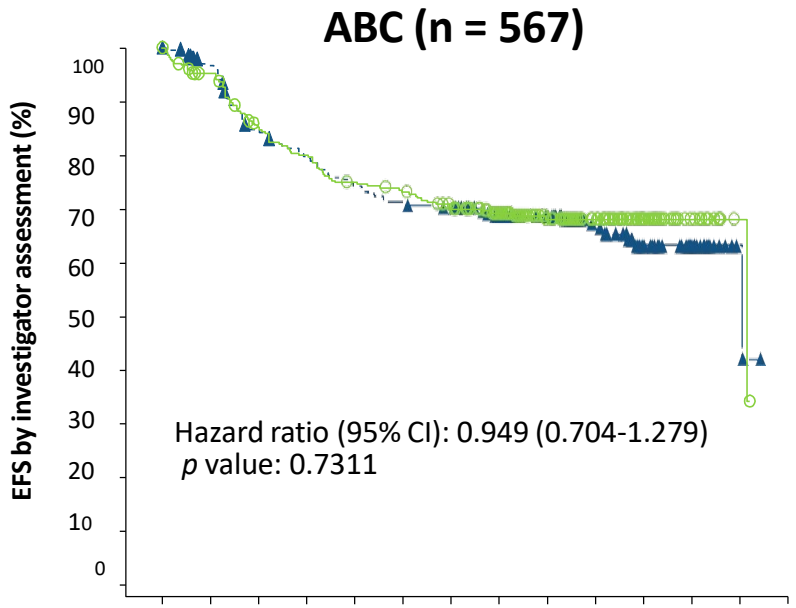
- Newly diagnosed DLBCL of non-GCB type
- Stage II to IV
- IPI ≥ 2; ECOG PS ≤ 2; Age >18
- Primary Endpoint = EFS
- N = 838

Primary end point

- EFS in ITT for non- GCB and ABCsubgroup

Secondary end points

- PFS, CR rate, OS, safety

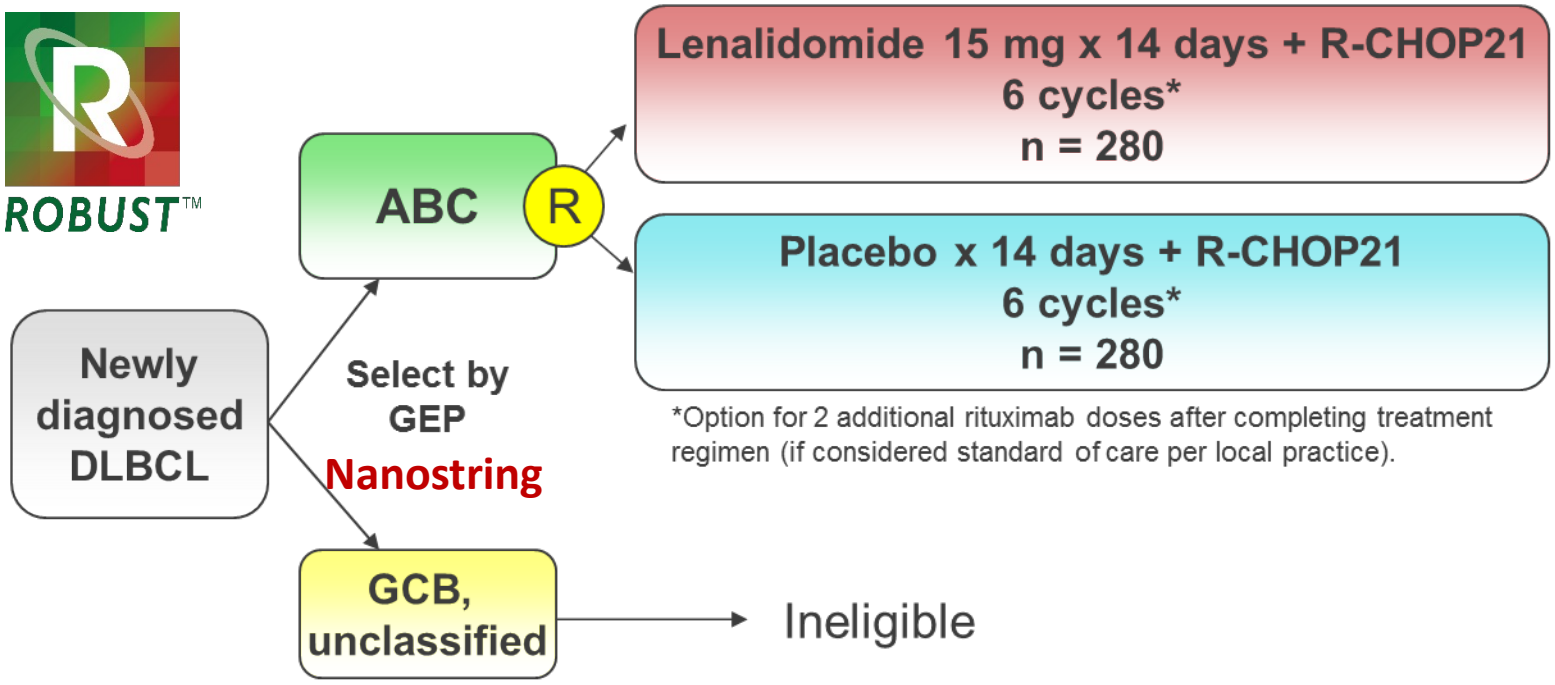


Younes A, JCO 2019

RCHOP +/- lenalidomide

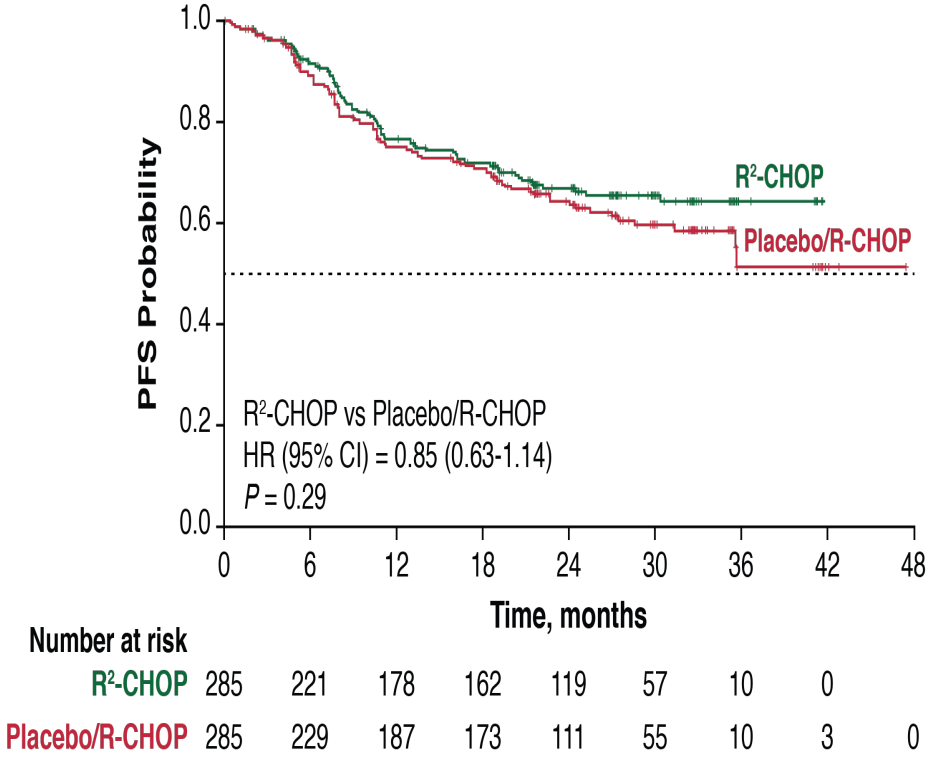
DLC-002 (ROBUST): Phase III Randomized Efficacy and Safety Study of Lenalidomide Plus R-CHOP vs. Placebo Plus R-CHOP in Patients With Untreated ABC-type Diffuse Large B-cell Lymphoma

Sponsor: Celgene Corporation. Team leader: FIL and Mayo Clinic. PIs: U. Vitolo, T. Witzig. Writing committee: U. Vitolo, A. Chiappella, M. Spina, T. Witzig, G. Nowakowski.

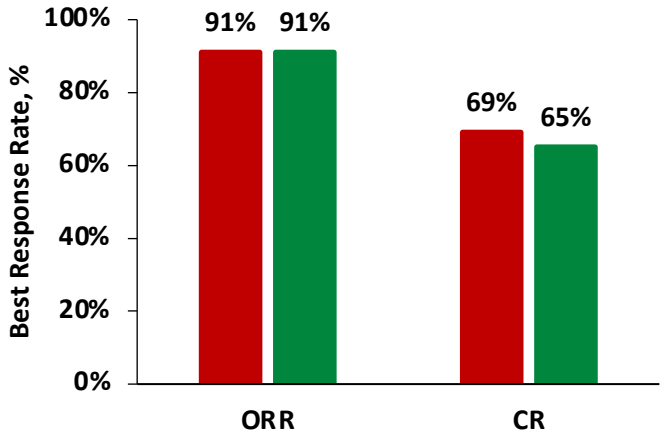


- **Newly diagnosed ABC DLBCL; IPI ≥ 2; ECOG PS ≤ 2; age ≥ 18 years**
- **Primary endpoint = PFS; N = 560**
- **90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)**

Primary Endpoint: Progression-Free Survival (ITT, IRAC)



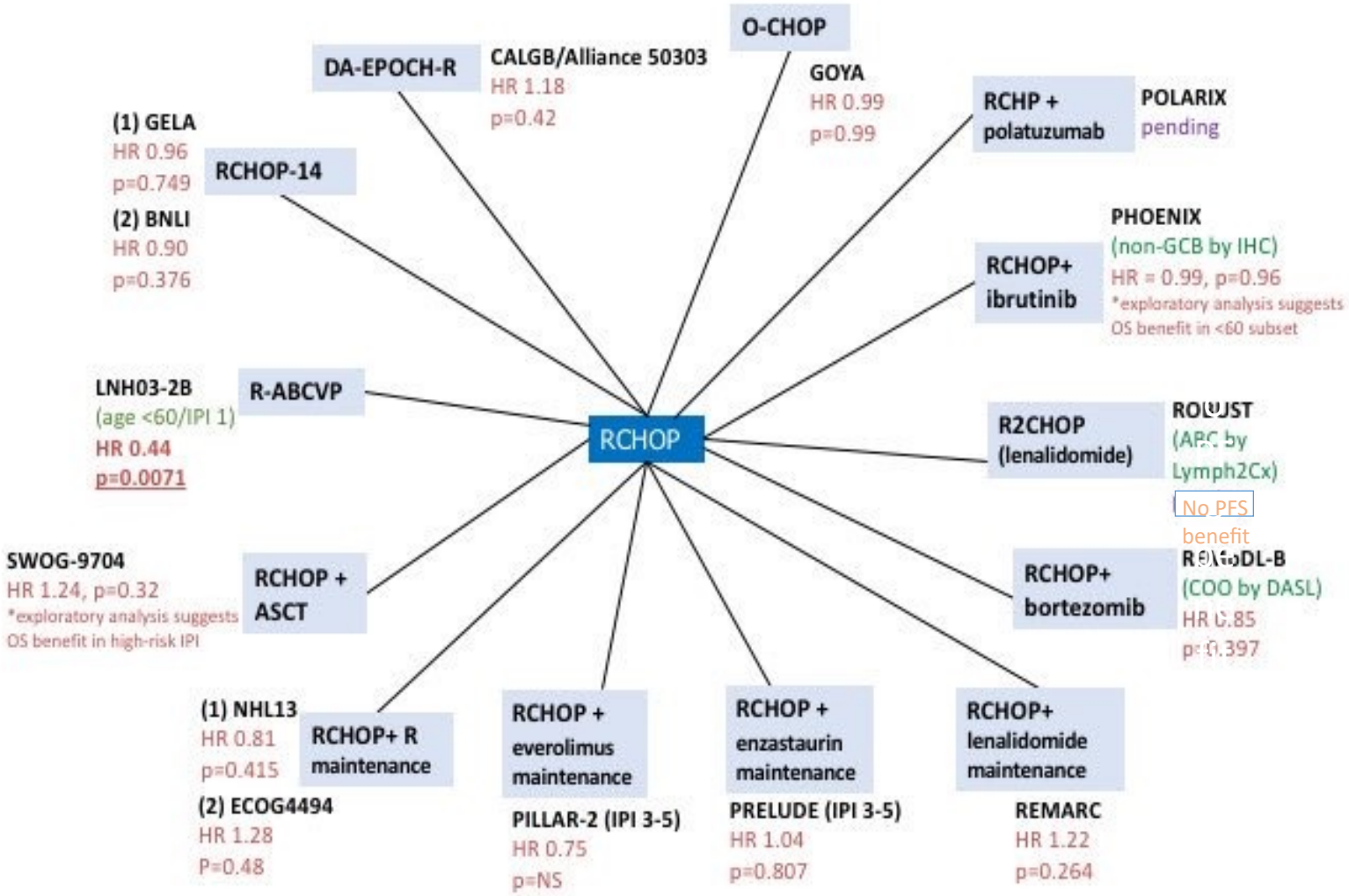
PFS Rates	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	77%	75%
2-y	67%	64%



