Nuevo algoritmo terapéutico para el linfoma difuso de célula grande B

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10 Noviembre 2022

Conflicto de intereses

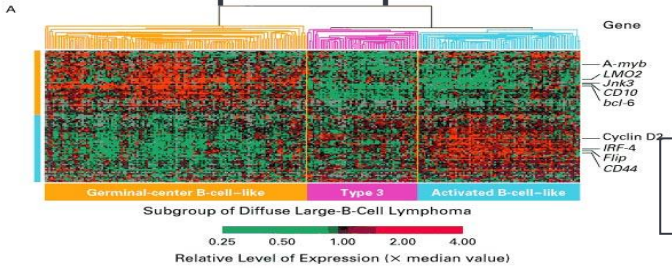
Consultancy: Janssen, Abbvie, Gilead, Kiowa, EUSAPharma, Incyte, Lilly, Beigene, Novartis

Speaker: Janssen, Abbvie, Takeda, Roche, EUSAPharma, Astra-Zeneca, Incyte

Travel: Janssen, Abbvie, Roche, EUSAPharma

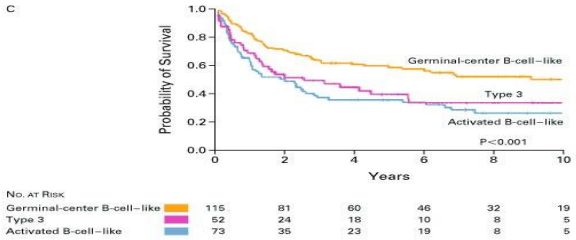
Biological heterogeneity of DLBCL

Gene expression profile



B

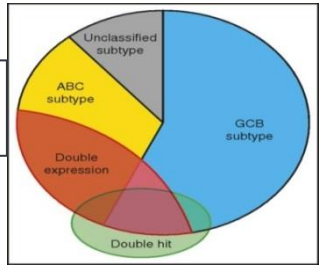
Oncogenic Abnormality	Germinal-center B-cell–like	Type 3	Activated B-cell–like
	no. of samples		
c-rel amplification	17	0	0
bcl-2 t(14;18)	26	0	0

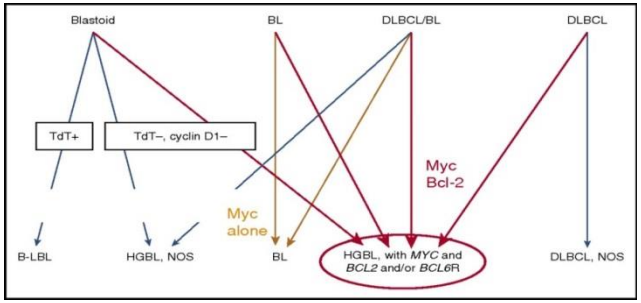


Double hit (DH) / Triple hit (TH)

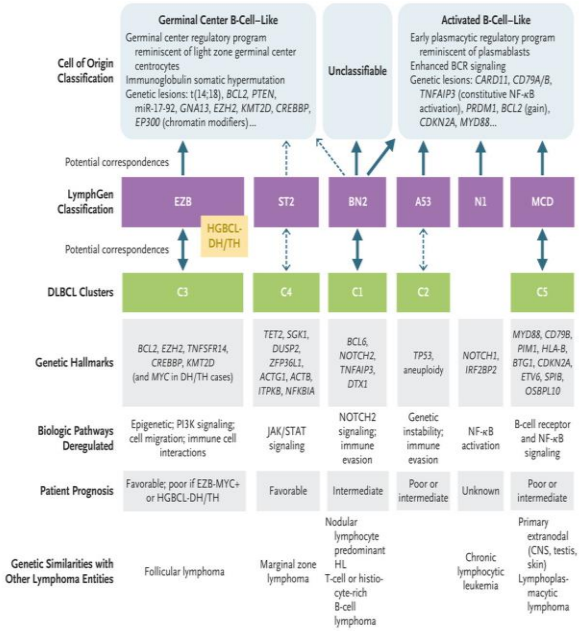
4-14% of DLBCL.

MYC/BCL2	62%
MYC/BCL6	8%
MYC/BCL2/BCL6	16%





Genétic subtypes



International NHL project, N Engl J Med 1993
Swerdlow et al, Blood 2016 127:2375-2390

Schmith et al, N Engl J Med. 2018 Apr 12;378(15):1396-1407
Chapuy et al, Nat Med. 2018 May;24(5):679-690

Clasificación de la OMS 2022

LBDCG NOS

1. **Variantes morfologicas**: centroblásticos, inmunoblásticos, anaplásicos
2. **Variantes inmunofenotípicas**: CD5+, doble expresores MYC/BCL2
3. **Variantes genéticas**: ABC vs CGB
4. **Variantes moleculares / citogenéticas**

Subtipos ABC extranodal

- Primario SNC
- Primario testicular
- Primario cutáneo de las piernas
- Intravascular
- Mama, suprarrenal…

Subtipos provisionales

LBDCG con alteraciones de 11q
Linfoma primario de cavidades HHV8 - y VEB -

Subtipos

Linfoma B predominio linfocítico nodular
Linfoma B rico en células T
LBDCG ALK+
Linfoma plasmablástico
Linfoma B primario mediastínico
LBDCG asociado a inflamación crónica (asociado a fibrina)

Asociados virus

Linfoproliferaciones asociadad a **VEB**

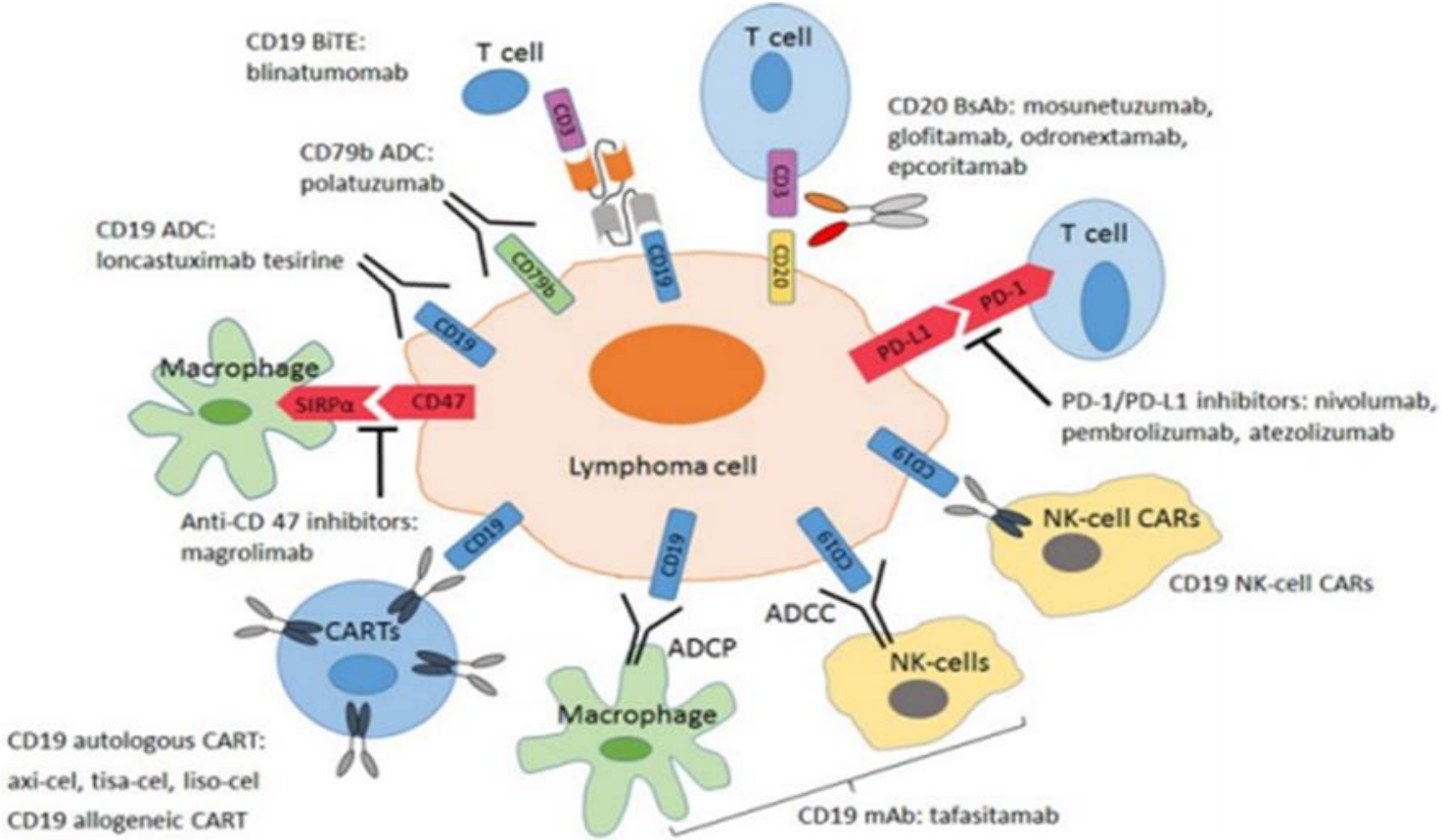
- Sd linfoproliferativo polimorfo VEB + NOS
- LBDCG VEB + NOS
- Úlcera mucocutanea VEB +
- Granulomatosis linfomatoide VEB+

Linfoproliferaciones asociadad a **HHV-8**

- LBDCG HHV8+ NOS
- Castleman multicéntrico
- Linfoma primario de cavidades
- Sd linfoproliferativo germinotropo HHV8+

Campo E, et al. Blood 2022;140(11):1229-1253

INMUNOTERAPIA



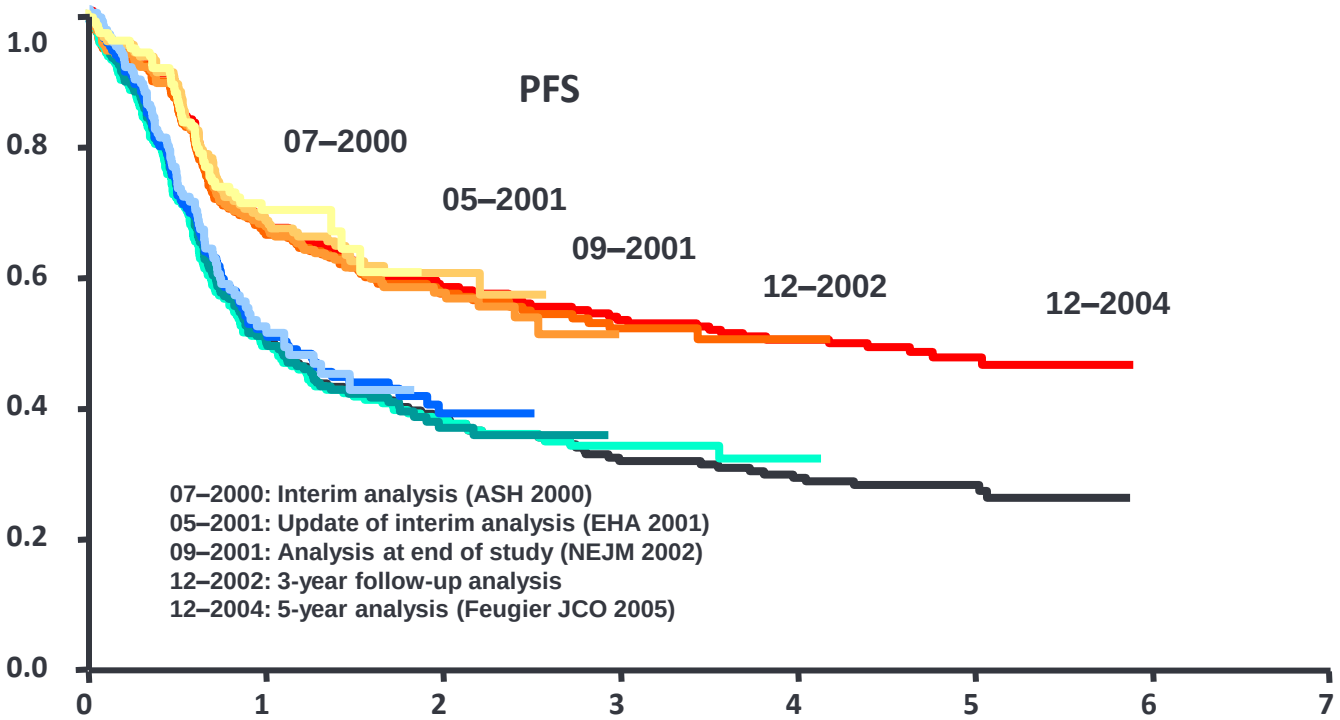
Karmali, ASH educational program 2021

FIRST LINE

RITUXIMAB: anti CD20

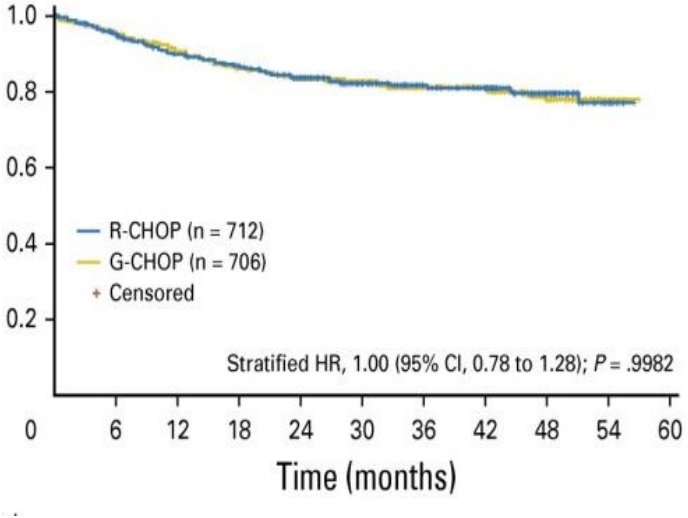
R-CHOP

399 patients > 60 yr R-CHOP/21 x 8 vs CHOP/21 x 8

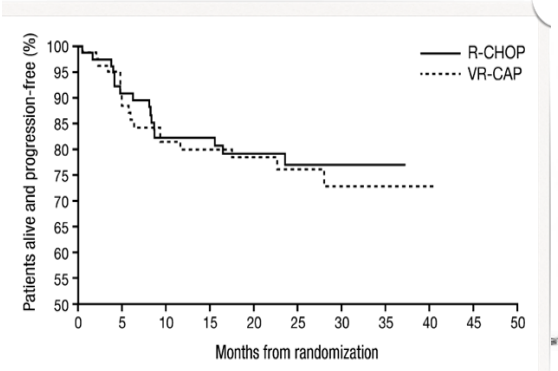


Coiffier, GELA, NEJM 2002; 346:235
Feugier P, *et al. J Clin Oncol*. 2005; 23:4117–4126

