EVENTO FAD

LINFOMI AGGRESSIVI:

Questioni Aperte

2 OTTOBRE 2020

Linfomi diffusi a grandi cellule B: focus sul management del sottotipo ABC e delle varianti con riarrangiamento del cMYC

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Struttura Complessa di Ematologia

Presidio Ospedaliero di Treviso

Disclosures of Dr. Piero Maria Stefani

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ROCHE							**X**
TAKEDA							**X**
GENTILI							**X**
PFIZER							**X**

Studi retrospettivi

- Copie-Bergman JCO 2009 RCHOP GELA. Algoritmo di Hans non ha significato prognostico, il riarrangiamento di BCL6 ma non di BCL2 condiziona la prognosi. Se presenti almeno due tra FOXP1, MUM1/IRF4 e BCL6, in multivariata hanno valore prognostico.
- Copie-Bergman Blood 2015 GELA/LYSA. In multivariata MYC-R ma in particolare SH e MYC/BCL2 DH hanno valore prognostico indipendente per PFS e OS assieme a IPI e algoritmo di Hans. MYC-IG è associato a prognosi peggiore.
- Cunningham Lancet 2013 RCHOP14 vs. RCHOP21. MYC-R è prognostico per OS solo in univariata, DH non prognostico anche in multivariata. COO , MIB1, BCL2 e BCL6 riarrangiati hanno prognosi migliore con RCHOP14.
- Petrella Ann Onc 2017 LNH03-6B trial: BCL2 positività e algoritmo di Hans impattano su OS e PFS.

Studi retrospettivi

•Kuhnl 2017 Ann Oncol 2017. COO definita secondo Hans non ha significato prognostico. MYC-R e DH hanno OS peggiore indipendentemente da IPI e braccio di trattamento. Riarrangiamento di BCL2 e BCL6 non ha significato prognostico.

•McPhail 2018 Haematologica 2018. I casi DH/THL trasformati hanno una prognosi peggiore (median OS 10.8 mesi e EFS12 10%) e sono tutti con BCL2 ± BCL6 riarrangiati.

I DH BCL6 riarrangiati sono sempre solo *de novo* e sono sia GCB che non CGB.

Nei DH/THL il fallimento dell'induzione è precoce specie nei pazienti < 60 aa.

R-CODOX-M/IVAC sembra preferibile nei pazienti < 60 aa..

La bassa espressione di MYC in IHC non dovrebbe comportare per definizione l'omissione della FISH: 14% dei casi risultava riarrangiato anche se con positività < 40%. Non è noto se questa situazione abbia significato prognostico. Nessuna correlazione tra la prognosi e partner di riarrangiamento di MYC.

Clinical Impact of the Cell-of-Origin Classification and the *MYC/BCL2* Dual Expresser Status in Diffuse Large B-Cell Lymphoma Treated Within Prospective Clinical Trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group

Annette M. Staiger, Marita Ziepert, Heike Horn, David W. Scott, Thomas F.E. Barth, Heinz-Wolfram Bernd,

J Clin Oncol 35:2515-2526. © 2017 by American Society of Clinical Oncology

- **Concordanza Hans vs. GEP 82% per RICOVER60 e 73% per RMegaCHOEP.**
- **DE più frequenti nel gruppo ABC (esclusi unclassified).**
- **BCL2 o MYC riarrangiati e DH sono prevalentemente GCB.**
- **BCL6 riarrangiati e MYC/BCL6 DH ugualmente rappresentati sia nel tipo ABC (prevalenti) che GCB.**
- **Nessuna differenza di EFS/OS in funzione di COO in entrambi gli studi (multivariata).**
- **Espressione di MYC e di BCL2 ha significato prognostico prevalentemente per GCB se inclusi i DH/TH.**
- **DE status (dopo esclusione di DH) ha impatto prognostico indipendentemente da COO.**
- **DE nel gruppo ABC: EFS 5-year 34% vs. 65% (p=0.02); PFS 39% vs. 68% (p=0.03); OS 42% vs. 75% (p=0.008) e rispetto a GCB non DE.**
- **I Pazienti non DE hanno prognosi peggiore nel gruppo ABC: EFS 5-year 65% vs. 80% (p=0.06); PFS 68% vs. 85% (p=0.04); OS 75% vs. 88% (p=0.12).**

Prognostic Significance of MYC Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium. Andreas Rosenwald. J Clin Oncol 37:3359-3368. 2019

•2.383 patients; MYC-R was present in 264 (11%).
•associated with a significantly shorter progression-free and overall survival, within the first 24 months after diagnosis.
•The adverse prognostic impact of MYC-R was only evident in patients with a concurrent rearrangement of BCL2 and/or BCL6 and an IG partner (p= 0.001).
•Patients with MYC-SH (either IG or non-IG) and those with MYC-DH/TH non-IG had an outcome comparable with those with DLBCL without MYC-R.
•MYC-SH DLBCL in the non-GCB subgroup have an inferior outcome compared with MYC-SH DLBCL in the GCB subgroup (P = .076 for OS).
•The survival rate for patients with MYC-DH/TH lymphoma with DLBCL morphology. may be significantly better (approximately 60% after 5 years) compared with those with MYC-DH/TH lymphoma with Burkitt-like or blastoid morphology.

Molecular background delineates outcome of double protein expressor diffuse large B-cell lymphoma

blood advances 11 AUGUST 2020 · VOLUME 4, NUMBER 15

Leo Meriranta,[1-3] Annika Pasanen,[1-3,*] Amjad Alkodsi,[1,*] Jari Haukka,[4] Marja-Liisa Karjalainen-Lindsberg,[5] and Sirpa Leppä[1-3]

$BCL2^{TL}$ e $BCL2^{GA}$ sono mutualmente esclusivi.

$BCL2^{TL}$ e MYC^{TL} sono altamente specifici del sottotipo GCB ed associati a stadio avanzato.

I casi con MYC^{OE} presentano MYC^{TL} nel 53% dei casi e concomitano più frequentemente alterazioni di TP53 .

MYC^{TL} si associa a varianti strutturali di BCL2 (double alteration B-cell lymphomas [DA BCL]) e a mutazioni di TP53, CREBBP e EZH2.

•Analogamente $BCL2^{GA}$ si associa al sottipo ABC.

$BCL6^{TL}$ sono più frequenti nel gruppo non-GCB DLBCLs.

Non-GCB DPE possono originare sia da BN2 o MCD-like ABC.

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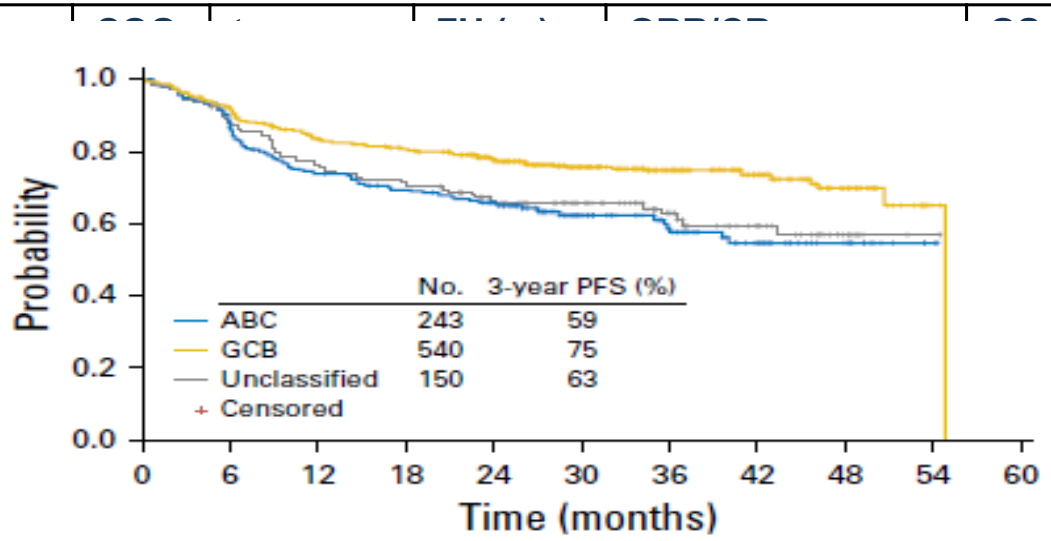
- **DPE è associata a high risk disease più spesso ABC/non-GCB DLBCLs.**
- **Oltre al "classico" DHIT, vi sono casi di DPE GCB con combinazione di MYC^{TL} e $BCL2^{GA}$. Costituiscono il 58% dei DPE GCBs e si associa alterazione di TP53.**
- **I casi con MYC^{TL} probabilmente identificano un sottotipo compreso tra EZB/C3 e C2/A53.**
- **MYC^{OE} e DPE status (spesso con alterazione di TP53) sono fattori predittivi indipendenti nei non-GCB DLBCL.**

Obinutuzumab CHOP vs. Rituximab CHOP

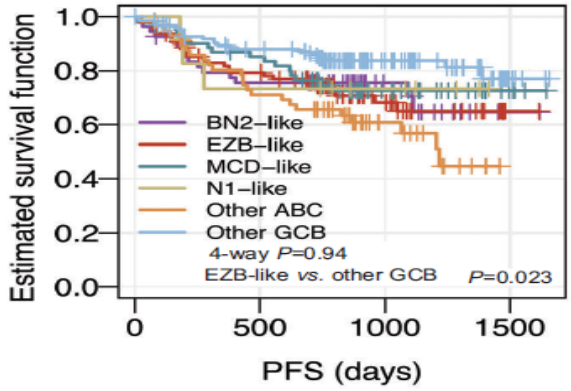
Ref.	n.	ag					%	PFS %
Vitolo Ph2 GOYA 2017	706 vs. 16	62					vs	72,5 vs. 70,6
Sharman Ph2 GATHER 2019	100	62						GCB 75,9 vs. ABC 66,5

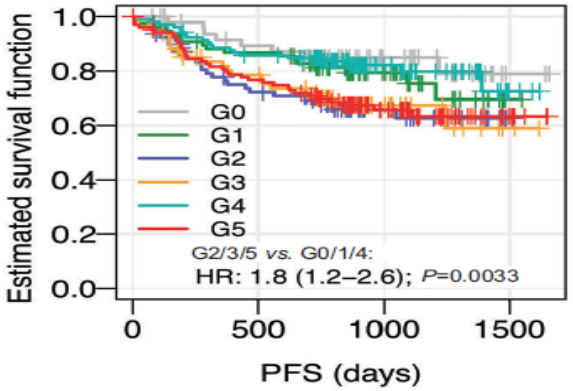


Prognostic impact of somatic mutations in diffuse large B-cell lymphoma and relationship to cell-of-origin: data from the phase III GOYA study

Haematologica 2020
Volume 105(9):2298-2307

Christopher R. Bolen,[1*] Magdalena Klanova,[2,3,4*] Marek Trnény,[2]





- Lo studio ha evidenziato sia clusters molecolari (Schmitz and Chapuy), in parte riconducibili a sottotipi di COO come GCB (EZB-like, G3), o ABC (MCD- o N1-like, G5), o Unclassified (BN2- like), sia cluster indipendenti da COO.

- Prognosi peggiore per i clusters C2, C3 and C5 (according to Chapuy).

- Solo alterazioni di BCL2 risultavano significativamente associate alla prognosi indipendentemente da COO.

MONOCLONALI BISPECIFICI

BLINATUMUMAB

Dufner Blood Advances 2019.
Long-term outcome of patients With relapsed/refractory B-cell non-Hodgkin lymphoma treated with blinatumomab. Ph1.
38 patients, 5 (13%) with DLBC
No evidence for long-term toxicities, mOS was 4.6 years.
Responding patients who had received >60 mg/m2/d achieved a median OS of 7.7 years.
5 DLBCL only 1 responding

MOSUNETUZUMAB

Schuster. Blood 2019 134 S1:6.
DLBCL R/R after CAR-T. Phase I/Ib.
DLBCL pts (87 +29 trFL), 23 prior CAR-T. 16 were efficacy evaluable (7 DLBCL, 5 tFL, 4 FL).
Expansion of previously administered CAR-Ts after M administration was detected
ORR /CR: 64.1% (41/64)/42.2% (27/64) in iNHL pts and 34.7% (41/119)/18.6%, (22/119) in aNHL pts.