- At a median follow-up of 27.1 mo (range, 0-47), THE primary endpoint of PFS was not met (medians not reached)
- ORR and CR rates were high in both arms
- **Median time from diagnosis to treatment was 31 days for each arm**

- Data cut-off 15Mar2019.
  Complete response (CR) was assessed by 2014 IWG criteria with CT-PET (Cheson 2014)).

FOREVER RCHOP ?



ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

Hervé Tilly, M.D., Franck Morschhauser, M.D., Ph.D., Laurie H. Sehn, M.D., M.P.H., Jonathan W. Friedberg, M.D., Marek Trněný, M.D., Jeff P. Sharman, M.D., Charles Herbaux, M.D., John M. Burke, M.D., Matthew Matasar, M.D., Shinya Rai, M.D., Ph.D., Koji Izutsu, M.D., Ph.D., Neha Mehta-Shah, M.D., et al.

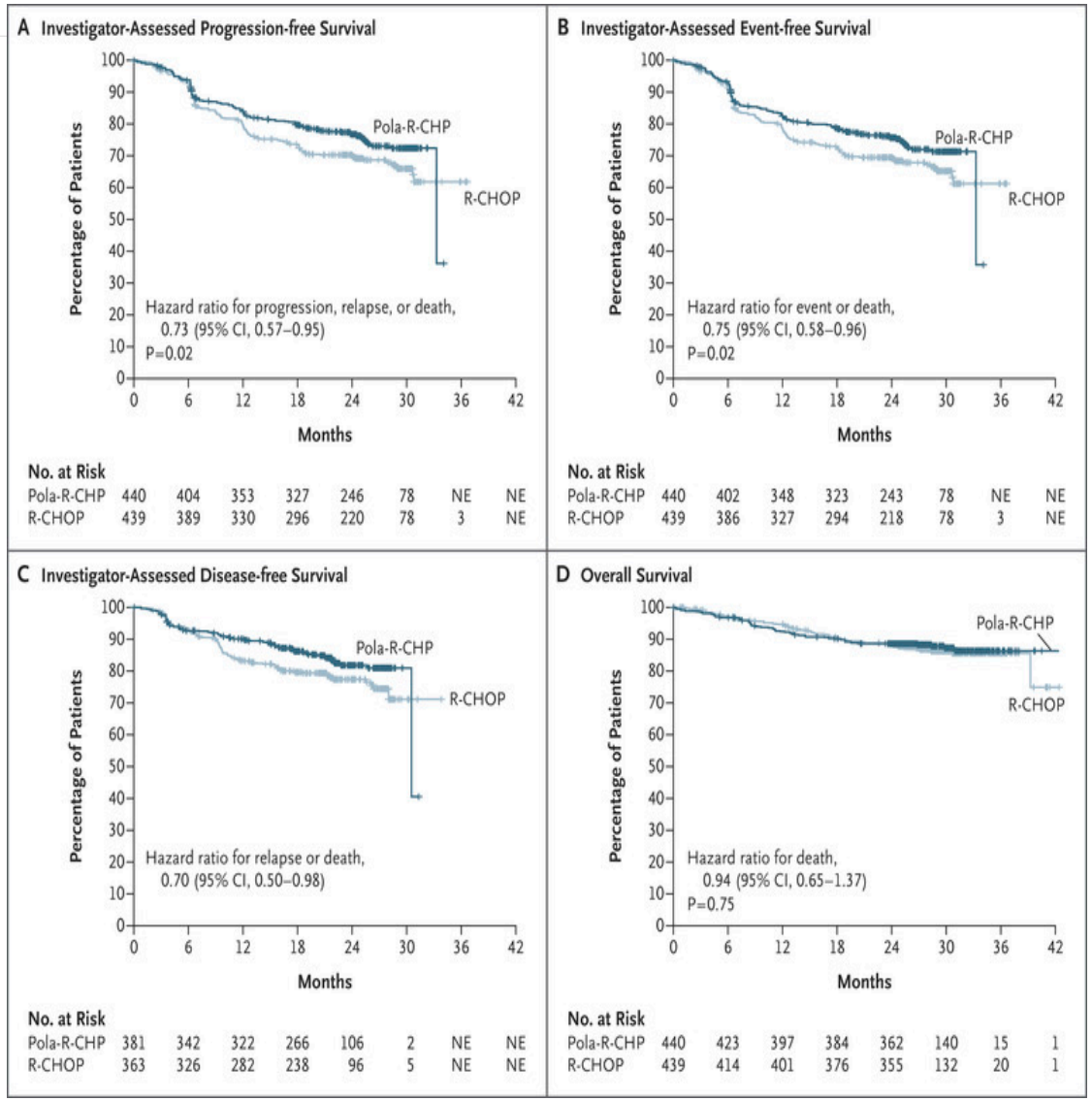
January 27, 2022
N Engl J Med 2022; 386:351-363
DOI: 10.1056/NEJMoa2115304

37 References 34 Citing Articles

Table 1. Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

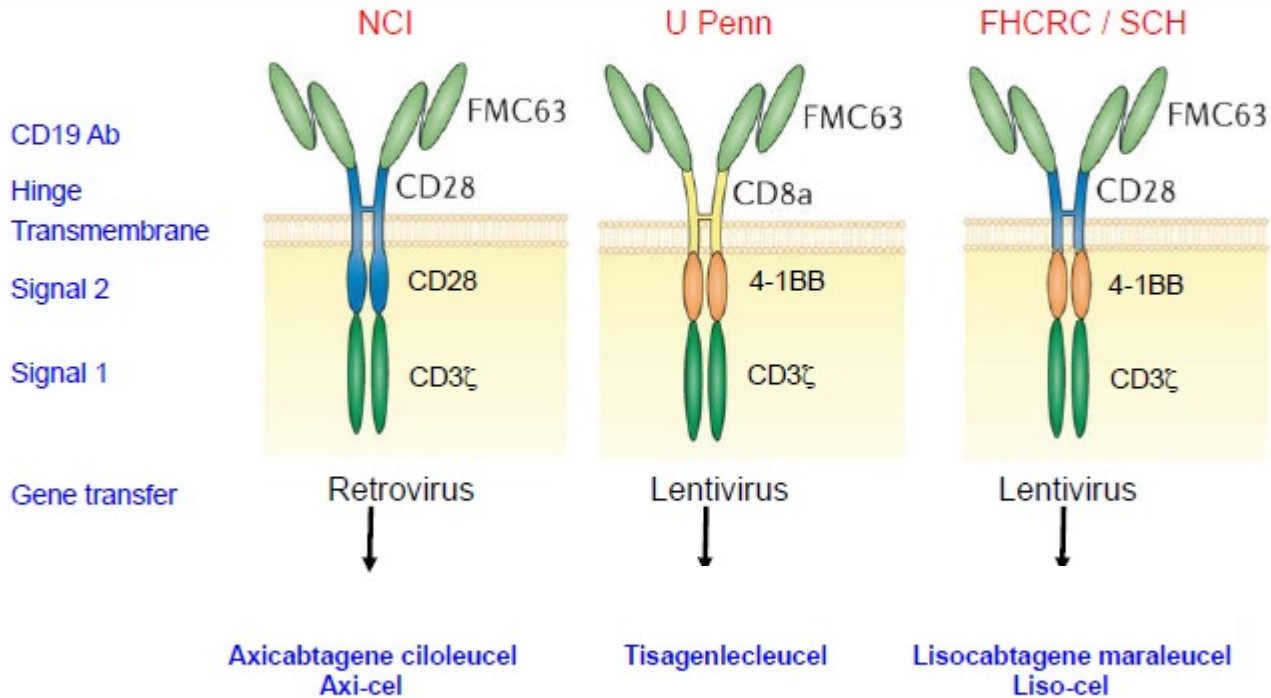
Characteristic	Pola-R-CHP (N=440)	R-CHOP (N=439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)
ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

PFS 24 MONTHS: Pola-R-CHP 76,7 vs R-CHOP 70,2 %
....6,5%....



THE LIVING DRUGS

CD19 CAR T products in pivotal trials in NHL



Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

Response rate

JULIET[1]

tisa-cel in

adult R/R DLBCL or TrFL or HGBCL

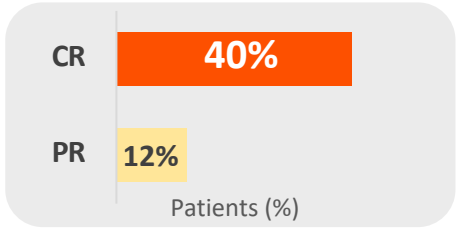
Median follow-up

14 months (range 0.1–26.0)

ORR 52%

95% CI 41–62%

n/N=48/93



ZUMA-1[2]

axi-cel in

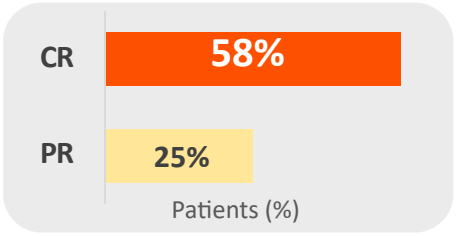
adult R/R DLBCL or PMBCL or trFL or HGBCL

Median follow-up

27.1 months (IQR 25.7–28.8)

ORR 83%

n/N=84/101



TRANSCEND-001[3]

liso-cel in

R/R DLBCL or PMBCL or Tr. Indolent L or HGBCL

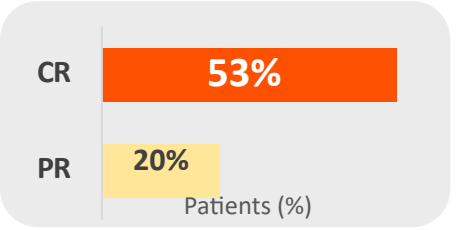
Median follow-up

18.8 months (95% CI 15.0–19.3)

ORR 73%

95% CI 66.8–78.0%

n/N=186/256



Durable response → Cure for some patients?