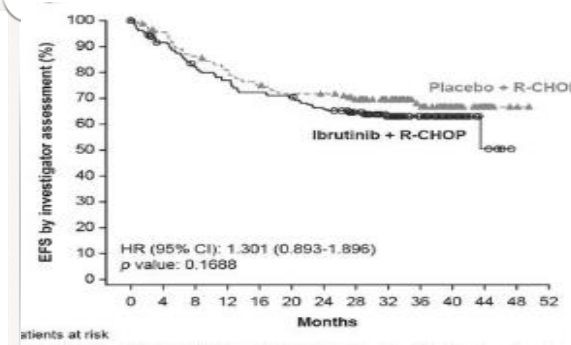
Different antiCD20:
Obinutuzumab CHOP(GOYA)



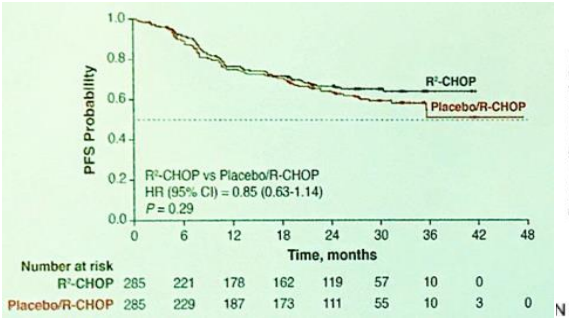
Bortezomib in ABC



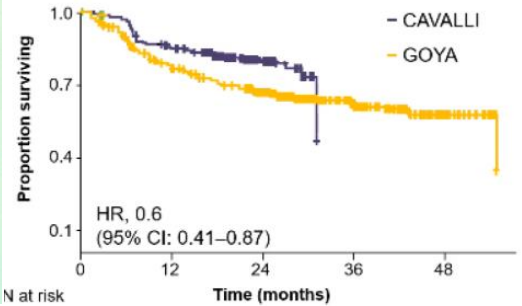
Ibrutinib in ABC (PHOENIX)



Lenalidomida in ABC (ROBUST):



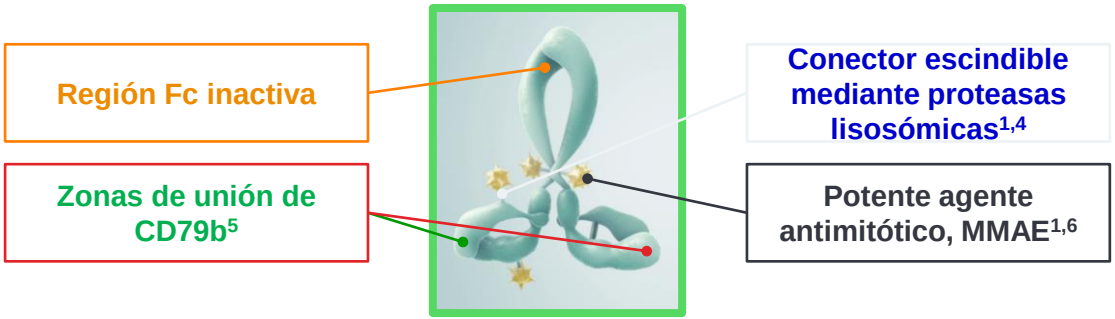
Venetoclax (Phase 2,CAVALLI):



Offner F, et al. Blood 2015;126:1893–901 (VR-CAP)
Vitolo U et al J Clin Oncol 2017;35(31):3529–3537 (GOYA)
Younes et al, J Clin Oncol 2019;37(15):1285-1295 (Ibrutinib)
Morschhauser et al, Blood 2018;132:782 (ASH meeting) (Venetoclax)
Zelenetz et al, Blood 2019;133(18):1964-1976.(Venetoclax)
Nowakowski GS et al, Future Onclol 2016 ;12(13):1553-63. (Lenalidomida)

POLATUZUMAB

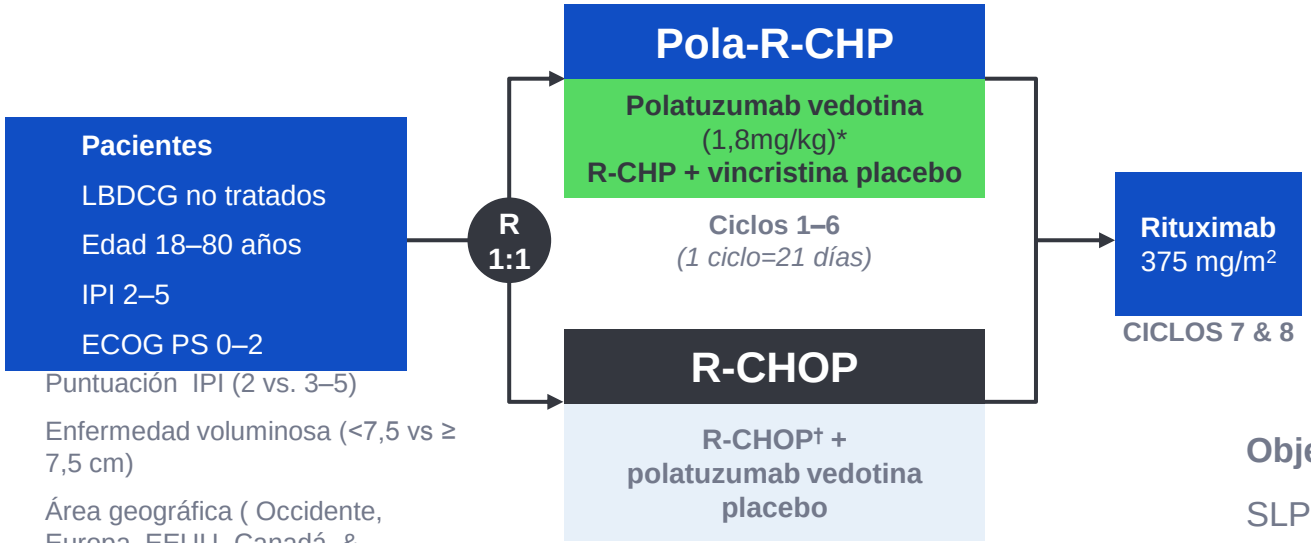
- Anticuerpo conjugado dirigido contra CD79b[1]
- **Potente agente antimitótico (MMAE)**



Sehn LH, et al. J Clin Oncol. 2020 Jan 10;38(2):155-165. doi: 10.1200/JCO.19.00172**. 3.** Tilly H, et al. Lancet Oncol. 2019 Jul;20(7):998-1010. doi: 10.1016/S1470-2045(19)30091-9. **4.** Dornan D, et al. Blood. 2009 Sep 24;114(13):2721-9. doi: 10.1182/blood-2009-02-205500. **5.** Polson A.G, et al. Expert Opin Investig Drugs. 2011 Jan;20(1):75-85. doi: .1517/13543784.2011.539557. **6.** Doronina S.O, et al. Nat Biotechnol. 2003 Jul;21(7):778-84. doi: 10.1038/nbt832

POLARIX (GO39942): estudio fase III, aleatorizado, doble ciego, controlado con placebo

879 pacientes fueron aleatorizados: 440 a polatuzumab R-CHP y 439 a R-CHOP



Objetivo primario:

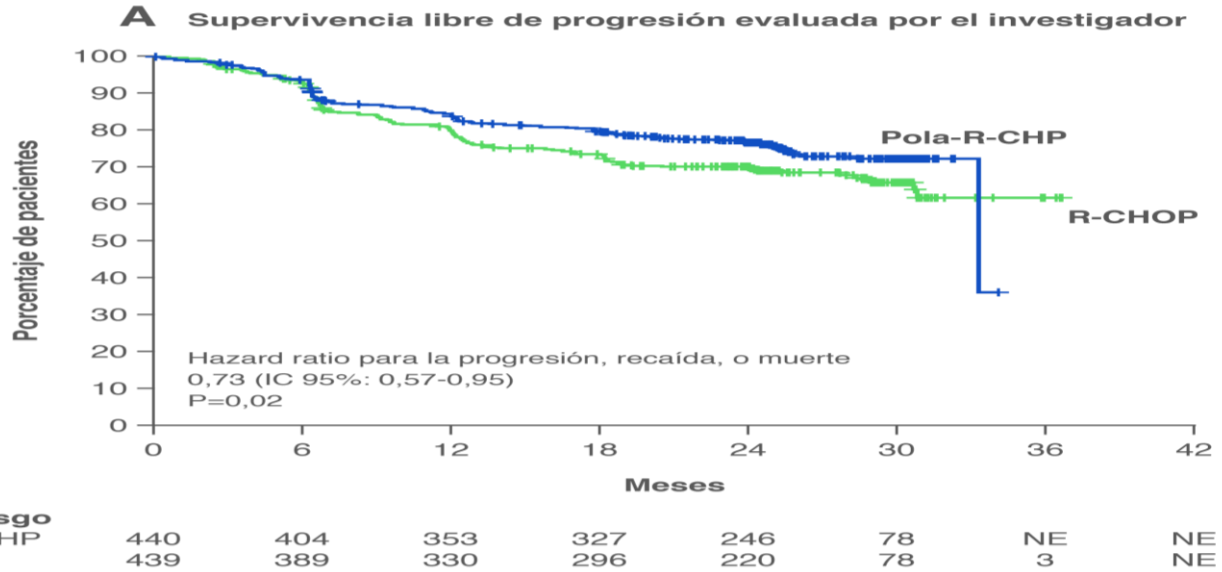
SLP evaluada por el investigador

Objetivo secundario:

SG y seguridad

Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363.

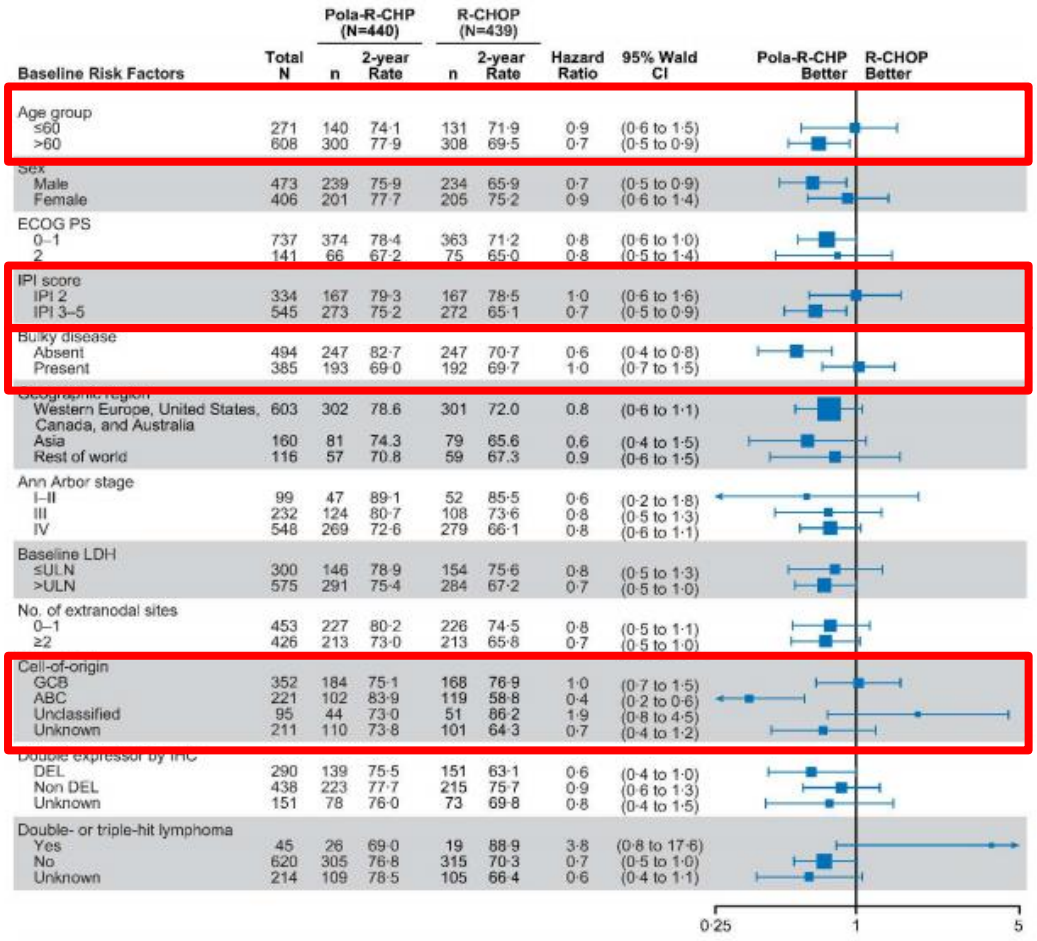
Objetivo primario: SLP



HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363. doi: 10.1056/NEJMoa2115304.
Tilly H, et al. **Late Breaking Abstracts , comunicación oral** en el 63rd ASH Annual Meeting 2021.