Lenalidomide RCHOP vs. RCHOP

Ref.	n.	age	COO by	tx	FU (m)	ORR/CR	OS %	PFS %
Vitolo Ph2 REAL07 2014	49	69	Hans	L 15 mg d1-14 RCHOP	28	92/86	92	74
Nowakowski Ph2 2019	64	65	GEP	L 25 mg d1-10 RCHOP	23,5	98/80	90	70

Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non–Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study

Grzegorz S. Nowakowski, Betsy LaPlant, William R. Macon, Craig B. Reeder, James M. Foran, Garth D. Nelson,

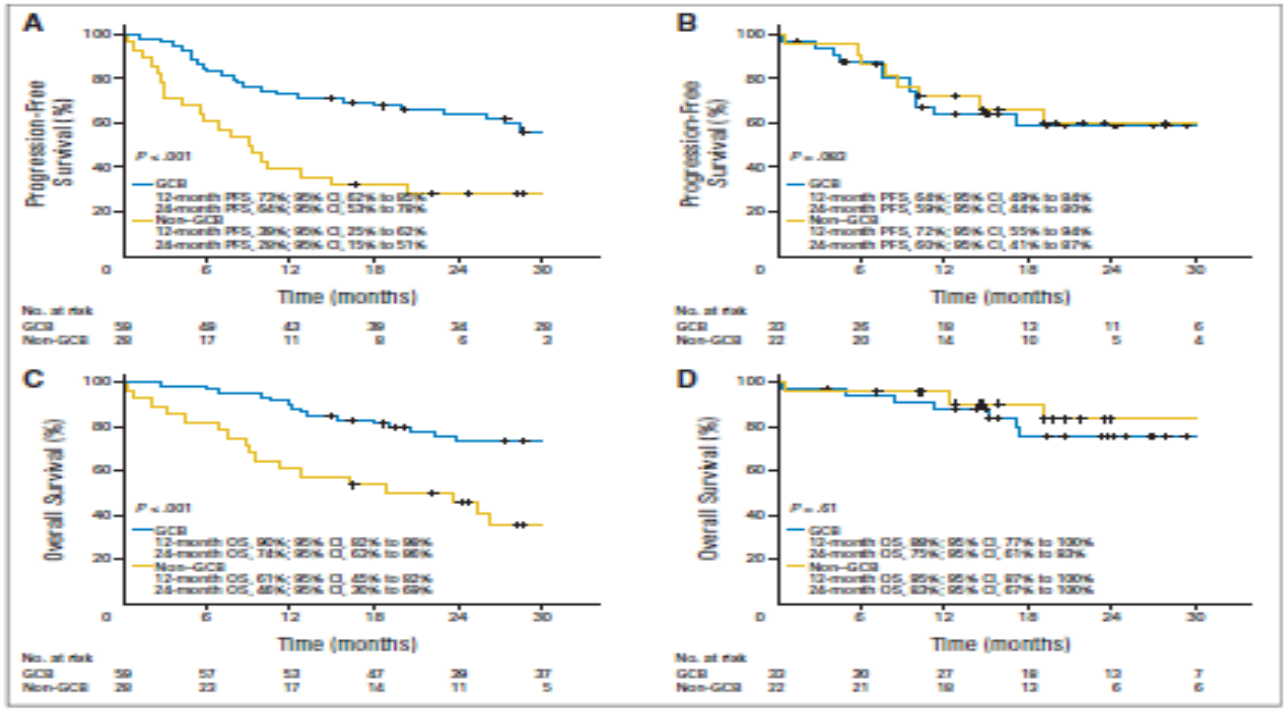


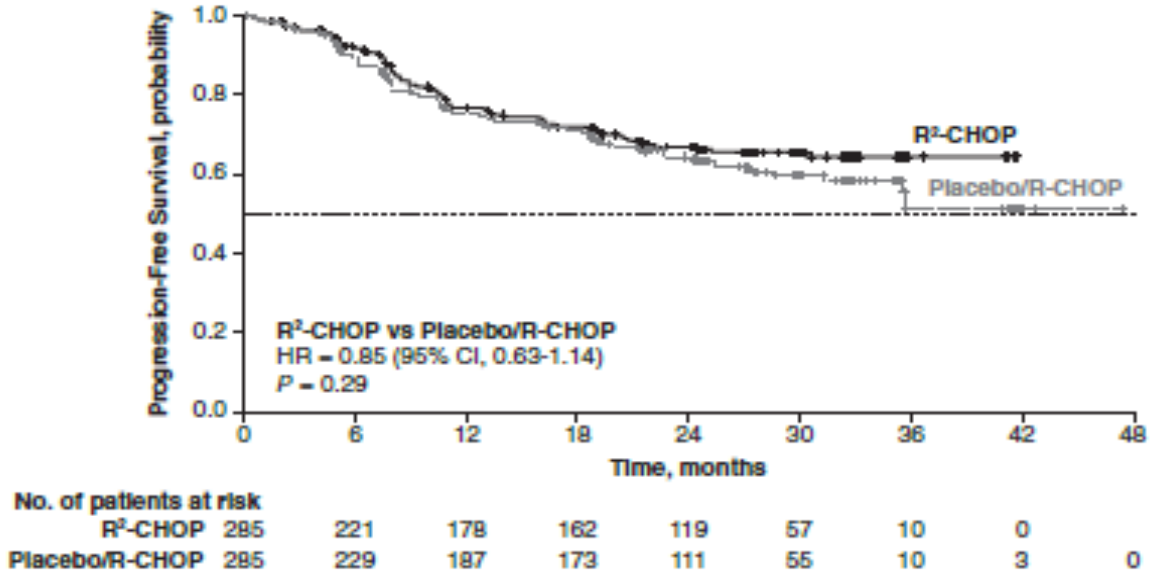
Fig 2. Outcomes of historical control patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and study patients treated with R2CHOP (lenalidomide added to R-CHOP) based on germinal center B-cell (GCB) versus non-GCB diffuse large B-cell lymphoma (DLBCL) subtype. (A) Progression-free survival in patients treated with R-CHOP in non-GCB versus GCB DLBCL. (B) Progression-free survival in patients treated with R2CHOP in non-GCB versus GCB DLBCL. (C) Overall survival in patients treated with R-CHOP in GCB versus non-GCB DLBCL. (D) Overall survival of patients treated with R2CHOP in non-GCB versus GCB DLBCL.

J Clin Oncol 33:251-257. © 2014 by American Society of Clinical Oncology

ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. U. Vitolo Lugano 2019.

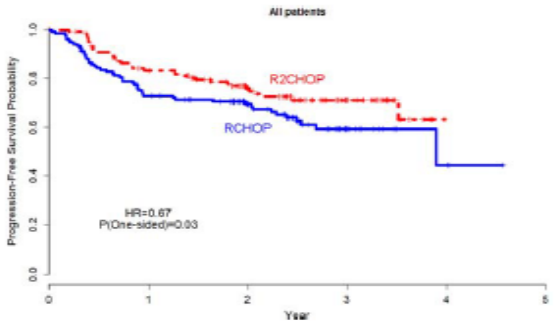
A total of 570 ABC-DLBCL patients met eligibility criteria andwere enrolled in ROBUST (n = 285 per arm)

Overall, the ROBUST study did not meet the primary endpoint of PFS for R 2-CHOP vs. placebo/R-CHOP in previously untreated patients with ABC-DLBCL, although a positive trend fa and higher risk patients. Th f individual medicines, and tion



ADDITION OF LENALIDOMIDE TO R-CHOP (R2CHOP) IMPROVES OUTCOMES IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FIRST REPORT OF ECOG-ACRIN1412 A RANDOMIZED PHASE 2 US INTERGROUP STUDY OF R2CHOP VS R-CHOP. G.S. Nowakowski Lugano 2019.

280 patients (145 R2CHOP, 135 RCHOP) were evaluable; 94 were ABC-DLBCL; 122 GCB-DLBCL and 18 Unclassfied. ORR/CR 92%/67% in R-CHOP vs. 97%/72 (p=0.12) in R2-CHOP arm, median FU 2.4 years; 33% reduction in risk of progression/ death vs.RCHOP: p =0.03. The 2-year overall survival was 87% and 80%, respectively.



Targeting of inflammatory pathways with R2CHOP in high-risk DLBCL

Keenan T. Hartert[1] · Kerstin Wenzl[1] · Jordan E. Krull[1] · Michelle Manske[1] · Vivekananda Sarangi[2] · Yan Asmann[3]

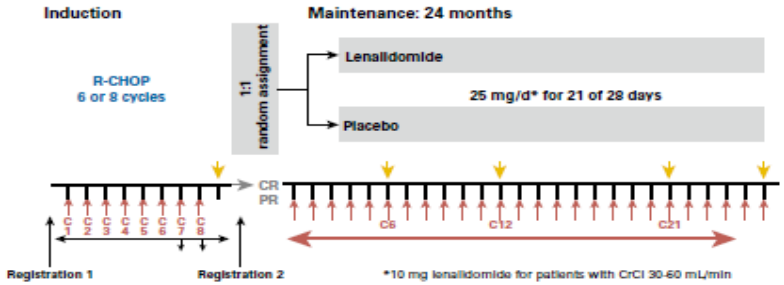
The R2CHOP cases that achieved EFS24 were enriched for genes involved in cell cycle, IL6, JAKSTAT, IL2, and STAT3 pathways. Patients who failed R2CHOP were enriched for genes involved in PI3K-AKT, RAS, MAPK, WNT, and EGFR signaling, pathways recently highlighted as mechanisms of lenalidomide resistance in multiple myeloma.

These data suggest that the C1 and C5 subtypes were responsive to R2CHOP. This is most likely due to the fact that C1 is enriched for SPEN mutations and C5 is enriched for MYD88 and PIM1 mutations.

Leukemia
https://doi.org/10.1038/s41375-020-0766-4

Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Catherine Thieblemont, Hervé Tilly, Maria Gomes da Silva, Rene-Olivier Casasnovas, Christophe Fruchart,



Analysis of outcomes on the basis of COO (Hans criteria) only showed a statistically significant difference in median PFS in favor of lenalidomide (60.9 months) over placebo (52.7 months) in patients with a GCB profile (p=0.04). No significant difference was seen in patients with a non-GCB profile (p=0.75). For OS, there was no difference in either the GCB (p=0.92) or the non-GCB (p=0.07) groups.
Per NanoString, there was no difference in PFS for patients with GCB-like, ABC-like, or unclassified DLBCL (p=0.15, p=0.82, and p=0.31, respectively) and no difference in OS. 18 (21%) patients converted from PET-positive to PET-negative in the lenalidomide arm versus 13 (14%) patients in placebo arm (p=0.20).

J Clin Oncol 35:2473-2481. © 2017.

Long-lasting efficacy and safety of lenalidomide maintenance in patients with relapsed diffuse large B-cell lymphoma who are not eligible for or failed autologous transplantation

Andrés J. M. Ferreri[1] | Marianna Sassone[1] | Piera Angelillo[1] | Francesco Zaja[2] |

After a median follow-up of 65 (range 39-124) months, 22 patients remain progression free, with a 5-year PFS of 48% ± 7%. The duration of response to lenalidomide was longer than response to prior treatment in 30 (65%) patients. Benefit was observed both in de novo and transformed DLBCL, germinal center- B-cell and non germinal-center-B-cell subtypes. Twenty-six patients are alive (5-year OS 62% ± 7%).

Hematological Oncology. 2020;38:257–265.