24-month PFS 33% N=115

Ongoing response at 24 months 36% n/N=36/101

Estimated 24-month PFS 42%

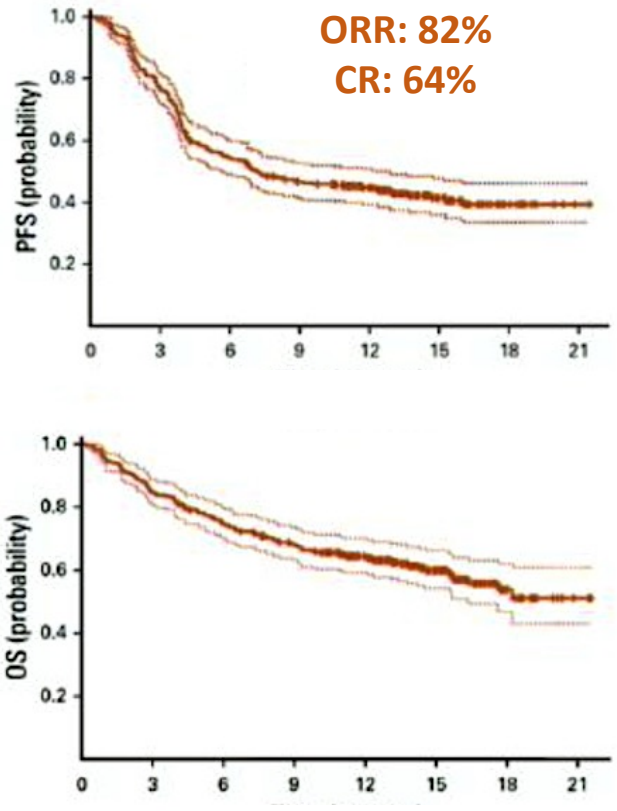
Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

CAR-T in R/R LBCL – Real-Word Studies vs ZUMA 1: outcomes

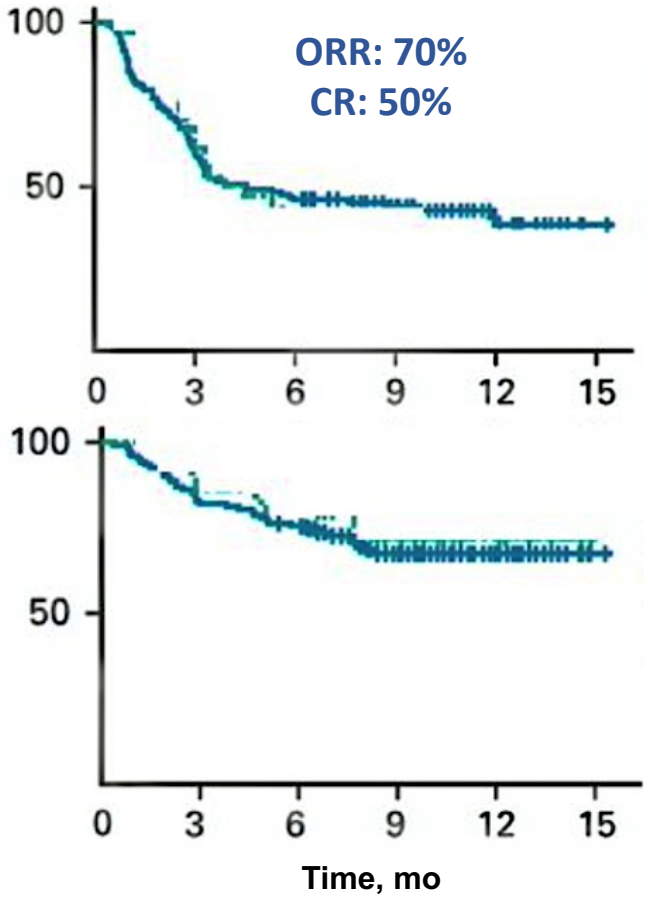
PFS

OS

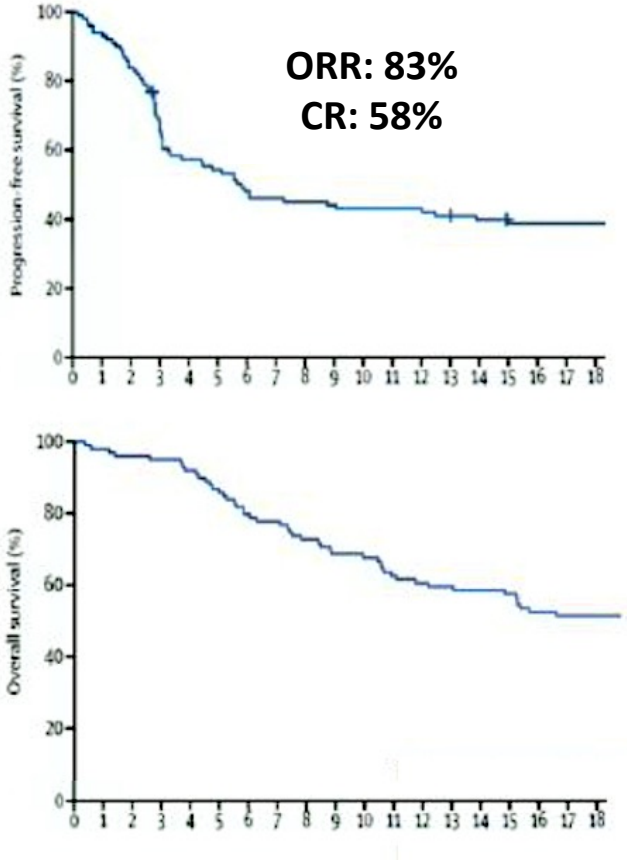
US Lymphoma **CAR T Consortium**[1]



7 US Academic Centers[2]



ZUMA-1[3]



Time, mo

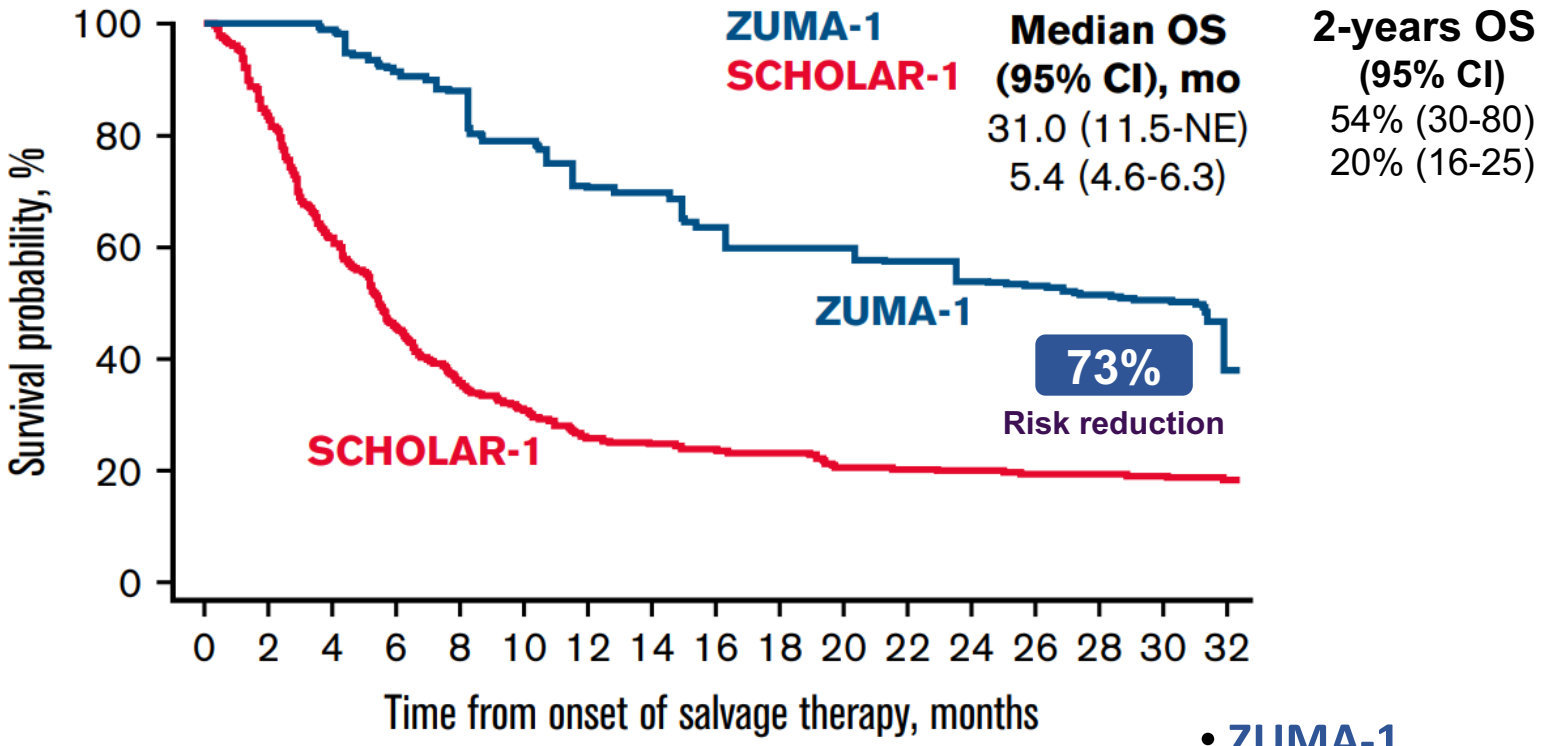
Time, mo

Time, mo

1. Nastoupil LJ, et al. J Clin Oncol. 2020; 2. Jacobson CA, et al. J Clin Oncol. 2020; 3. Locke FL, et al. Lancet Oncol. 2019.