> 60 yr

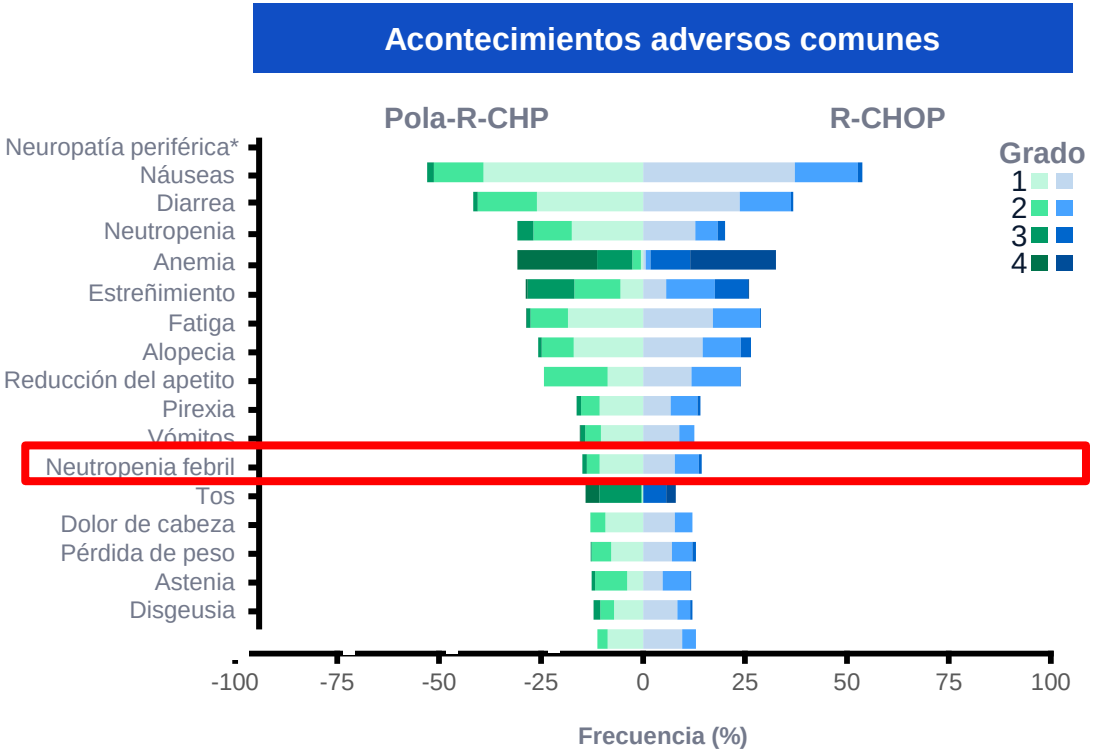
IPI 3-5

Non bulky

COO ABC

Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363. doi: 10.1056/NEJMoa2115304.
Tilly H, et al. **Late Breaking Abstracts , comunicación oral** en el 63rd ASH Annual Meeting 2021.

Seguridad



Aprobado por EMA

Neutropenia febril mayor con **Pola-R-CHP: no se tradujo en una mayor incidencia global de infecciones, discontinuaciones** del tratamiento, o **reducciones de dosis**

No se identificaron nuevas señales de seguridad

Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363. doi: 10.1056/NEJMoa2115304.
Tilly H, et al. **Late Breaking Abstracts , comunicación oral** en el 63rd ASH Annual Meeting 2021.

R/R SECOND LINE

I. Patients not eligible for transplant
II. Patients eligible for transplant
III. Very high-risk patients

I. Patients not eligible for ASCT

- **R-GEMOX**
- **R-Bendamustine**
- R-DHAP / R-ICE / R-ESHAP
- Cyclophosphamide
- Steroids

Median PFS: 5 months
Median OS: 10 months

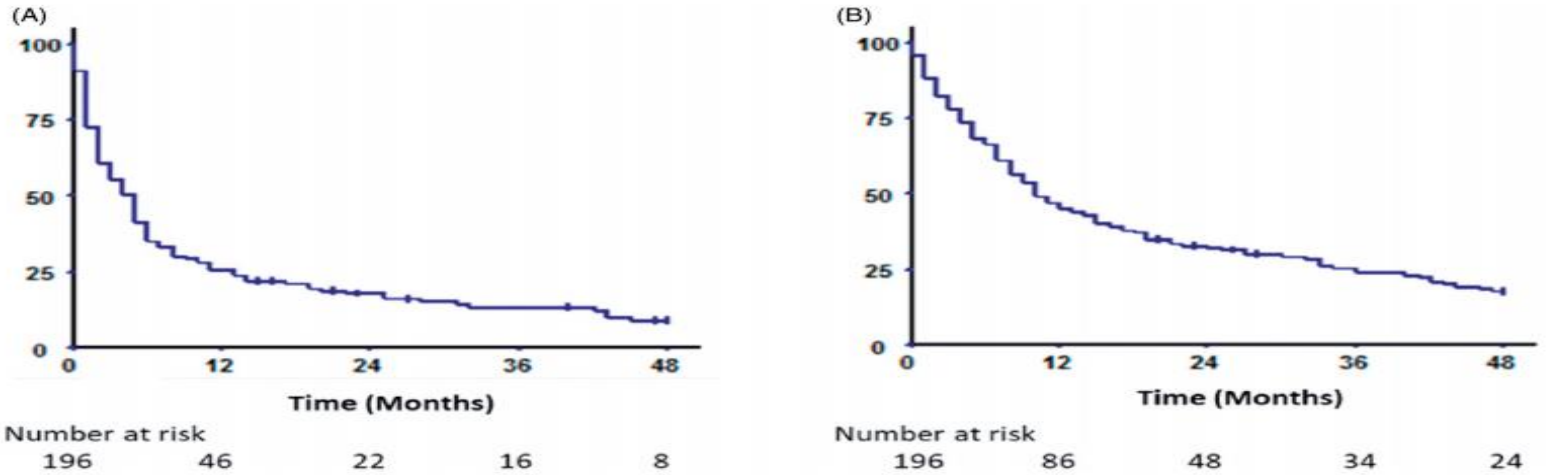


Figure 2. Outcome of the population. (A) PFS; median: 5 months. (B) OS; median: 10 months.

Cazelles et al, LEUKEMIA & LYMPHOMA 2021;62(9):2161–2168

Anticuerpos monoclonales en LBDCG R/R

- **Polatuzumab**: anticuerpo anti CD79b conjugado con monometilauristatina

  Enero 2020: EMA concede la autorización condicional de comercialización para polatuzumab, en combinación con bendamustina y rituximab.

  Noviembre 2020: AEM aprobacion de uso en riesgo compartido

- **Tafasitamab**: anticuerpo anti CD19

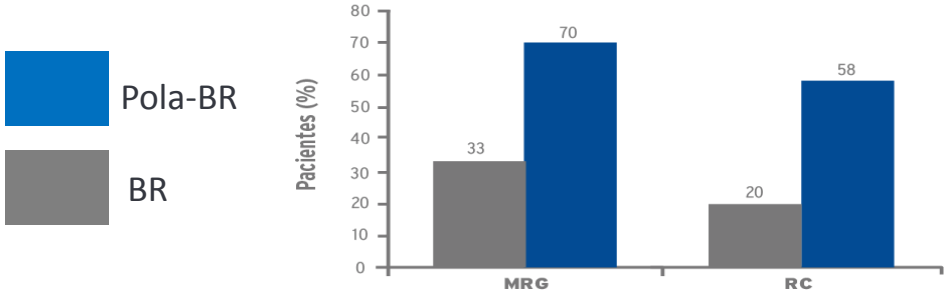
  Junio 2021: EMA concede autorización condicional de comercialización para la tafasitamab en combinación con lenalidomida seguido de tafasitamab ev en monoterapia

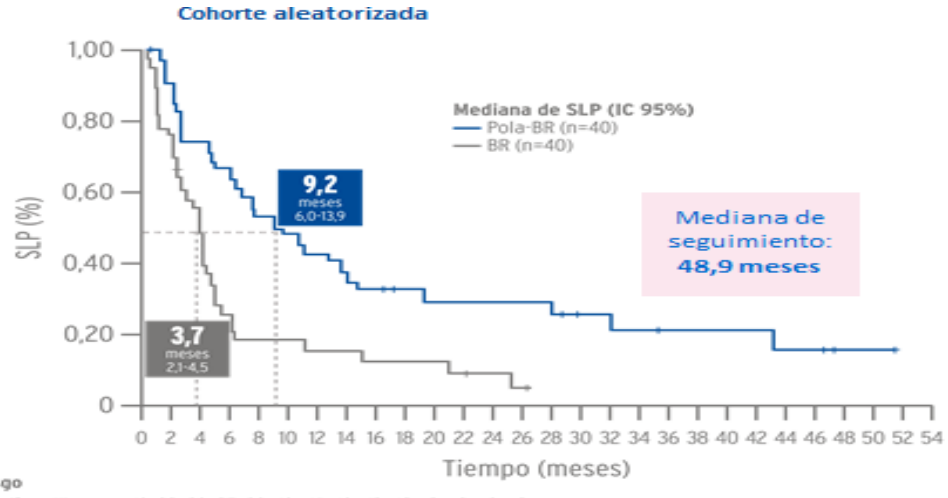
  Programa de uso expandido gratuito en España hasta septiembre 2022

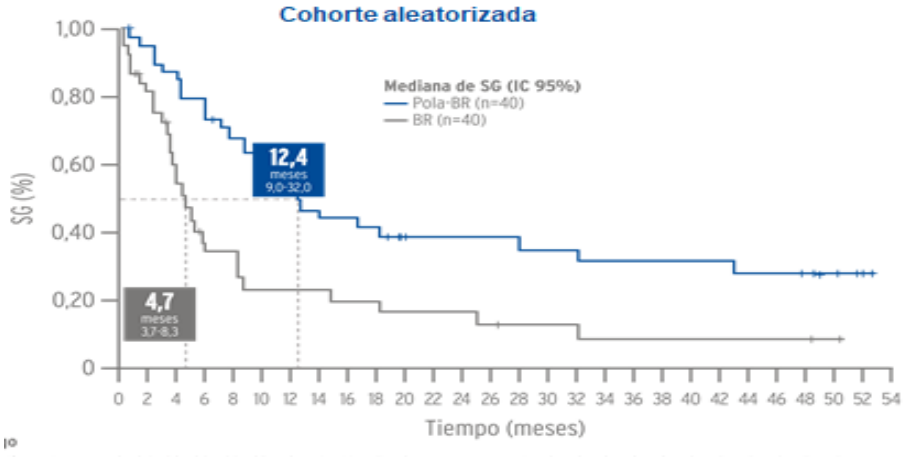
Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (not candidates for transplant) Phase Ib, phase II randomized trial, phase II extension trial

Sehn et al, J Clin Oncol 2020;38(2):155-165.

Efficacy





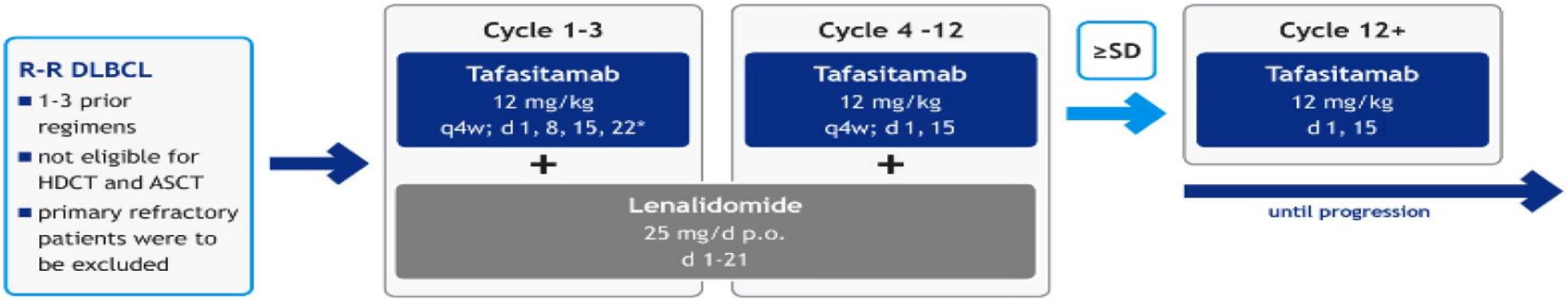


Maddocks KJ, et al. American Society of Hematology 2020 Annual Meeting. Abstract 3021.

Safety: hematological

	Pola-BR (n = 39)*		BR (n = 39)*	
Adverse Event	**All Grades, No. (%)**	**Grades 3-4, No. (%)**	**All Grades, No. (%)**	**Grades 3-4, No. (%)**
Blood and lymphatic system disorders				
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
GI disorders				
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
General disorders and administration site conditions				
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0
Peripheral neuropathy				
Peripheral neuropathy†	17 (43.6)	0	3 (7.7)	0

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

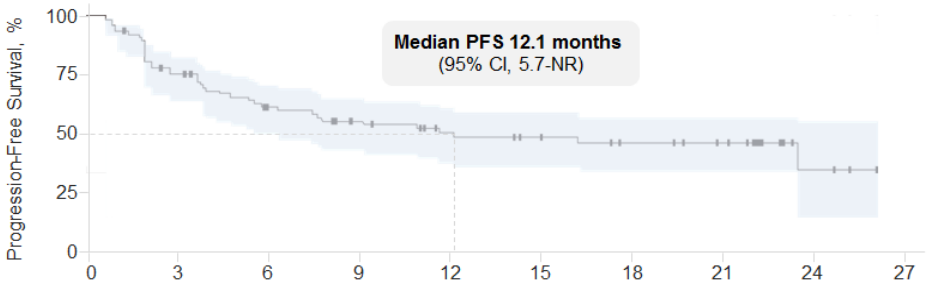


80 patients included

Salles et al. Lancet Oncol 2020;21(7):978-988.
Duell J, et al. Haematologica. 2021;106(9):24-17-2426.