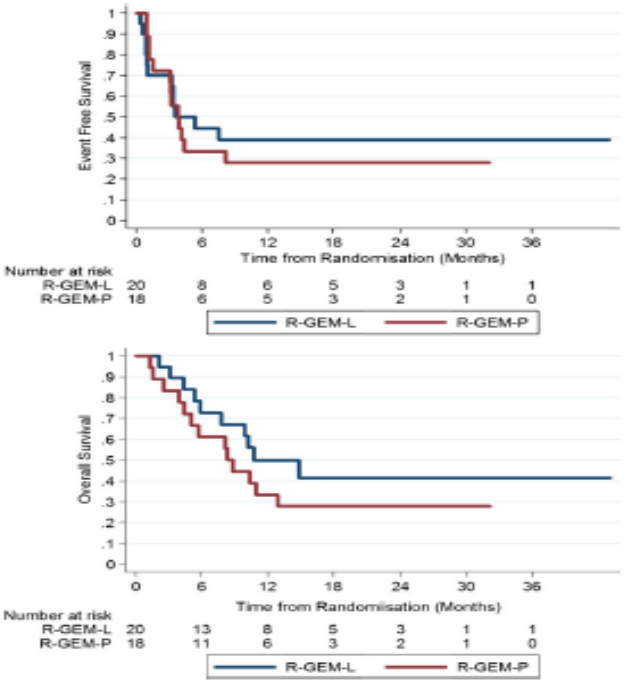
R-GEM-Lenalidomide versus R-GEM-P as second-line treatment of diffuse large B-cell lymphoma: results of the UK NRCI phase II randomised LEGEND trial

Andrea Kühnl [1,2] · Clare Peckitt [1] · Bijal Patel [1] · Kirit M. Ardeshna [3] · Marian P. Macheta [4] · John Radford [5]

Table 3 Most common grade ≥ 3 toxicities. Adverse events that occurred in more than one patient of either arm at grade ≥ 3 are shown

	R-GEM-L ($N = 21$)		R-GEM-P ($N = 18$)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All toxicities	21 (100%)	11 (52%)	18 (100%)	15 (83%)
Neutropenia	11 (52.4%)	6 (29.0%)	7 (27.7%)	4 (22.2%)
Thrombocytopenia	16 (72.7%)	3 (14.3%)	10 (55.5%)	7 (38.9%)
Anaemia	14 (66.7%)	1 (4.8%)	13 (72.2%)	3 (16.7%)
Infection	6 (28.6%)	3 (14.3%)	8 (44.4%)	5 (29.4%)
Fever	5 (23.8%)	3* (14.3%)	6 (33.3%)	1# (5.9%)
Thromboembolism	1 (4.8%)	1 (4.8%)	4 (22.2%)	3 (16.7%)
Fatigue	17 (81.0%)	0 (0%)	11 (61.1%)	2 (11.1%)

	Evaluable patients ($N = 34$)	
End of treatment response*	R-GEM-L ($N = 18$) n (%)	R-GEM-P ($N = 16$) n (%)
Complete response	7 (38.9)	3 (18.8)
Partial response	3 (16.7)	3 (12.5)
Stable disease	1 (5.6)	1 (6.3)
Progressive disease	7 (38.9)	9 (62.5)
Clinically assessed	4	3
Not done/evaluable	na	na
Overall response rate	10 (55.6)	6 (37.5)



Annals of Hematology (2020) 99:105–112

#8019 Lenalidomide plus R-GDP (R2-GDP) in Relapsed/Refractory Diffuse Large B Cell Lymphoma. Final results of the R2-GDP-GOTEL Trial.

ASCO 2020

Luis de la Cruz Merino, Alejandro Martin, Esteban Nogales Fernández, Fernando Carnicero González, Eduardo Ríos Herranz, Fátima de la Cruz-Vicente, Guillermo Rodríguez, Concepción Nicolás, Natividad Martínez-Banaclocha, Josep Gumá, José Gómez-Codina, Antonio Salar Silvestre, Delvys Rodríguez-Abreu, Christina Quero Blanco, Jorge Labrador Gómez, María Guirado, Natalia Palazón Carrión, Pablo Espejo García, Mariano Provencio-Pulla, Antonio Rueda Domínguez. Hospital Virgen Macarena, Seville, Spain; Hospital Universitario de Salamanca and IBSAL, CIBERONC, Salamanca, Spain; Hospital San Pedro de Alcántara, Cáceres, Spain; Hospital Universitario de Valme, Seville, Spain; Hospital Virgen del Rocío, Seville, Spain; Hospital Universitario Central de Asturias, Oviedo, Spain; Hospital Universitario de Alicante, Alicante, Spain; Hospital Universitario Sant Joan de Reus, IISPV, Universitat Rovira i Virgili, Reus, Spain; Hospital La Fe, Valencia, Spain; Hospital del Mar, Barcelona, Spain; Hospital Universitario Insular de Gran Canaria, Las Palmas De Gran Canaria, Spain; UGC Oncología Intercentros. Hospitales Universitarios Regional y Virgen de la Victoria de Málaga. Instituto de Investigaciones Biomédicas de Málaga (IBIMA), Málaga, Spain; Hospital Universitario de Burgos, Burgos, Spain; General University Hospital de Elche, Alicante, Spain; Instituto Investigación Sanitaria Puerta De Hierro-Segovia De Arana, Hospital Universitario Puerta De Hierro-Majadahonda, Madrid, Spain; Hospital Costa del Sol de Marbella, Málaga, Spain.

Background:

Relapsed/Refractory Diffuse Large B Cell Lymphoma **(R/R DLBCL)** patients, not suitable for autologous stem cell transplant (ASCT), represent a group of DLBCL with extremely dismal prognosis. Newer strategies are eagerlly needed in this setting.

Lenalidomide (LEN) is an immunomodulatory drug that could reverse rituximab refractoriness in lymphoma patients.

We pursued to test the activity of LEN plus R-GDP in R/R DLBCL not suitable for ASCT.

A translational substudy was carried out in peripheral blood along the trial to monitor the evolution of some key elements of the anti-lymphoma immune response: immunosuppressive myeloid derived suppressor cells (MDSC), activated (OX-40+) and inhibiting (PD-1+) CD4 and CD8 T lymphocytes.

Methods:

Open label multicenter **phase 2 trial** testing the **efficacy and toxicity** of a combination of lenalidomide and rituximab (R2) plus GDP schedule **(R2-GDP).**

R/R DLBCL ≥ 1 line of biochemotherapy including rituximab, and not candidates for ASCT, were eligible.

Treatment:

- ✓ **Induction phase:** Lenalidomide (LEN) 10 mg po d1-14, rituximab 375 mg/m2 iv d1, cisplatin 60 mg/m2 iv d1, gemcitabine 750 mg/m2 iv d1 and d8 and dexamethasone 20 mg d1-3, up to a maximum of 6 cycles. G-CSF was administered in every induction cycle from d+2 to d+6 and from d+9 to d+14.
- ✓ **Maintenance phase:** LEN 10 mg, or last LEN dose received in the induction phase, d1-21 in cycles every 28 days.
- **Primary endpoint** was overall response rate (ORR).
- **Secondary endpoints** included disease free survival (DFS), event free survival (EFS), overall survival (OS), safety and response by cell of origin (COO), type of DLBCL (double-triple hit) and other microenvironment and genomic biomarkers. In the **translational analysis, MDSC, CD4+ and CD8+ T lymphocytes (expressing OX-40 or PD-1)** were measured in peripheral blood by flow cytometry and correlated with **Clinical Benefit (CB: partial/complete response, PR/CR + disease stabilization, DS)** vs **Progressive Disease (PD)**.

Results:

After the run-in phase period, independent Data Safety Monitoring Board (DSMB) deemed the R2-GDP Schedule as safe starting with an initial dose of LEN of 10 mg.

Median age was 70 years (range 23-86), 48.7% women. Median FUP of 13 months.

- In the **ITT analysis** (n=78), ORR was 59.0%, with 32.1% CR and 26.9% PR. In the **PPP analysis** (n=59) ORR 74,6%, with 40,7% CR and 33,9% PR. FIGURE 1, TABLE 1.
- In the **primary refractory population** (n = 33), ORR was 45.5%, with 21.2% CR and 24.3% PR. FIGURE 2.
- There were no statistically significant differences in ORR with respect to COO.
- In **Double-Hit R/R DLBCL** (n = 16), ORR was 37.5% with 25% CR and 12.5% PR. FIGURE 3.
- **Median OS (ITT)** was 12.0 months (6.9-17.0). FIGURE 4.

Graphics:

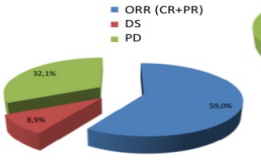


Figure 1. ITT responses.

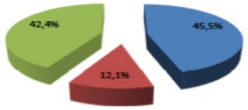


Figure 2. Primary Refractory ORR

Figure 3. Double-Hit ORR

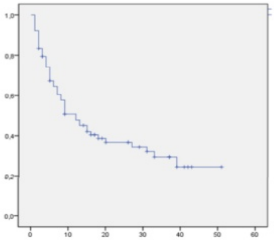


Figure 4. Overall survival. Cumulative Proportion Surviving

Overall Response Rate	R/R DLBCL ITT (%) N=78	R/R DLBCL PPP (%) N=59	Primary Refractory DLBCL ITT (%) N=33	Primary Refractory DLBCL PPP (%) N=20
ORR	59,0	74,6	45,5	65,0
CR	32,1	40,7	21,2	30
PR	26,9	33,9	24,3	35
SD	8,9	10,2	12,1	20
PD	32,1	15,2	42,4	10

Table 1. Overall Response Rate (ORR) by Intention to Treat (ITT) and Per Protocol (PPP)

Hematologic events (%)	NON – hematologic events (%)
Trombocytopenia (60.2%)	Asthenia (19.2%)
Neutropenia (60.2%)	Infection (15.3%)
Anemia (26.9%)	Renal insufficiency (6.4%)
Febrile Neutropenia (14.1%)	*4 toxic deaths related to R2- GDP schedule*

Table 2. Most common grade 3/4 (G3/4) adverse events.
Toxic deaths were related to sepsis (3) and febrile neutropenia (1)

CONCLUSIONS:

- LEN with R-GDP (R2-GDP) is feasible and highly active n R/R DLBCL.
- R2-GDP induced 4 toxic deaths (5,1%) due to sepsis or febrile neutropenia notwithstanding primary prophylaxis with G-CSF.
- Results in the primary refractory DLBCL population are particularly promising.
- Analysis of COO did not revealed differences in response rates.
- Responders induced a favourable immune profile in peripheral blood, with a clear and statistically significant drop in MDSC and PD1+ T lymphocytes, whilst CD4+OX40+ T lymphocytes levels increased dramatically.
- Immune monitoring could be useful to predict responses and, furthermore, it allow a glimpse of new targets with therapeutic purposes in R/R DLBCL.

Translational analysis. Results:

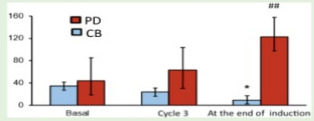


Figure 5. MDSC (cells/ul) counts. PD (progressive disease). CB (clinical benefit).
*,p≤0.05 compared with basal.
##, p≤0.01 compared with CB.

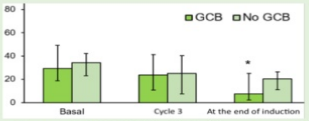


Figure 6. MDSC (cells/ul) counts of GCB and no GCB patients. *, p≤0.05 compared with basal.

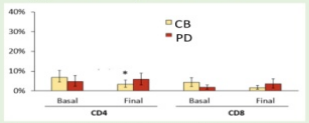


Figure 7. CD4+PD1+ and CD8+PD1+ T lymphocyte counts.
PD (progressive disease).
CB (clinical benefit).
*, p≤0.05 compared with basal.

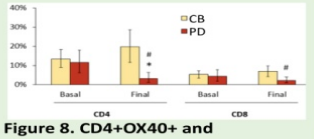


Figure 8. CD4+OX40+ and CD8+OX40+ T lymphocyte counts of CB and PD patients in response to systemic therapies.
*,p≤0.05 compared with basal.
#,p≤0.05 compared with CB.

- **MDSC levels significantly decrease in patients with CB vs those with PD.**
- **MDSC levels significantly decrease in Germinal Center B (GCB) patients vs those with no-GCB.**
- **PD1+ T lymphocytes % decrease in patients with CB vs those with PD.**
- **OX40+ T lymphocytes % increase in patients with CB vs those with PD.**

References:
1. Crump M et alt. Cancer. 2004;101(8):1835. 2. López A et alt. Eur J Haematol. 2008;80(2):127. 3. Corazzelli G et alt. Cancer Chemother Pharmacol. 2009;64(5):907. 4. Witzig TE et alt. Ann Oncol. 2011;22(7):1622.