How has CAR-T therapy improved survival for patients with R/R-DLBCL

Retrospective and comparative analysis of confounder-adjusted OS between ZUMA1 (axi-cel) vs SCHOLAR-1 (SOC)



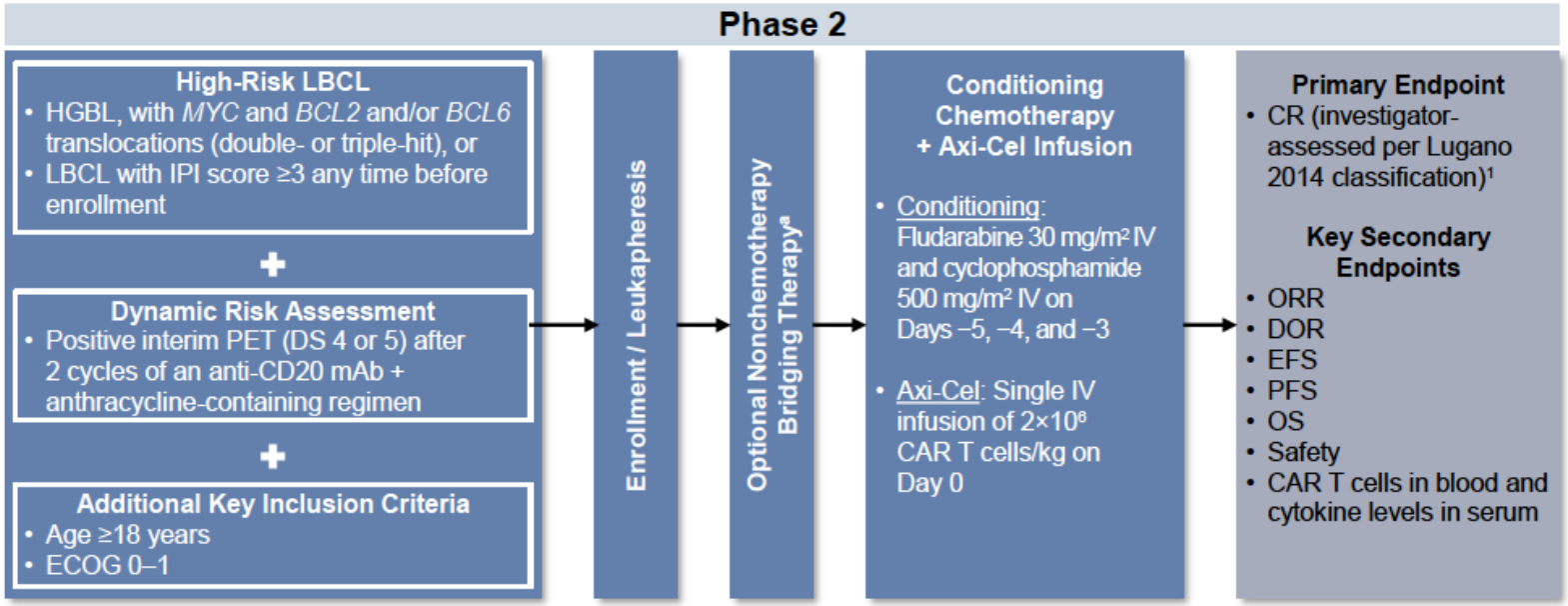
- **SCHOLAR-1**
- N = 636
- **ORR = 26%; CR rate = 7%**
- Median OS = 6.3 months

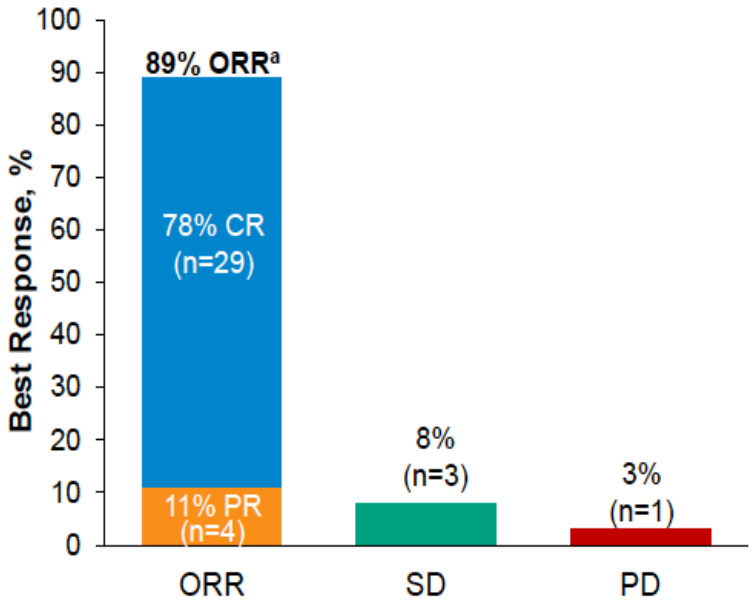
Crump et al. Blood 2017

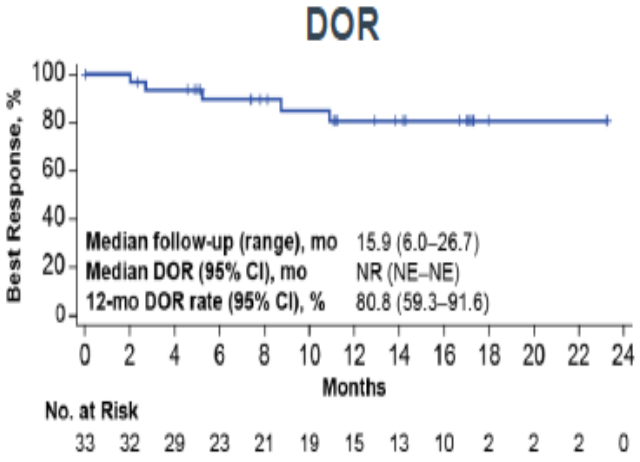
- **ZUMA-1**
- N = 108
- **ORR = 83%; CR rate = 58%**
- Median OS = >18 months

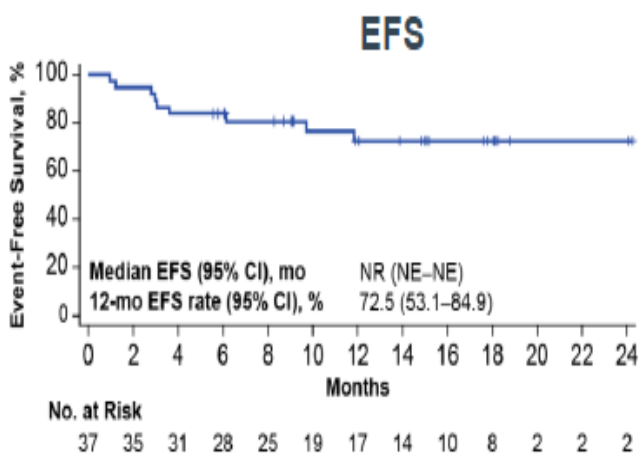
Neelapu et al. N Eng J Med 2017

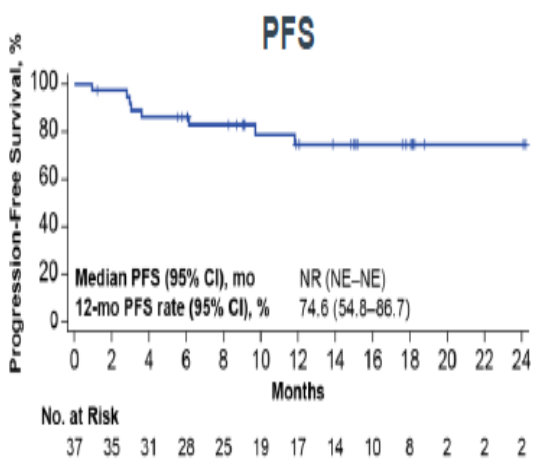
Primary Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients With High-Risk Large B-Cell Lymphoma

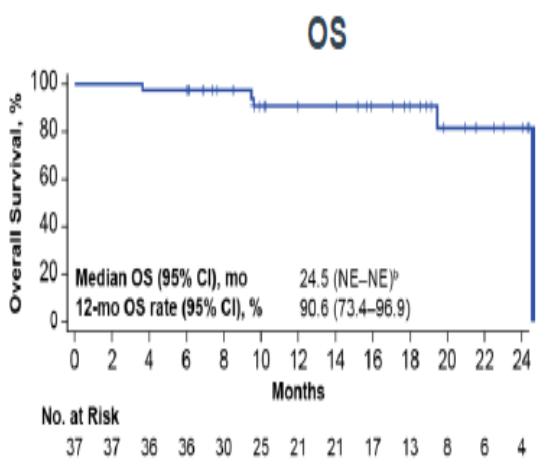












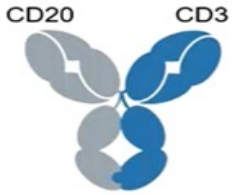
Neelapu SS, et al. Abstract #739, ASH 2021.

New targets

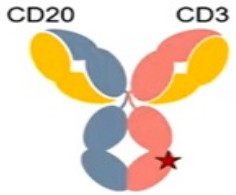
Overview of select CD3xCD20 bsAb

Epcoritamab
DuoBody-CD3×CD20
IgG1

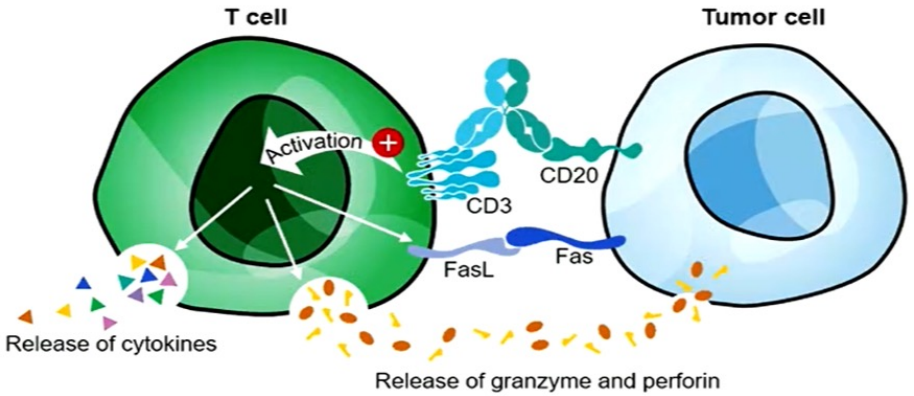
Glofitamab
2+1 CrossMab
IgG1



Mosunetuzumab
Knob-in-hole
IgG1



Odronextamab
VELOCI-Bi
IgG4

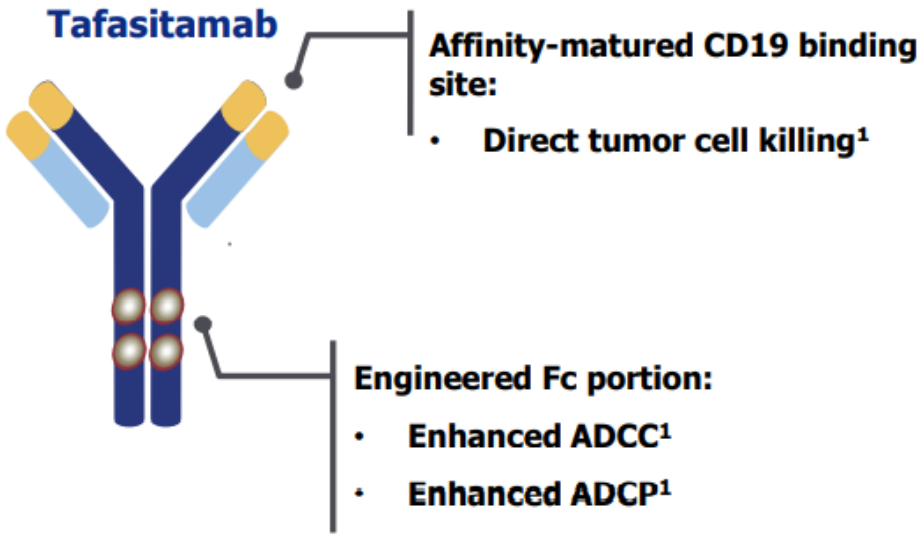


- Simultaneous binding to tumor antigen and CD3ε chain of TCR independent of peptide-MHC complex
- **T cell engagement, activation and killing** of tumor cells by cytotoxic granules
- **T cell proliferation** (expansion) at site of activation (blood? Lymph nodes): **4 x 10^{11} in the circulation**
- **Serial killing of tumor cells, activity at low effector-to-target (E:T) ratio**
- **T cell killing independent of specificity, activation and differentiation**

Schuster SJ Hematological Oncology 2021; You G et al, Vaccines 2021, Engelberts PJ et al, EBioMedicine 2020

