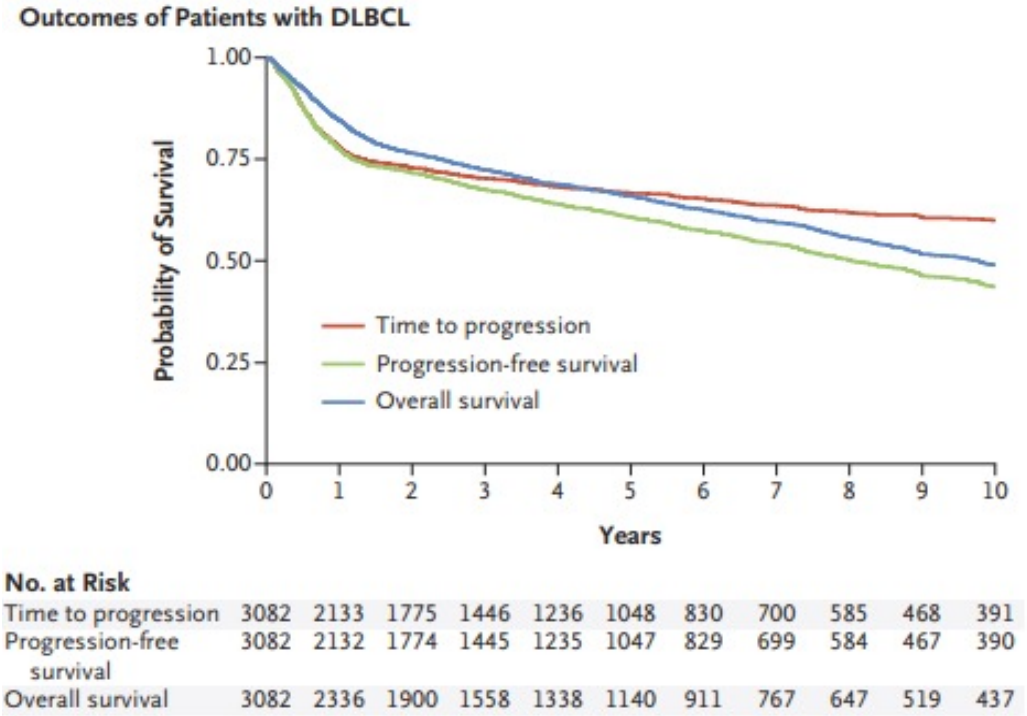
CATANIA 11.07.22

Il razionale biologico delle combinazioni nei linfomi non Hodgkin

Caterina Stelitano
GOM-Ematologia
Reggio Calabria

Relapsed/refractory DLBCL: the size of the issue



No. at Risk

Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437

35-40% failures after

R-CHOP first line therapy

Sehn LH and Salles G, NEJM 2021.

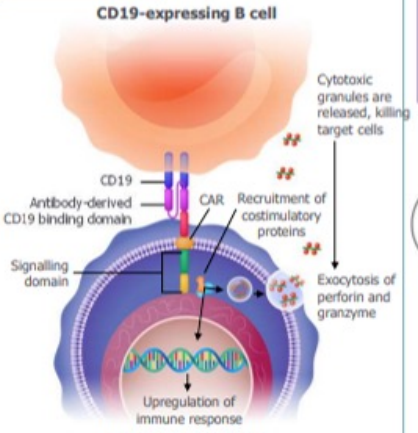
How to improve response in 1 L or in R/R DLBCL?

Rituximab

Monoclonal Antibodies (mAbs)[1]

Sono stati sviluppati mAb multipli per il trattamento delle neoplasie ematologiche. Gli mAb possono mediare la morte cellulare attraverso meccanismi come l'apoptosi, l'inibizione della crescita cellulare, la citotossicità complemento-dipendente (CDC), la citotossicità cellulare anticorpo-dipendente (ADCC), la sensibilizzazione alla chemioterapia o alle radiazioni

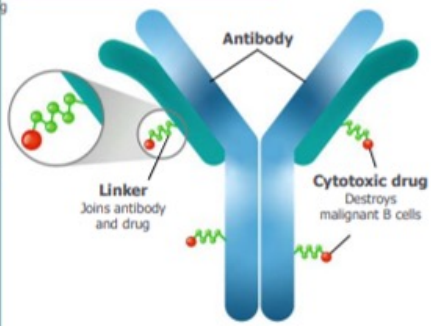
Kymriah
Yescarta



CAR T-cell therapy[2]

La terapia con cellule T del recettore dell'antigene chimerico (CAR) prende le cellule T dell'ospite e le ingegnerizza geneticamente per esprimere la CAR. I linfociti CAR T riconoscono e dirigono una risposta immunitaria contro le cellule mirate che mostrano un antigene specifico

Loncastuximab
Polatuzumab
Brentuximab



Antibody–drug conjugates (ADCs)[3]

Gli ADC sono costituiti da un mAb mirato, un linker covalente e un farmaco citotossico. Dopo il legame dell'anticorpo all'antigene, il complesso antigene-ADC viene interiorizzato e il farmaco citotossico viene rilasciato, con conseguente morte cellulare

Copanlisib
Ibrutinib
Selinexor
Acalabrutinib

Small molecule inhibitors[4]

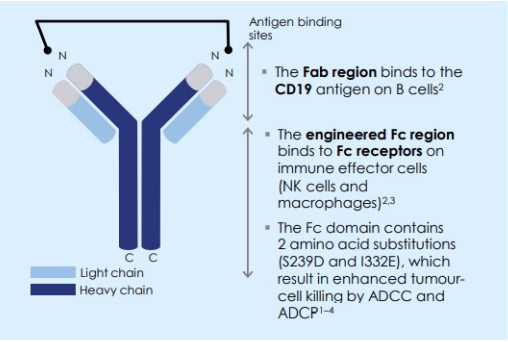
Gli inibitori di piccole molecole inibiscono le molecole di segnalazione responsabili dell'attivazione delle vie che mediano la proliferazione e la sopravvivenza delle cellule B

Glofitamab
Epcoritamab
Mosunetuxumab

Bispecific antibodies[5]

Queste proteine artificiali agiscono legandosi contemporaneamente a due diversi tipi di antigene, portando a morte mirata delle cellule tumorali

Tafasitamab



Fc-engineered IgG monoclonal antibody

How to improve R-CHOP

- ✓ Dose- dense RCHOP : RCHOP 14 ?
- ✓ Rituximab modulation : smart R-CHOP- sex-R-CHOP?
- ✓ Front line intensification : ASCT front line ?
- ✓ Wen and for whon CNS prophylaxis?
- ✓ R and different regimen : DA-EPOCH-R
- ✓ Anti CD20 augmentation : obinutuzumab, G-CHOP?
- ✓ R-CHOP + X
- ✓ Can we identify an unfavourable group of patients based on clinical or biological factors?
- ✓ Wen we can consider an alternative therapy to R-CHOP?