EudraCT 2014-001620-29

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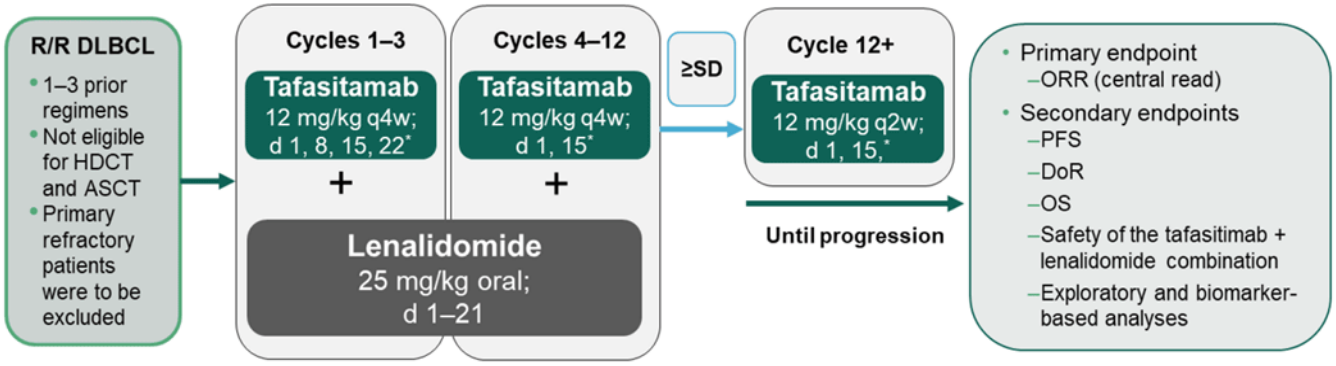
Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles*, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr,

L-MIND: Study Design



- Phase 2 single-arm, open-label, multicentre study (NCT02399085)
  - Sample size suitable to detect ≥15% absolute increase in ORR for tafasitamab/lenalidomide combination vs lenalidomide monotherapy at 85% power, 2-sided alpha of 5%
  - Long-term outcomes analysis with data cut-off 30 Nov 2019; minimum follow-up 2 years

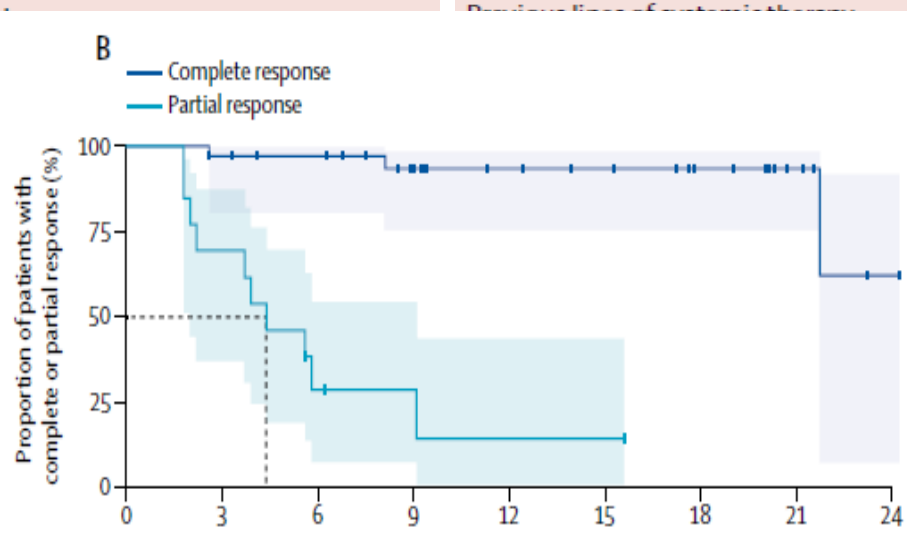
*A leading dose of tafasitamab was administered on day 4 of cycle 1.
ASCT: autologous stem-cell transplantation; DoR: duration of response; HDCT: high-dose chemotherapy; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R/R: relapsed/refractory.

Lancet Oncol 2020; 21: 978–88

Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr,*

Cell of origin by immunohistoche	
Germinal centre B cell	2 (1–4)
Non-germinal centre B cell	40 (50%)
Unknown	35 (43%)
Cell of origin by gene-expression	5 (6%)
Germinal centre B cell	1 (1%)
Non-germinal centre B cell	
Unclassified	81 (100%)
Unknown	0 (0%)
Patients with DLBCL arising from previous indolent lymphoma	81 (100%)
Reasons for ASCT ineligibility	0 (0%)
Aged >70 years	
Chemorefractory†	15 (19%)
Refusal	66 (81%)
Comorbidities‡	11 (14%)
Other§	1 (1%)



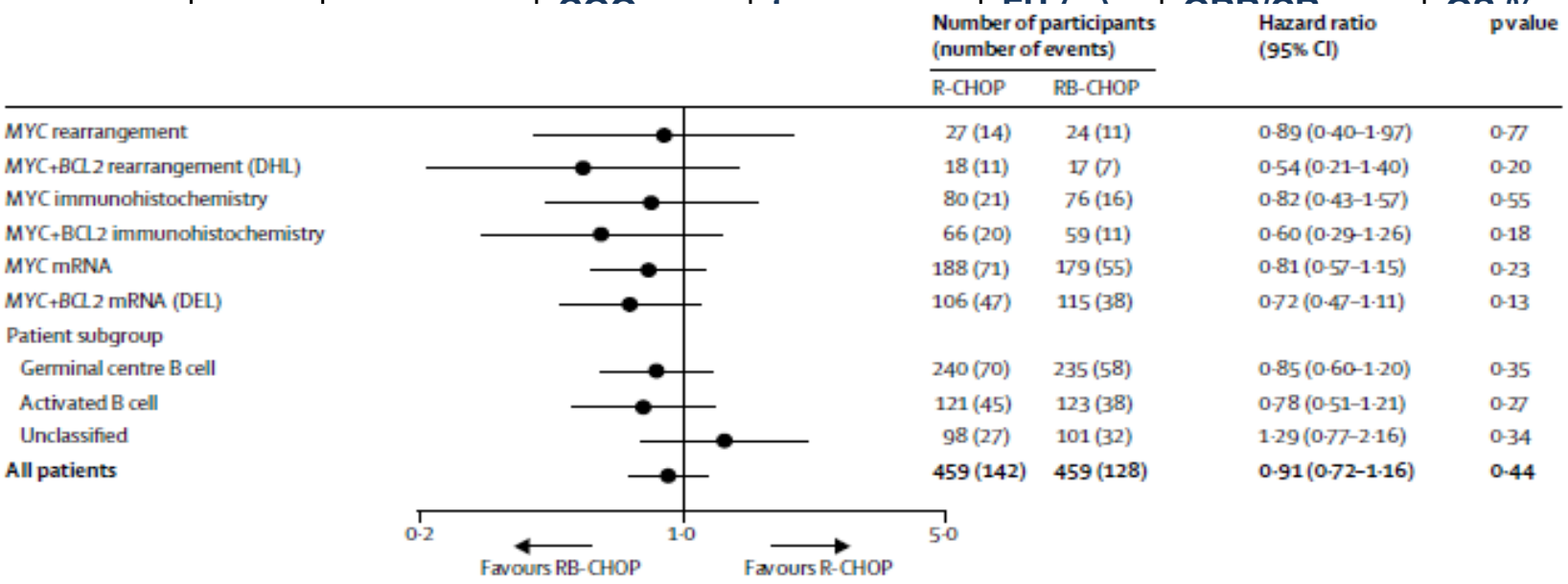
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)

mDOR in the 48 responding was 21,7 m.
Among the 34 patients with a CR, the mDOR was not reached.
For the 14 patients with a PR, the mDOR was 4,4 m.
At a median followup of 17,3 m, median PFS was 12,1 m

Lancet Oncol 2020; 21: 978–88

Protocolli RCHOP like + bortezomib

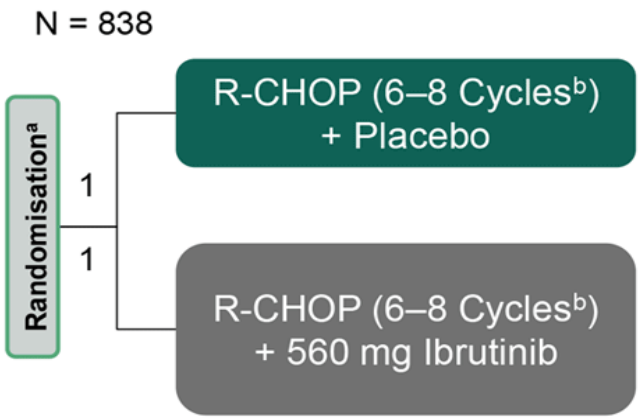
Ref.								PFS %
Offner P								76,2 vs 77,1
Leonard PYRAMI 2017								82 vs.77,6
Davies REMoDL-B Ph3 2019	918	63/65	GEP	VrCHOP vs RCHOP	29,7	n.a.	83,6 vs. 82,7	74,3 vs. 70,1



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];

PHOENIX: Ibrutinib With R-CHOP



Key Eligibility Criteria[1]

- Untreated non-GCB DLBCL
  - Determined by Hans-based immunohistochemistry at a central laboratory
  - Retrospectively analysed for ABC subtype using GEP
- Stage II to IV measurable disease
- R-IPI ≥1
- ECOG PS ≤2

Endpoints

- Primary endpoint: EFS[c] in ITT (non-GCB) and ABC subgroup
- Secondary endpoints: PFS, CR, OS, and safety
- Response assessed per Revised Response Criteria for Malignant Lymphoma[2]

[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. [b] As prescribed by site. [c] EFS: time from randomisation 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 of death.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: event-free survival; GEP: gene expression profiling; ITT: inention-to-treat; OS: overall survival; PFS: progression-free survival; PS: performance status; R-IPI: revised International Prognostic Index.

1. Younes A et al. *J Clin Oncol.* 2019;37:1285-1295. 2. Cheson BD et al. *J Clin Oncol.* 2007;25:579-586.

J Clin Oncol 37:1285-1295.

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];

Paz < 60	ITT	ABC
EFS		
p	0,0099	0,0233
36-month EFS	75,4 vs.64,6	76,9 vs. 64,5
PFS		
p	0,75	0,0043
36-month PFS	77,4 vs.66,3	80,5 vs. 64,5
OS		
p	0,0013	0,0099
36-month OS	93,2 vs. 80,9	92,8 vs. 80,9

J Clin Oncol 37:1285-1295.

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J Clin Oncol 37:1285-1295. © 2019 by American Society of Clinical Oncology

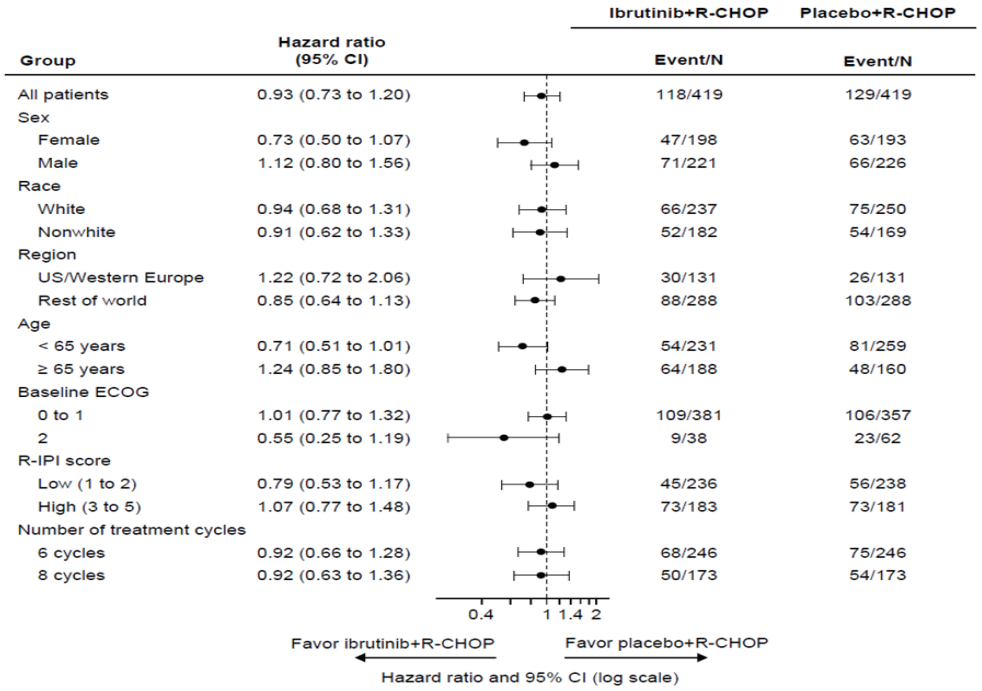
No. (%)

	Safety Population		< 60 Years		≥ 60 Years	
SAE	Ibrutinib + R-CHOP (n = 416)	Placebo + R-CHOP (n = 418)	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
Overall	221 (53.1)	142 (34.0)	55 (35.7)	53 (28.6)	166 (63.4)	89 (38.2)
Febrile neutropenia	78 (18.8)	44 (10.5)	22 (14.3)	17 (9.2)	56 (21.4)	27 (11.6)
Diarrhea	15 (3.6)	4 (1.0)	1 (0.6)	2 (1.1)	14 (5.3)	2 (0.9)
Neutropenia	17 (4.1)	13 (3.1)	2 (1.3)	4 (2.2)	15 (5.7)	9 (3.9)
Pneumonia*	28 (6.7)	14 (3.3)	6 (3.9)	4 (2.2)	22 (8.4)	10 (4.3)
Anemia	15 (3.6)	5 (1.2)	3 (1.9)	2 (1.1)	12 (4.6)	3 (1.3)
Atrial fibrillation	13 (3.1)	1 (0.2)	2 (1.3)	1 (0.5)	11 (4.2)	0
Lung infection*	14 (3.4)	7 (1.7)	1 (0.6)	2 (1.1)	13 (5.0)	5 (2.1)
Pyrexia	12 (2.9)	11 (2.6)	3 (1.9)	4 (2.2)	9 (3.4)	7 (3.0)
Dehydration	8 (1.9)	2 (0.5)	1 (0.6)	0	7 (2.7)	2 (0.9)
Sepsis	7 (1.7)	3 (0.7)	0	0	7 (2.7)	3 (1.3)
Pneumonitis*	6 (1.4)	3 (0.7)	4 (2.6)	2 (1.1)	2 (0.8)	2 (0.9)
Thrombocytopenia	9 (2.2)	1 (0.2)	0	0	9 (3.4)	1 (0.4)
Interstitial lung disease*	7 (1.7)	4 (1.0)	4 (2.6)	2 (1.1)	3 (1.1)	2 (0.9)