Tafasitamab

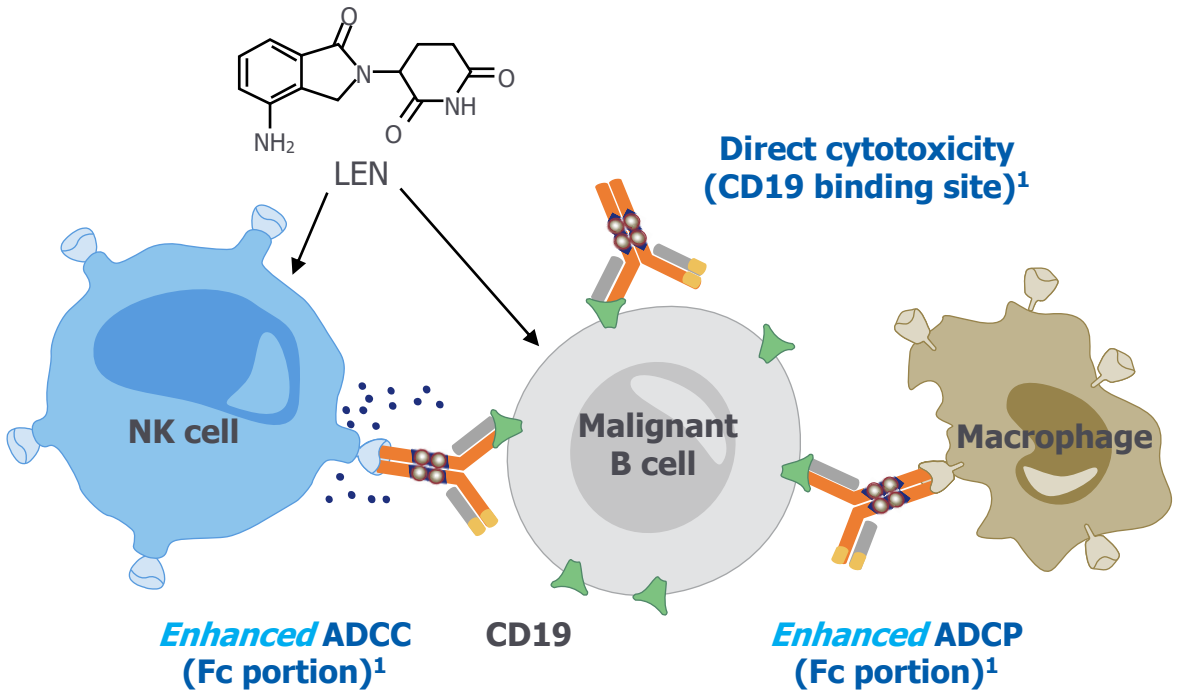
- Tafasitamab is novel Fc-engineered monoclonal antibody directed against human CD19 receptor
- The heavy chain constant region has been engineered with the introduction of two amino acid changes, S239D and I332E, in the CH2 domain, resulting in increased binding affinity for Fcγ receptors (FcγRs).



The Fc-modification of tafasitamab is **intended to lead to a significant potentiation of ADCC and ADCP activity, thus enhancing two key mechanisms of tumor cell killing.**

Zinzani PL, Minotti G. J Cancer Res Clin Oncol.

Tafasitamab & lenalidomide : rationale for a sinergistic activity



Tafasitamab (Fc-enhanced, anti-CD19 mAb)[1–3]

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single-agent activity in patients with R/R DLBCL and iNHL

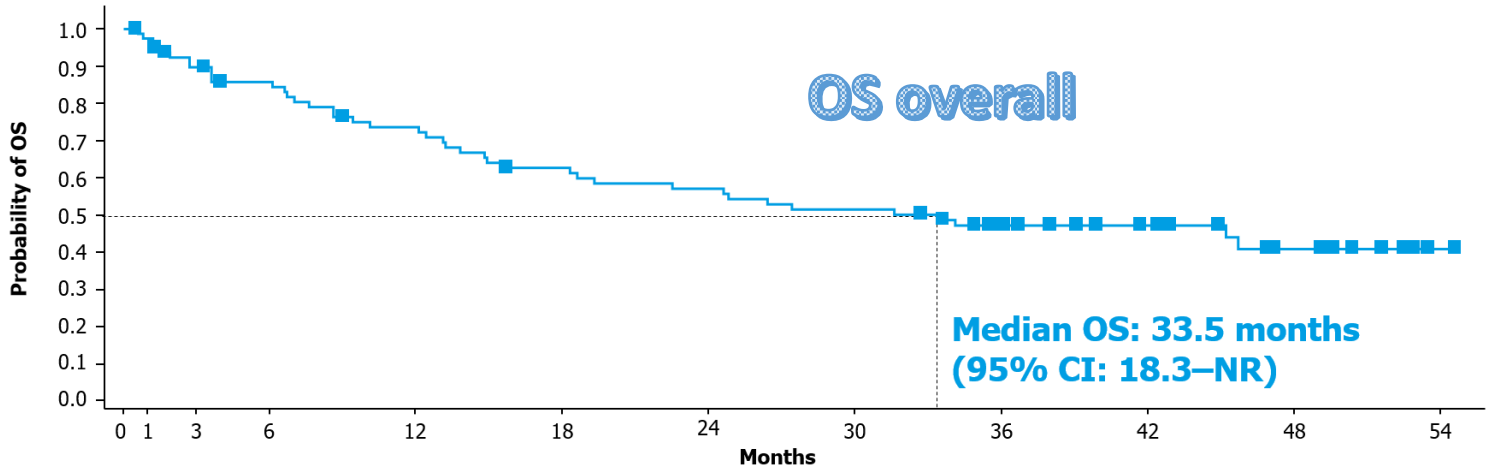
LEN[4,5]

- T-cell and NK-cell activation/expansion
- Direct cell death
- Well-studied as an antilymphoma agent, alone or in combination

The L-MIND trial provided clinical evidence supporting the efficacy and synergy of the combination of tafasitamab and lenalidomide in which **the affinity of tafasitamab for both effector and target cells is magnified by the immunomodulating effects of lenalidomide** (such as stimulation of NK cell proliferation, as well as activation and enhancement of NK-mediated ADCC)[6]

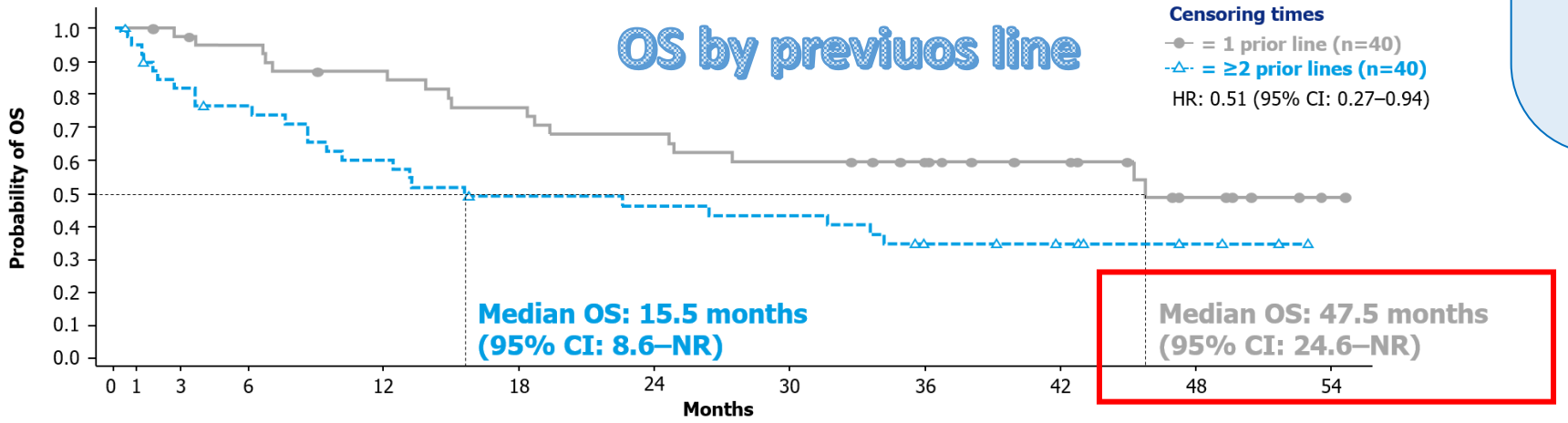
1. Horton HM, et al. Cancer Res. 2008;68:8049–57; 2. Woyach JA, et al. Blood. 2014;124:3553–60; 3. Jurczak W, et al. Ann Oncol. 2018;29:1266–72; 4. Witzig TE, et al. Ann Oncol. 2015;26:1667–77; 5. Czuczman MS, et al. Clin Cancer Res. 2017;23:4127–37; 6. Zinzani PL, Minotti G. J Cancer Res Clin Oncol. 2021;148:177–90.

L-MIND outcome: Overall Survival



Number of patients still at risk

Overall	80	77	69	64	54	45	41	37	28	21	10	1



Number of patients still at risk

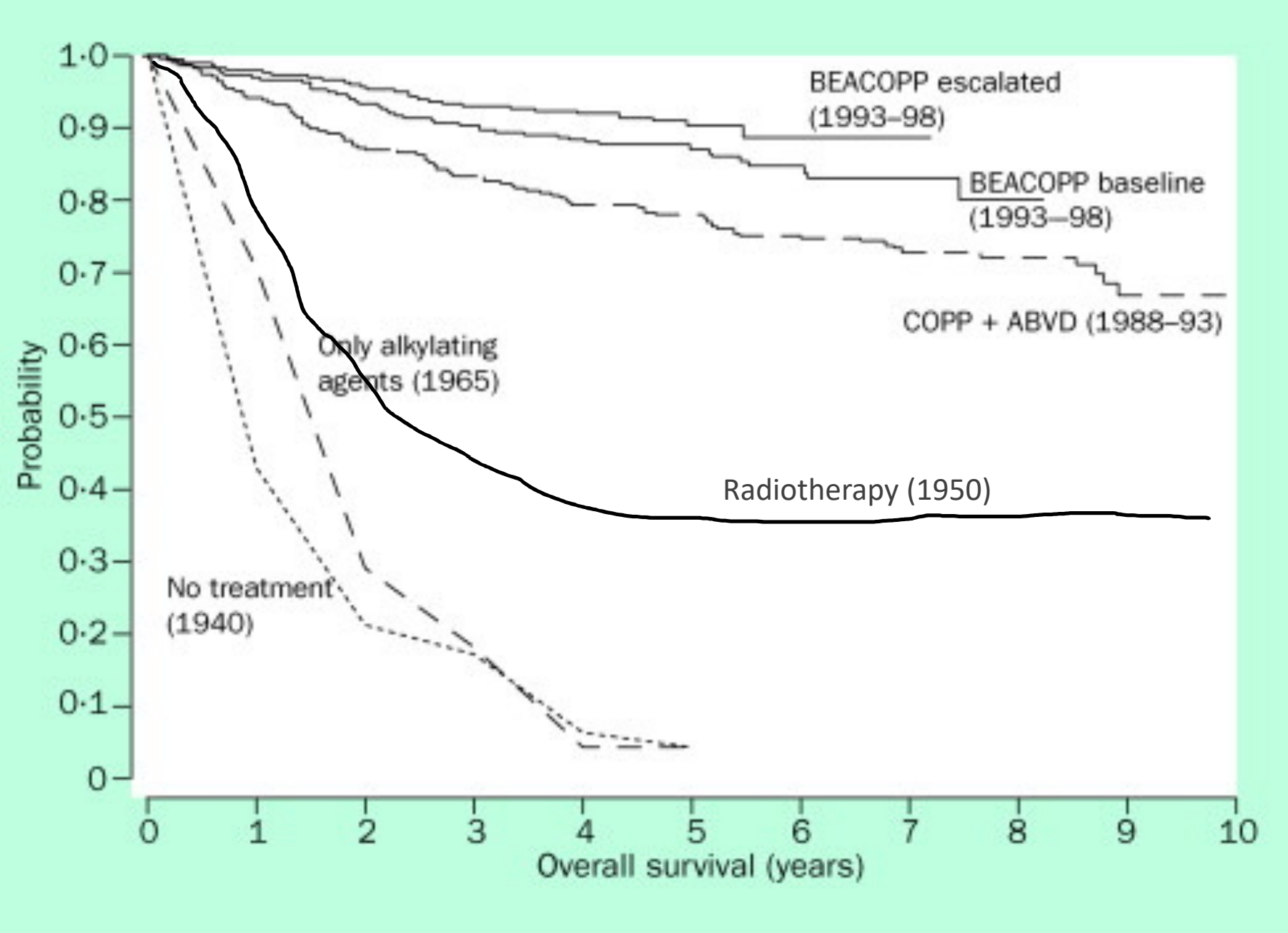
1 prior line	40	40	38	36	32	28	25	22	18	14	7	1
≥2 prior lines	40	37	31	28	22	17	16	15	10	7	3	0