Beyond RCHOP

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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

International, open-label, randomized Phase III study in 1L DLBCL pts
Scientific support from the Fondazione Italiana Linfomi

GOYA (BO21005)

Previously untreated DLBCL

- Age ≥18 years
- IPI ≥2 or IPI 1 not due to age alone or IPI 0 with bulky disease (one lesion ≥7.5cm)
- Adequate hematologic function
- ≥1 bi-dimensionally measurable lesion
- ECOG PS ≤2
- Target enrolment: 1400

Randomized 1:1

G-CHOP arm

G 1000mg C1 D1/8/15 and C2–8 D1
CHOP 6 or 8 cycles every 21 days

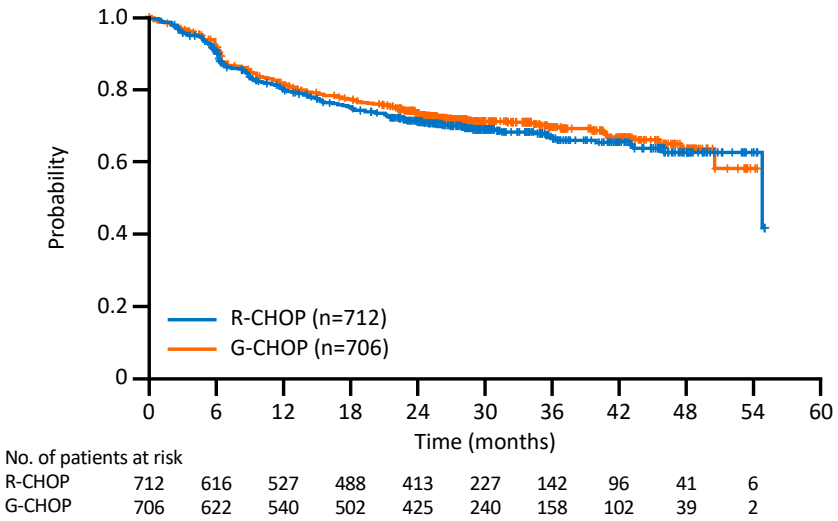
R-CHOP arm

R 375mg/m^2 C1–8 D1
CHOP 6 or 8 cycles every 21 days

Primary endpoint

PFS (INV-assessed) *Statistical assumption: G-CHOP vs R-CHOP, HR=0.75*

GOYA RESULTS



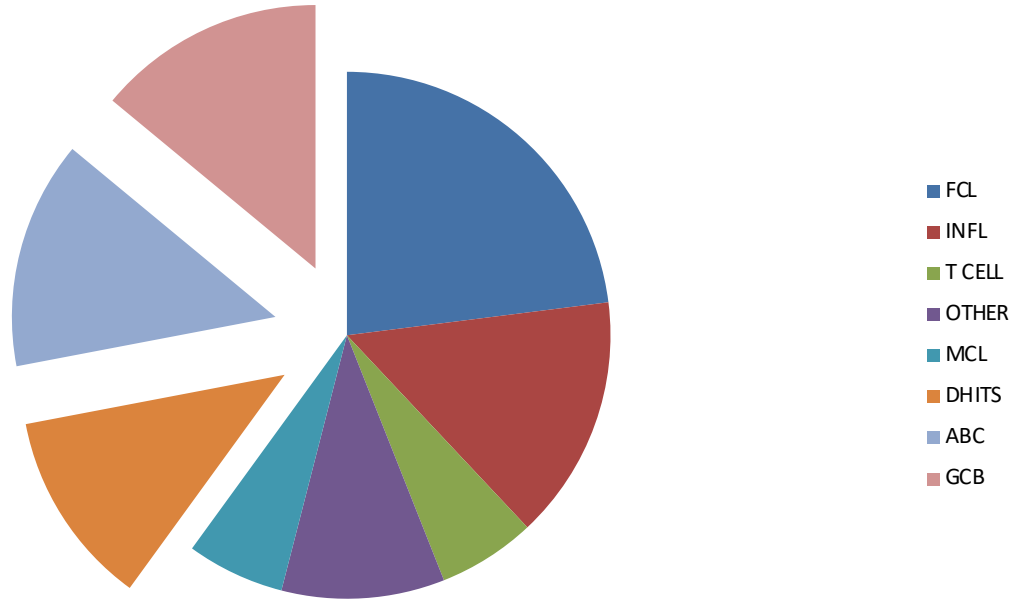
	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	

