2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:

Marco Ladetto (Alessandria)

Umberto Vitolo (Candiolo-TO)

How I treat high risk DLBCL in first line

Annalisa Chiappella

Division of Hematology

Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy

Disclosures

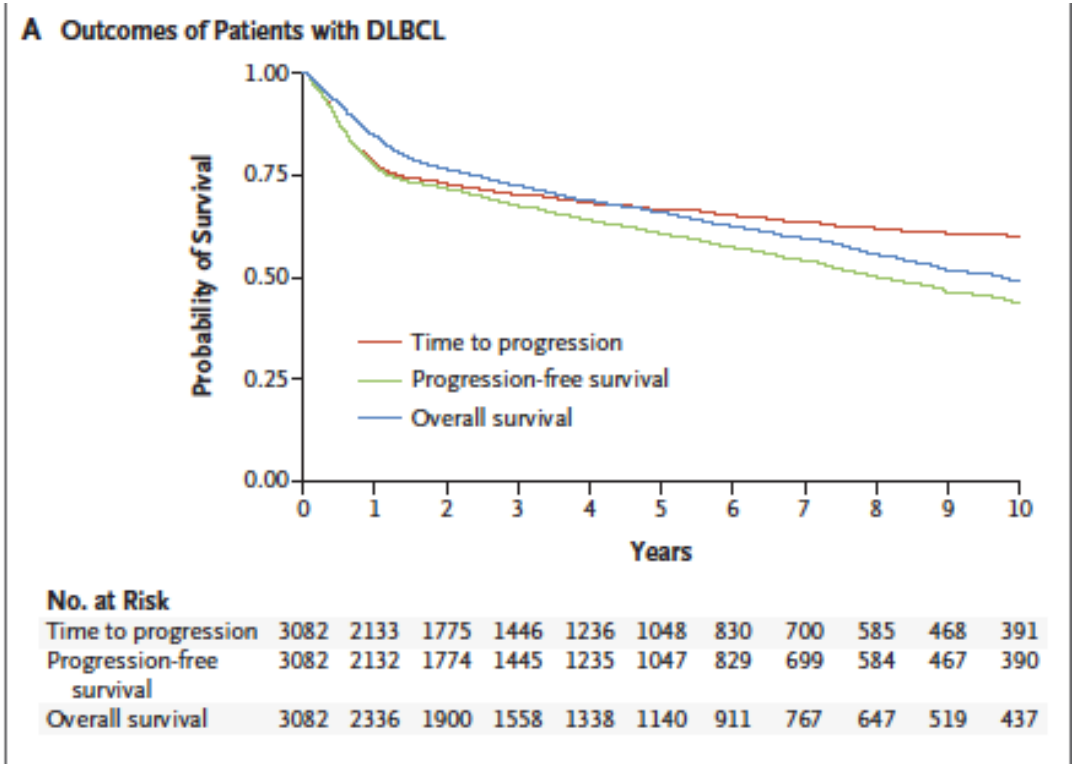
Scientific Advisory Board:

- Celgene-BMS, Clinigen, Gilead-Kite, Janssen, Roche, Takeda

Lecture fees/Educational Activities:

- Astrazeneca, Celgene-BMS, Clinigen, Gilead-Sciences, Incyte, Janssen, Novartis, Roche, Servier, Takeda

R-CHOP is the standard treatment in DLBCL



No. at Risk											
Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437

R-CHOP is insufficient in 35% of DLBCL:

- High-Risk “Clinical” (IPI 3-5)
- High-Risk “Biological”

Sehn LH and Salles G, NEJM 2021.

How to move beyond R-CHOP in aggressive lymphoma?

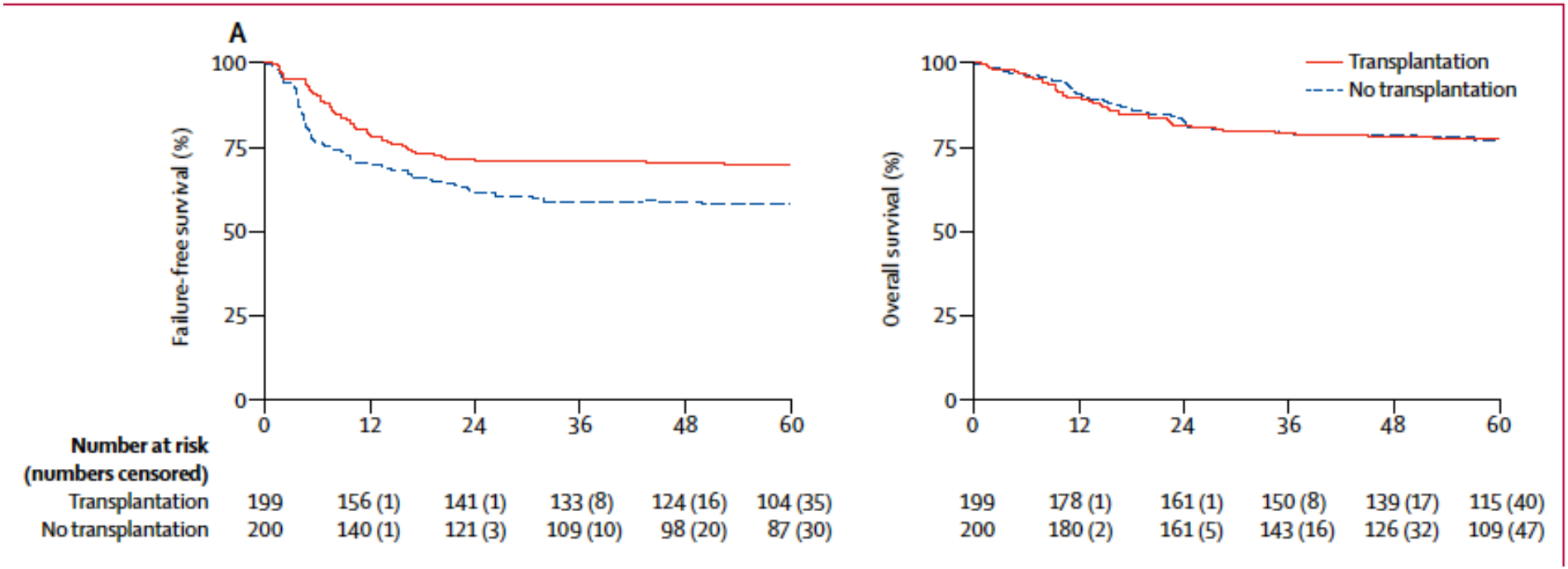
… targeting all DLBCL

- Intensified chemotherapy
- Different MAb

Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study

Annalisa Chiappella, Maurizio Martelli*, Emanuele Angelucci, Ercole Brusamolino†, Andrea Evangelista, Angelo Michele Carella, Caterina Stelitano, Giuseppe Rossi, Monica Balzarotti, Francesco Merli, Gianluca Gaidano, Vincenzo Pavone, Luigi Rigacci, Francesco Zaja, Alfonso D'Arco, Nicola Cascavilla, Eleonora Russo, Alessia Castellino, Manuel Gotti, Angela Giovanna Congiu, Maria Giuseppina Cabras, Alessandra Tucci, Claudio Agostinelli, Giovannino Ciccone, Stefano A Pileri, Umberto Vitolo*