- Survival rate at 36 months was 47.3% in the overall L-MIND population
- Higher survival rates were observed at each timepoint in patients who received 1 versus 2 or more prior lines of treatment

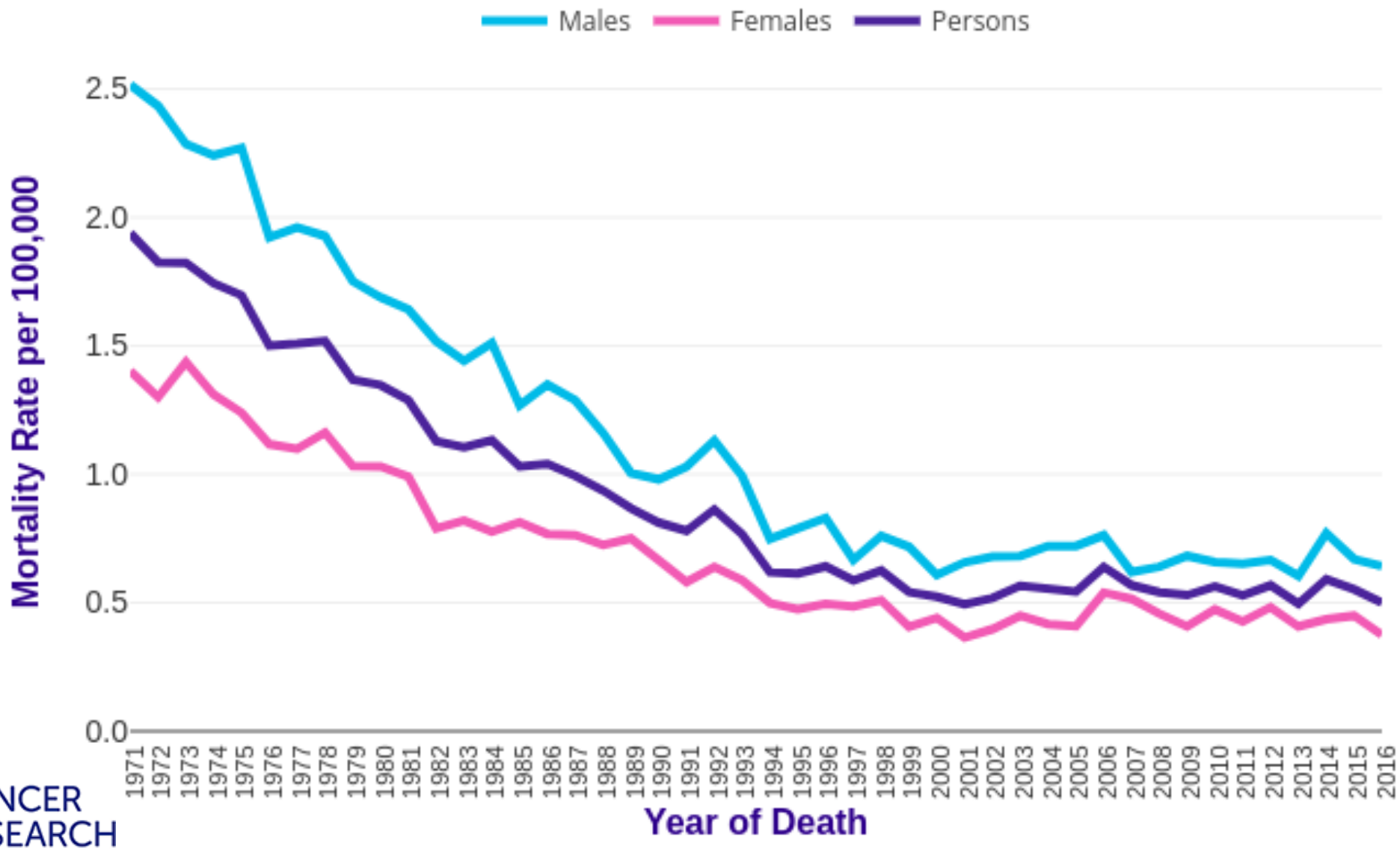
Duell J, et al. Oral presentation at Virtual ICML 2021; Abstract 28; Duell et al Haematologica 2021

LINFOMA DI HODGKIN

a successful history

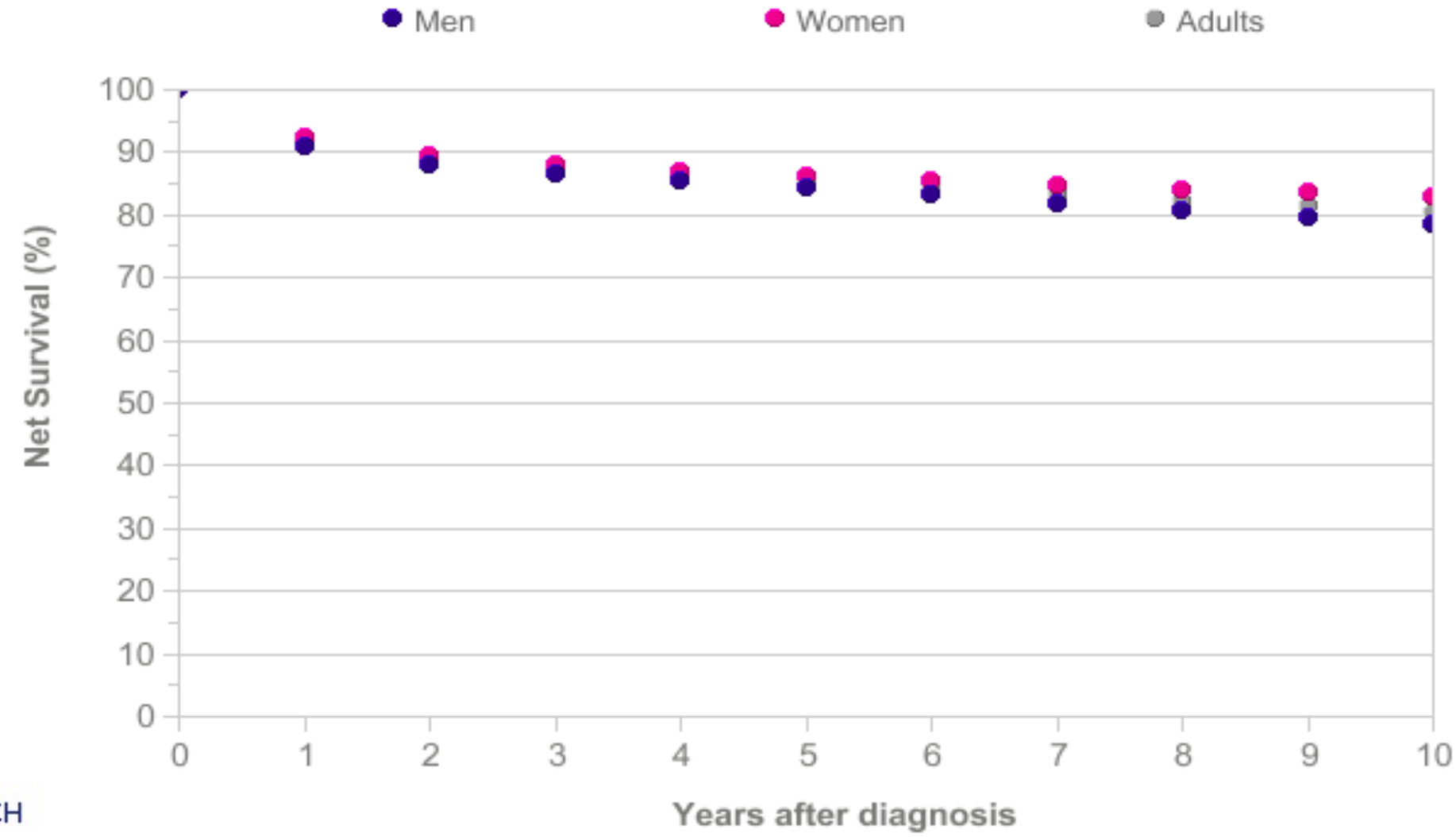


Mortality Has Fallen Over 30 Years



CANCER RESEARCH UK

Survival up to Ten Years after Diagnosis



CANCER RESEARCH UK

Overall Therapeutic Results

- Cured with first line therapy, >90%
  - 90-95% in early stages, 80% in advanced stages
- Alive at 10 years, 80-85% of patients
- Deaths from causes other than HL
  - Disease control may not mean survival

The optimal treatment for HL remains controversial:

Present Open Questions

1) Reduction of therapy in the most favourable subset

TOO LITTLE?

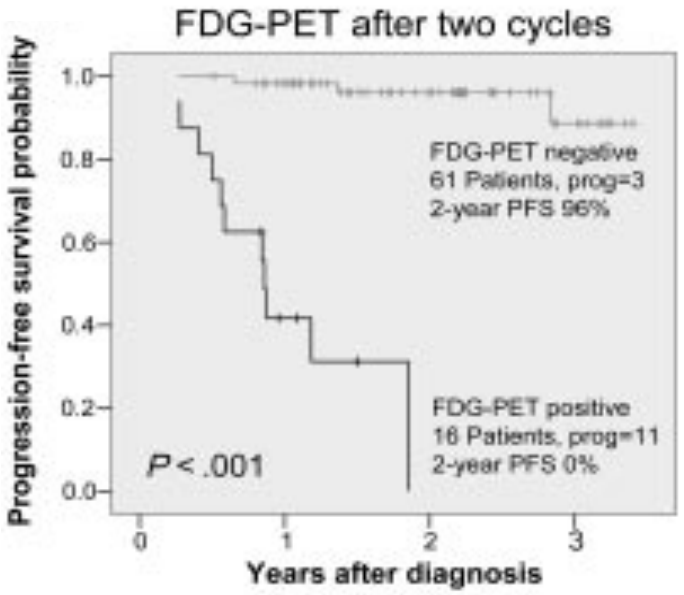
RELAPSE RISK AND ADDITIONAL TOXIC THERAPY

2) New approaches for those who have a high risk of failure

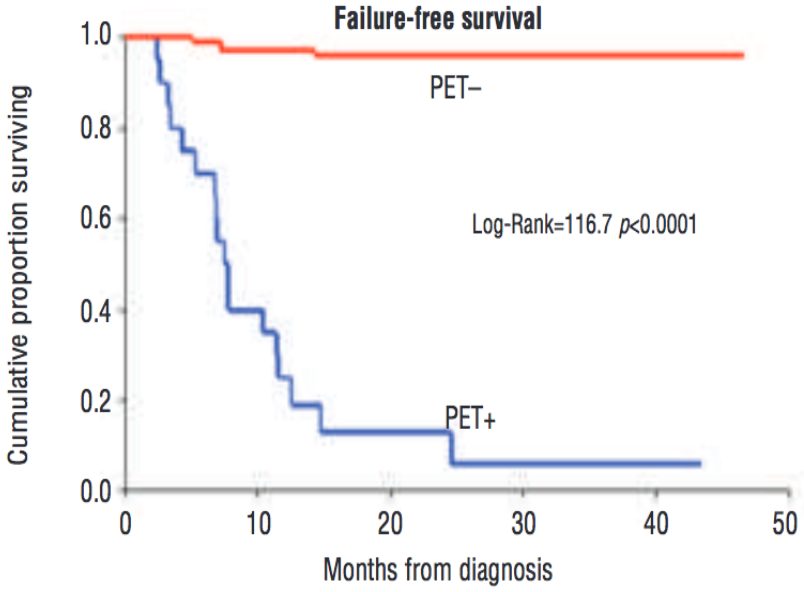
TOO MUCH?