Vitolo, JCO 2017

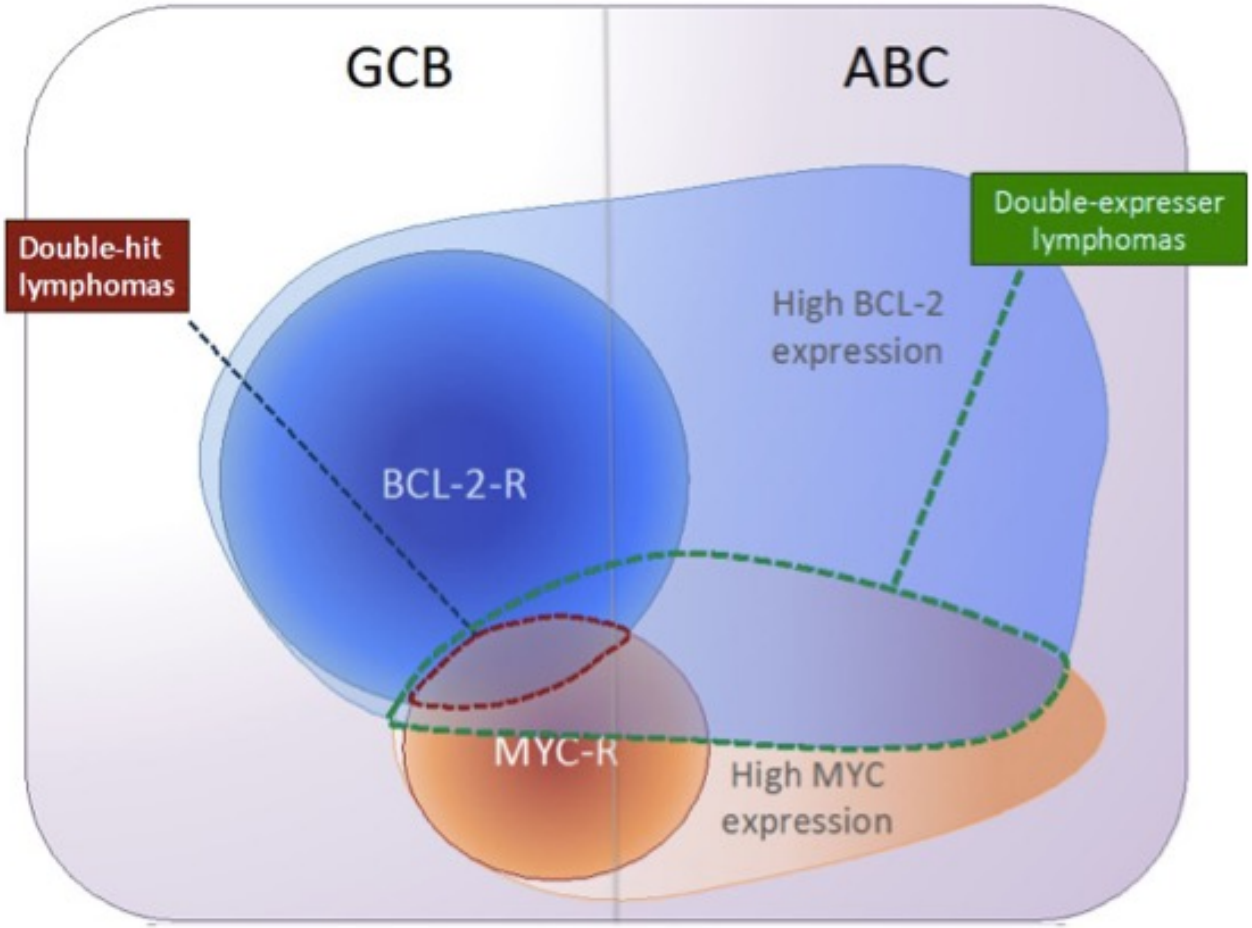
DLBCL : NOT a single disease

DLBCL 40%

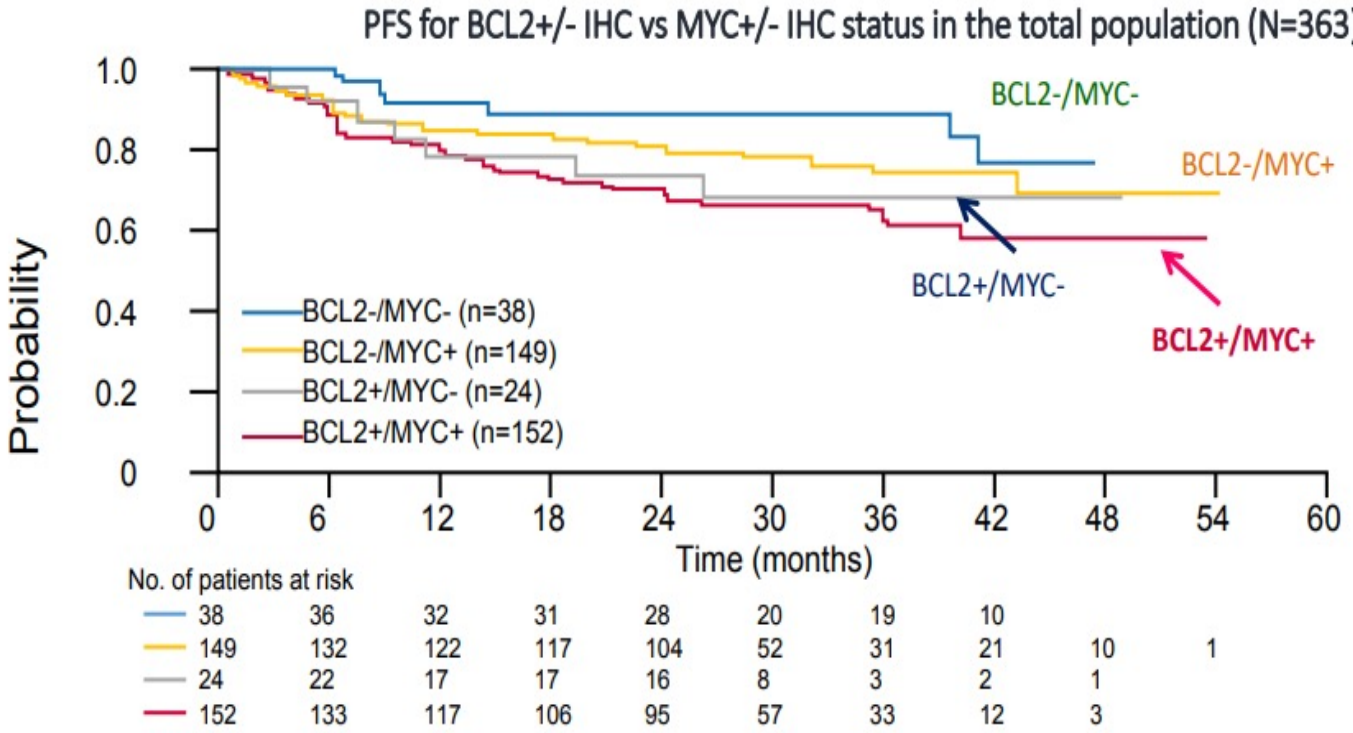
- ABC
- GCB
- DH-TH
- DE
- EBV+
- ALCL
- CD30+



A biological stratification for a biological-based treatment approach



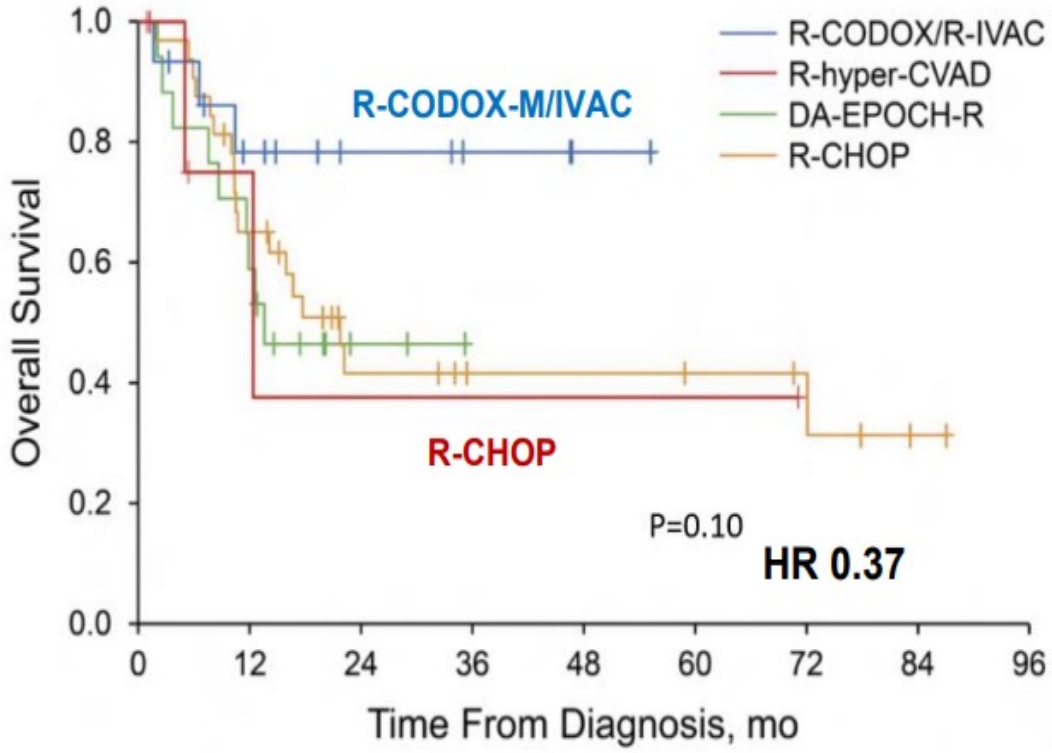
Prognostic impact of double BCL2 and MYC expression (DE) in the Goya study



	BCL2-/MYC-, n=38	BCL2-/MYC+, n=149	BCL2+/MYC- n=24	BCL2+/MYC+, n=152
3-yr PFS, % (95% CI)	88.6 (72.5, 95.6)	73.9 (64.1, 81.4)	68.1 (44.2, 83.4)	63.1 (53.8, 71.0)

Vitolo U, et al. Presented at ICML 2017. Hematol Oncol;35:131-3.