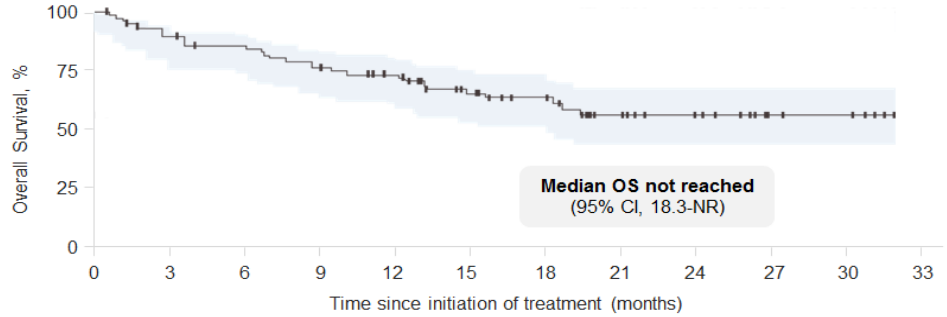
Survival

Results from 3-Year Follow-up



Number at risk (number censored)										
All treated patients	80(3)	56(5)	42(9)	35(12)	26(18)	22(23)	17(25)	13(29)	3(38)	0(41)

PFS Rates	
12 months	50% (95% CI, 38-61)
18 months	46% (95% CI, 33-57)

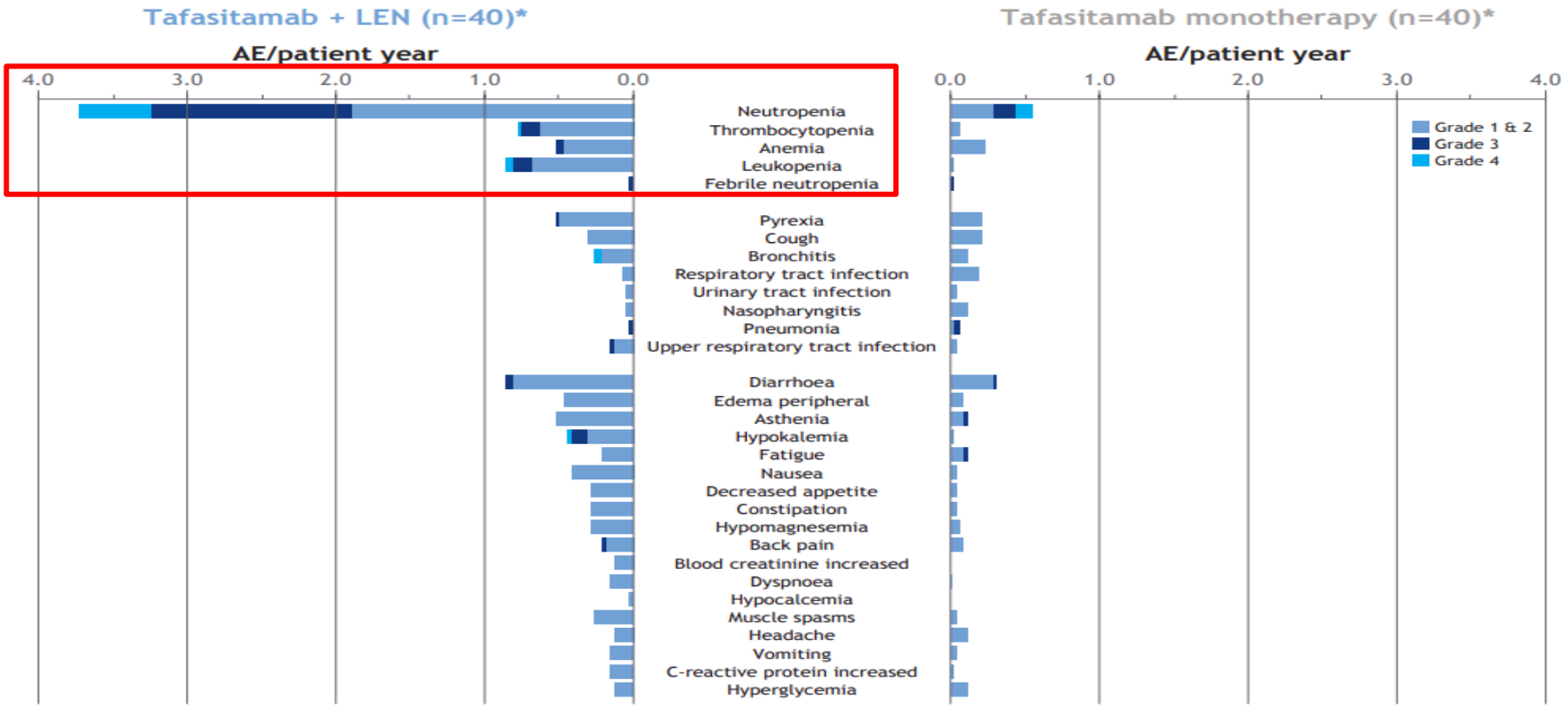


Number at risk (number censored)											
All treated patients	80(0)	69(3)	64(5)	57(6)	50(10)	35(20)	29(26)	20(32)	14(37)	6(45)	5(46)	0(51)

OS Rates	
12 months	74% (95% CI, 62-82)
18 months	64% (95% CI, 51-74)

Maddocks KJ, et al. American Society of Hematology 2020 Annual Meeting. Abstract 3021.

Safety

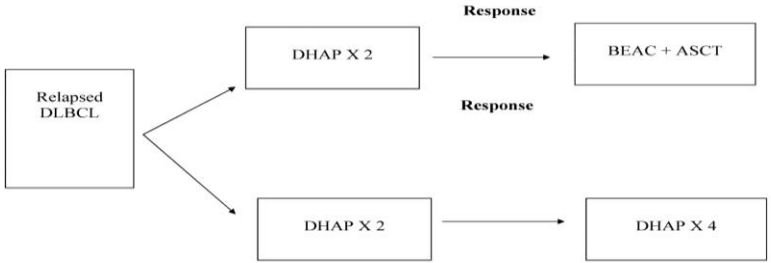


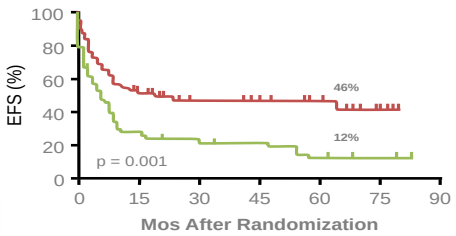
AE, adverse event. Data are based on a cumulative exposure total of 11,625 days or 19,880 days for tafasitamab + LEN or tafasitamab monotherapy study phases, respectively.
*Patients who had data from the tafasitamab monotherapy phase as well as the combination treatment phase.

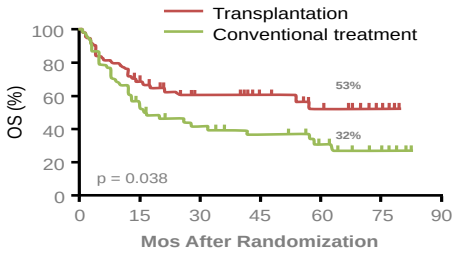
II. Patients eligible for transplat (ASCT)

SOC Salvage therapy followed by autologus stem cell transplantation

- **30-40% patients relapse or progress** (10-15% primary refractory)
- **PARMA study: pre-rituximab era**







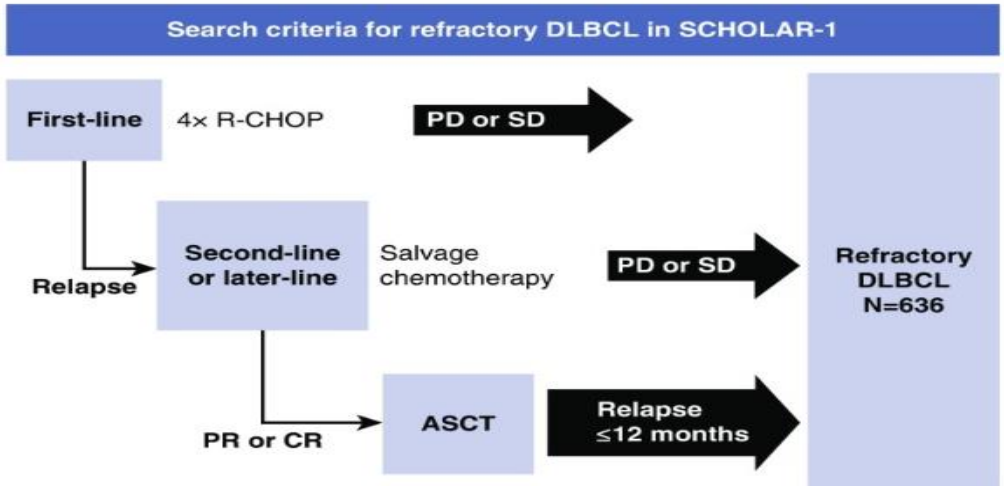
- **Different salvage therapies in the rituximab era**

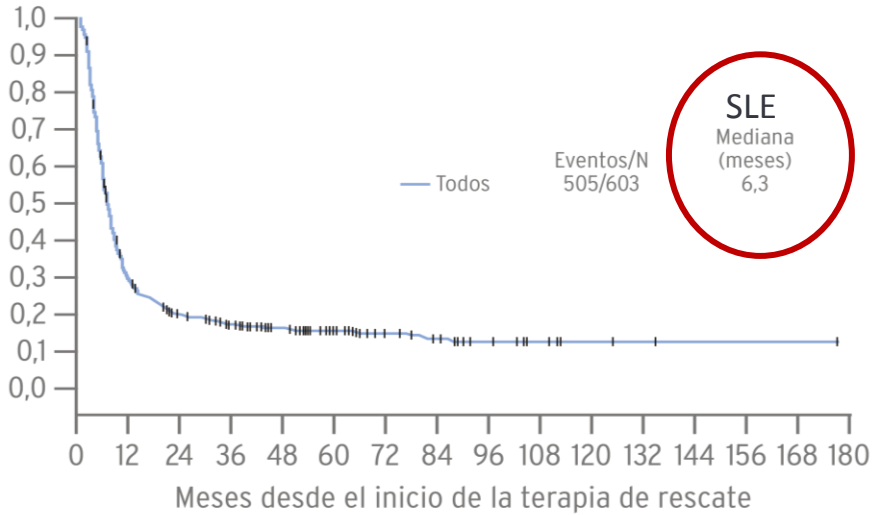
Estudio	n	Régimen	RR (%)	TPH (%)	SLE (3-4a)	SG (3-4a)
CORAL	396	R-DHAP R-ICE	63 64	54 50	35% 26%	51% 47%
NCIC-CTG LY12	619	R-DHAP R-GDP	44 45	49 52	26% 26%	39% 39%

Philip T, et al. N Engl J Med 1995;333:1540–5
Gisselbrecht et al, J Clin Oncol 2010; 28:4184
Crump M, et al. J Clin Oncol 2014;32:3490–6

III. Very high risk patients

SCHOLAR-1: refractarios o recaídos en menos de 12 meses

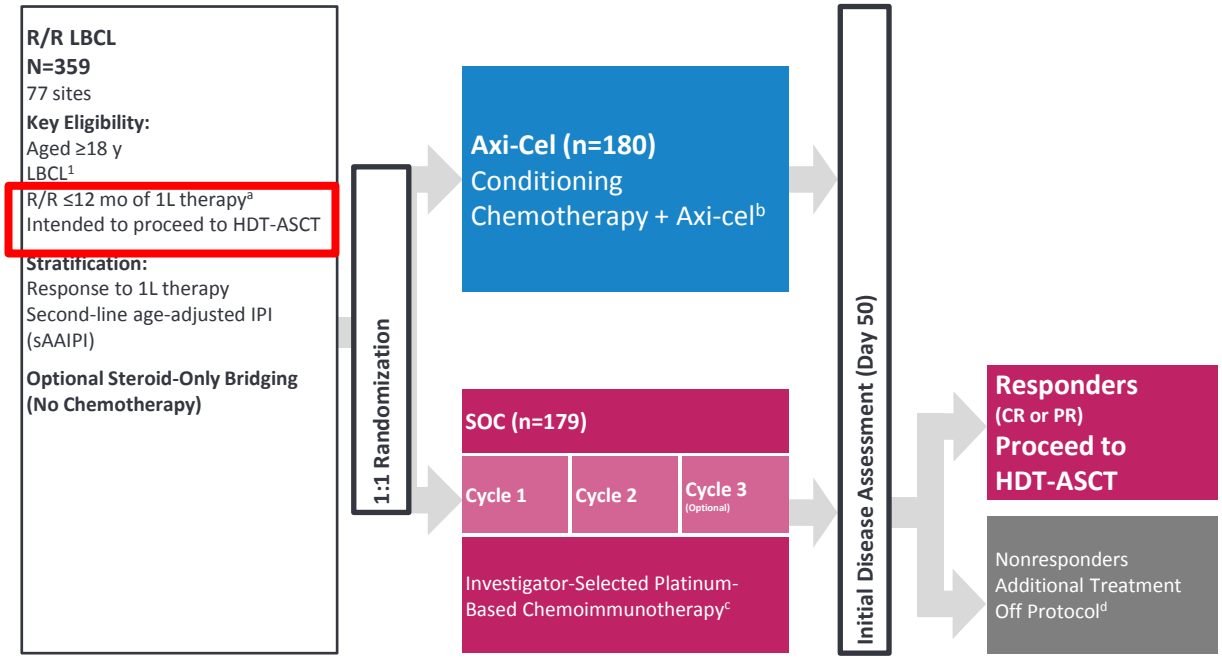




Gráfica extraída de Crump M, et al. Blood. 2017.