LONG TERM CONSEQUENCES/TOXICITIES

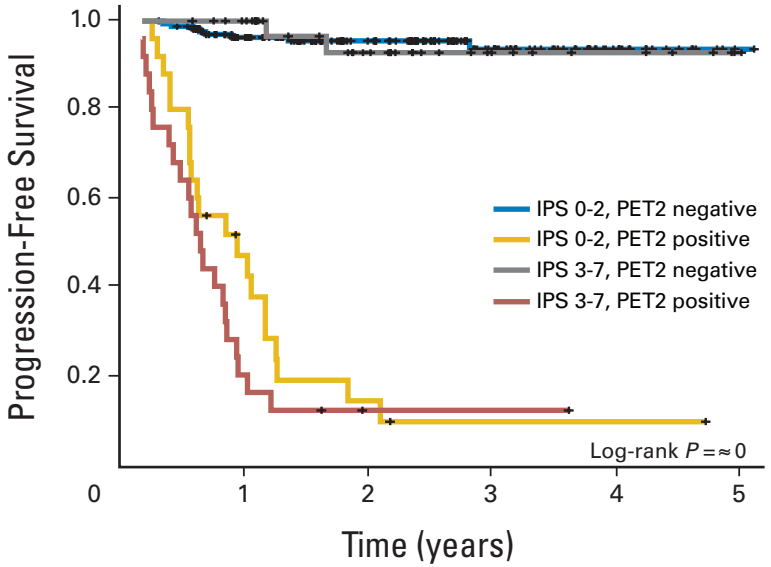
Prognostic Relevance of Positive iPET



Hutchings, Blood 2006



Gallamini Haematologica 2006



Gallamini JCO 2007

Interim PET as a tool to distinguish good vs bad disease

PET response-adapted strategies

Advanced Stage:PET-driven studies

Intensification

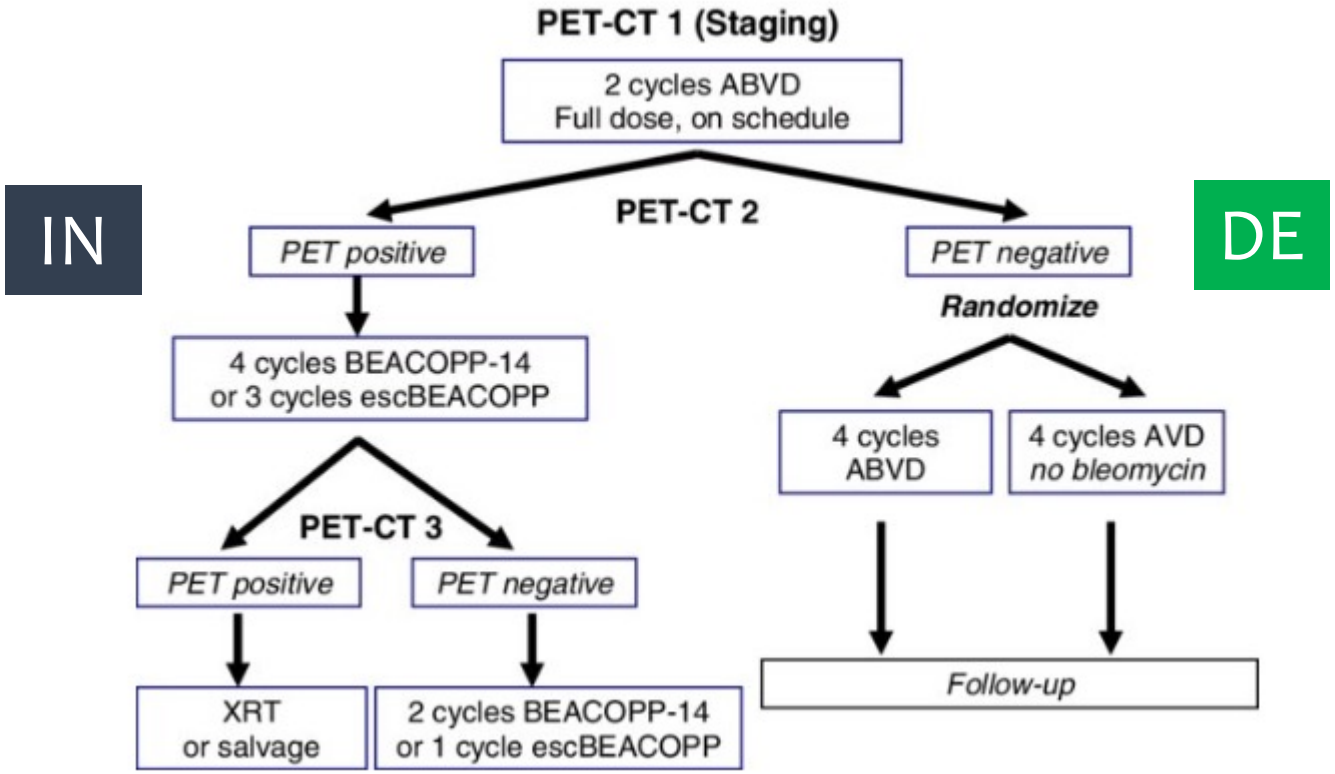
DE-Escalation

- HD0801 (FIL) Zinzani PL et al, JCO 2016
- HD0607 (GITIL/FIL) Gallamini A, JCO 2018
- RATHL (UK) Johnson P et al, NEJM 2016
- S0816 (SWOG) Stephens D. et al, ASH 2018
- HD18 (GHSG) Borchmann P et al, Lancet 2017
- AHL2011 (Lysa) Casasnovas et al, Lancet Oncol 2019

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma

Johnson P et al, NEJM 2016

RATHL Study



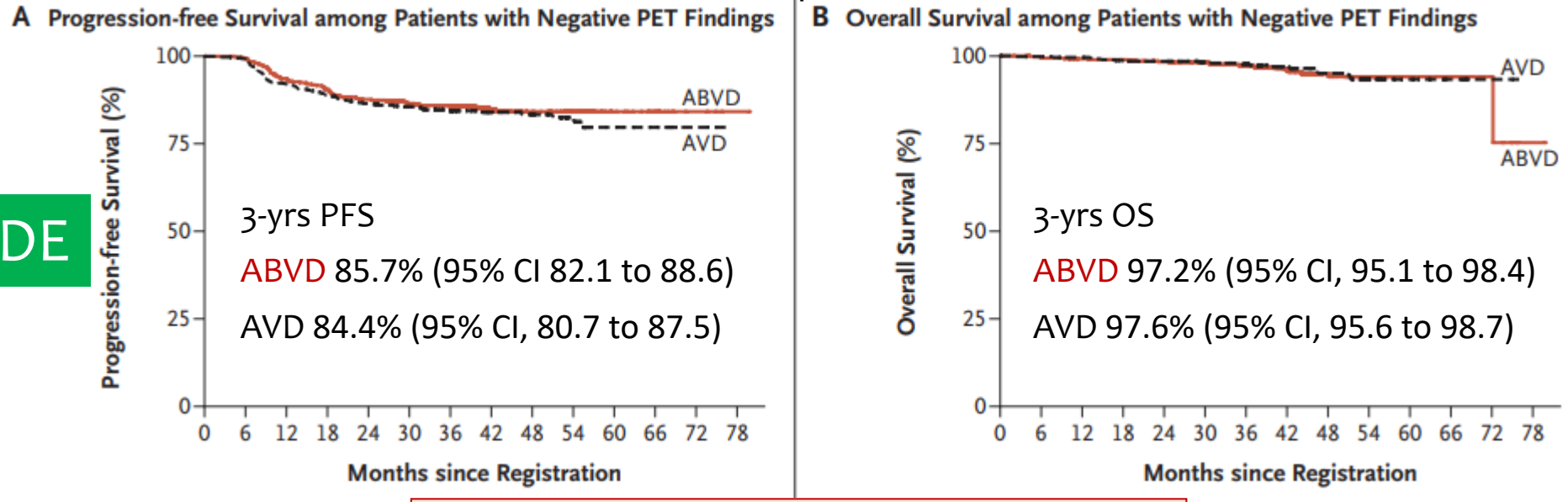
Primary outcome: 3-yrs PFS between randomized groups (non inferiority comparison)

RATHL Study: outcome

Johnson P et al, NEJM 2016

median follow-up of 41 months

DE



3-yrs PFS

ABVD 85.7% (95% CI 82.1 to 88.6)

AVD 84.4% (95% CI, 80.7 to 87.5)

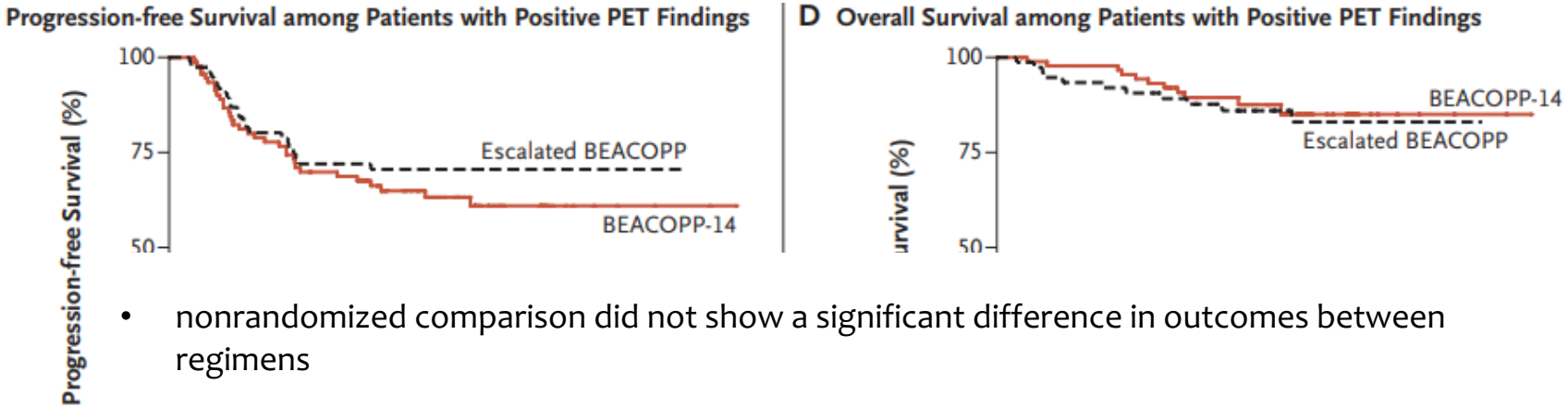
3-yrs OS

ABVD 97.2% (95% CI, 95.1 to 98.4)