DHL and THL: retrospective CALGB study front-line treatment



100 patients with DHL

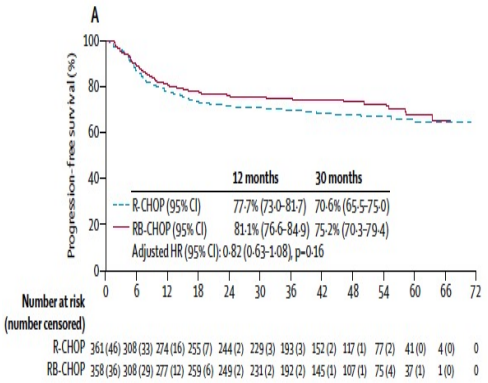
>60 years, in 53% pts

R-CHOP 36%
R-EPOCH 17%
R-CODOX-M/IVAC 17%
R-hyper-CVAD 6%

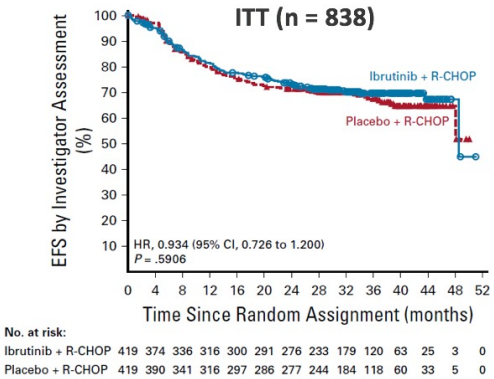
McPhail et al. Hematologica 2018

COO-ABC approach

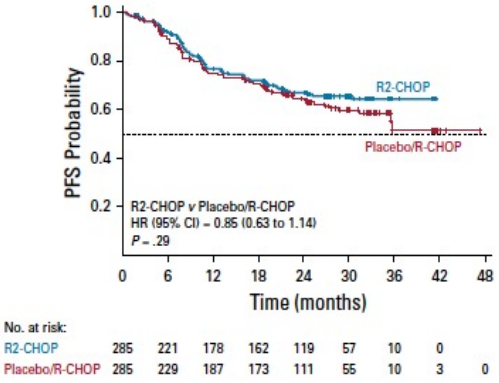
R-CHOP + Bortezomib



R-CHOP + Ibrutinib



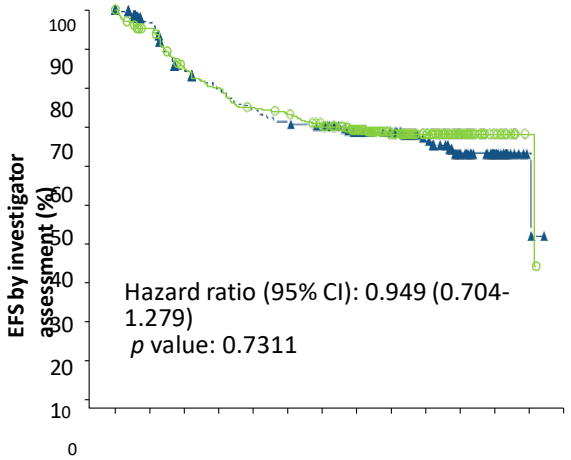
R-CHOP + Lenalidomide



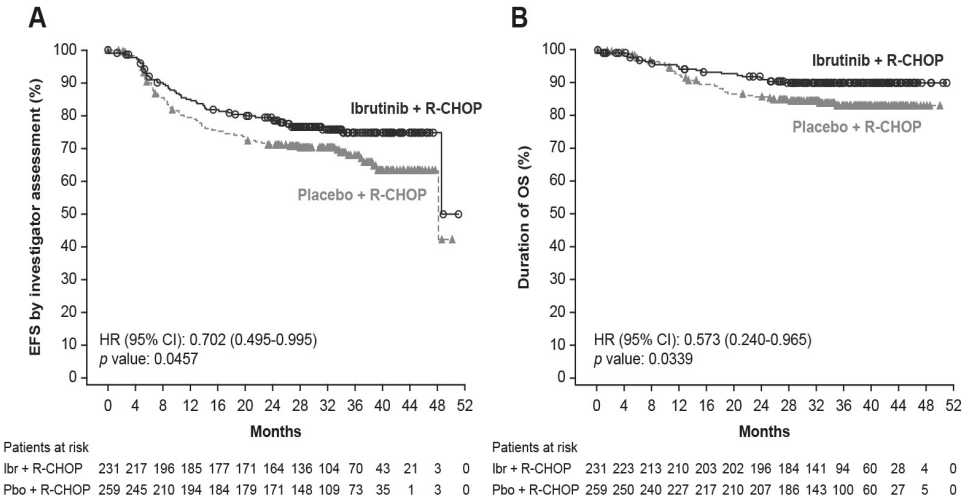
Davies A, et al. Lancet Oncol 2019; Younes A, et al. J Clin Oncol 2019; Nowakowski G, et al. J Clin Oncol 2021.

How to **NOT** treat elderly DLBCL: RCHOP +IBRUTINIB

Whole serie- ABC-n= 567



EFS and OS in patients < 60 years

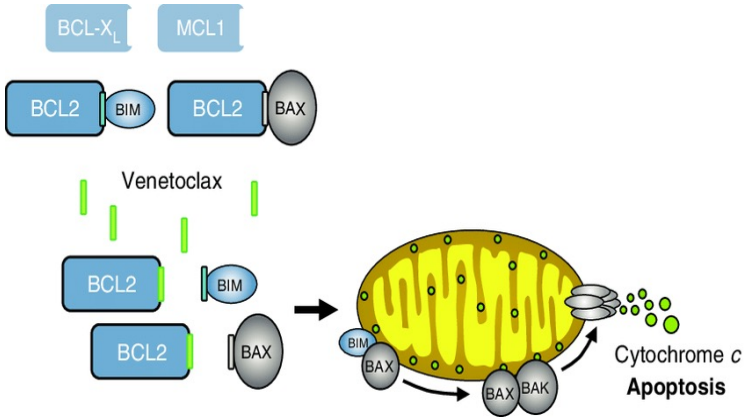


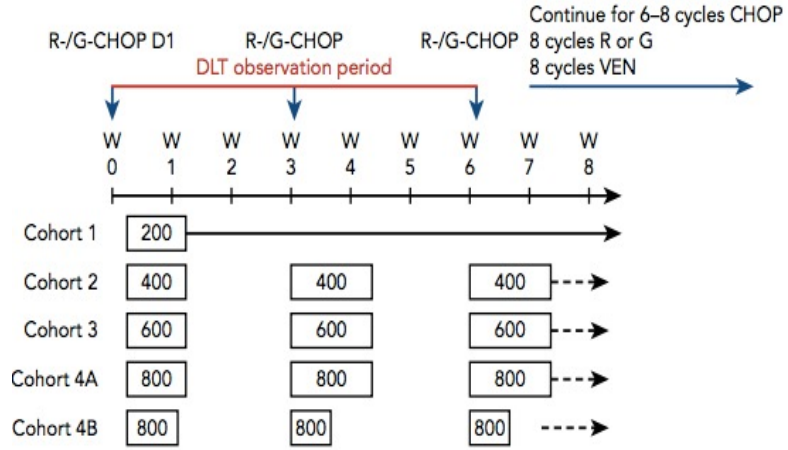
*In **patients ≥ 60 years**, addition of ibrutinib to R-CHOP **increased rates of SAEs and AEs leading to R-CHOP discontinuation**, which compromised treatment exposure and likely decreased efficacy*