399 DLBCL, aa-IPI 2-3



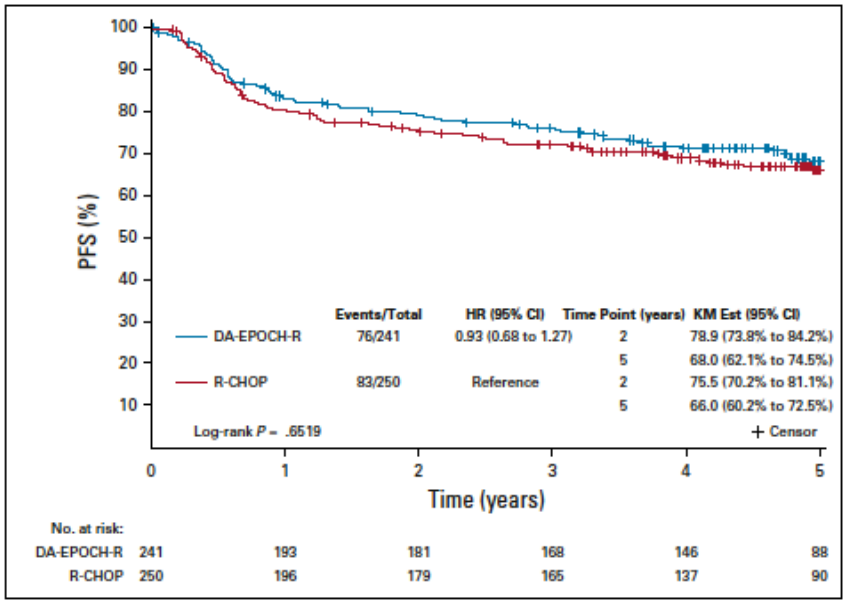
Chiappella A, Martelli M et al, Lancet Oncol 2017.

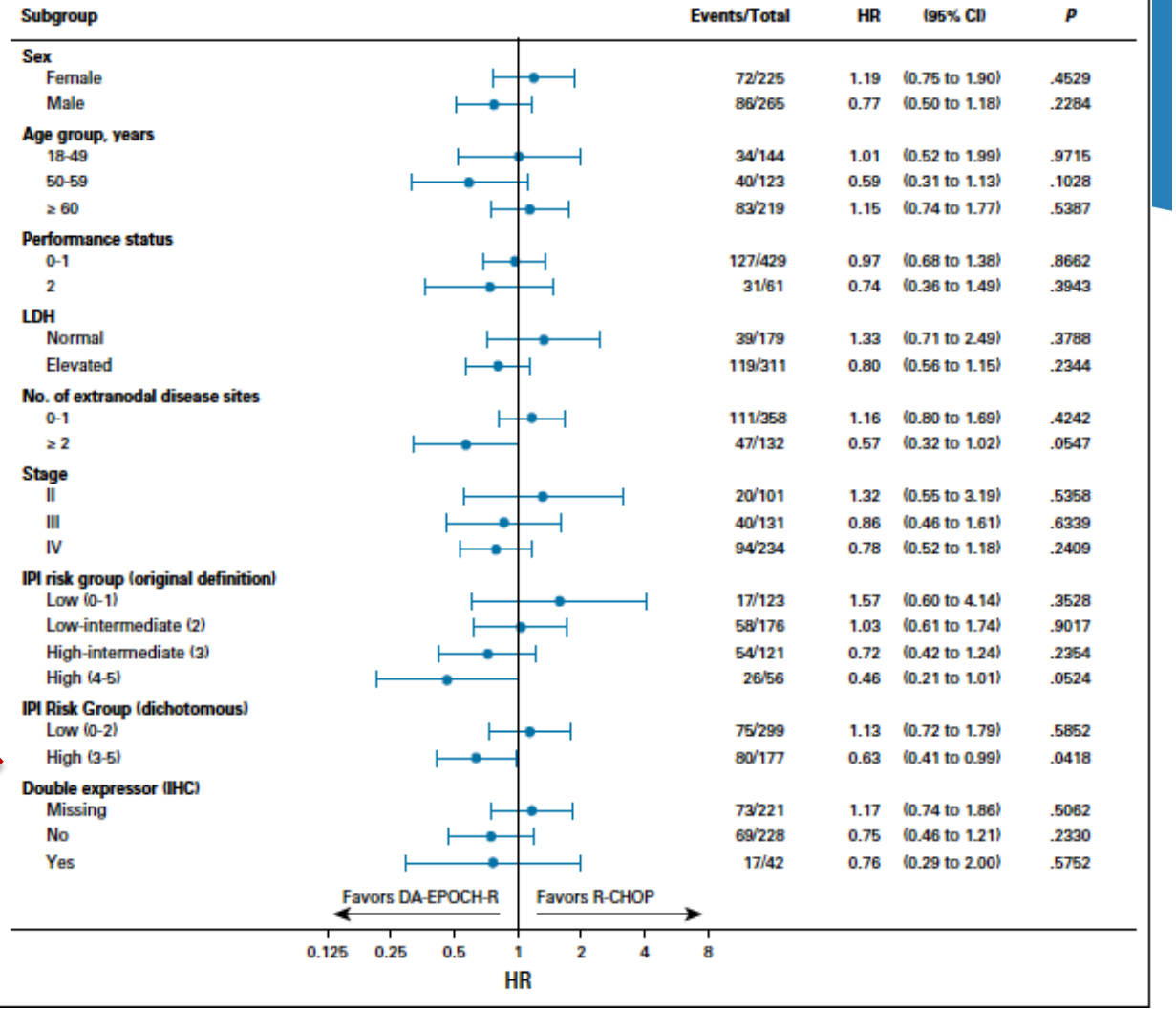
Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303

Nancy L. Bartlett, MD[1]; Wyndham H. Wilson, MD, PhD[2]; Sin-Ho Jung, PhD[3]; Eric D. Hsi, MD[4]; Matthew J. Maurer, MS[5]; Levi D. Pederson, MS[5]; Mei-Yin C. Polley, PhD[5]; Brandelyn N. Pitcher, MS[3]; Bruce D. Cheson, MD[6]; Brad S. Kahl, MD[1]; Jonathan W. Friedberg, MD[7]; Louis M. Staudt, MD, PhD[2]; Nina D. Wagner-Johnston, MD[1]; Kristie A. Blum, MD[8]; Jeremy S. Abramson, MD[9]; Nishitha M. Reddy, MD[10]; Jane N. Winter, MD[11]; Julie E. Chang, MD[12]; Ajay K. Gopal, MD[13]; Amy Chadburn, MD[14]; Susan Mathew, PhD[14]; Richard I. Fisher, MD[15]; Kristy L. Richards, MD, PhD[16]; Heiko Schöder, MD[17]; Andrew D. Zelenetz, MD, PhD[17]; and John P. Leonard, MD[14]

J Clin Oncol 37:1790-1799. © 2019 by American Society of Clinical Oncology

PFS





Bartlett NL et al, JCO 2019.

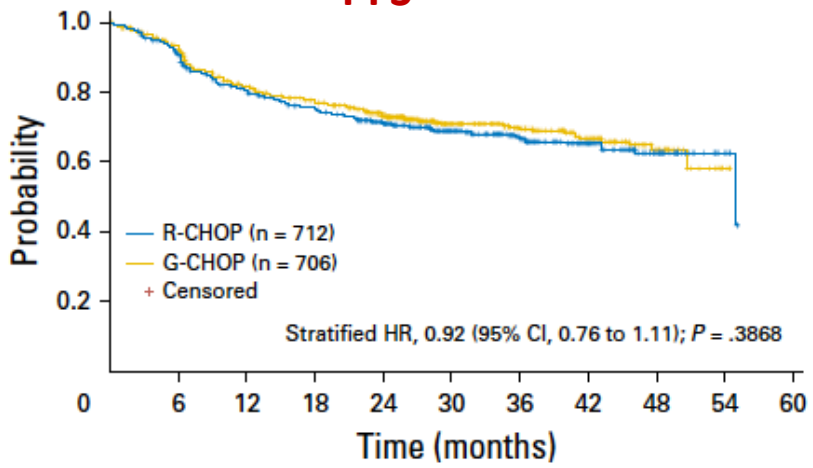
Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma

Umberto Vitolo, Marek Trněný, David Belada, John M. Burke, Angelo Michele Carella, Neil Chua, Pau Abrisqueta, Judit Demeter, Ian Flinn, Xiaonan Hong, Won Seog Kim, Antonio Pinto, Yuan-Kai Shi, Yoichi Tatsumi, Mikkel Z. Oestergaard, Michael Wenger, Günter Fingerle-Rowson, Olivier Catalani, Tina Nielsen, Maurizio Martelli, and Laurie H. Sehn

J Clin Oncol 35. © 2017 by American Society of Clinical Oncology

A

PFS



No. at risk:

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

A

Stratification Factors	Total No.	R-CHOP (n = 712) No.	R-CHOP Events	R-CHOP 1-Year KM Rate	G-CHOP (n = 706) No.	G-CHOP Events	G-CHOP 1-Year KM Rate	HR	95% Wald CI
All patients	1,418	712	215	79.778	706	201	81.614	0.92	0.76 to 1.12
No. of planned CHOP cycles									
6	1,049	526	152	80.789	523	142	83.449	0.91	0.73 to 1.15
8	369	186	63	76.949	183	59	76.480	0.96	0.6 to 1.37
IPI									
Low-intermediate	785	409	99	84.168	376	86	87.510	0.93	0.70 to 1.24
High-intermediate	413	192	71	75.013	221	62	81.669	0.68	0.48 to 0.95
High	220	111	45	71.577	109	53	61.460	1.27	0.85 to 1.90
Geographic region									
Eastern Europe	196	99	28	77.354	97	32	80.726	1.10	0.66 to 1.82
Western Europe	426	215	61	79.653	211	51	85.429	0.79	0.54 to 1.14
North America	216	107	27	87.556	109	25	83.972	1.00	0.58 to 1.73
Asia	518	258	87	77.830	260	87	76.484	1.01	0.75 to 1.36
Other	62	33	12	77.047	29	6	93.103	0.46	0.17 to 1.22

B

Baseline Factors	Total No.	R-CHOP (n = 712) No.	R-CHOP Events	R-CHOP 1-Year KM Rate	G-CHOP (n = 706) No.	G-CHOP Events	G-CHOP 1-Year KM Rate	HR	95% Wald CI
All patients	1,418	712	215	79.778	706	201	81.614	0.92	0.76 to 1.12
Cell of origin									
GCB	540	269	74	81.022	271	55	86.062	0.72	0.5 to 1.01
ABC	243	118	47	73.714	125	45	74.634	0.86	0.57 to 1.29
Unclassified	150	75	27	73.973	75	27	80.572	1.02	0.60 to 1.75
Missing	485	250	627	83.214	235	74	80.634	1.18	0.85 to 1.64

Vitolo U et al, JCO 2017.

How to move beyond R-CHOP in aggressive lymphoma?

Table 2. Biologic Factors Associated with Outcomes in Patients with DLBCL.*

Biomarker	Methodology	Prognostic Significance	Other Implications
Cell-of-origin molecular classification	Various technologies (gene array, digital expression profiling, multiplex RT-PCR–based methods)	ABC subtype is associated with poor prognosis	ABC subtype may be associated with an increased risk of CNS relapse
Cell-of-origin IHC-based algorithms	Various IHC-based algorithms to assign molecular subtype; most commonly the Hans algorithm†	Non-GCB subtype is associated with poor prognosis, although this is not confirmed in some studies	Dichotomizes patients into GCB and non-GCB subgroups and represents an approximation of molecular subtype as assessed by GEP
Double- or triple-hit rearrangement involving *MYC* and either *BCL2* or *BCL6* or both	FISH is used primarily in clinical practice; the use of break-apart probes is recommended; GEP-based assays may identify additional cases with double-hit signature undetected by FISH with similar biologic features and outcome‡	Double- or triple-hit cases are associated with poor prognosis; poor prognosis may be limited to cases in which the *MYC* translocation partner is an immunoglobulin gene locus	Now classified by the WHO as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements; majority of cases are GCB subtype; may benefit from more intensive therapies
MYC and BCL2 protein expression	IHC measurement to estimate the percentage of cells expressing MYC or BCL2 protein or both; 40% cutoff threshold for MYC and 50% for BCL2	Double expression of MYC and BCL2 or expression of BCL2 alone is associated with worse prognosis	May have prognostic significance mainly in GCB-type DLBCL; MYC-BCL2 double expression may be associated with an increased risk of CNS relapse
Proliferation index	IHC measurement of proliferation marker Ki67; no established cutoff threshold	Higher proliferation may be associated with poorer prognosis, although it has not consistently been shown to be an independent prognostic marker	High proliferation rate (>80%) may increase suspicion that patient has high-grade B-cell lymphoma (with or without double- or triple-hit rearrangements)
TP53	PCR, NGS, or gene array for detection of mutation or deletion of *TP53*	*TP53* mutations in the DNA-binding domain are associated with poor prognosis	May cluster with a genetic subset of DLBCL

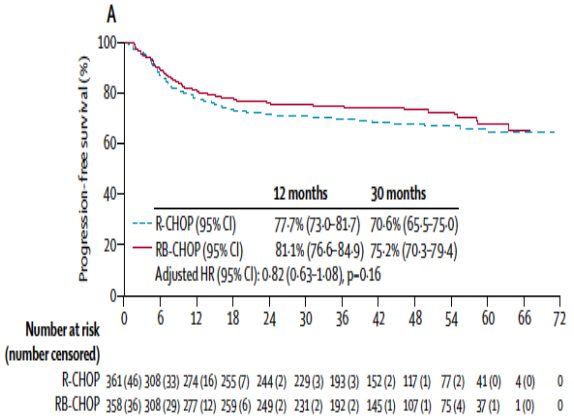
… targeting “biological high risk”:

- COO-ABC
- Double or Triple-hit
- Double expressor
- TP53 mutations

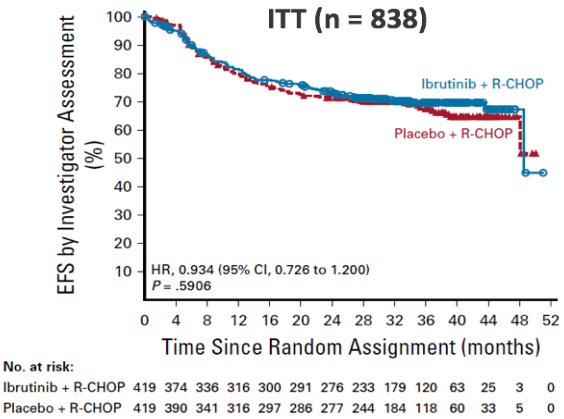
Sehn LH and Salles G, NEJM 2021.

COO-ABC

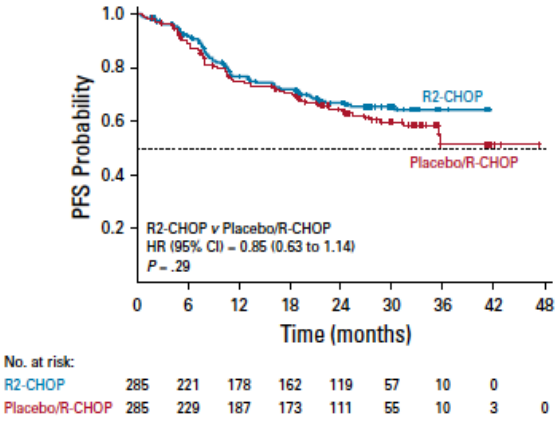
R-CHOP + Bortezomib



R-CHOP + Ibrutinib



R-CHOP + Lenalidomide



Davies A, et al. Lancet Oncol 2019; Younes A, et al. J Clin Oncol 2019; Nowakowski G, et al. J Clin Oncol 2021.