CAR T-CELL THERAPY

ZUMA-7 : A Phase 3 Randomized Trial of Axicabtagene Ciloleucel Versus Standard-Of-Care Therapy in Patients With Relapsed/Refractory Large B-Cell Lymphoma.



Primary Endpoint
Event-free survival by blinded central review

Key Secondary Endpoints
ORR
OS

Secondary Endpoints
PFS
Safety
PROs

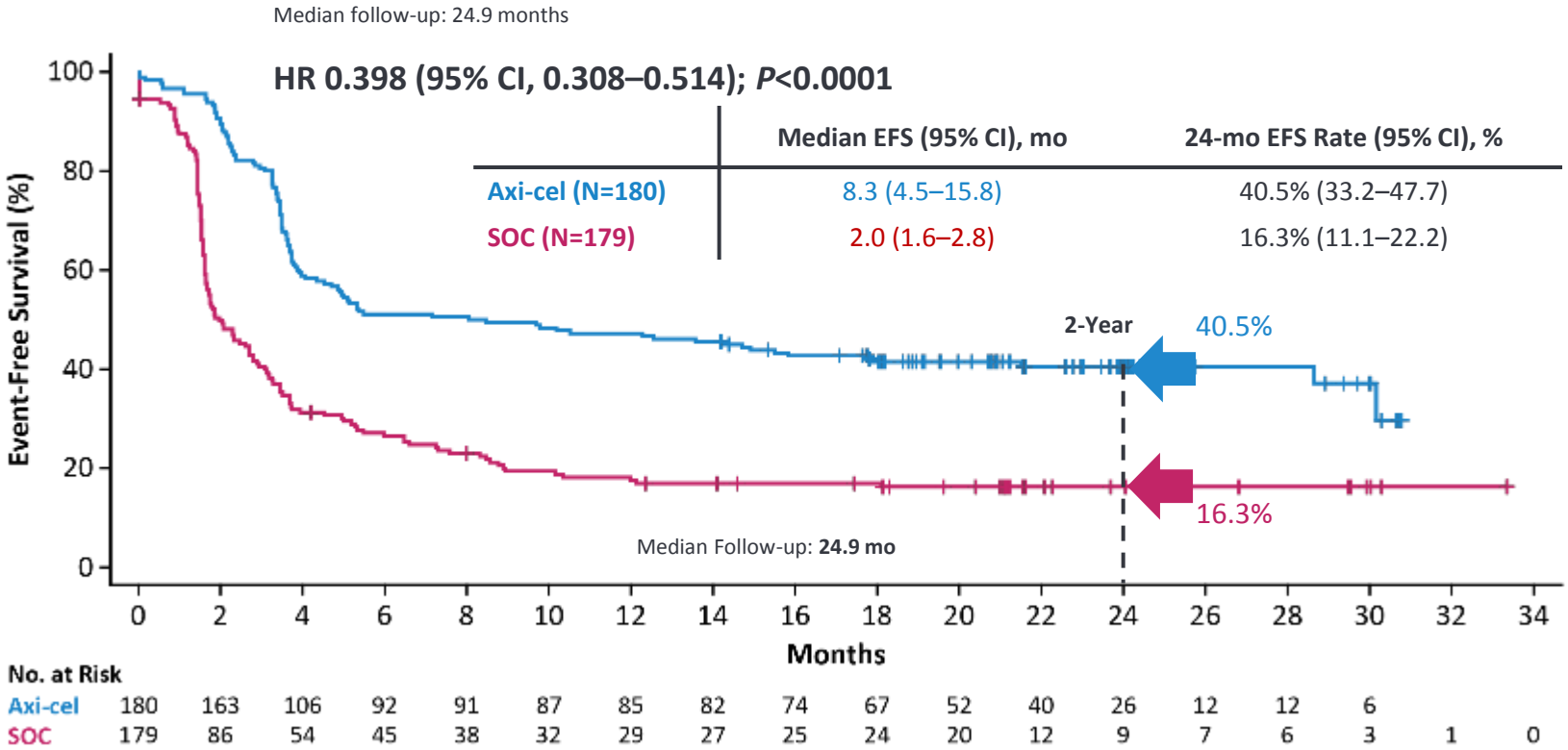
No Protocol-Specified Crossover

Locke et al. N Engl J Med. 2022 Feb 17;386(7):640-654.

Baseline Characteristics

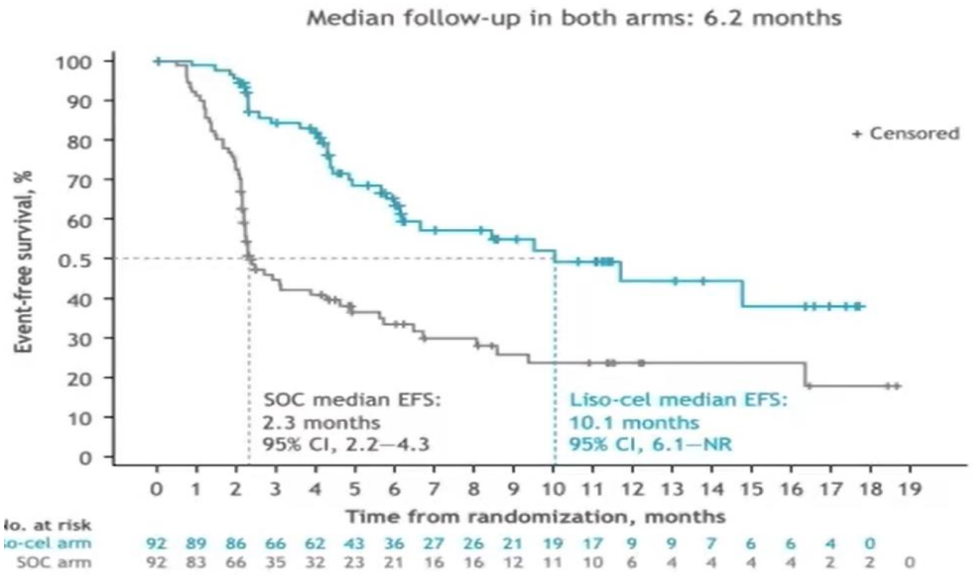
Characteristic	Axi-cel n=180	SOC n=179	Overall N=359
Median age (range), years	58 (21–80)	60 (26–81)	59 (21–81)
≥65 years, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III–IV, n (%)	139 (77)	146 (82)	285 (79)
sAAIPI of 2–3[a], n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy[a], n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤12 mo of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker per central laboratory, n (%)			
HGBL (including double-/triple-hit)	31 (17)	25 (14)	56 (16)
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[b]	101 (56)	94 (53)	195 (54)

Primary EFS Endpoint



Other CAR T-Cells

TRANSFORM. Lisocabtagene Maraleucel (liso-cel), a CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy, Versus Standard of Care (SOC) with Salvage Chemotherapy (CT) Followed By Autologous Stem Cell Transplantation (ASCT) As Second-Line (2L) Treatment in Patients (Pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL): Results from the Randomized Phase 3 Transform Study.

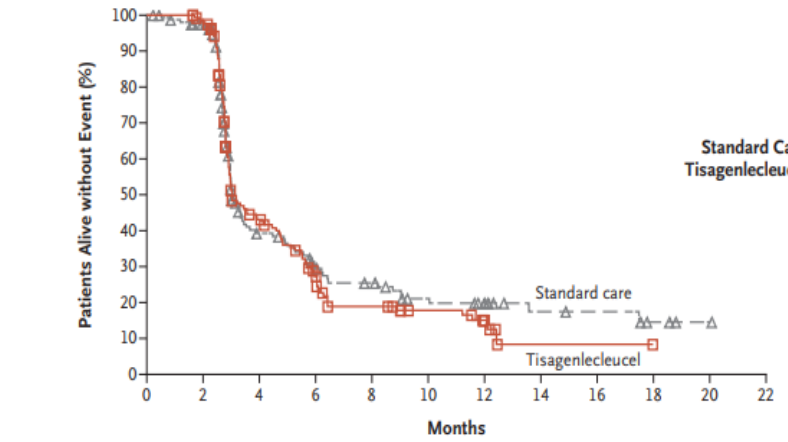


	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229—0.530)	
	$P < 0.0001$	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0—74.7	23.0—43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4—59.6	13.4—34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

Kamdar et al Lancet. 2022 Jun 18;399(10343):2294-2308.

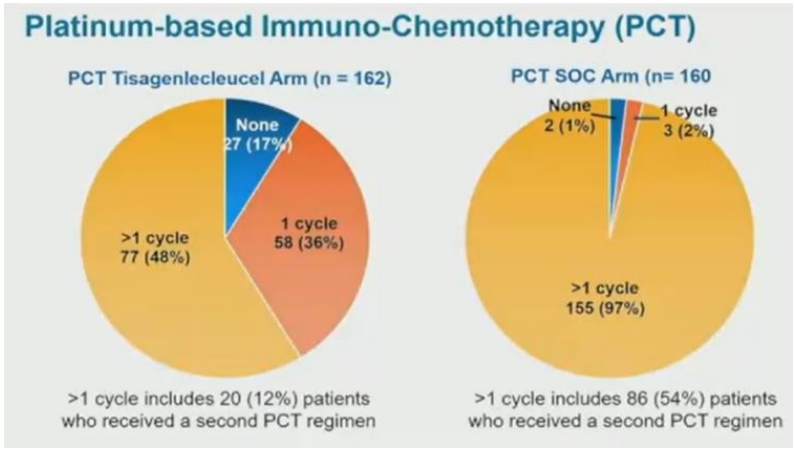
BELINDA: Tisagenlecleucel Vs Standard of Care As Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III Belinda Study.



No. at Risk												
Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

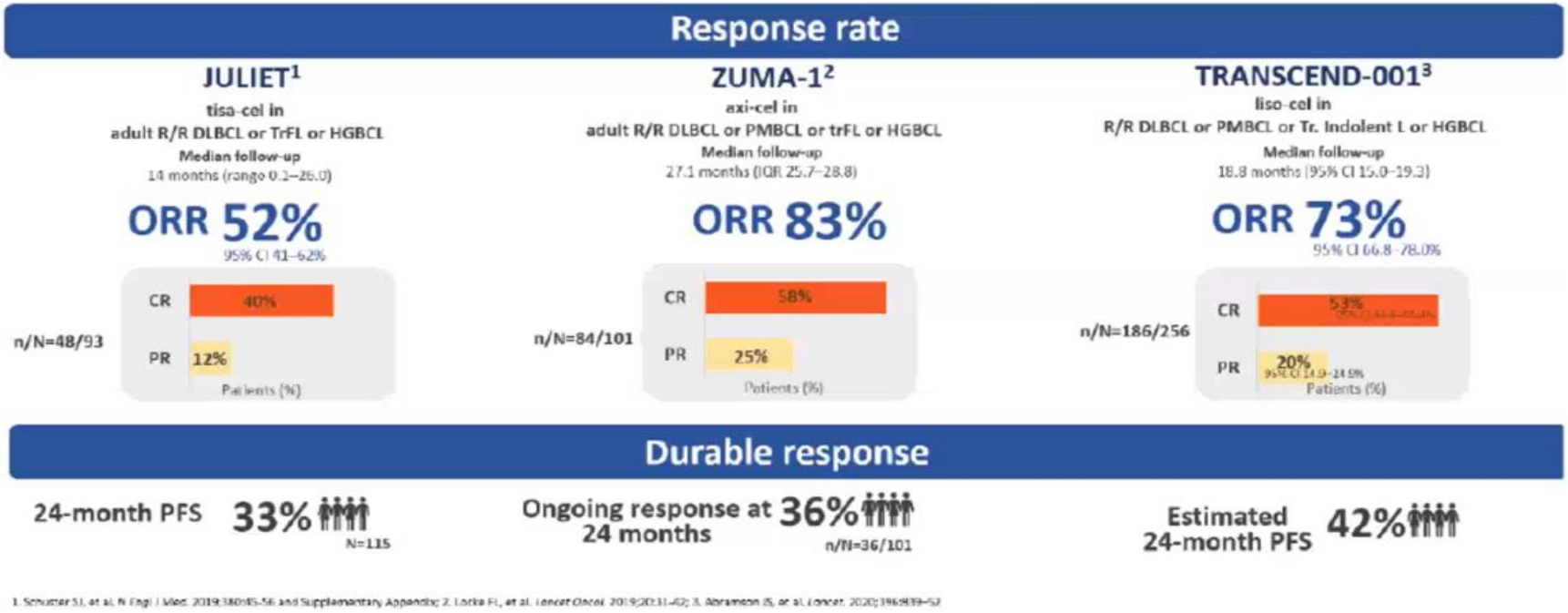


- Median time to CART infusion: 52 days
- Patients in progression previous to CART infusion: 26%

Bishop et al, N Engl J Med. 2022 Feb 17;386(7):629-639

R/R ≥ THIRD LINE

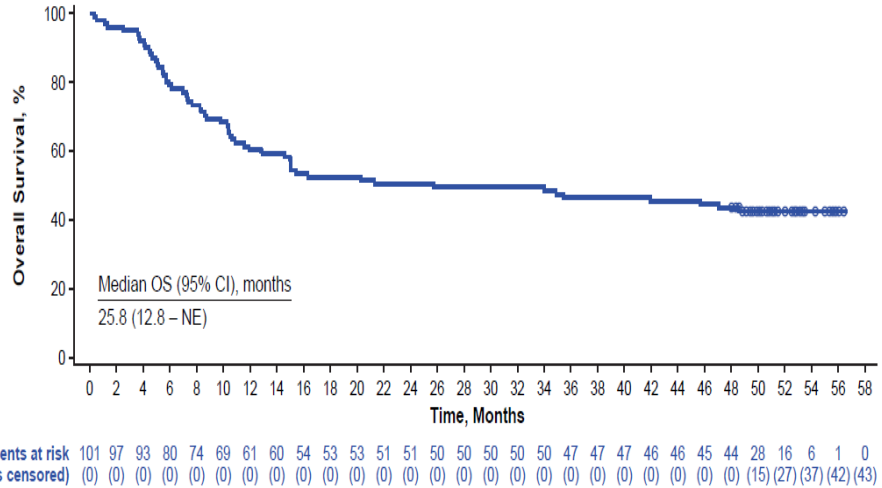
CARTs para pacientes en 3ra línea o posteriores



1. Schuster SJ, et al. N Engl J Med. 2019;380:45-56 and Supplementary Appendix; 2. Locke FL, et al. Lancet Oncol. 2019;20:31-42; 3. Abramson JS, et al. Lancet. 2020;396:839-52

Neelapu et al, N Engl J Med 2017; 377:2531-2544
Schuster SJ et al. N Engl J Med 2017; 377: 2545-2554
Locke FL et al. Lancet Oncol 2019; 20:31-42
Schuster SJ et al. N Engl J Med 2019; 380:45-56.