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

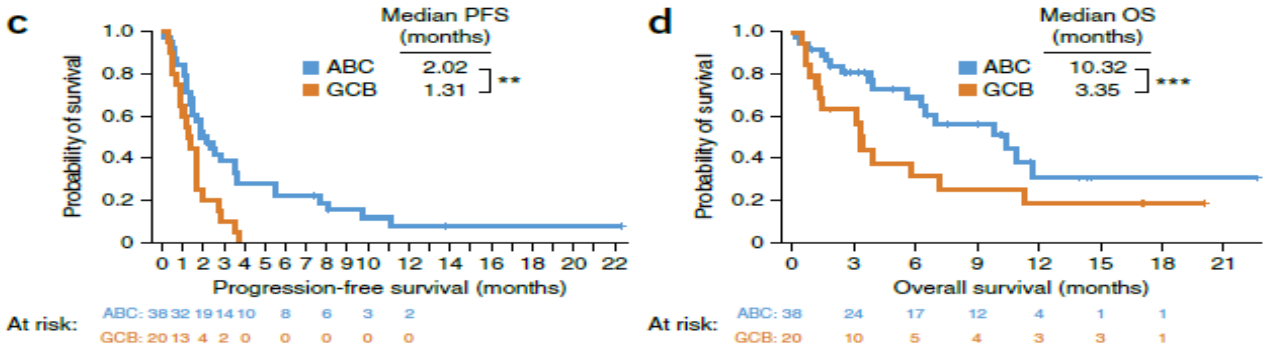
Anas Younes, MD[1]; Laurie H. Sehn, MD[2]; Peter Johnson, MD[3]; Pier Luigi Zinzani, MD, PhD[4]; Xiaonan Hong, MD[5]; Jun Zhu, MD[6];

J Clin Oncol 37:1285-1295.



Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma

Wyndham H Wilson[1], Ryan M Young[1], Roland Schmitz[1], Yandan Yang[1], Stefania Pittaluga[2], George Wright[3],

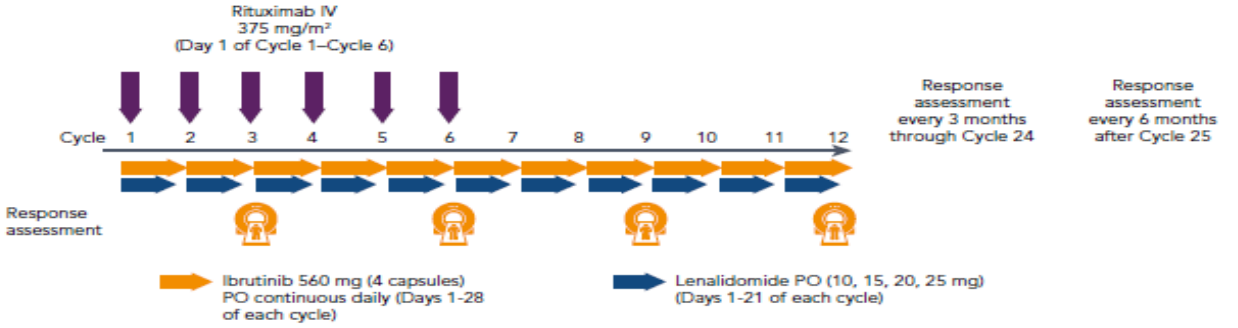


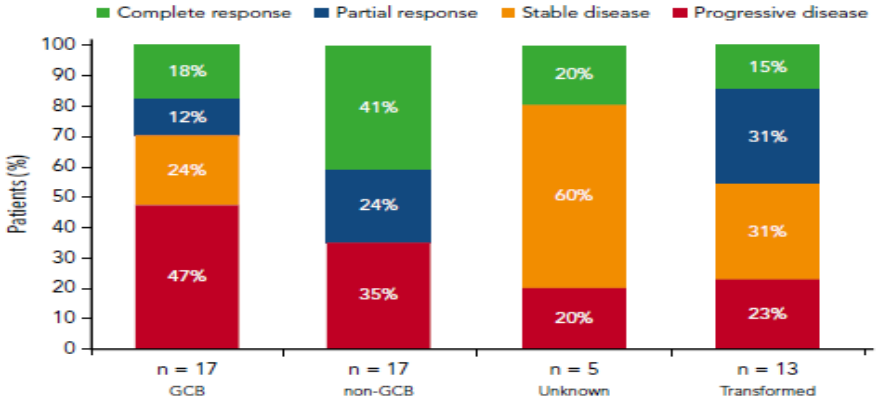
Ph 1/2 clinical trial: 80 subjects with R/R DLBCL, ibrutinib 560 mg/d until progression/intolerance produced CR/PR in 37% (14/38) of those with ABC DLBCL, but in only 5% (1/20) of subjects with GCB DLBCL (p= 0.0106). ABC tumors with BCR mutations responded to ibrutinib frequently (5/9; 55.5%), especially those with concomitant MYD88 mutations (4/5; 80%), a result that is consistent with in vitro cooperation between the BCR and MYD88 pathways.
However, the highest number of responses occurred in ABC tumors that lacked BCR mutations (9/29; 31%), suggesting that oncogenic BCR signaling in ABC does not require BCR mutations and might be initiated by non-genetic mechanisms.

VOLUME 21 | NUMBER 8 | AUGUST 2015 NATURE MEDICINE

Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non–germinal center B-cell–like DLBCL

Andre Goy,[1] Radhakrishnan Ramchandren,[2] Nilanjan Ghosh,[3] Javier Munoz,[4] David S. Morgan,[5] Nam H. Dang,[6] Mark Knapp,[7]



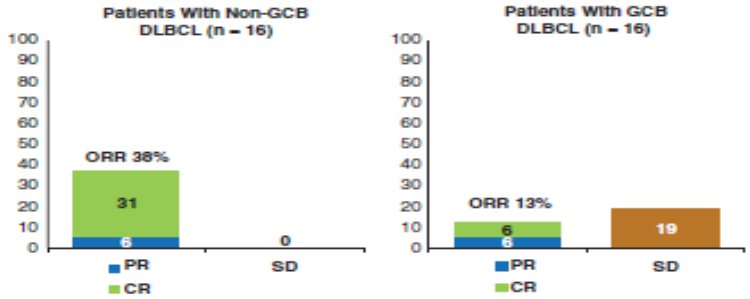


- **Median PFS/OS among all patients was 5.5/9.5 months, and for responders it was 18.8 months/not reached.**
- **Among patients with non-GCB DLBCL, median OS/PFS was 10.7/3.9months.**
- **Among patients with GCB DLBCL, median OS/PFS was 7.1/5.5 months.**
- **Among patients with transformed DLBCL, median OS/PFS was 12/5.9 months.**

(*Blood.* 2019;134(13):1024-1036)

Safety and activity of ibrutinib in combination with durvalumab in patients with relapsed or refractory follicular lymphoma or diffuse large B-cell lymphoma

Alex F. Herrera[1] | Andre Goy[2] | Amitkumar Mehta[3] |

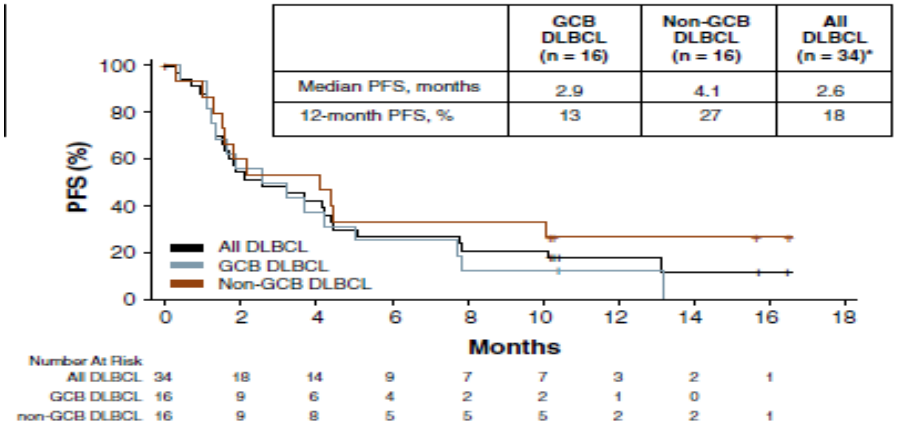


ORR among R/R DLBCL was 38% for patients with the non-GCB subtype and 13% for those with the GCB subtype.

The differential response rates between these subtypes is probably explained by chronic active B-cell receptor signaling, which activates the NF-κB pathway through BTK in non-GCB tumors but not in GCB tumors and by the high PD-L1 expression only observed in non-GCB subtypes.

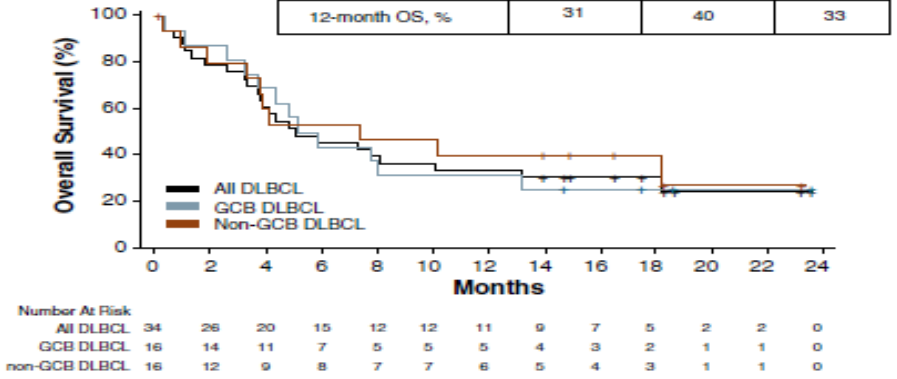
(B)

	GCB DLBCL (n = 16)	Non-GCB DLBCL (n = 16)	All DLBCL (n = 34)*
Median PFS, months	2.9	4.1	2.6
12-month PFS, %	13	27	18



(D)

	GCB DLBCL (n = 16)	Non-GCB DLBCL (n = 16)	All DLBCL (n = 34)*
Median OS, months	5.5	7.3	5.1
12-month OS, %	31	40	33



Am J Hematol. 2020;95:18–27.

Opzioni trapiantologiche

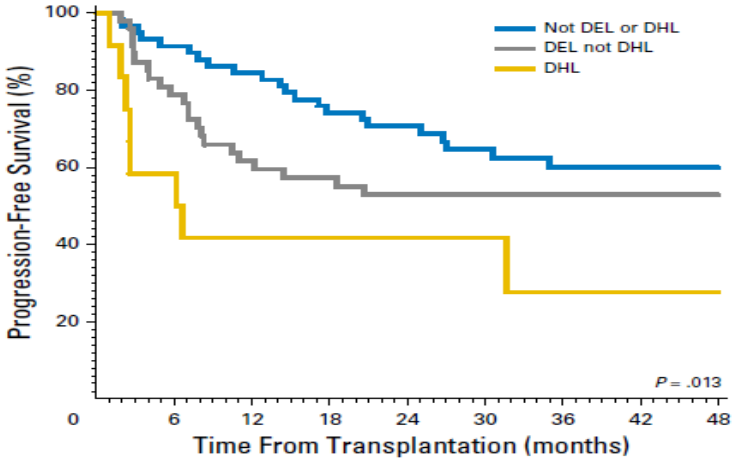
• Blood 2014, Petrich. Studio retrospettivo. 311 DH PFS/OS 10.9/21.9 m. Intensive induction was associated with improved PFS/OS. Role of SCT?

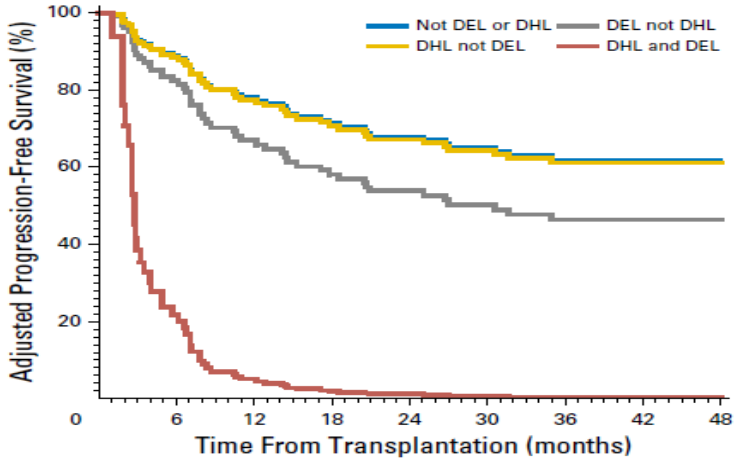
• BCJ 2016, Maura. Studio retrospettivo. 140 paz. di cui 38 DE. Intensive induction followed by ASCT 5-years EFS 49.4 vs 71.5 (non DE) p=0.06, and not different OS.