DEL and DHL: poor outcome with standard treatment

Review Article

Double Hit and Double Expressors in Lymphoma: Definition and Treatment

Peter A. Riedell, MD; and Sonali M. Smith, MD

Cancer 2018;124:4622-4632.

TABLE 1. Outcomes of Patients With DHL and DEL in Select Studies

Source	Focus	Patients, No.	Treatment, No.	PFS/EFS	OS
Johnson 2012[15]	DHL	14	R-CHOP: 14	PFS: 18% at 5 y	OS: 27% at 5 y
Johnson 2009[19]	DHL	54	R-CHOP: 11	N/A	Median OS: 1.4 y
Petrich 2014[46]	DHL	311	R-CHOP: 100	Median PFS: 7.8 mo	N/A
			R-EPOCH: 64	Median PFS: 21.6 mo	N/A
Oki 2014[51]	DHL	129	R-CHOP: 57	EFS: 20% at 5 y	OS: 22% at 5 y
			R-EPOCH: 28	N/A	N/A
Johnson 2012[15]	DEL	55	R-CHOP: 55	PFS: 32% at 5 y	OS: 36% at 5 y
Green 2012[43]	DEL	54	R-CHOP: 54	PFS: 39% at 3 y	OS: 43% at 3 y
Hu 2013[44]	DEL	157	R-CHOP: 157	PFS: 27% at 5 y	OS: 30% at 5 y

Abbreviations: DEL, double-expressor lymphoma; DHL, double-hit lymphoma; EFS, event-free survival; N/A, not available; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

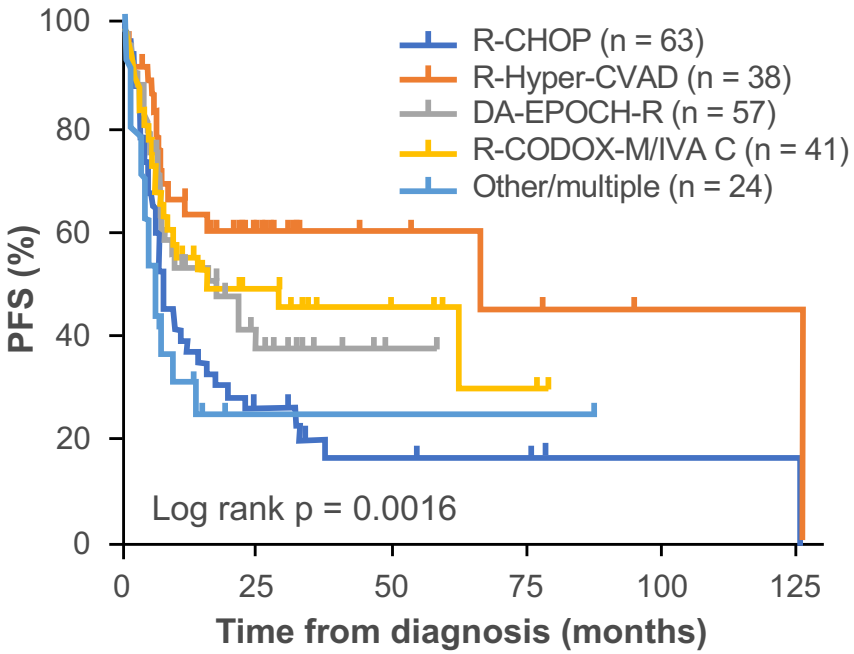
Riedell PA, et al. Cancer 2018.

DHL

- 311 DHL patients; median age 60 years (19–87)
  - 50% patients had DLBCL; 48% patients had BCLU
  - 87% patients had a *BCL2* translocation
  - 5% patients had a *BCL6* translocation
  - 8% patients had triple-hit lymphoma
  - 58% patients had a GCB COO

Induction regimen	Patients, n (%)
R-CHOP	100 (32)
R-Hyper-CVAD	66 (21)
DA-EPOCH-R	64 (21)
R-CODOX-M/IVAC	42 (14)
R-ICE	9 (3)
Others	31 (10)

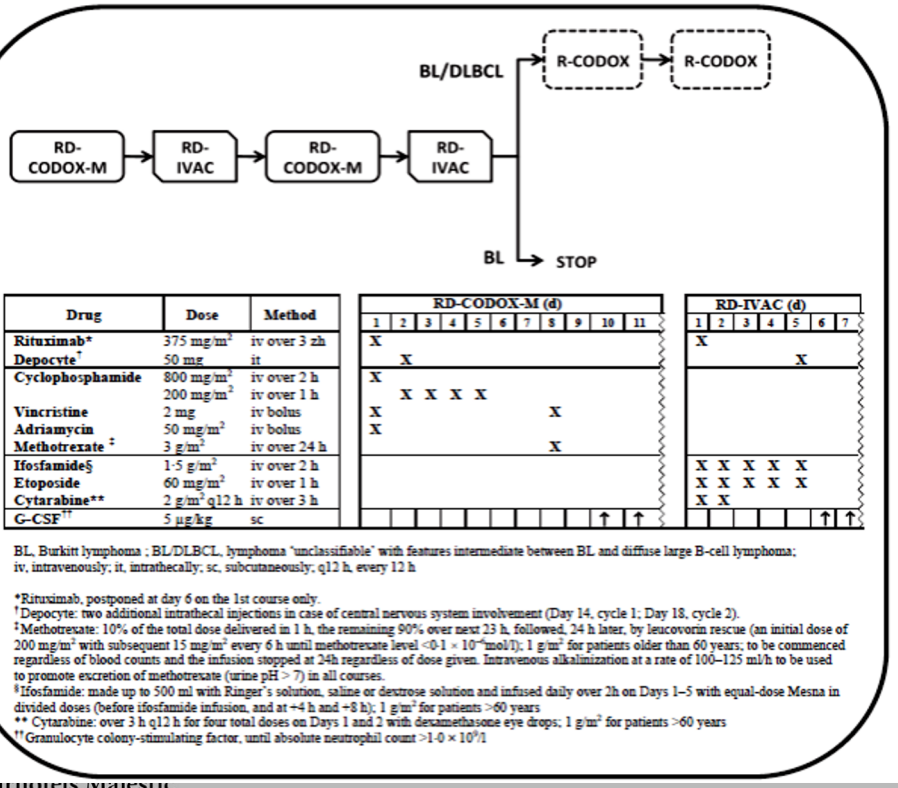
R-CHOP is not adequate in DHL



Petrich AM, et al. Blood 2014.

DHL

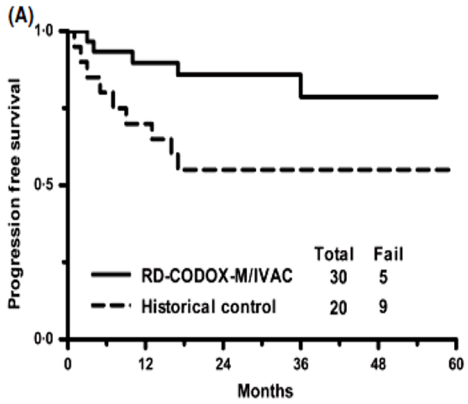
RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and 'unclassifiable' highly aggressive B-cell lymphoma