Zuma-1. Overall survival at 4 years: long-lasting responses.



Treated patients (mITT, n=101), **4-year OS rate was 44%**
Enrolled population (ITT, n=111), **4-year OS rate was 41%**

CI, confidence interval; ITT, intention-to-treat; mITT, modified intention-to-treat; NE, not evaluable; OS, overall survival.

ZUMA-1: Summary of Adverse Events

AE, n (%)	Primary Analysis N = 101	Updated Analysis N = 108
Grade ≥ 3 AE	96 (95)	105 (97)
Grade ≥ 3 SAE	43 (43)	50 (46)
Grade ≥ 3 CRS	13 (13)	13 (12)
Grade ≥ 3 NE	28 (28)	33 (31)
Grade 5 AE	3 (3)[a]	4 (4)[b]

Neurological events (NE)
- Delirium
- Encephalopathy
- Aphasia
- Seizure

Cytokine release syndrome (CRS)
- Fever
- Hypotension
- Respiratory insufficiency

Jacobson CA et al. *Clin Advances Hematol & Oncol* 2021;19 (3) Suppl 10.

NEW OPTIONS…IMMUNOTHERAPY

LONCASTUXIMAB

BISPECIFIC ANTIBODIES

Loncastuximab tesirine:

Humanized anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin

LOTIS·1
LOncastuximab Tesirine-lpyl Clinical AsSessment

[402-101] – A Phase 1 Dose-escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients With Relapsed or Refractory B-cell Lineage Non-Hodgkin Lymphoma (B-NHL)

NCT02669017
COMPLETED

LOTIS·2
LOncastuximab Tesirine-lpyl Clinical AsSessment

[402-201] – A Phase 2 Open-label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine-lpyl in Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

NCT03589469
ACTIVE, NOT RECRUITING

Resultados preliminares

LOTIS·5
LOncastuximab Tesirine-lpyl Clinical AsSessment

[402-311] – A Phase 3 Randomized Study of Loncastuximab Tesirine-lpyl Combined With Rituximab Versus Immunochemotherapy in Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

NCT04384484
RECRUITING

R-Lonca vs R-GEMOX

LOTIS·7
LOncastuximab Tesirine-lpyl Clinical AsSessment

A Phase 1b, Open-label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine-lpyl in Combination With Other Anticancer Agents in Patients with Relapsed or Refractory B-cell Lineage Non-Hodgkin Lymphoma (B-NHL)

NCT04970901
RECRUITING

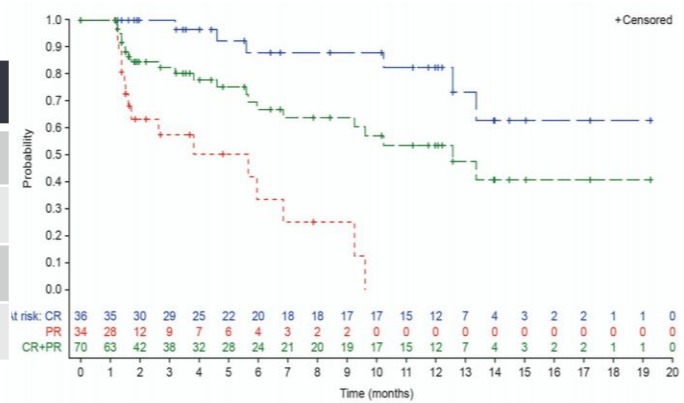
Lonca + Polatuzumab

LONCASTUXIMAB TESIRINE phase 2 study of loncastuximab tesirine in relapsed or refractory diffuse large b-cell lymphoma.

- Lonca 150 µg/kg every 3 weeks (Q3W) for 2 cycles, then 75 µg/kg Q3W thereafter

DLBCL/PML/HGBCL/TL	145 pts
Age (median, limits)	66 (23-94)
Previous lines (median)	3 (2-7)
Refractory to last Tx, (%)	57
Toxicity (%)	
- Increased GGT	41.4
- Neutropenia	40.0
- Thombocytopenia	33.1
- Anemia	26.1

Outcome	
ORR	48.3%
CR	24.8%
PFS	4.9 mo
OS	9.5 mo

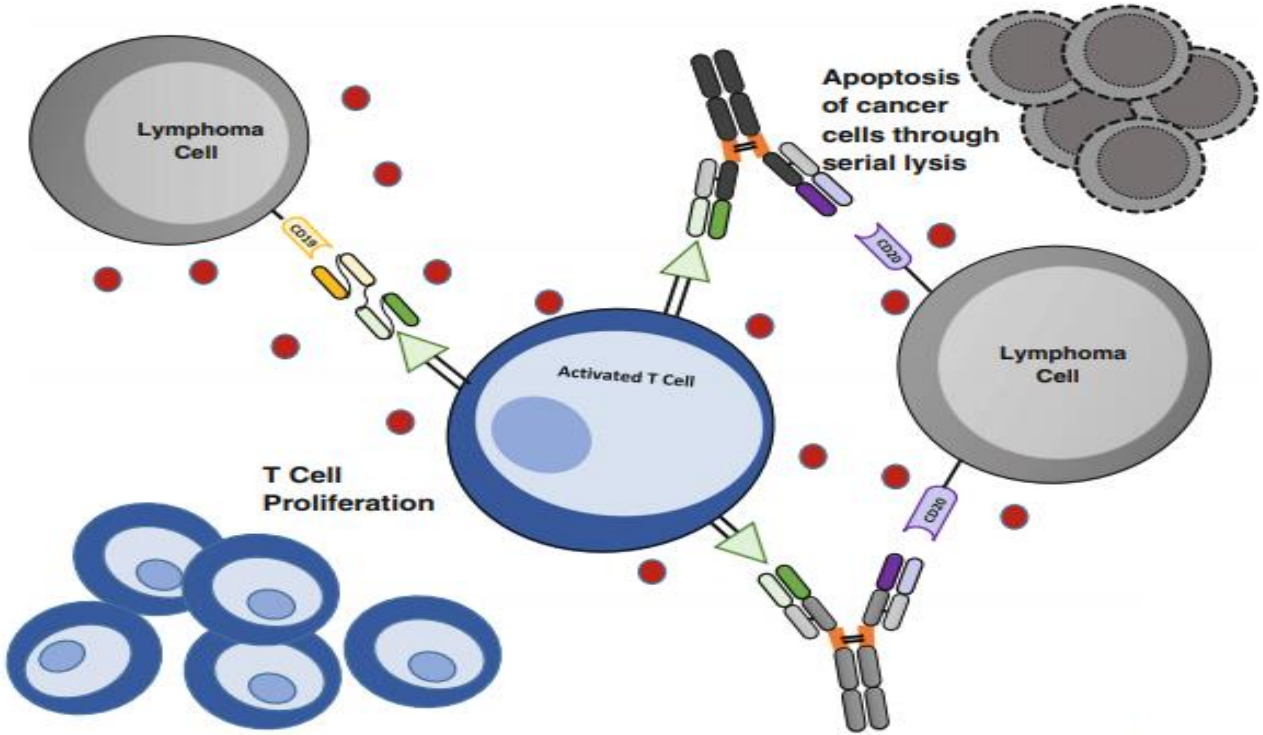


- 15 pts received after lonca a CD19-directed CART therapy with ORR of 46.7%
- 11 pts proceeded to SCT as consolidation.

CONCLUSIONS: durable responses to Lonca in heavily pre-treated pts. No new safety concerns reported.

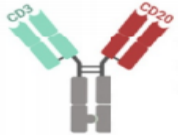
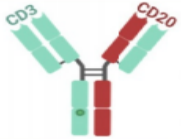
Zinzani, et al. Lugano 2021. Abstract #177

BISPECIFIC ANTIBODIES



Doraiswamy et al, Current Hematologic Malignancy Reports (2021) 16:72–81

BISPECIFIC ANTIBODIES

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield

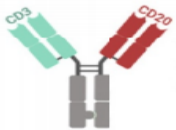
Schuster SJ. Hematological Oncology. 2021;39(S1):113–116.

Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

Lihua E. Budde, MD[1]; Sarit Assouline, MD[2]; Laurie H. Sehn, MD[3]; Stephen J. Schuster, MD[4]; Sung-Soo Yoon, MD, PhD[5]; Dok Hyun Yoon, MD, PhD[6]; Matthew J. Matasar, MD[7]; Francesc Bosch, MD, PhD[8]; Won Seog Kim, MD, PhD[9]; Loretta J. Nastoupil, MD[10]; Ian W. Flinn, MD, PhD[11]; Mazyar Shadman, MD, MPH[12]; Catherine Diefenbach, MD[13]; Carol O'Hear, MD, PhD[14]; Huang Huang, MSc[15]; Antonia Kwan, MBBS, PhD[14]; Chi-Chung Li, PhD[14]; Emily C. Piccione, PhD[14]; Michael C. Wei, MD, PhD[14]; Shen Yin, PhD[14]; and Nancy L. Bartlett, MD[16]

J Clin Oncol 2021;40:481-491

mosunetuzumab CD20 x CD3



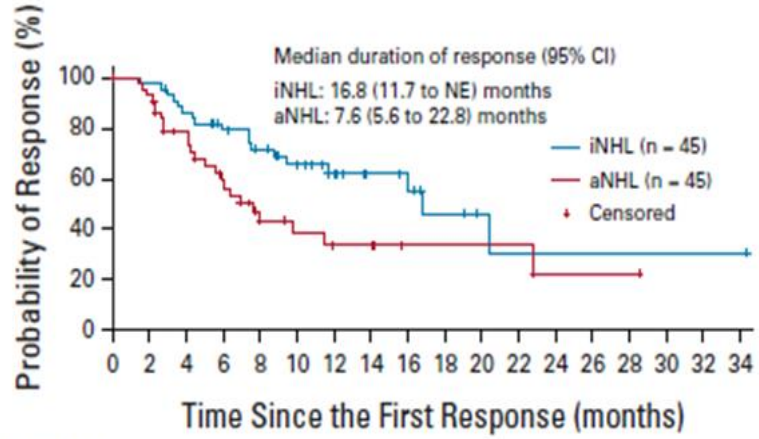
- humanized mouse heterodimeric IgG1-based antibody
- monovalent CD20 and monovalent CD3ε binding
- modified Fc devoid of FcγR and complement binding

Mosunetuzumab was given 21-day cycles up to 8 cycles for patients with a CR and 17 cycles for hose with PR or SD.

- In group A, mosunetuzumab was administered intravenously on day 1 of each 21-day cycle.
- In group B, mosunetuzumab was administered intravenously as low and intermediate step-up doses on days 1 and 8 of cycle 1, with the target dose on day 15 and on day 1 of subsequent 21-day cycles.

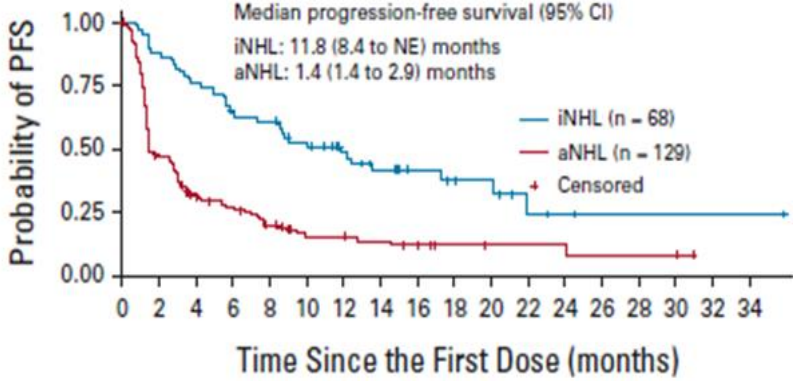
Efficacy

	Mosunetuzumab NCT02500407 Ph 1/1b (dose escalation / expansion)	
Patients	129 aNHL	68 iNHL
Prior LoT, median Refractory to last therapy Prior CAR T-cell therapy	3 (1-14) 106 (82%) 15 (12%)	3 (1-11) 43 (63%) 4 (6%)
ORR / CR	34.9% / 19.4%	66.2% / 48.5%
Prior CART ORR / CR	36.8% / 26.3%	



No. at risk:

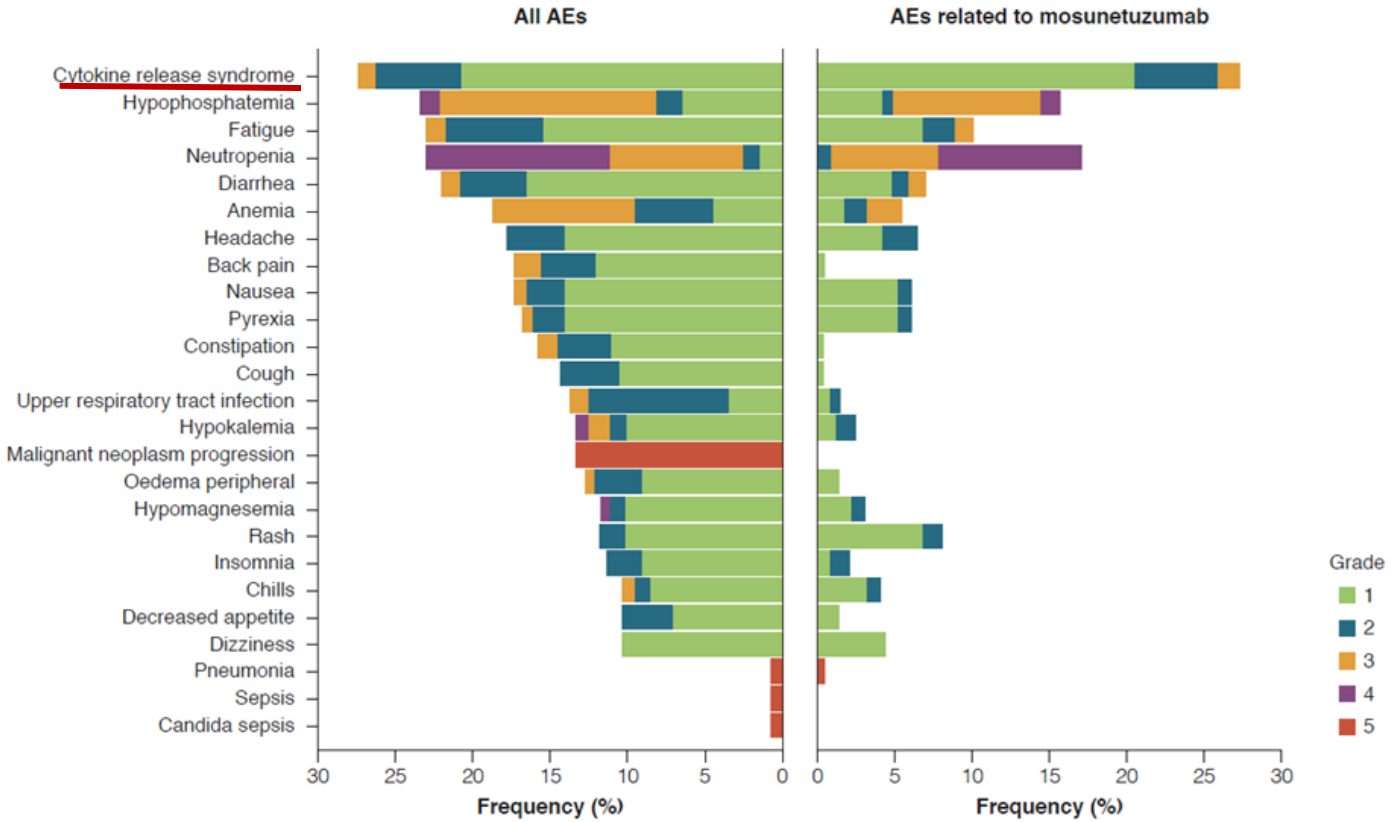
iNHL	45	44	38	32	27	22	16	10	9	5	3	2	1	1	1	1	1	1
aNHL	45	41	29	20	10	8	6	6	3	3	3	3	1	1	1			



No. at risk:

iNHL	68	59	51	42	40	29	22	17	10	8	7	3	2	1	1	1	1	1
aNHL	129	58	35	29	20	11	11	9	7	4	3	3	3	2	2	2	0	0

PRIMARY OBJECTIVE: MTD and SAFETY

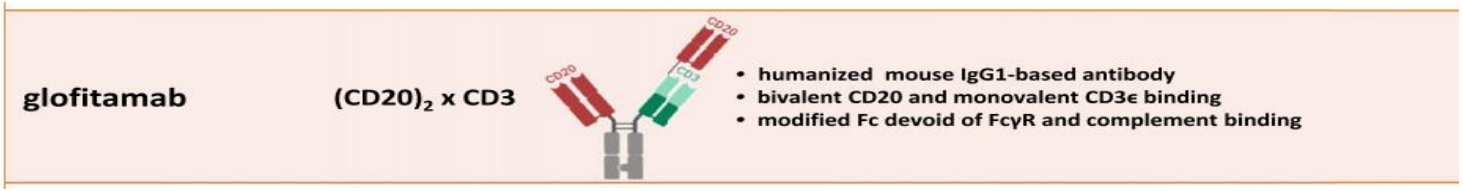


ICAN grade 1-2: Headache 18%, insomnia 11%, dizziness 10%; grade 3: 4.1%

Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD[1]; Franck Morschhauser, MD, PhD[2]; Gloria Iacoboni, MD[3,4]; Carmelo Carlo-Stella, MD[5]; Fritz C. Offner, MD, PhD[6]; Anna Sureda, MD, PhD[7]; Gilles Salles, MD[8]; Joaquín Martínez-Lopez, MD, PhD, MBA[9]; Michael Crump, MD[10]; Denise N. Thomas, MSc[11]; Peter N. Morcos, PharmD[11]; Cristiano Ferlini, MD[11]; Ann-Marie E. Bröske, PhD[12]; Anton Belousov, PhD[13]; Marina Bacac, PhD[13]; Natalie Dimier, PhD[14]; David J. Carlile, PhD[14]; Linda Lundberg, PhD[15]; David Perez-Callejo, MD, PhD[15]; Pablo Umaña, PhD[13]; Tom Moore, MD[12]; Martin Weisser, MD[12]; and Michael J. Dickinson, MBBS, DMedSci[16]

J Clin Oncol 2021;39:1959-1970



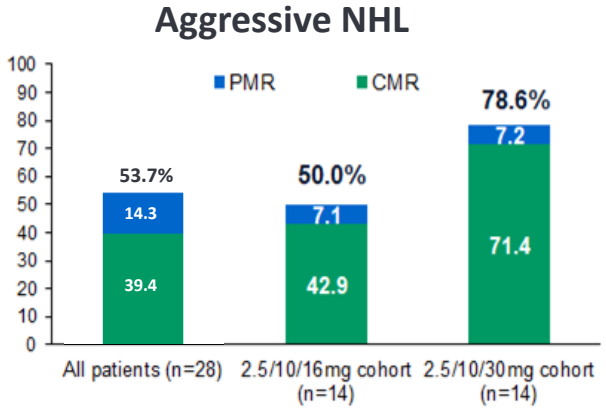
Glofitamab was given 21-day cycles up to 12 cycles.

- Dose escalation was guided by a Bayesian-modified continuous reassessment method with overdose control
- 2.5 mg (C1D1), 10 mg (C1D8), and 30 mg (C2D1)
- Seven days before 1,000 mg obinutuzumab to deplete peripheral and tissue based B cells and mitigate serious AE.

TABLE 1. Patient Demographics and Baseline Disease Characteristics in Patients Who Received Glofitamab at Any Dose and at the RP2D (Safety-Evaluable Patients)

Characteristic	All Glofitamab Cohorts (N = 171)	RP2D Glofitamab Cohort 2.5/10/30 mg (n = 35)
Age, years		
Median	64	66
Range	22-85	44-85
Male sex, No. (%)	100 (58.5)	17 (48.6)
Histology subtype, No. (%)		
DLBCL	73 (42.7)	5 (14.3)
FL grades 1-3A	44 (25.7)	21 (60.0)
DLBCL arising from FL	29 (17.0)	3 (8.6)
Richter's transformation	10 (5.8)	2 (5.7)
PMBCL	3 (1.8)	0
Others[b]	12 (7.0)	4 (11.4)
Prior autologous stem-cell transplant, No. (%)	41 (24.0)	9 (25.7)
Prior CAR-T therapy, No. (%)	3 (1.8)	1 (2.9)
Prior lines of therapy, No.		
Median	3	3
Range	1-13	1-12
Refractory to any prior therapy, No. (%)		
Refractory	155 (90.6)	29 (82.9)
Relapsed	16 (9.4)	6 (17.1)

Efficacy



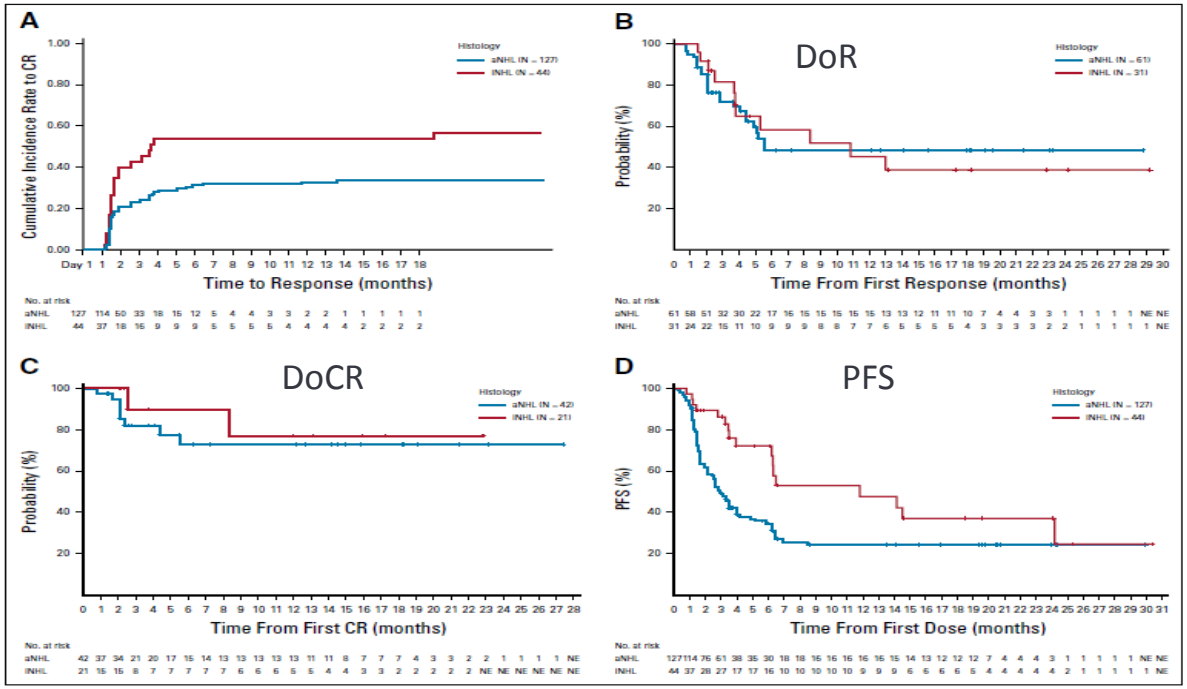
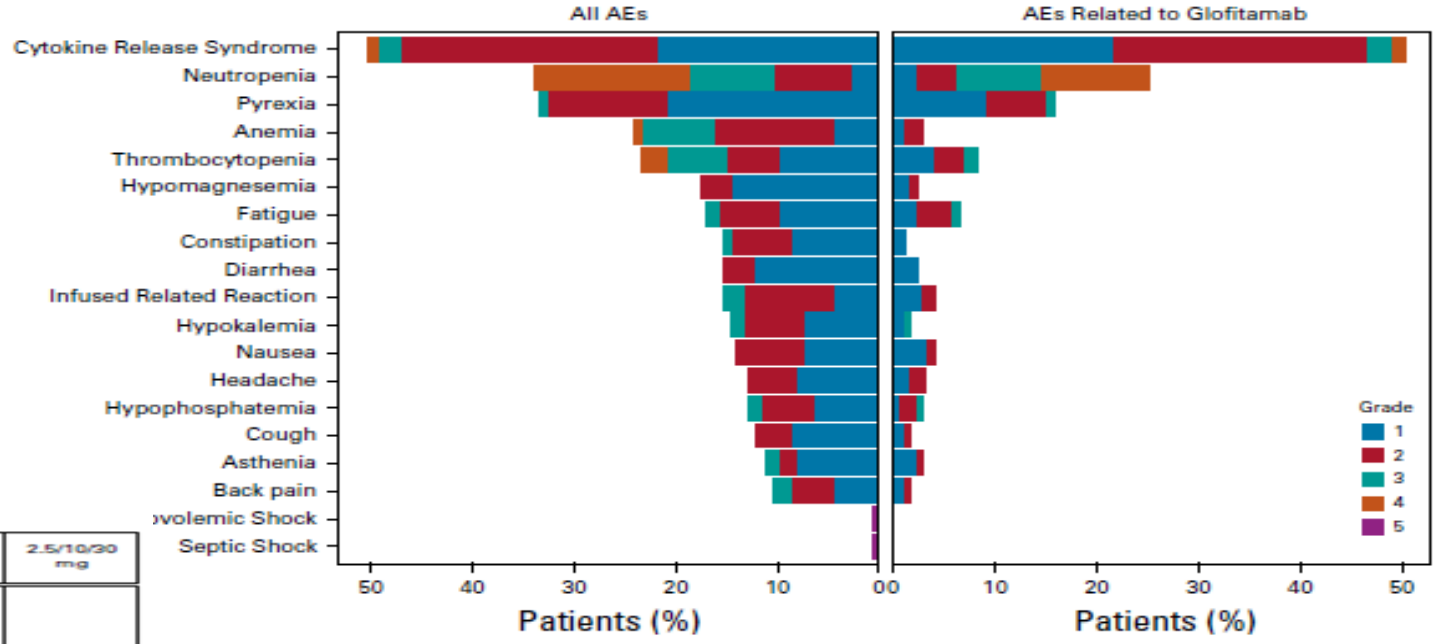
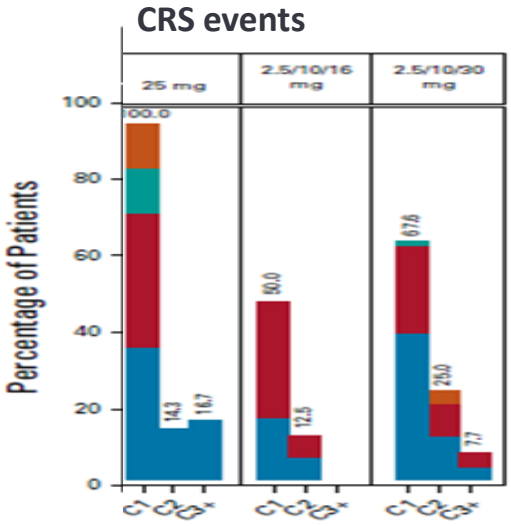


FIG 3. (A) Represents the cumulative incidence of time to CR. Kaplan-Meier curves for (B) DOR (PR and CR), (C) duration of CR, and (D) PFS. aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; DOR, duration of response; iNHL, indolent non-Hodgkin lymphoma; NE, not estimable; PFS, progression-free survival; PR, partial response.