•JCO 2017, achieving CR1 is not signi ddition, patients receiving R line therapy".

•JCO 2017 vs. 59/67: p=0.049/0.

•Annals of n GCB. No differer non GCB (80.8/80.8





Outcomes after Allogeneic Stem Cell Transplantation in Patients with Double-Hit and Double-Expressor Lymphoma

Alex F. Herrera [1,*], Scott J. Rodig [2], Joo Y. Song [3], Young Kim [3], Gabriel K. Griffin [2],

Biol Blood Marrow Transplant 24 (2018) 514–520

Double-hit lymphomas (DHLs) and double-expressor lymphomas (DELs) are associated with resistance to front-line and salvage immunochemotherapy, as well as autologous stem cell transplantation (SCT). We hypothesized that allogeneic SCT (alloSCT) could overcome the chemoresistance associated with DEL/DHL. We retrospectively studied the impact of DEL/DHL status in a multicenter cohort of patients who underwent alloSCT for relapsed/refractory (rel/ref) aggressive B cell non-Hodgkin lymphoma (B-NHL). Seventy-eight patients transplanted at 3 centers in whom tumor tissue was available for immunohistochemistry and fluorescence in situ hybridization were enrolled; 47% had DEL and 13% had DHL. There were no significant differences in 4-year progression-free (PFS) or overall survival (OS) between patients with DEL compared with patients without DEL (PFS 30% versus 39%, $P = .24$; OS 31% versus 49%, $P = .17$) or between patients with DHL compared with patients without DHL (PFS 40% versus 34%, $P = .62$; OS 50% versus 38%, $P = .46$). The lack of association between DEL or DHL and outcome was confirmed in multivariable models, although inadequate sample size may have limited our ability to detect significant differences. In our cohort alloSCT produced durable remissions in patients with rel/ref aggressive B-NHL irrespective of DEL and DHL status, justifying its consideration in the treatment of patients with rel/ref DEL/DHL.

DA-EPOCH and Rituximab

- Haematologica 2012, Wilson 69 paz. Ph II. FU 62 m; ORR/CR 95%/84%, 5yrs % OS/EFS 100/94 GCB vs 67/58 non GCB, p=0.008. (1 SAE G5)
- BJH 2014, Purroy (PETHEMA) 85 paz. Ph II : FU64 m, ORR/CR 73/65TTTF 6 m. 10 yrs % OS/EFS/DFS 63.6/47.8/59. (0 SAE G5) BCL2R hanno prognosi peggiore.
- BJH 2014, Oki. studio retrospettivo 129 paz. solo DH, R-DA-EPOCH hanno EFS/OS migliore rispetto a RCHOP.
- BJH 2016, Howlett metanalisi. Solo DH: R-DA-EPOCH conferisce PFS migliore rispetto a RCHOP, OS non migliore
- Lancet Haematol 2018, Dunleavy. Ph II. 53 paz affetti da DLBCL MYC-R di cui 34 HGBL e 18 DLBCL. FU 55.6 m, 4yrs % EFS/OS 71.8/76. HGBL vs. DLBCL 4yrs % EFS/OS 70.8/77 vs. 69.6/75 (3 SAE G5).
- Leukemia 2019, Dodero: studio retrospettivo 114 paz solo DE, R-DA-EPOCH hanno PFS/OS migliore rispetto a RCHOP.

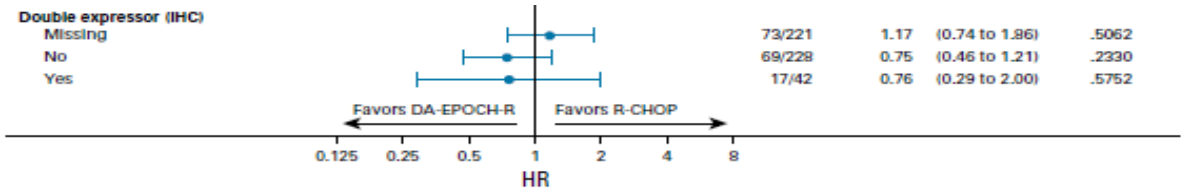
Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303

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[3];

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

TABLE 2. Progression-Free Survival for All Patients and According to Treatment Arm

Parameter	Event/Total	Hazard Ratio (95% CI)*	Survival Estimates (95% CI), %†	P
All patients	159/491		2 Years: 77.1 (73.5 to 81.0)	
			3 Years: 73.9 (70.1 to 77.9)	
			5 Years: 67.1 (62.8 to 71.6)	
Treatment arm				.6519‡
DA-EPOCH-R	76/241	0.93 (0.68 to 1.27)	2 Years: 78.9 (73.8 to 84.2)	
			3 Years: 75.8 (70.5 to 81.5)	
			5 Years: 68.0 (62.1 to 74.5)	
R-CHOP	83/250	Reference	2 Years: 75.5 (70.2 to 81.1)	
			3 Years: 72.0 (66.6 to 77.9)	
			5 Years: 66.0 (60.2 to 72.5)	
Double expressor (IHC)				
Missing			73/221 1.17 (0.74 to 1.86)	.5062
No			69/228 0.75 (0.46 to 1.21)	.2330
Yes			17/42 0.76 (0.29 to 2.00)	.5752



"We found no differences by treatment arm in the MYC rearranged or patients with the DE phenotype, though, again, this subset was of insufficient size for statistical comparison.
On the basis of encouraging phase II results with DA-EPOCH-R in patients with double-hit and Burkitt lymphoma compared with historical R-CHOP data, the results of Alliance/CALGB 50303 should not discourage use of DA-EPOCH-R in these settings"

Phase I Study of the Bcl-2 Inhibitor Venetoclax with DA-EPOCH-R as Initial Therapy for Aggressive B-cell Lymphomas

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**These authors contributed equally*

Treatment Schedule

Dose Level	Venetoclax Dose	Cycle 1 Schedule	Cycles 2-6 Schedule
-1	400 mg PO QD	Days 3-7	Days 1-5
1	400 mg PO QD	Days 3-12	Days 1-10
2	600 mg PO QD	Days 3-12	Days 1-10
3	800 mg PO QD	Days 3-12	Days 1-10
2B	600 mg PO QD	Days 3-7	Days 1-5

DA-EPOCH-R for 6 cycles every 3 weeks per standard protocol

Dose adjustments of EPOCH based on CBC checked twice weekly

No intra-patient escalation of venetoclax

All subjects received pegfilgrastim, filgrastim, or formulary equivalents

Best response by intention to treat

Response	Total	DL1 (N=3)	DL2 (N=9)	DL3 (N=6)	DL2B (N=12)
CR[1]	**27**	3	9	4	11
PR[2]	**2**			1	1
PD[3]	**0**				
NE[4]	**1**			1	

ORR[5] 97%, CR rate 90%

- 24/27 remain in CR with median follow up of 13.5 months
- 3 subjects progressed after a response
- 2 subjects died (1 in a car accident of unclear reasons, 1 of sepsis during cycle 3)

[1]Complete response
[2]Partial response
[3]Progressive disease
[4]Not evaluable
[5]Overall response rate

Best response by selected subgroup

Response	DHL (N=15)	DEL[1] (N=2)	*BCL2* rearranged (N=14)	BCL2+ by IHC (N=21)
CR	13	2	13	19
PR	1		1	1
NE	1			1

DHL: ORR 93%, CR rate 87%

- Of 13 DHL with CR, 10 remain in CR with median follow up of 11 months; 2 progressed and 1 died
- 2/2 DEL remain in CR with follow up of 27 and 29 months

[1]Double expressor lymphoma

Venetoclax Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP) Improves Outcomes in BCL2-Positive First-Line Diffuse Large B-Cell Lymphoma (DLBCL): First Safety, Efficacy and Biomarker Analyses from the Phase II CAVALLI Study . Franck Morschhauser. *Blood* (2018) 132 (Supplement 1): 782.

Tx: 6 R-CHOP21 + 800 mg Ven daily for 10 days (D1-10, except Cycle 1: D 4-10), followed by two 3-w cycles of 800mg Ven on D1-10 + R on Day 1.
P.E.: PET-CT response 6-8 weeks after the last R dose (EoT)(Lugano 2014 criteria).
S.E. PFS and safety.
208 pts evaluable. The EoT CRR in all pts did not differ significantly between CAVALLI and GOYA (69.2% vs 62.8%, respectively), but was improved in BCL2-positive subgroups, specifically in *BCL2* FISH-positive (70.0% vs 47.5%) and DH (71.4% vs. 25.0%) pts. With 20 m median follow-up in CAVALLI, PFS improvement was observed in BCL2 IHC-positive pts, including within both ABC and GCB. No PFS benefit was observed in BCL2 IHC-negative GCB pts.
The higher rate of AEs in CAVALLI led to dose interruptions/discontinuations of both Ven and R-CHOP; 61% of pts had >90% relative dose intensity (RDI) of Ven.

Abstract #8053: Atezolizumab + Obinutuzumab + Venetoclax in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphomas: Primary Analysis of a Phase 2 Trial from LYSA.

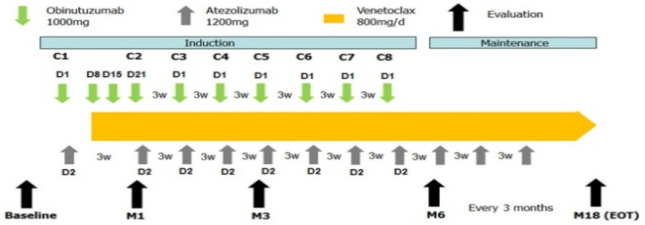
Herbaux C[1], Casasnovas O[2], Feugier P[3], Damaj G[4], Bouabdallah R[5], Guidez S[6], Ysebaert L[7], Tilly H[8], Le Gouill S[9], Fornecker LM[10], Daguindau N[11], Morineau N[12], Haioun C[13], Gyan E[14], Sibon D[15], Gressin R[16], Houot R[17], Salles G[18], Morschhauser F[1], Cartron G[19].
1/ CHU Lille 2/ CHU Dijon 3/ CHU Nancy 4/ CHU Caen 5/ Institut Paoli-Calmettes, Marseille 6/ CHU Poitiers 7/ Institut Universitaire du Cancer de Toulouse 8/Centre Henri Becquerel, Rouen 9/ CHU Nantes 10/ CHU Strasbourg 11/ CH Annecy Genevois 12/ CHD Vendée, La Roche Sur Yon 13/ Henri Mondor University Hospital, Créteil 14/ CHU Tours 15/ Hôpital Necker- Enfants Malades, Paris 16/ Institut Albert Bonniot, Grenoble 17/ CHU Rennes 18/ Centre Hospitalier Lyon Sud 19/ CHU de Montpellier. All centers are in France.

Background/Methods:

- **Relapsed/Refractory** (R/R) **diffuse large B-cell lymphomas** (DLBCL) treatment remains challenging
- **Atezolizumab** (ATZ) and **obinutuzumab** (OBZ) are monoclonal antibodies acting respectively to inhibit T-lymphocyte exhaustion or by inducing lymphoma cells cytotoxicity, whereas **venetoclax** (VEN) is a small molecule inhibiting BCL-2
- Combining tumor-targeted therapies with agents that enhance anti-tumor immunity represents an attractive treatment paradigm
- This is a LYSA sponsored **multicenter phase 2** trial **NCT03276468**

Methods:

- Patients ≥18 years with biopsy-confirmed R/R DLBCL who failed at least 1 line of therapy
- Primary endpoint was the **Overall Metabolic Response Rate** (OMRR) at the end of induction (EOI) or at premature treatment discontinuation.