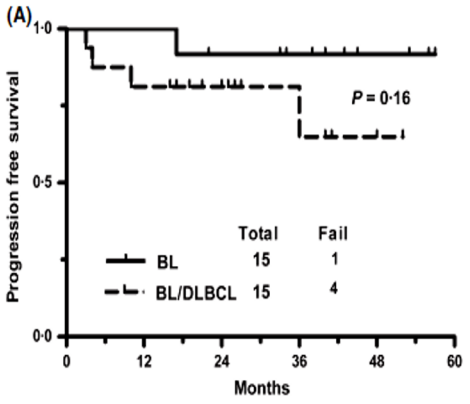


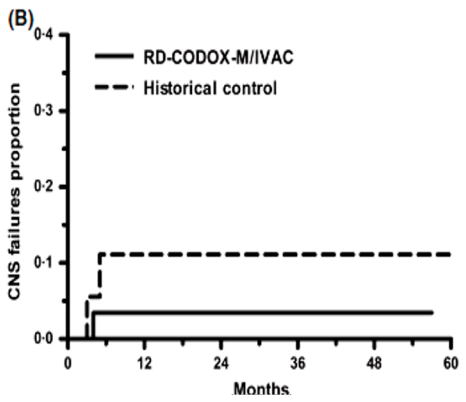
Drug	Dose	Method	RD-CODOX-M (d) 1 2 3 4 5 6 7 8 9 10 11	RD-IVAC (d) 1 2 3 4 5 6 7
Rituximab*	375 mg/m²	iv over 3 zh	X	X
Depocyte†	50 mg	it	X	X
Cyclophosphamide	800 mg/m²	iv over 2 h	X	
	200 mg/m²	iv over 1 h	X X X X	
Vincristine	2 mg	iv bolus	X X	
Adriamycin	50 mg/m²	iv bolus	X X	
Methotrexate ‡	3 g/m²	iv over 24 h	X	
Ifosfamide§	1·5 g/m²	iv over 2 h		X X X X X
Etoposide	60 mg/m²	iv over 1 h		X X X X X
Cytarabine**	2 g/m² q12 h	iv over 3 h		X X
G-CSF††	5 µg/kg	sc	↑ ↑	↑ ↑

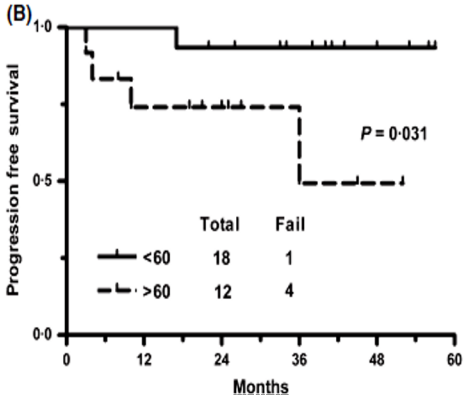
BL, Burkitt lymphoma ; BL/DLBCL, lymphoma 'unclassifiable' with features intermediate between BL and diffuse large B-cell lymphoma; iv, intravenously; it, intrathecally; sc, subcutaneously; q12 h, every 12 h

*Rituximab, postponed at day 6 on the 1st course only.
†Depocyte: two additional intrathecal injections in case of central nervous system involvement (Day 14, cycle 1; Day 18, cycle 2).
‡Methotrexate: 10% of the total dose delivered in 1 h, the remaining 90% over next 23 h, followed, 24 h later, by leucovorin rescue (an initial dose of 200 mg/m² with subsequent 15 mg/m² every 6 h until methotrexate level <0·1 × 10^{-6}mol/l); 1 g/m² for patients older than 60 years; to be commenced regardless of blood counts and the infusion stopped at 24h regardless of dose given. Intravenous alkalinization at a rate of 100–125 ml/h to be used to promote excretion of methotrexate (urine pH > 7) in all courses.
§Ifosfamide: made up to 500 ml with Ringer's solution, saline or dextrose solution and infused daily over 2h on Days 1–5 with equal-dose Mesna in divided doses (before ifosfamide infusion, and at +4 h and +8 h); 1 g/m² for patients >60 years
** Cytarabine: over 3 h q12 h for four total doses on Days 1 and 2 with dexamethasone eye drops; 1 g/m² for patients >60 years
††Granulocyte colony-stimulating factor, until absolute neutrophil count >1·0 × 10^9/l









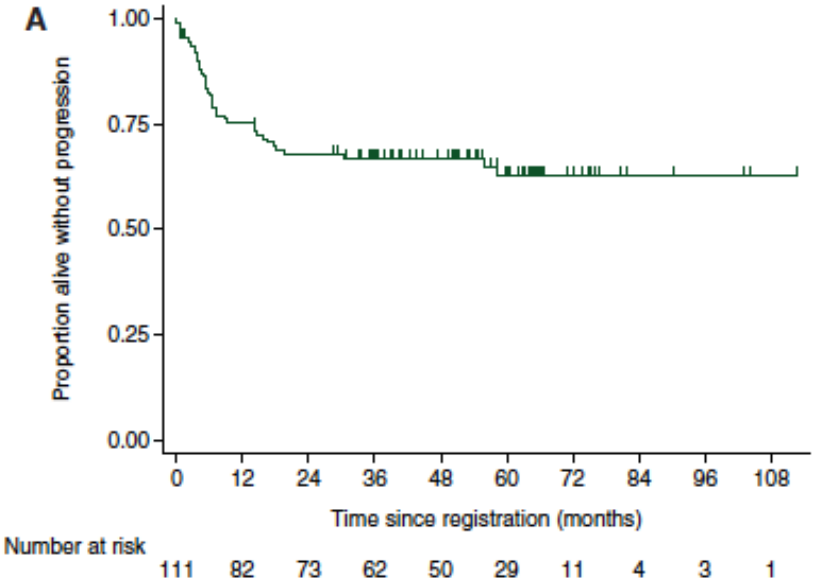
Corazzelli et al, BJH 2011.

ESMO
ANNALS OF ONCOLOGY

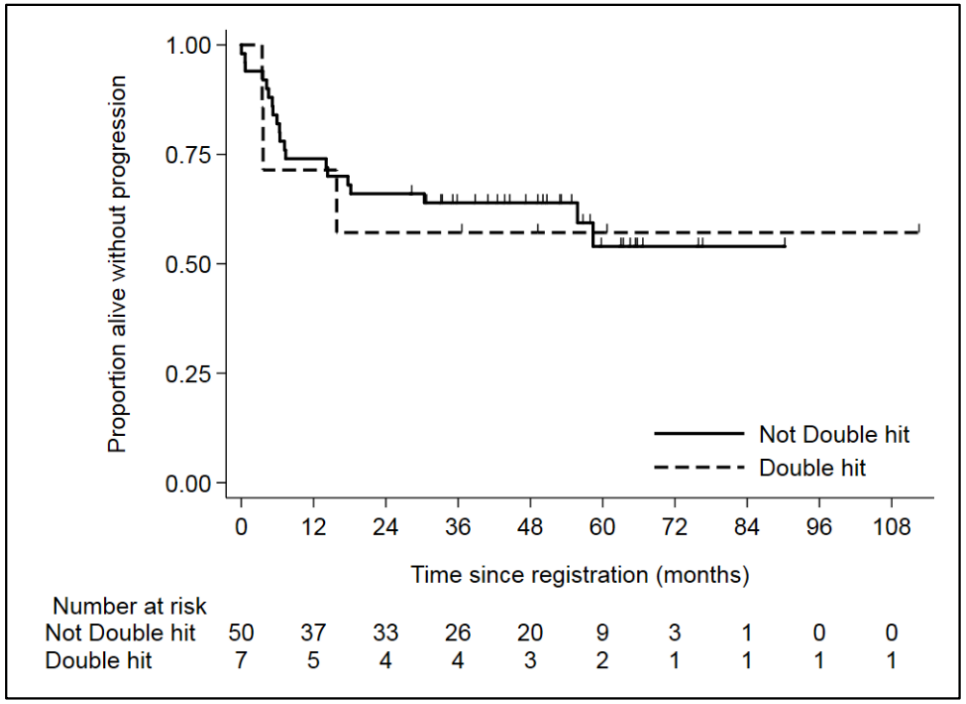
ORIGINAL ARTICLE

Favourable outcomes for high-risk diffuse large B-cell lymphoma (IPI 3—5) treated with front-line R-CODOX-M/R-IVAC chemotherapy: results of a phase 2 UK NCRI trial☆