AVD 97.6% (95% CI, 95.6 to 98.7)

AVD: lower incidence of pulmonary toxic effects

IN



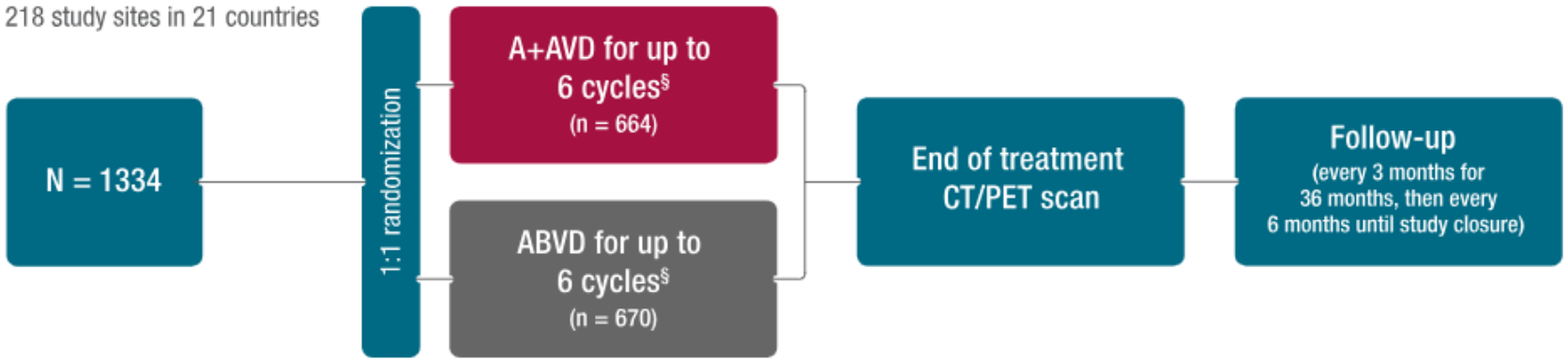
- nonrandomized comparison did not show a significant difference in outcomes between regimens
- toxic effects were broadly similar, except for higher rates of thrombocytopenia and febrile neutropenia with escalated BEACOPP

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

ECHELON-1

Connors JM et al, NEJM 2018

Phase 3, Randomized, Multicenter, Open-label Superiority Trial[1,3,4]



- A+AVD (brentuximab vedotin 1.2 mg/kg, doxorubicin 25 mg/m², vinblastine 6 mg/m², dacarbazine 375 mg/m²)
- ABVD

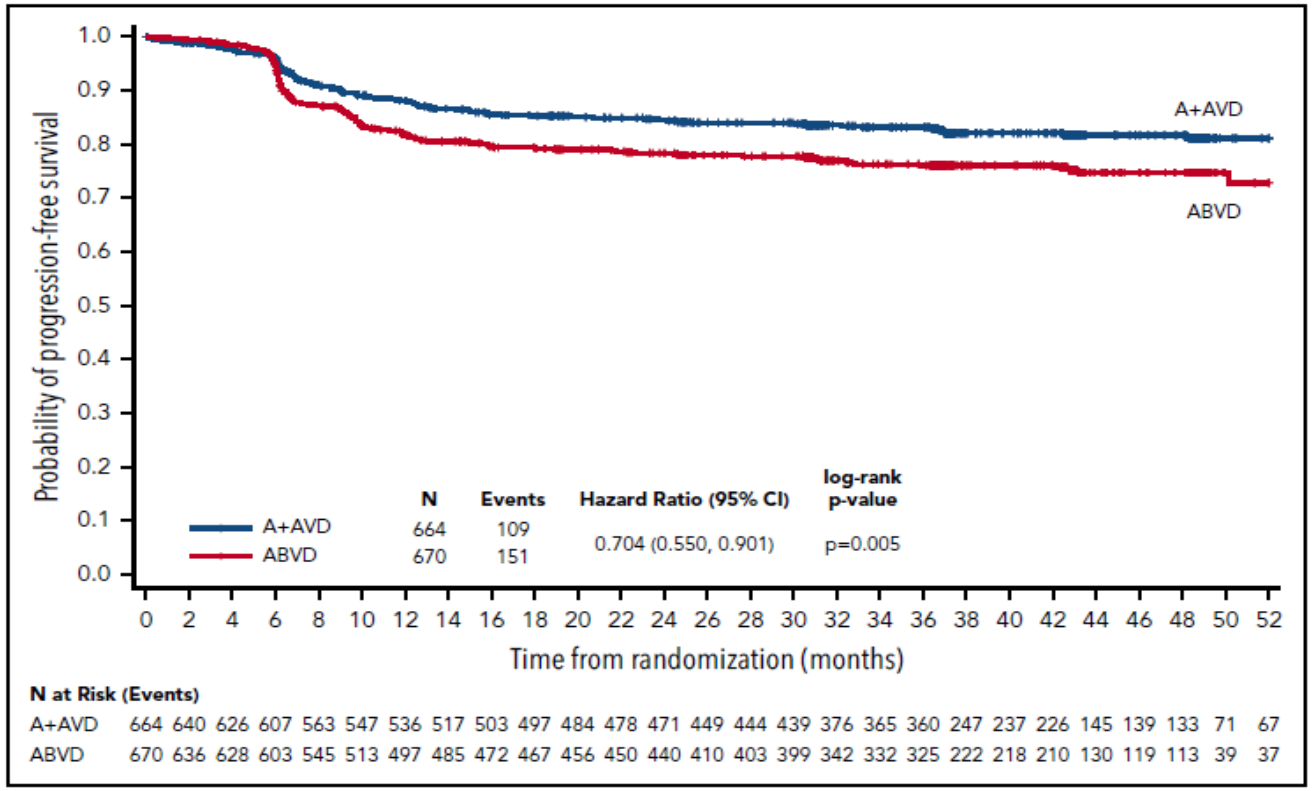
IV on Days 1 and 15 of each 28-day cycle for up to 6 cycles

Primary endpoint: modified PFS per IRC
Defined as first of: progression, death from any cause, PET6 with Deauville score 3-5 after frontline tx and subsequent anticancer tx

Secondary endpoints: response, OS, PET negativity per IRC, safety

ECHELON-1: Primary Endpoint

Median follow-up: 37.1 mos



CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study

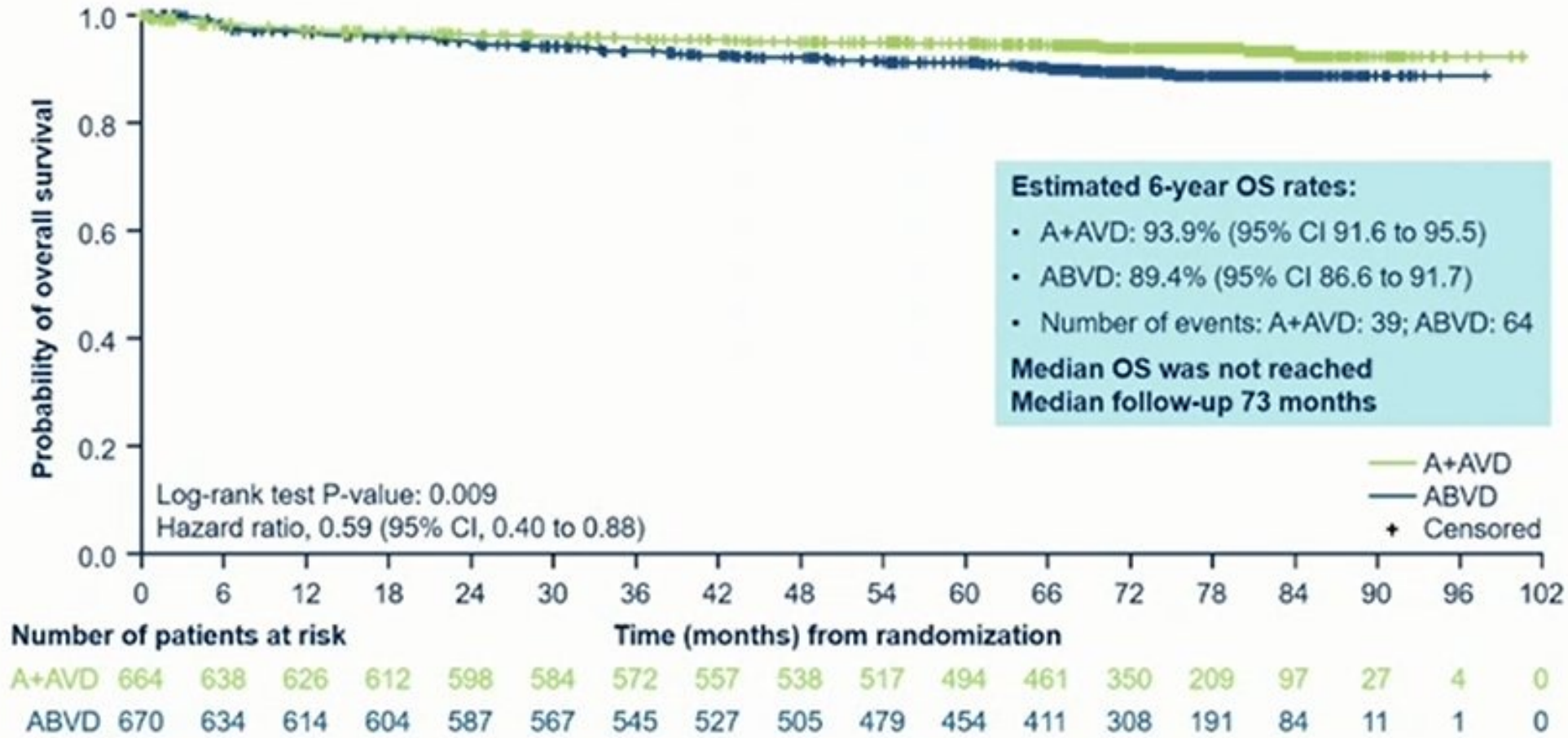
David J. Straus,[1] Monika Długosz-Danecka,[2] Sergey Alekseev,[3] Árpád Illés,[4] Marco Picardi,[5] Ewa Lech-Maranda,[6] Tatyana Feldman,[7] Piotr Smolewski,[8] Kerry J. Savage,[9,10] Nancy L. Bartlett,[11] Jan Walewski,[12] Radhakrishnan Ramchandren,[13] Pier Luigi Zinzani,[14] Martin Hutchings,[15] Joseph M. Connors,[9,10] John Radford,[16,17] Javier Munoz,[18] Won Seog Kim,[19] Ranjana Advani,[20] Stephen M. Ansell,[21] Anas Younes,[1] Harry Miao,[22] Rachael Liu,[22] Keenan Fenton,[23] Andres Forero-Torres,[23] and Andrea Gallamini[24]

2-yrs modified PFS:

- A+AVD 83,1% (95%CI 79.9-85.9)
- ABVD 76.0% (95%CI 72.4-79.2)

blood® 5 MARCH 2020 | VOLUME 135, NUMBER 10

A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD



Conclusions

- ✓ In less than 10 years the treatment landscape of Non Hodgkin and Hodgkin lymphoma has dramatically changed
- ✓ New treatment targets have emerged
- ✓ We are progressively moving towards a chemo –free approach
- ✓ Despite a rapidly increasing of knowledge on the results of the new approaches, we have to minimize therapies in order to avoid side effects
- ✓ These will probably represent the object of both clinical and translational research in the next future