The ATZ, OBZ and VEN combination is well tolerated with an efficacy comparable with currently available treatment options in R/R DLBCL

Acknowledgements: this study was financially supported by Roche and AbbVie

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Results/Graphs/Data:

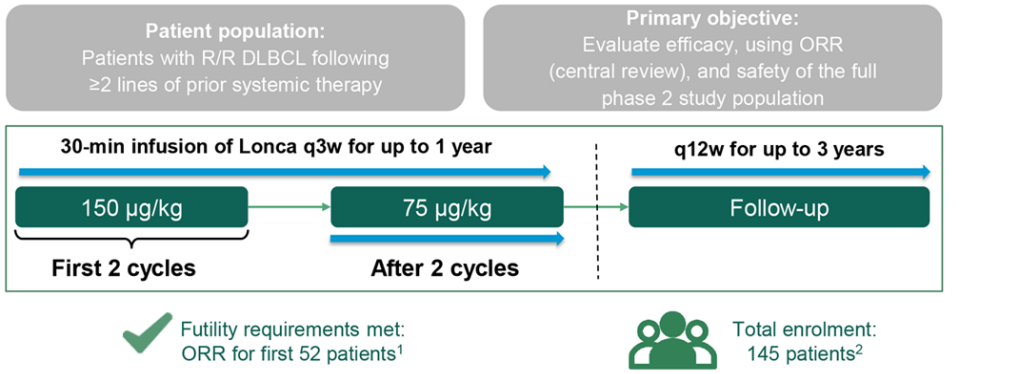
- At the time of the primary analysis (03 Jan 2020), **58 pts** were enrolled and the **median follow-up was 9 months** [6.9-11.8]
  - ➢ Ann Arbor Stage IV, 84.5%
  - ➢ aaIPI (≥2), 63.2%
  - ➢ > 2 prior lines of therapy, 83.6%
  - ➢ Refractory to last therapeutic line, 63.6%
- The OMRR at EOI: **23.6%** [14.58%-34.93%], including **18% of CMR**
- A total of **48 pts (84.2%)** experienced grade 3–4 adverse event (AE)
- AE of grade ≥3 in at least 20% of patients:
  - ➢ neutropenia (33.3%)
  - ➢ lymphopenia (35.1%)
- A grade 3 **autoimmune colitis** and a grade 1 **hypothyroidism** occured during induction.

Future Directions for Research:

- Follow-up to confirm the durability of responses
- Recruitment is complete for the other two cohorts:
  - ➢ Follicular Lymphoma
  - ➢ Indolent NHL

Interim Futility Analysis of a Phase 2 Study of Loncastuximab Tesirine, a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients with Relapsed or Refractory. ASCO 2020 C. Carlo-Stella

Study Design: Single-Arm, Open-Label Phase 2 Study



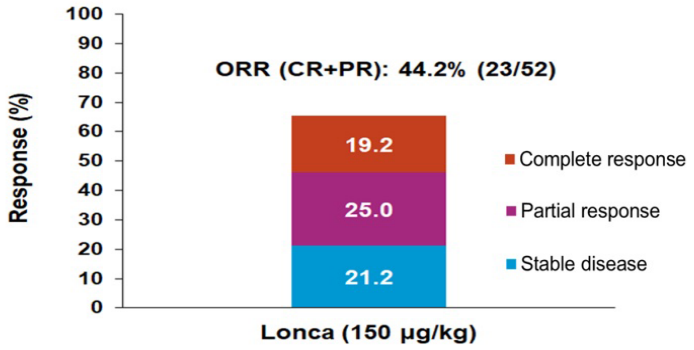
1. Carlo-Stella C, et al. *Blood.* 2019;134(Suppl 1):757. 2. Carlo-Stella C et al. EHA 2020; Abstract S233.

Table 1. Baseline demographics and clinical characteristics

Characteristic	Total (N=52)
Sex, n (%)	
Female	14 (26.9)
Male	38 (73.1)
Race, n (%)	
White	48 (92.3)
Black or African American	2 (3.8)
Asian	1 (1.9)
Other	1 (1.9)
Age, years, median (min, max)	62.5 (24, 84)
Histology	
Diffuse large B-cell lymphoma, NOS	44 (84.6)
High-grade B-cell lymphoma	5 (9.6)
Primary mediastinal B-cell lymphoma	3 (5.8)
Double-hit (myc and bcl-2), n (%)	3 (5.8)
Triple-hit (myc, bcl-2 and bcl-6), n (%)	0 (0.0)
Transformed disease, n (%)	8 (15.4)
Follicular	7 (13.5)
Richter's	1 (1.9)
Disease stage, n (%)	
I	5 (9.6)
II	9 (17.3)
III	8 (15.4)
IV	30 (57.7)
First-line prior chemotherapy response, n (%)	
Relapsed	32 (61.5)
Refractory	16 (30.8)
Other	4 (7.7)
Last-line prior chemotherapy response group, n (%)	
Relapsed	16 (30.8)
Refractory	27 (51.9)
Other	9 (17.3)
Number of prior systemic therapies, median (min, max)	3 (2, 7)
Prior stem cell transplantation, n (%)	9 (17.3)
Allogeneic	0 (0.0)
Autologous	8 (15.4)
Both	1 (1.9)

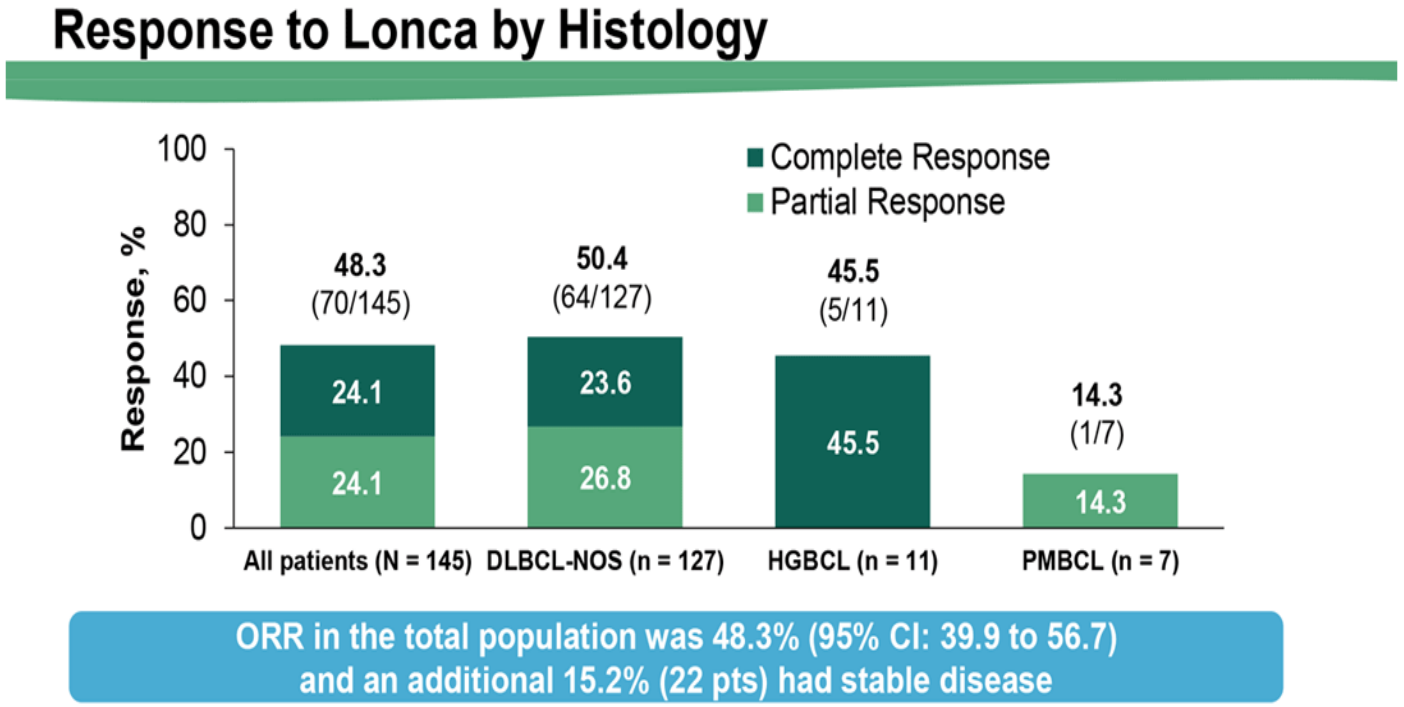
NOS, not otherwise specified.

Figure 1: Bar graph showing response to Lonca in pts with R/R DLBCL (Futility Analysis Set).



CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; pts, patients; R/R, relapsed/refractory.

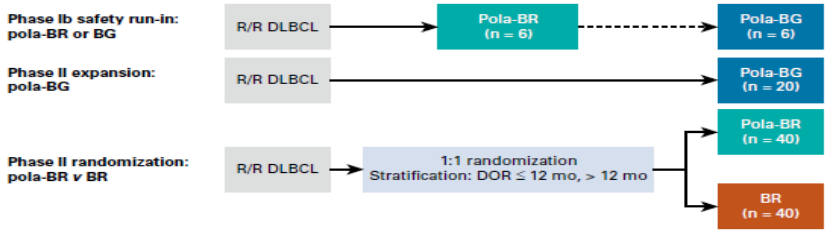
Interim Futility Analysis of a Phase 2 Study of Loncastuximab Tesirine, a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients with Relapsed or Refractory. ASCO 2020 C.Carlo-Stella



Data cut-off: 06 April 2020. Response assessed by independent reviewer.
HGBCL: high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; PMBCL: primary mediastinal B-cell lymphoma.
Carlo-Stella C et al. EHA 2020; Abstract S233.

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; J Clin Oncol 38:155-165. © 2019



	Phase Ib Safety Run-In	Phase Ib/II Expansion	Phase II Randomized	
Outcome	**Pola-BR (n = 6)**	**Pola-BG (n = 27)***	**Pola-BR (n = 40)**	**BR (n = 40)**
Best responses (IRC)				
Objective response	3 (50.0)	13 (48.1)	25 (62.5)	10 (25.0)
Complete response	3 (50.0)	10 (37.0)	20 (50.0)	9 (22.5)
Partial response	0	3 (11.1)	5 (12.5)	1 (2.5)
Stable disease	2 (33.3)	5 (18.5)	5 (12.5)	9 (22.5)
Progressive disease	1 (16.7)	4 (14.8)	6 (15.0)	8 (20.0)
Missing or unevaluable	0	5 (18.5)	4 (10.0)	13 (32.5)
Median duration of response, months (95% CI)				
IRC	NE (NE)	28.4 (15.0 to 31.9)	12.6 (7.2 to NE)	7.7 (4.0 to 18.9)
INV assessed	NE (NE)	28.4 (3.0 to 31.9)	10.3 (5.6 to NE)	4.1 (2.6 to 12.7)
Median progression-free survival, months (95% CI)				
IRC	NE (5.6 to NE)	6.3 (3.5 to 30.4)	9.5 (6.2 to 13.9)	3.7 (2.1 to 4.5)
INV assessed	NE (1.8 to NE)	5.4 (2.8 to 30.4)	7.6 (6.0 to 17.0)	2.0 (1.5 to 3.7)
Median overall survival, months (95% CI)	NE (5.6 to NE)	10.8 (5.8 to 33.8)	12.4 (9.0 to NE)	4.7 (3.7 to 8.3)

Baseline risk factors	Total No.	Pola-BR (Ph II) No.	Pola-BR (Ph II) Events	Pola-BR (Ph II) Median (months)	BR (Ph II) No.	BR (Ph II) Events	BR (Ph II) Median (months)	HR	95% CI	
WHO 2016 DLBCL status										
ABC	38	19	15	4.7	19	12	12.8	0.34	0.15 to 0.74	
GCB	32	17	12	3.8	15	11	8.9	0.56	0.24 to 1.29	

Leukemia (2020) 34:2184–2197
https://doi.org/10.1038/s41375-020-0743-y

ARTICLE

Lymphoma

Single-agent activity of phosphatidylinositol 3-kinase inhibition with copanlisib in patients with molecularly defined relapsed or refractory diffuse large B-cell lymphoma

Georg Lenz[1] · Eliza Hawkes[2] · Gregor Verhoef[3] · Corinne Haioun[4] · Soon Thye Lim[5] · Dae Seog Heo[6] ·

Table 2 Tumor response based on investigator assessment. a Tumor response in the overall cohort; b objective response rate in molecular DLBCL subtypes in the overall cohort and PPS.