A. K. McMillan[1*†], E. H. Phillips[2,3†], A. A. Kirkwood[2], S. Barrans[4], C. Burton[4], S. Rule[5], R. Patmore[6], R. Pettengell[7], K. M. Ardeshna[8], A. Lawrie[2], S. Montoto[9], S. Paneesha[10], L. Clifton-Hadley[2] & D. C. Linch[2,11]



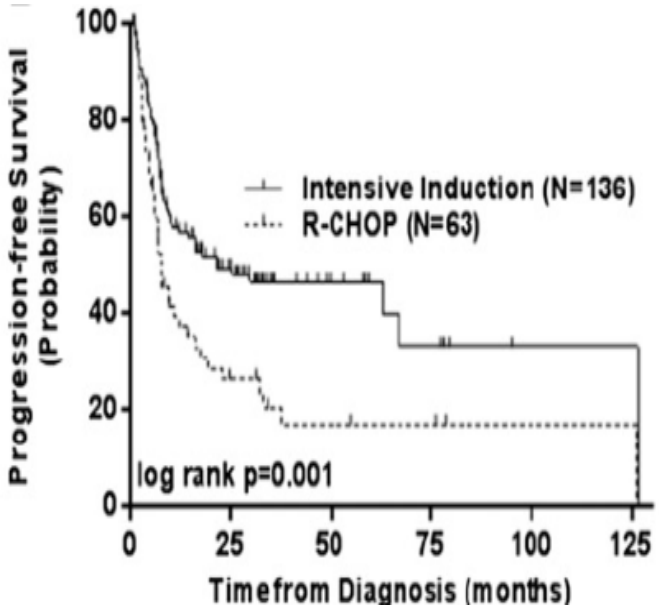
DHL

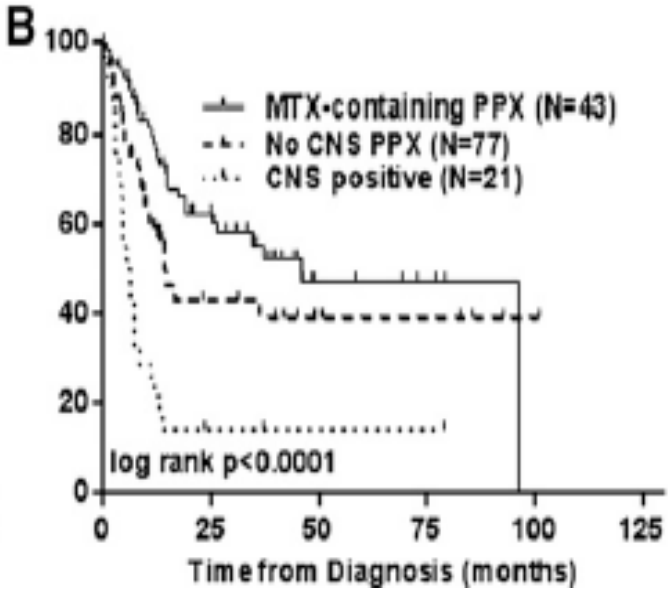


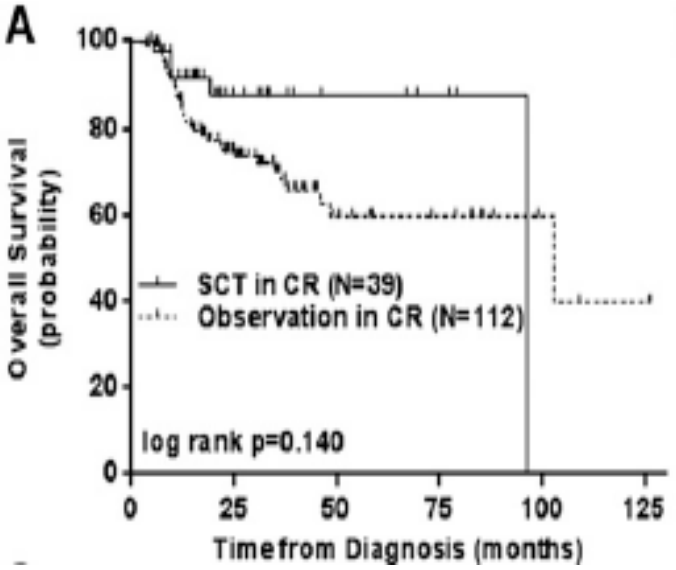
McMilln AK, et al. Ann Oncol 2020.

DHL

Consolidation with ASCT?





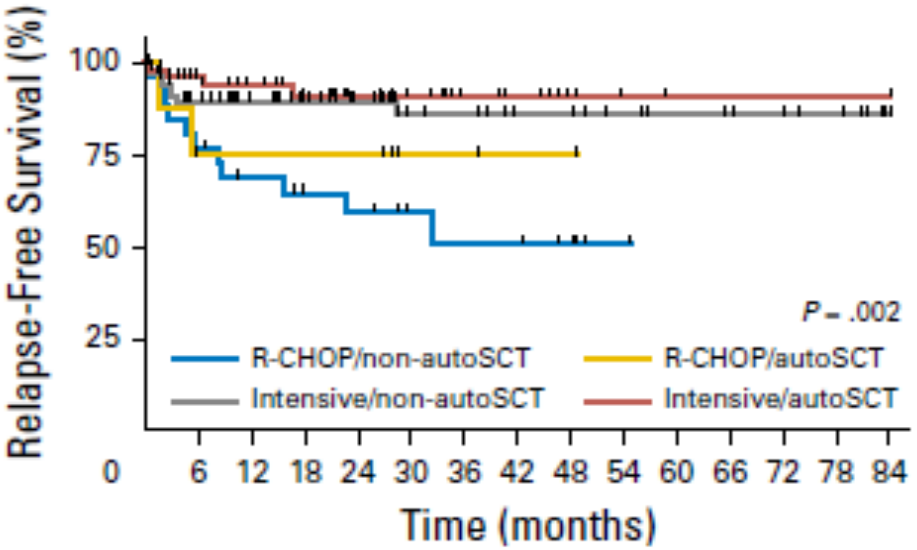


Petrich AM, et al. Blood 2014.

DHL

Consolidation with ASCT?

Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission



159 patients: 62 autoSCT; 97 no ASCT.

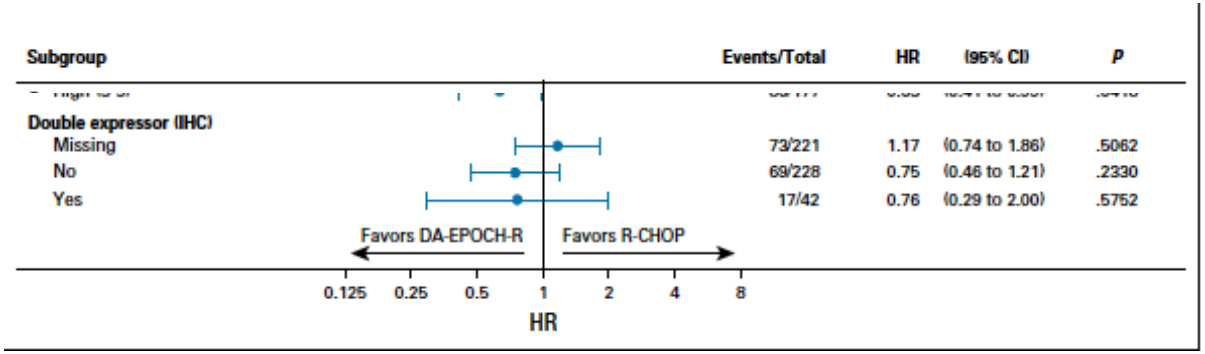
	R-CHOP n 35	R-DaEPOCH n 81	RhyperCVAD n 32	R-CODOXM/IVAC n 11	p
3y-EFS	56%	88%	87%	91%	0.003
3y-OS	77%	87%	90%	100%	0.36

Landsburg D, et al. JCO 2017.