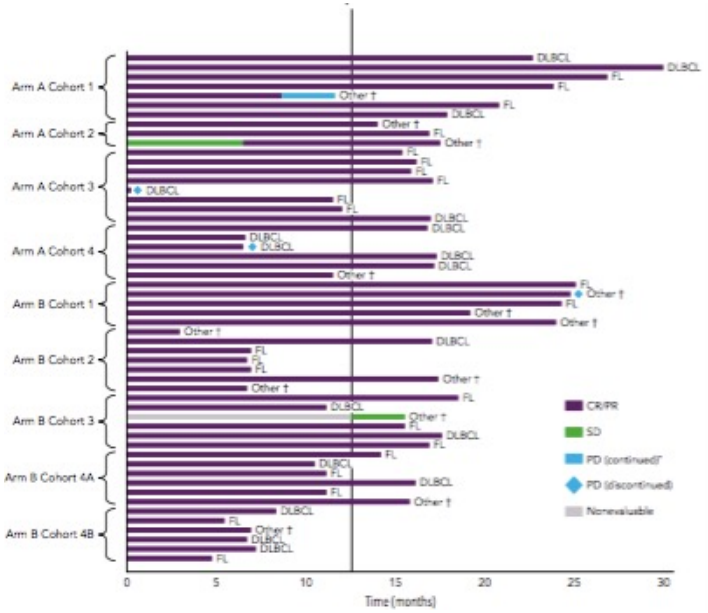
Younes A, JCO 2019

RCHOP +/- X

VENETOCLAX

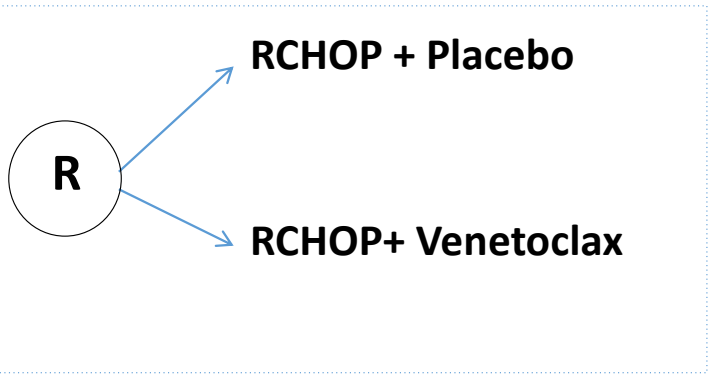




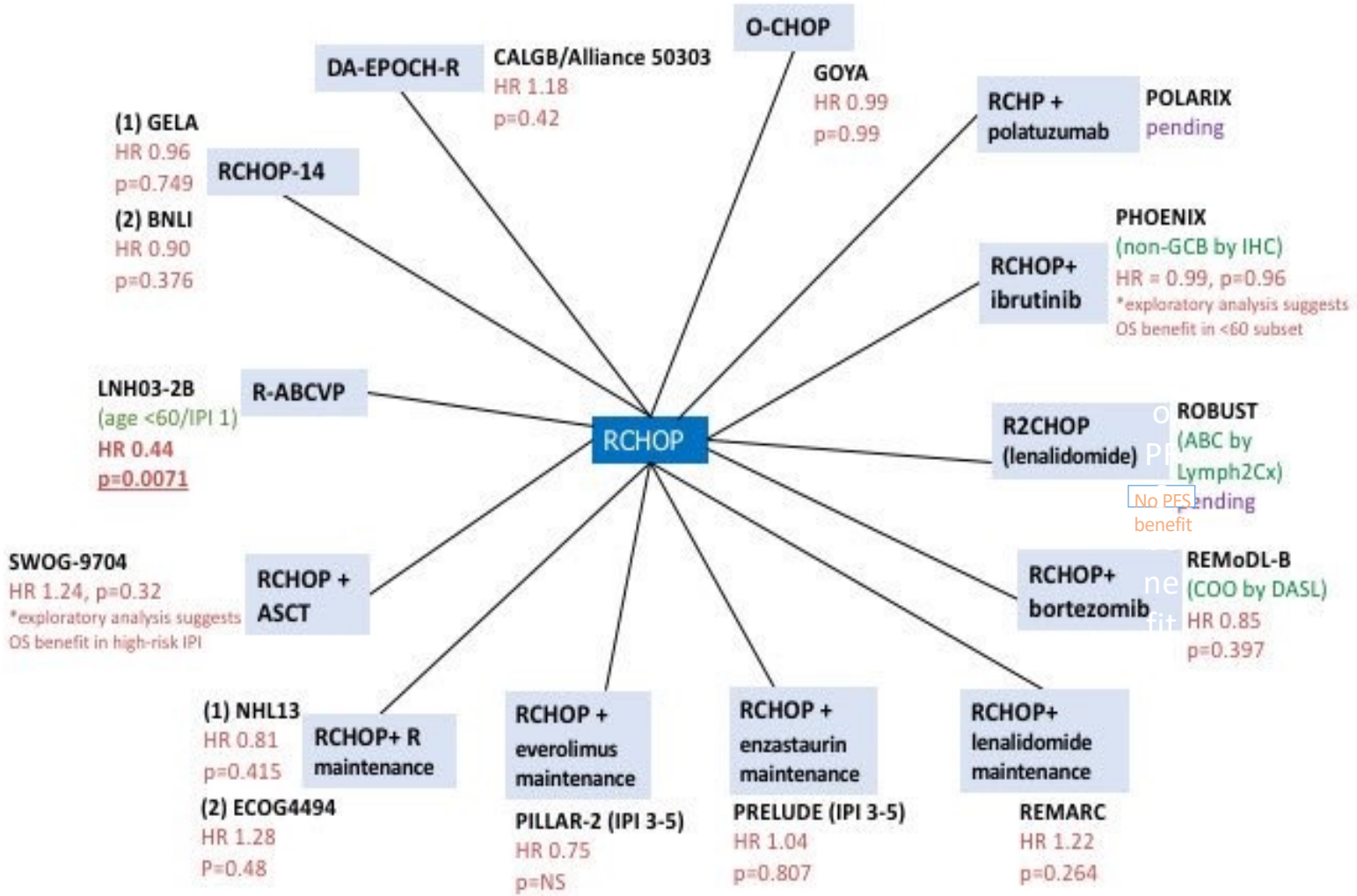


CAVALLI trial, Blood 2019

ONGOING



FOREVER RCHOP ?



Combination of novel molecular targeted agent plus R-CHOP-based regimen versus R-CHOP alone in previously untreated diffuse large B-cell lymphoma (DLBCL) patients: a systematic review and meta-analysis.

Guillermo Villacampa[1] · Rodrigo Dienstmann[1] · Francesc Bosch[2] · Pau Abrisqueta[2]

IMPROVING R-CHOP EFFICACY IN DLBCL

Randomized trials

….infusional therapy (R-EOCH)
….Rituximab maintenance
….obinutuzimab instead rituximab
….lenalidomide
….everolimus
….ibrutinib
….bortezomib

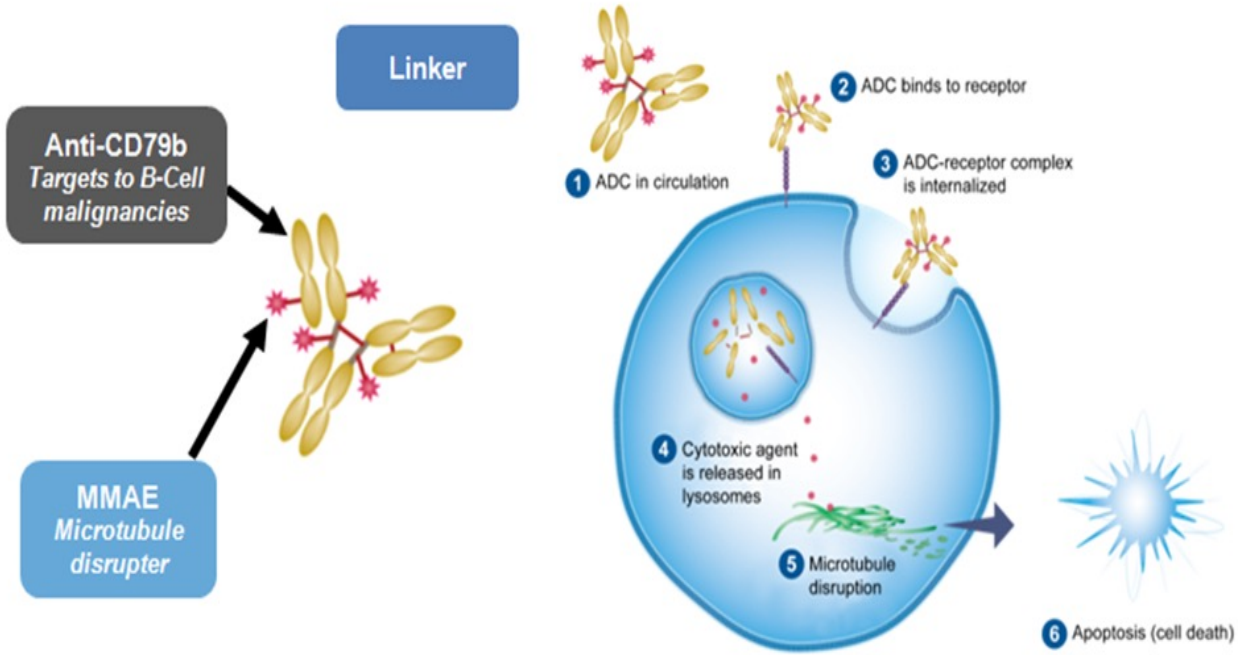
MORE SAES WITH SLIGHT PFS IMPROVEMENT IN YOUNG PATIENTS

Villacampa et al.Ann Hematol 2021

UPCOMING DATA

Polatuzumab Vedotin▼ (CD79b-ADC)