(A) Tumor response in the overall cohort

	Total $N=67$	*CD79B* mutational status $n=67$			DLBCL COO subgroup $n=67$			
		Mutant *CD79B* $n=9$	Wild-type *CD79B* $n=45$	Missing $n=13$	ABC DLBCL $n=19$	GCB DLBCL $n=30$	Unclassifiable $n=3$	Missing $n=15$
Best overall response, *n* (%)								
CR	5 (7.5)	1 (11.1)	4 (8.9)	0	4 (21.1)	1 (3.3)	0	0
PR	8 (11.9)	1 (11.1)	5 (11.1)	2 (15.4)	2 (10.5)	3 (10.0)	1 (33.3)	2 (13.3)
Stable disease	14 (20.9)	3 (33.3)	9 (20.0)	2 (15.4)	4 (21.1)	8 (26.7)	0	2 (13.3)
Progressive disease	30 (44.8)	4 (44.4)	17 (37.8)	9 (69.2)	7 (36.8)	13 (43.3)	2 (66.7)	8 (53.3)
Not evaluable/not available[a]	10 (14.9)	0	10 (22.2)	0	2 (10.5)	5 (16.7)	0	3 (20.0)
ORR, *n* (%)	13 (19.4)	2 (22.2)	9 (20.0)	2 (15.4)	6 (31.6)	4 (13.3)	1 (33.3)	2 (13.3)
90% CI	11.9, 29.1	4.1, 55.0	10.9, 32.3	2.8, 41.0	14.7, 53.0	4.7, 28.0	1.7, 86.5	2.4, 36.3
DCR, *n* (%)	27 (40.3)	5 (55.6)	18 (40.0)	4 (30.8)	10 (52.6)	12 (40.0)	1 (33.3)	4 (26.7)

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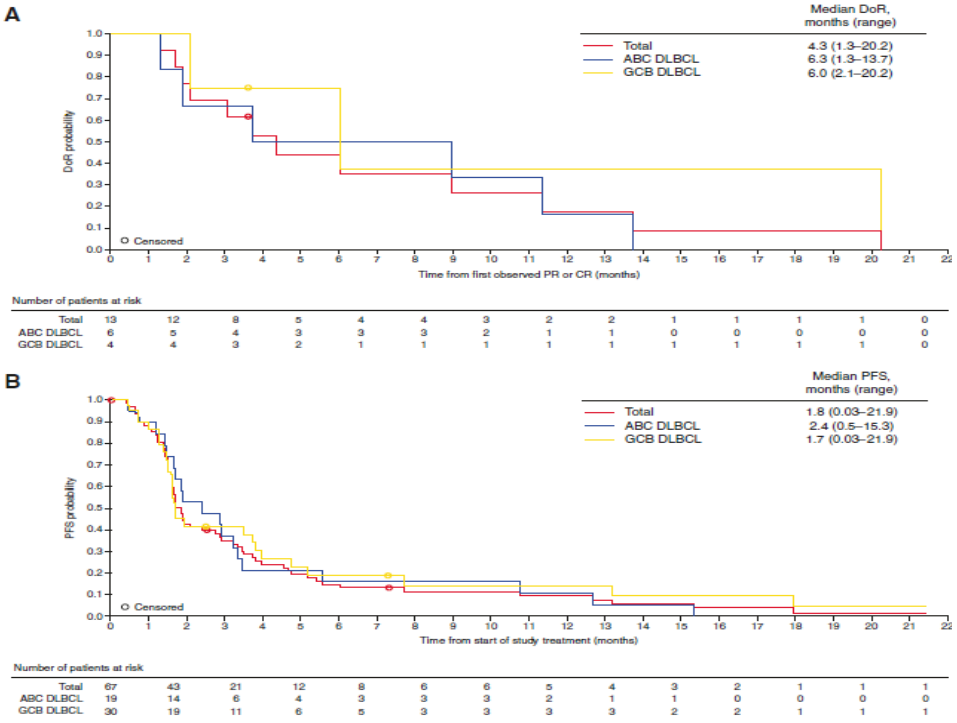

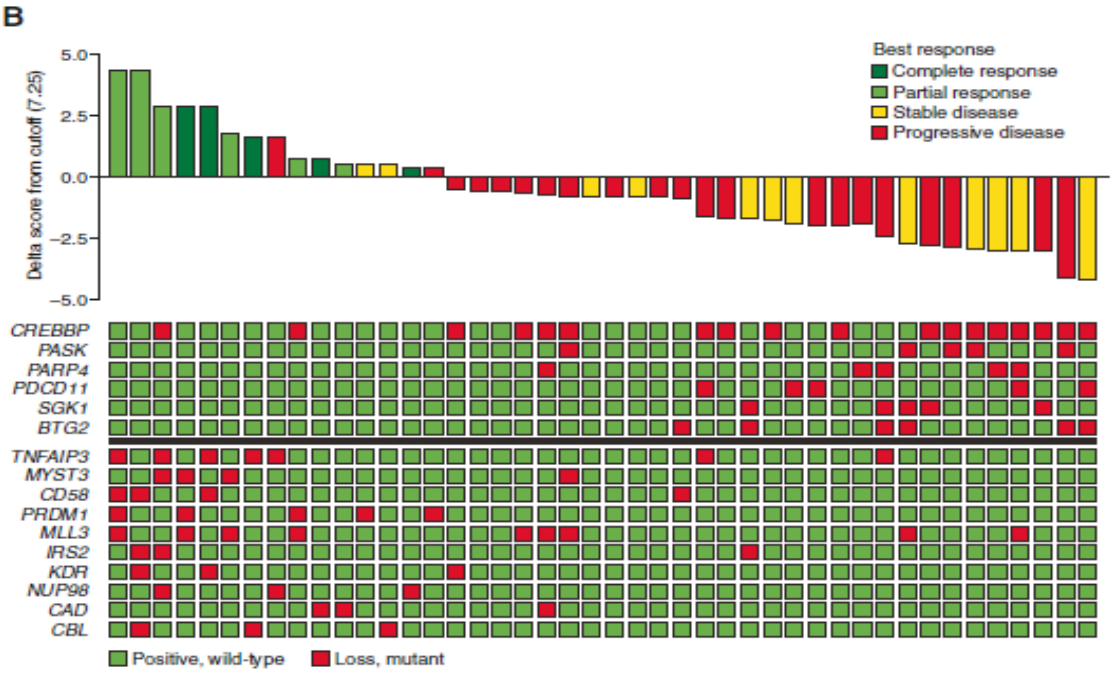

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In conclusion, single-agent copanlisib demonstrated modest anti-lymphoma activity in patients with relapsed/ refractory DLBCL with a numerically higher response rate in patients with ABC DLBCL vs. patients with GCB DLBCL, with similar activity in patients with and without CD79B mutations. A 16-gene mutation signature associated with improved outcomes was identified as a possible approach (with further validation) for selecting DLBCL patients for treatment with copanlisib. Copanlisib showed an acceptable safety profile, with the most common toxicities of hypertension and hyperglycemia being transient and manageable.

PROSPETTIVE

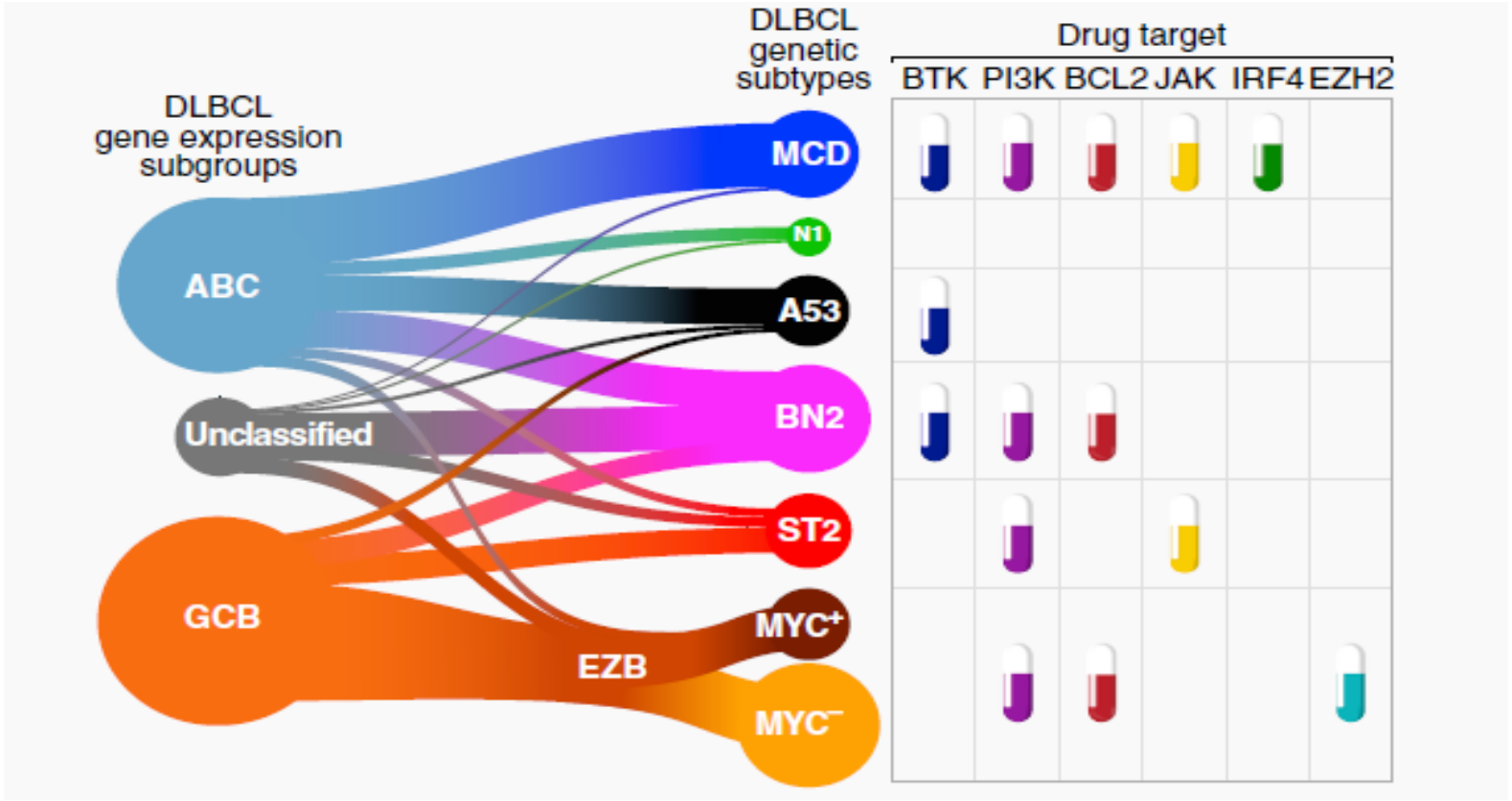
•STUDIO FIL: Copanlisib in combination with Rituximab-Bendamustine in patients with Relapsed Refractory Diffuse Large B-cell Lymphoma: a multicentric Phase II trial.
•Alisertib (inibitore Aurora kinasi), Kelly CCR 2020, Ph I (A + R + VCR), R/R DLBCL, 90/100 mg/die, 45 paz, 7 CR, 7 PR.
•Enzastaurina (inibitore PKC), Crump JCO 2016: mantenimento con E post-RCHOP in HR DLBCL: scarsa efficacia.
•Selinexor (SADAL), Kalakonda Lancet Haematol. 2020. Ph II 175 R/R DLBCL: ORR/CR 36/15, mDOR 9,3 m.
•Tazemetostat, Sarcozy CCR 2020, Ph Ib: median follow-up 20.6 months, 14.5 months, and 7.5 months in the 400, 600, and 800 mg cohort, respectively. mCR rate was 76.5% (13/17). During follow-up, 2 patients presented with a relapse. “The RP2D of tazemetostat combined with R-CHOP is 800 mg twice a day. The association presents safety and PK comparable with R-CHOP alone. Preliminary efficacy data are encouraging and further investigations in phase II trial are warranted”.
•Urelumumab (anti CD137), Timmerman AIH 2020: «Objective response rates/disease control rates were 6%/19% (DLBCL, n = 31), 12%/35% (FL, n = 17); durable remissions in heavily pretreated patients were achieved; however, many were observed at doses exceeding the MTD.
•Studi preclinici: inibitori IRAK4 (Chen EJMC 2020), inibitori di BCL6 (Cardenas JCI 2016)

CONCLUSIONI

A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications

Wright et al., 2020, Cancer Cell 37, 551–568
April 13, 2020 Published by Elsevier Inc.
https://doi.org/10.1016/j.ccell.2020.03.015

George W. Wright,[1] Da Wei Huang,[2] James D. Phelan,[2] Zana A. Coulibaly,[2] Sandrine Roulland,[2] Ryan M. Young,[2]



CONCLUSIONI

1.La distinzione in base a COO, DH/THL e DE non discrimina sottotipi con prognosi diverse ma soprattutto non identifica meccanismi patogenetici distinti, potenzialmente sensibili ad approcci biologici specifici.

2.Le strategie terapeutiche idealmente dovranno essere differenziate sulla base della rilevanza predittiva e prognostica dei dati genetici riconosciuti nell'ambito di trials prospettici.

3.I centri di riferimento nazionale devono contribuire in modo congiunto alla validazione e all'implementazione della diagnostica in modo che ogni paziente riceva una diagnosi corretta ed un trattamento il più possibile biologicamente orientato.