DEL

DA-EPOCH-R is superior to R-CHOP in DEL??

Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303



- lower incidence of the DE phenotype (15.6%)
- **no differences by treatment arm in the MYC rearranged or patients with the DE phenotype,** but this subset was of insufficient size for statistical comparison.

Bartlett NL et al, JCO 2019.

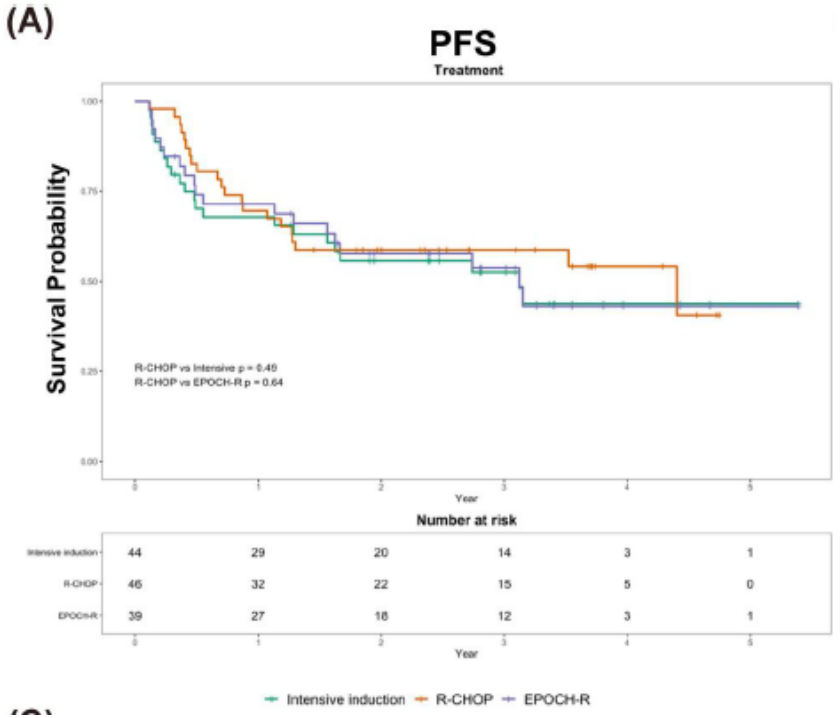
DEL

DA-EPOCH-R is superior to R-CHOP in DEL??

Impact of initial chemotherapy regimen on outcomes for patients with double-expressor lymphoma: A multi-center analysis

Christopher R. D'Angelo[1] | Walter Hanel[2] | Yi Chen[3] | Menggang Yu[3] | David Yang[4] | Ling Guo[5] | Reem Karmali[6] | Madelyn Burkart[6] | Colleen Ciccosanti[7] | Kevin David[8] | Zachary Risch[5] | Carlos Murga-Zamalloa[9] | Sumana Devata[10] | Ryan Wilcox[11] | Malvi Savani[12] | Elizabeth L. Courville[13] | Veronika Bachanova[14] | Emma Rabinovich[9] | David Peace[9] | Fauzia Osman[3] | Narendranath Epperla[5] | Vaishalee P. Kenkre[4]

	Total N = 90	R-CHOP N = 46	Intensive therapy N = 44	p-value
Median followup (year, IQR)	2.7 (1.5–3.7)	3.0 (1.98–3.71)	2.4 (1.2–3.4)	0.041
Expressor status (%)				
DEL	30 (33)	15 (33)	15 (34)	1
TEL	60 (67)	31 (67)	28 (66)	



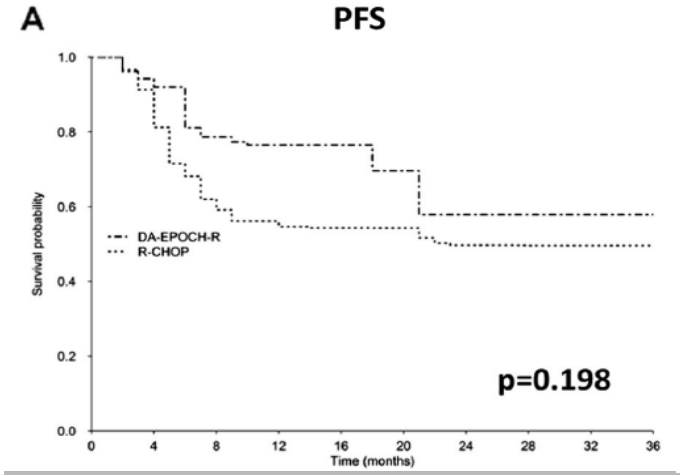
D'Angelo CR et al, Hematol Oncol 2021.

DEL

DA-EPOCH-R is superior to R-CHOP in DEL??

Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma

A. Dodero[1] · A. Guidetti[1,2] · A. Tucci[3] · F. Barretta[4] · M. Novo[5] · L. Devizzi[1] · A. Re[3] · A. Passi[3] · A. Pellegrinelli[6] · G. Pruneri[2,6] · R. Miceli[4] · A. Testi[6] · M. Pennisi[1] · M. C. Di Chio[1] · P. Matteucci[1] · C. Carniti[1] · F. Facchetti[7] · G. Rossi[3] P. Corradini[1,2]



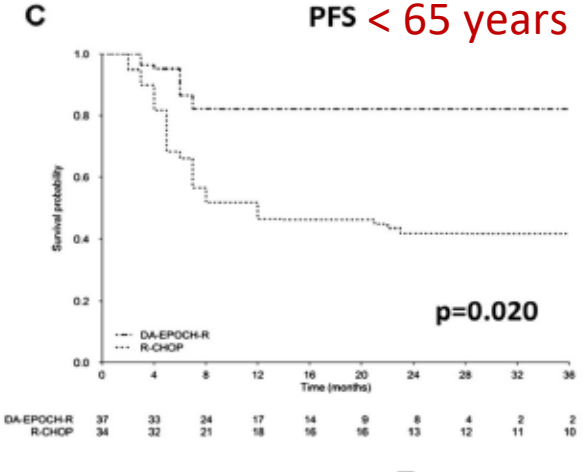


Table 1 Clinical and biological characteristics

Variable	ALL N = 114	DA-EPOCH-R N = 51	R-CHOP N = 63	SMD before/after
Age				
Median	62 years	58 years	65 years	0.296/<0.001
Range	29–81	29–79	36–81	
Age > 65 years	43 (38%)	14 (27%)	29 (46%)	
Sex				
Male	70 (62%)	32 (63%)	38 (60%)	0.049/0.018
Female	44 (38%)	19 (37%)	25 (40%)	
Histology				
DLBCL	106 (93%)	47(92%)	59 (94%)	
Transformed	8 (7%)	4 (8%)	4 (6%)	—
Stage				
I–II	28 (25%)	8 (16%)	20 (32%)	0.850/0.079
III–IV	86 (75%)	43 (84%)	43 (68%)	
IPI				
1–2	62 (54%)	24 (47%)	38 (60%)	0.332/0.101
3–5	52 (46%)	27 (53%)	25 (40%)	
BM involvement				
Yes	22 (19%)	16 (32%)	6 (10%)	0.552/0.421
No	92 (81%)	35 (68%)	57 (90%)	
Extranodal involvement[a]				
Yes	69 (60%)	46 (90%)	23 (36%)	—
No	45 (40%)	5 (10%)	40 (64%)	
CNS involvement				
Leptomeningeal	3 (3%)	2 (4%)	1 (1%)	—
Cytogenetic abnormalities				
DE-only	58 (51%)	18 (35%)	40 (63%)	0.749/0.119
DE with SH	29 (25%)	16 (31%)	13 (21%)	
DE with DH/TH	10 (9%)	8 (16%)	2 (3%)	
DE with atypical DH	15 (13%)	9 (18%)	6 (10%)	
Missing	2 (2%)	0 (0%)	2 (3%)	

Dodero A et al, Leukemia 2019.