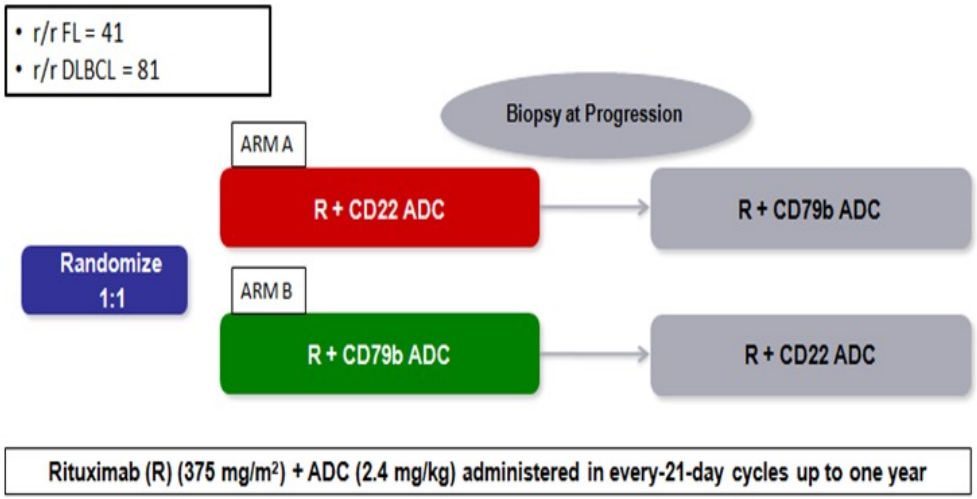
- ADC comprising potent microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



▼*Polatuzumab vedotin è sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 dell'RCP per informazioni sulle modalità di segnalazione delle reazioni avverse.*

Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS)

Franck Morschhauser, Ian W Flinn, Ranjana Advani, Laurie H Sehn, Catherine Diefenbach, Kathryn Kolibaba, Oliver W Press*, Gilles Salles, Hervé Tilly, Andy I Chen, Sarit Assouline, Bruce D Cheson, Martin Dreyling, Anton Hagenbeek, Pier Luigi Zinzani, Surai Jones, Ji Cheng, Dan Lu, Elicia Penuel, Jamie Hirata, Michael Wenger, Yu-Waye Chu, Jeff Sharman



Morschhauser F et al, Lancet Hematology 2019

	DLBCL		FL	
	R+CD22 ADC (N=42)	R+CD79b ADC (N=39)	R+CD22 ADC (N=21)	R+CD79b ADC (N=20)
Objective response, n (%)	**24 (57%)**	**22 (56%)**	**13 (62%)**	**14 (70%)**
Complete Response	10 (24%)	**6 (15%)**	**2 (10%)**	**8 (40%)**
95% CI	[12%-39%]	[6%-31%]	[11%-30%]	[19%-64%]
Partial Response	14 (33%)	16 (41%)	11 (52%)	6 (30%)
95% CI	[20%-50%]	[26%-58%]	[30%-74%]	[12%-54%]
Stable disease, n (%)	3 (7%)	4 (10%)	6 (29%)	6 (30%)
Progressive disease, n (%)	7 (21%)	11 (30%)	1 (5%)	0
Unable to evaluate, n (%)	8 (19%)	2 (5%)	1 (5%)	0
Median Duration of Response, mo. (95% CI)	6.0 (2.9-12.2)	NR (2.6-NR)	5.8 (2.6-10.1)	*NR (5.7-NR)*

Pola-R-CHP: Polatuzumab Vedotin Combined with Rituximab, Doxorubicin, Cyclophosphamide, Prednisone for Patients with Previously Untreated DLBCL*

Hervé Tilly, Jeff Sharman, Nancy Bartlett, Franck Morschhauser, Corinne Haioun, Javier Munoz, Andy Chen, Thierry Lamy, Lijia Wang, Elicia Penuel, Jamie Hirata, Calvin Lee, Gilles Salles

Pola-R-CHP administration

Drug	Route	Dose	Days
Rituximab	IV	375 mg/m²	1
Cyclophosphamide	IV	750 mg/m²	1
Doxorubicin	IV	50 mg/m²	1
Vincristine	-	-	-
Prednisone	PO	100 mg/day	1–5
Polatuzumab vedotin	**IV**	**1.8 mg/kg**	**2** (cycle 1 and cycle 2) **1** (subsequent cycles)

6–8 cycles at 21-day interval
Response evaluation (CT and PET) after 4 cycles and end of treatment

Objectives
To assess safety, tolerability and efficacy of Pola-R-CHP

Tilly et al, Presentated at ICML 2017

Patient Baseline Characteristics

Characteristics	N = 45
Median age, yr (range)	**69** (45–80)
Sex	
Male, n (%)	22 (49)
Female, n (%)	23 (51)
ECOG PS, n (%)	
0–1	30 (67)
2	15 (33)
Stage III/IV disease, n (%)	**37 (82)**
International Prognosis Index (IPI), n (%)	
0–1	1 (2)
2	9 (20)
3	**18 (40)**
4–5	**17 (38)**
Available cell of origin, n = 34	
Activated B-cell, n (%)	12 (35)
Germinal center B-cell, n (%)	17 (50)
Unclassified, n (%)	5 (15)

Tilly et al,Presentated at ICML 2017

PET Response at End of Treatment

	Pola-R-CHP (N =45)	90% CI
Overall response rate, n (%)	41 (91)	[81, 97]
Complete response	35 (78)	[65, 87]
Partial response	6 (13)	[6, 25]
Progressive disease, n (%)	3 (7)	[2, 16]
Unevaluable/missing, n (%)	1 (2)	[0, 10]

Tilly et al,Presentated at ICML 2017

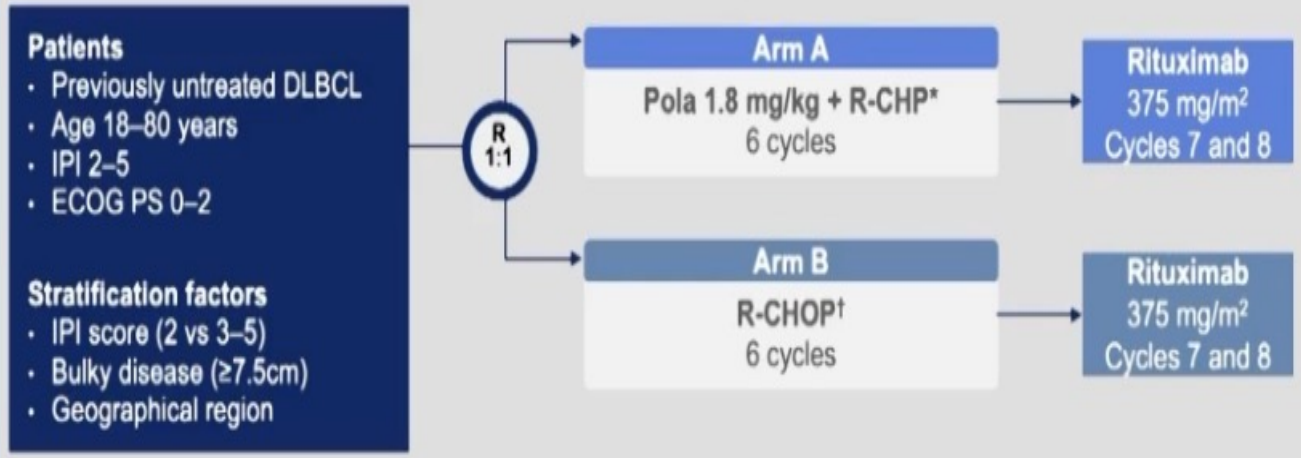
Phase III trial comparing efficacy and safety of Pola R-CHP vs R-CHOP in DLBCL*