PRIMARY OBJECTIVE: MTD and SAFETY





ICAN:

- **8 / 171 (4.8%), grade 3: 2 (1.8%); no grade 4-5**
- **All transient 3-72h**

Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study

Martin Hutchings, Rogier Mous, Michael Roost Clausen, Peter Johnson, Kim M Linton, Martine E D Chamuleau, David John Lewis, Anna Sureda Balari, David Cunningham, Roberto S Oliveri, Brian Elliott, Dena DeMarco, Ada Azaryan, Christopher Chiu, Tommy Li, Kuo-mei Chen, Tahamtan Ahmadi, Pieternella J Lugtenburg

Lancet 2021; 398: 1157–69

epcoritamab | **CD20 x CD3**

- humanized mouse IgG1-based heterodimeric antibody
- monovalent CD20 and monovalent CD3 binding
- IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield

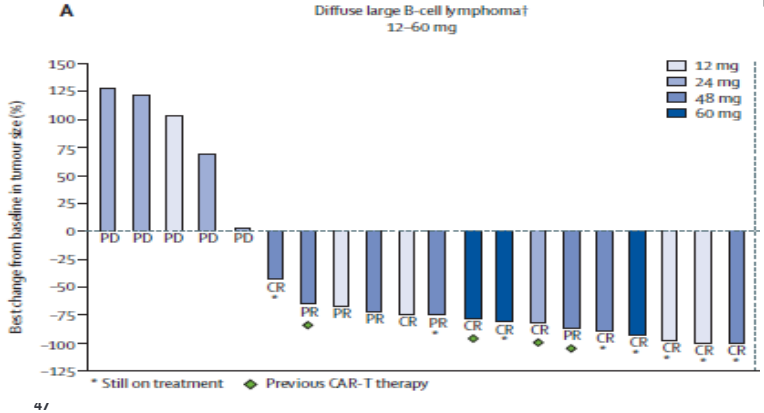
Subcutaneous epcoritamab (1 mL) was administered in 28-day cycles until disease progression or unacceptable toxicity

Weekly dosing in cycles 1 and 2 (days 1, 8, 15, 22)
Every 2 weeks in cycles 3–6 (days 1, 15)
Every 4 weeks from cycle 7 onward

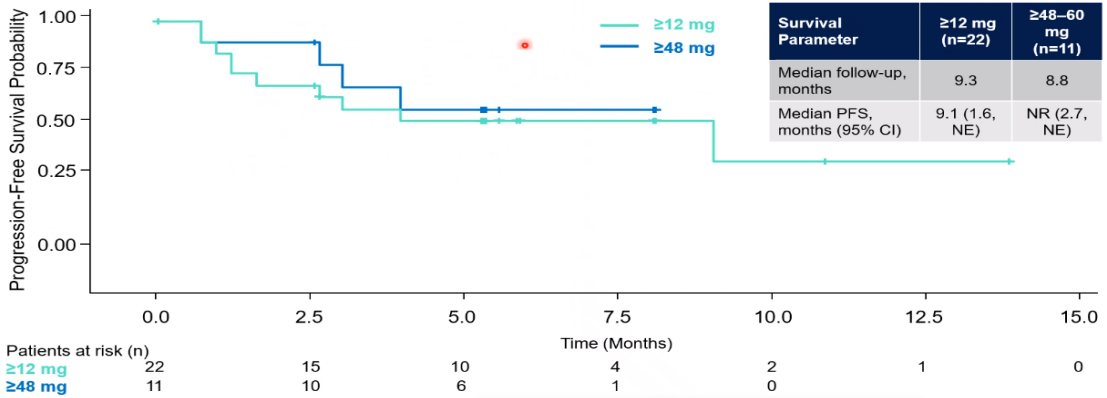
	Relapsed or refractory diffuse large B-cell lymphoma (n=46)	Relapsed or refractory follicular lymphoma (n=12)	All patients (n=68)*
Age, years	68 (55–74)	73 (63–76)	68 (57–75)
Sex			
Female	16 (35%)	4 (33%)	23 (34%)
Male	30 (65%)	8 (67%)	45 (66%)
ECOG performance status			
0	23 (50%)	6 (50%)	35 (51%)
1	21 (46%)	4 (33%)	29 (43%)
2	2 (4%)	1 (8%)	3 (4%)
3†	0	1 (8%)†	1 (1%)†
Ann Arbor stage			
I	3 (7%)	0	3 (4%)
II	5 (11%)	4 (33%)	12 (18%)
III	12 (26%)	4 (33%)	16 (24%)
IV	26 (57%)	4 (33%)	37 (54%)
Extranodal disease	29 (63%)	6 (50%)	42 (62%)
Time since diagnosis, months	25·4 (11·0–54·6)	61·5 (34·3–153·1)	29·7 (13·7–66·8)
Time since relapse or progression,	1·5 (1·1–2·3)	1·6 (1·2–2·6)	1·6 (1·1–2·3)
Number of lines of previous therapy	3·0 (2·0–4·0)	4·5 (2·5–8·0)	3·0 (2·0–4·5)
Previous therapies			
Anti-CD20 monoclonal antibody	46 (100%)	12 (100%)	68 (100%)
Anthracyclines	46 (100%)	9 (75%)	62 (91%)
Alkylating agents	46 (100%)	12 (100%)	67 (99%)
Autologous stem-cell transplantation	7 (15%)	1 (8%)	10 (15%)
CAR-T therapy	5 (11%)	0	6 (9%)
Treatment-refractory patients by therapy			
Last line of systemic therapy	41 (89%)	10 (83%)	58 (85%)
Alkylating agents	40 (87%)	9 (75%)	56 (82%)
Last anti-CD20 monoclonal antibody	41 (89%)	10 (83%)	59 (87%)

	Relapsed or refractory diffuse large B-cell lymphoma*			Relapsed or refractory follicular lymphoma†		Relapsed or refractory mantle cell lymphoma‡	
	12–60 mg (n=22)	48 mg (n=8)	60 mg (n=3)	0·76–48 mg (n=10)	48 mg (n=1)	0·76–48 mg (n=4)§	48 mg (n=1)
Overall response, n (%, 95% CI)	15 (68%, 45–86)	7 (88%, 47–100)	3 (100%, 29–100)	9 (90%, 55–100)	0 (0, 0–98)	2 (50%, 7–93)	1 (100%, 3–100)
Complete response	10 (45%)	3 (38%)	3 (100%)	5 (50%)	0	1 (25%)	0
Partial response	5 (23%)	4 (50%)	0	4 (40%)	0	1 (25%)	1 (100%)
Stable disease	1 (5%)	0	0	0	0	1 (25%)	0
Progressive disease	5 (23%)	0	0	1 (10%)	1 (100%)	0	0
Time to response, months	1·4 (1·3–2·6)	1·4 (1·3–2·6)	1·3 (1·1–1·4)	1·9 (1·5–3·5)	NA	1·4 (1·3–1·5)	1·3 (1·3–1·3)
Follow-up duration, months	9·3 (8·2–14·8)	8·2 (7·4–9·9)	9·2 (9·2–9·3)	13·6 (10·4–16·5)	6·6 (6·6–6·6)	10·2 (7·7–10·5)	7·7 (7·7–7·7)

Results - Efficacy



Progression-free survival in patients with R/R DLBCL



Survival Parameter	≥12 mg (n=22)	≥48–60 mg (n=11)
Median follow-up, months	9.3	8.8
Median PFS, months (95% CI)	9.1 (1.6, NE)	NR (2.7, NE)

PRIMARY OBJECTIVE: MTD and SAFETY

	Grade 1–2	Grade 3	Grade 4
Pyrexia*	43 (63%)	4 (6%)	0
Cytokine release syndrome	40 (59%)	0	0
Injection site reaction	32 (47%)	0	0
Fatigue	26 (38%)	4 (6%)	0
Diarrhoea	18 (26%)	0	0
Hypotension*	17 (25%)	4 (6%)	0
Dyspnoea	16 (24%)	0	1 (1%)
Tachycardia*	14 (21%)	0	0
Anaemia	7 (10%)	9 (13%)	0

*Most pyrexia, hypotension, and tachycardia events were associated with cytokine release syndrome.

Table 2: **Treatment-emergent adverse events that occurred in at least 20% of the full analysis population (n=68)**

ICAN: 4 (8%), grade 3: 2 (4%), no grade 4-5, all transient, median duration 3 days

Algoritmo terapéutico del paciente en recaída / refractario: Guía GELTAMO 2022

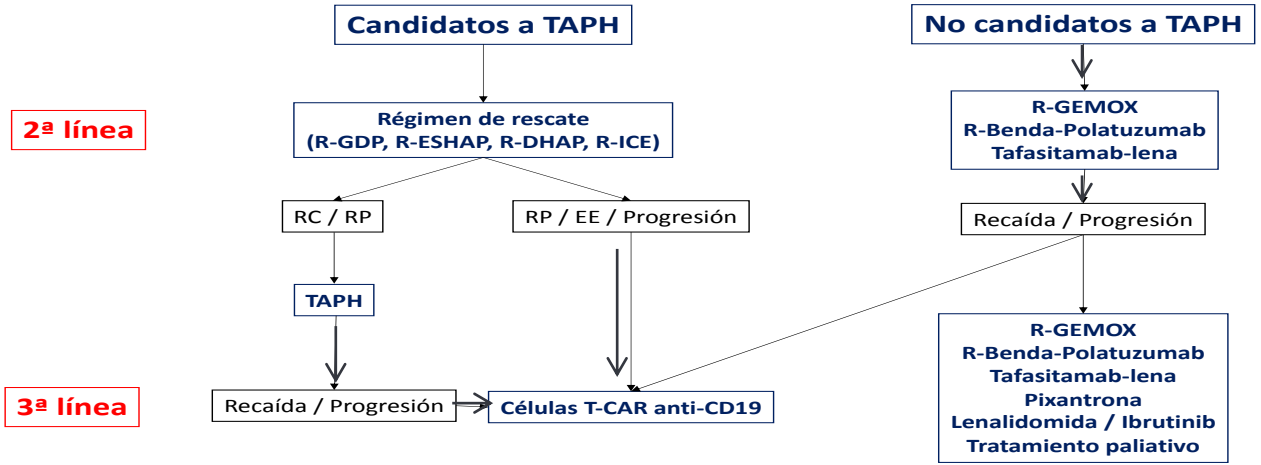
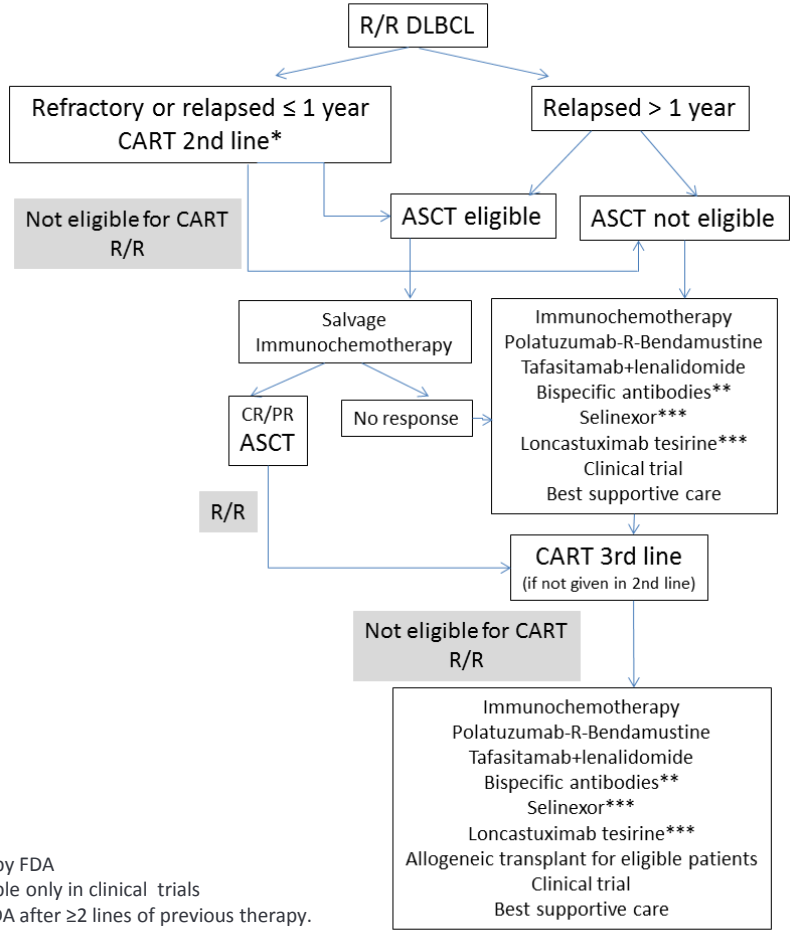


Figure 1. Proposed algorithm for the treatment of R/R DLBCL



*axi-cel approved by FDA
**currently available only in clinical trials
***approved by FDA after ≥2 lines of previous therapy.

- CART en segunda línea para los pacientes no candidatos a transplante

- Nuevas estrategias:
  - Anticuerpos biespecificos
  - Loncastuximab
  - Selinexor

Gonzalez-Barca E, Front Immunol. 2022, Jul 19;13:909008

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