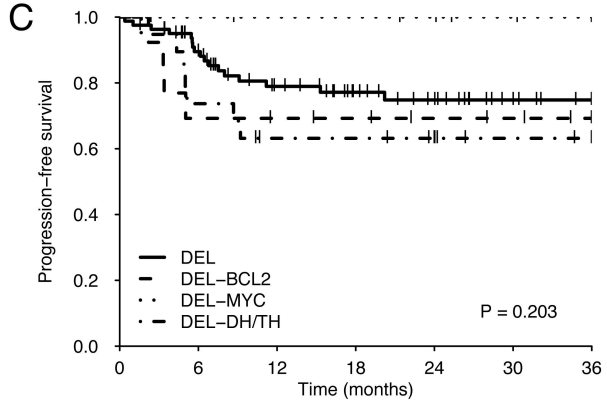
TP53

DA-EPOCH-R did not overcome the negative prognostic value of TP53 mutations

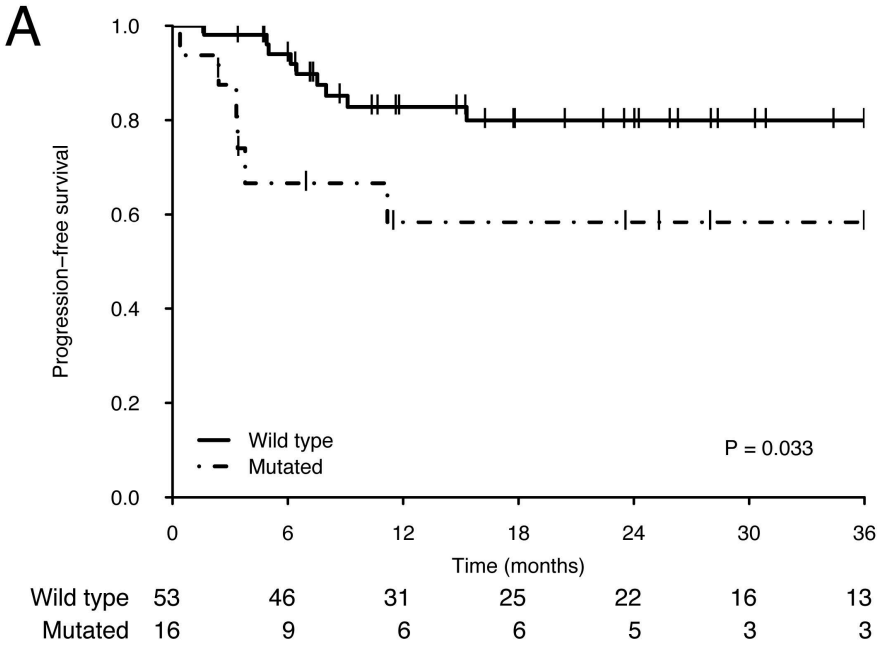
Dose-Adjusted Epoch and Rituximab for the treatment of double expressor and double hit diffuse large B-cell lymphoma: impact of TP53 mutations on clinical outcome

by Anna Dodero, Anna Guidetti, Fabrizio Marino, Alessandra Tucci, Francesco Barretta, Alessandro Re, Monica Balzarotti, Cristiana Carniti, Chiara Monfrini, Annalisa Chiappella, Antonello Cabras, Fabio Facchetti, Martina Pennisi, Daoud Rahal, Valentina Monti, Liliana Devizzi, Rosalba Miceli, Federica Cocito, Lucia Farina, Francesca Ricci, Giuseppe Rossi, Carmelo Carlo-Stella, and Paolo Corradini

C



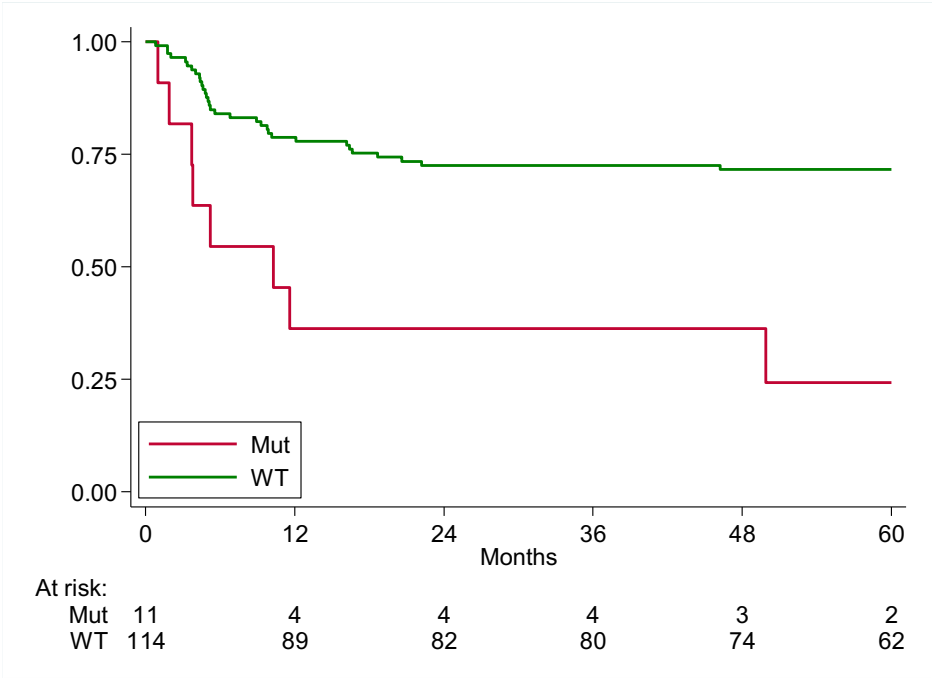
A



Dodero A, Guidetti A et al, Haematologica 2021.

TP53

Intensified therapy did not overcome the negative prognostic value of TP53 mutations



FIL-DLCL04

median follow-up 72 months

5-yrs FFS Mutated 24% 95%CI (4-52)
5-yrs FFS Wild Type 72% 95% CI (62-79)
HR 3.75 (1.72-8.16) p 0.001

No advantage in RCHOP+ASCT arm

Chiappella A et al, EHA 2018.

Conclusions

- R-CHOP is still the standard treatment in DLBCL
- The addition of Bortezomib, Lenalidomide, Ibrutinib to R-CHOP did not improve the outcome of ABC-DLBCL
- Treatment of Double Expressors Lymphomas is not yet established
- R-CHOP is not adequate in Double Hit Lymphomas and is associated with inferior outcome; intensified treatments are recommended
- “high risk” patients need to be better defined

Future directions

- Target Molecular Classification Subgroups
  - R-CHOP + X-Y-Z
    - Lenalidomide-Ibrutinib-R-chemo (CHOP/EPOCH): Smart Start, NCT02636322
    - Polatuzumab-R-CHOP: Polarix, NCT01992653
    - Tafasitamab-Lenalidomide-R-CHOP: FrontMIND, NCT04824092

Westin J, ICML 2019;

Aknowledgements

Hematology & Stem Cell Transplantation
Prof. Paolo Corradini

FONDAZIONE ITALIANA LINFOMI

Aggressive B-NHL committee
Monica Balzarotti
Maurizio Martelli
Umberto Vitolo