POLARIX

Objective

Multicenter, double-blind, placebo-controlled, randomized, Phase III trial to evaluate safety and efficacy of pola in combination with R-CHP, compared with R-CHOP alone, in patients with previously untreated DLBCL

Study Design



Endpoints

Primary: INV-assessed PFS
Secondary: PET-CT CR (by IRC) at EOT, EFS, 2-year PFS, OS, and safety

POLARIX: Key endpoints and analysis timing

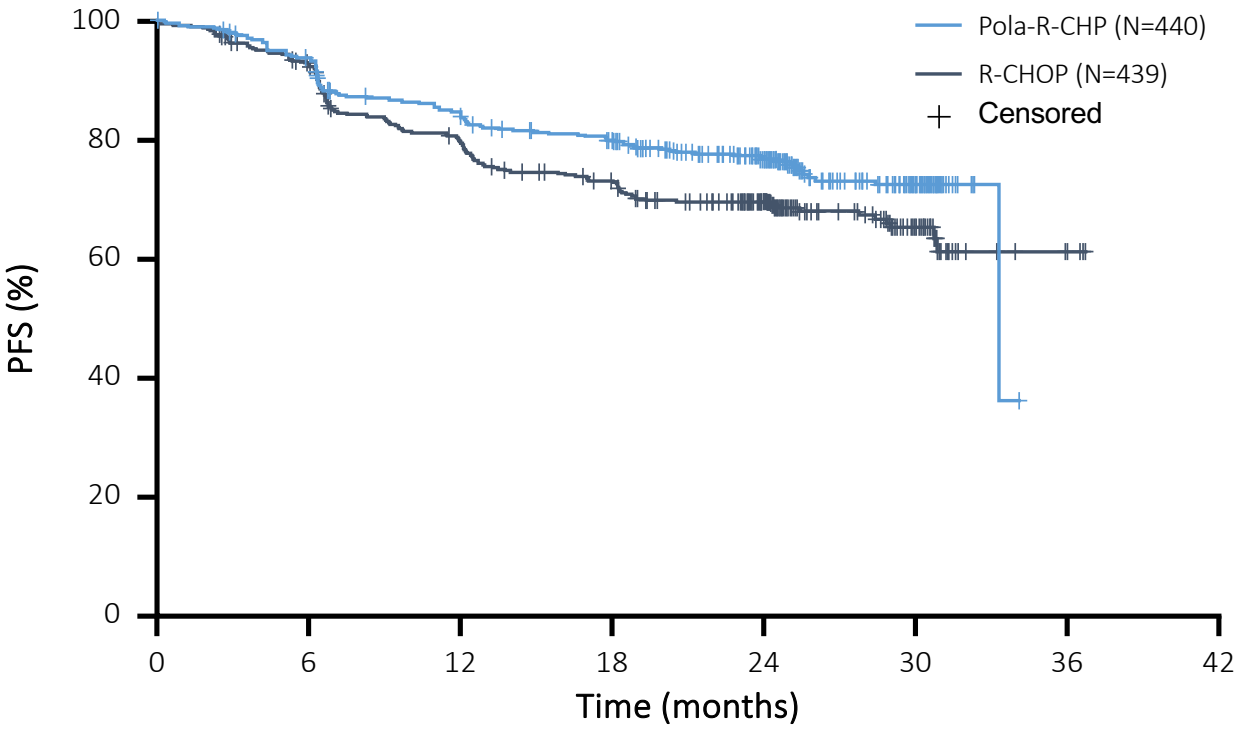
Key endpoints	
Primary endpoint	**Progression-free survival (Investigator-assessed)**
Secondary endpoints	Event-free survival Complete response rate at end of treatment (PET/CT, IRC-assessed) Disease-free survival Overall survival
Safety endpoints	Incidence, nature, and severity of adverse events

Statistical design and timing of primary analysis:

- 875 patients, all on study for ≥24 months with approximately 228 PFS events, were required for the primary analysis. This occurred on June 28, 2021 (clinical cut-off date)
- Median follow up at the primary analysis was 28.2 months

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 **(P<0.02)**

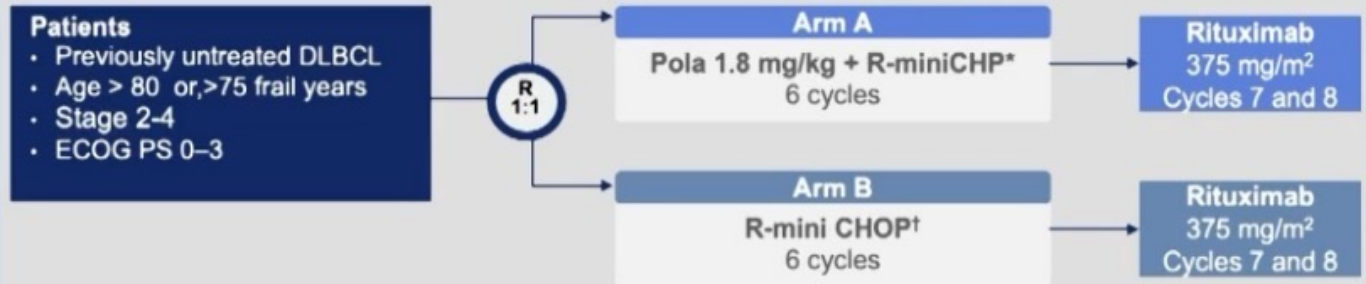
95% CI: 0.57, 0.95

- 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%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

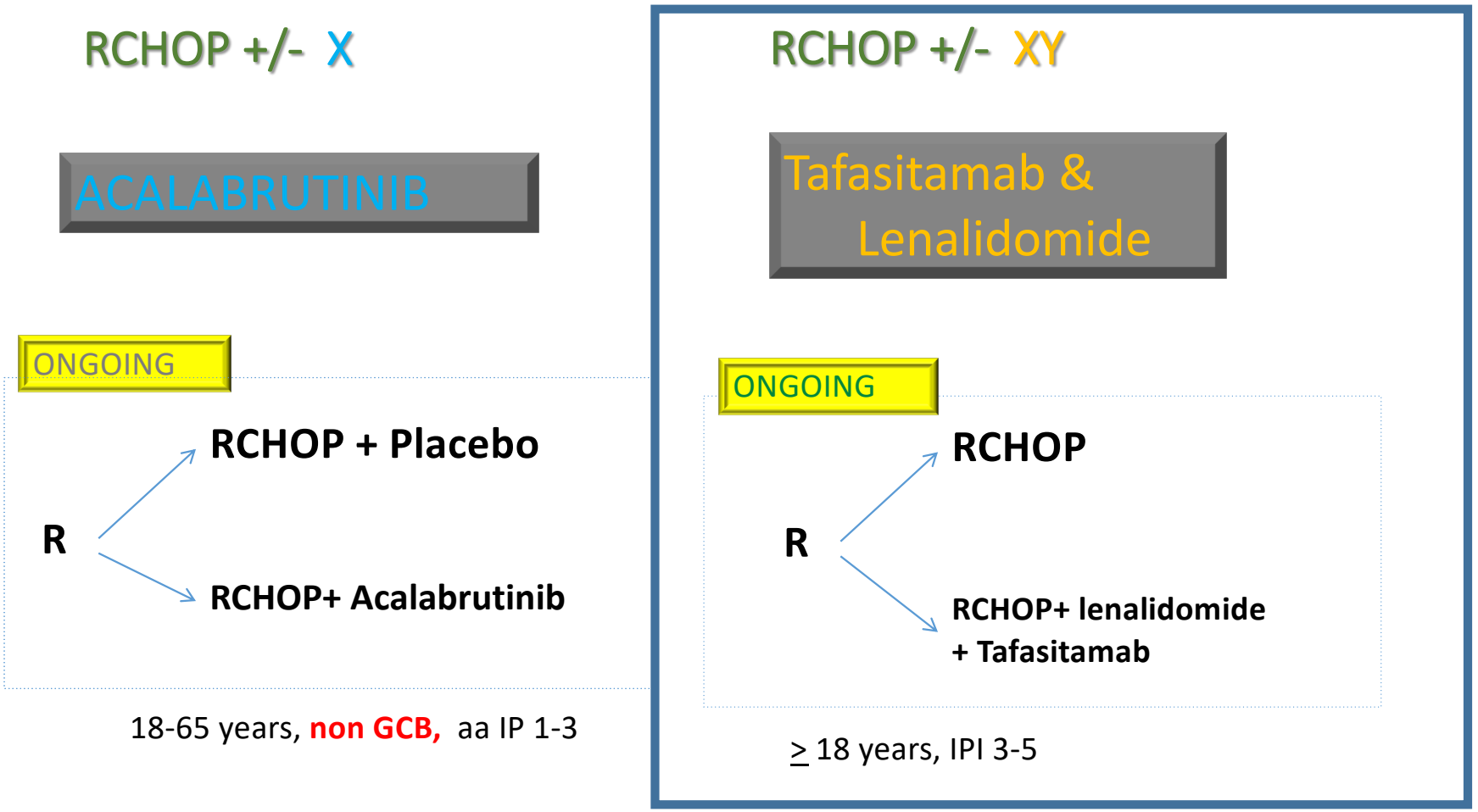
Phase III trial comparing efficacy and safety of Pola R-miniCHP vs R-miniCHOP in elderly DLBCL

POLA BEAR

Objective	Multicenter,, Phase III trial to evaluate safety and efficacy of pola in combination with R-miniCHP, compared with R-mini-CHOP alone, in elderly patients with previously untreated DLBCL
Study Design	
Endpoints	**Primary:** INV-assessed 24 months PFS **Secondary:** PET-CT CR (by IRC) quality of life and safety

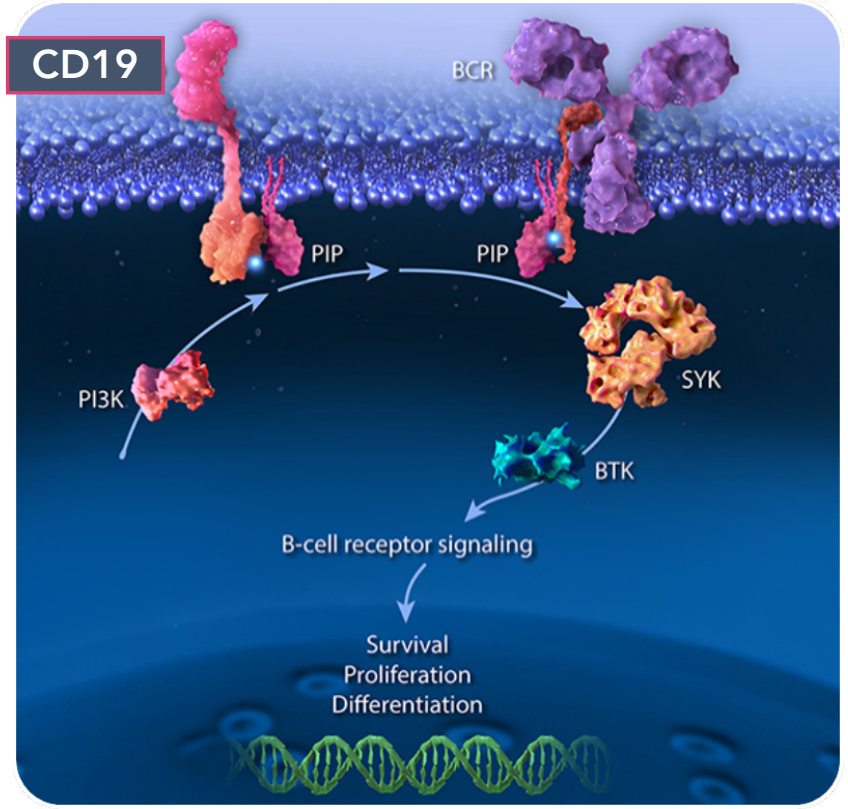
RCHOP+ X :

toward a clinical and/or biological tailored treatment



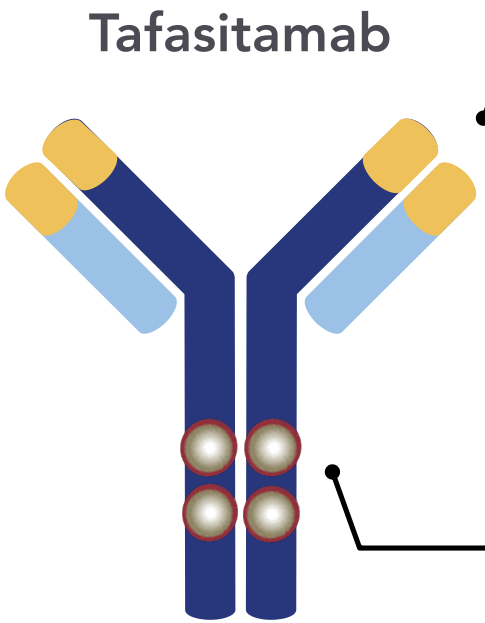
CD19 IN B-CELL BIOLOGY

- CD19 is a B-cell 95 kD transmembrane protein and signaling molecule involved in:
  - B-cell development and differentiation
  - B-cell proliferation
  - B-cell signaling
- CD19 works in complex with the B-cell receptor and other cell-surface molecules to trigger both direct and indirect recruitment and binding of various downstream protein kinases



TAFASITAMAB IS AN FC-ENGINEERED MONOCLONAL ANTIBODY

- Tafasitamab was generated by enhancing CD19 binding affinity and binding to Fc receptors on immune cells to increase Fc-mediated effector functions, such as ADCC and ADCP
- As CD19 is expressed on a broader range of B-cell subtypes, tafasitamab can target more B-cell subtypes than CD20-targeting therapies



Enhanced CD19 binding site in Fv region:

- Direct tumor-cell killing

Engineered Fc portion:

- Enhanced ADCC
- Enhanced ADCP

PRELIMINARY DATA FROM FIRST-MIND: A PHASE 1B, RANDOMISED STUDY TO ASSESS THE SAFETY AND PRELIMINARY EFFICACY OF TAFASITAMAB + LENALIDOMIDE IN ADDITION TO R-CHOP IN PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA

David Belada, Grzegorz Nowakowski, Juan Miguel Bergua Burgues, Marc André, Katerina Kopeckova, Don Stevens, Marek Trněný, Ernesto Persona, Perez Persona, Petra Pichler, Pia Klöpfer, Bettina Brackertz, Emanuel Lohrmann, Anirban Lahiry, Neha Shara, Günter Fingerie-Rowson, Wolfram Brugger, John Burke

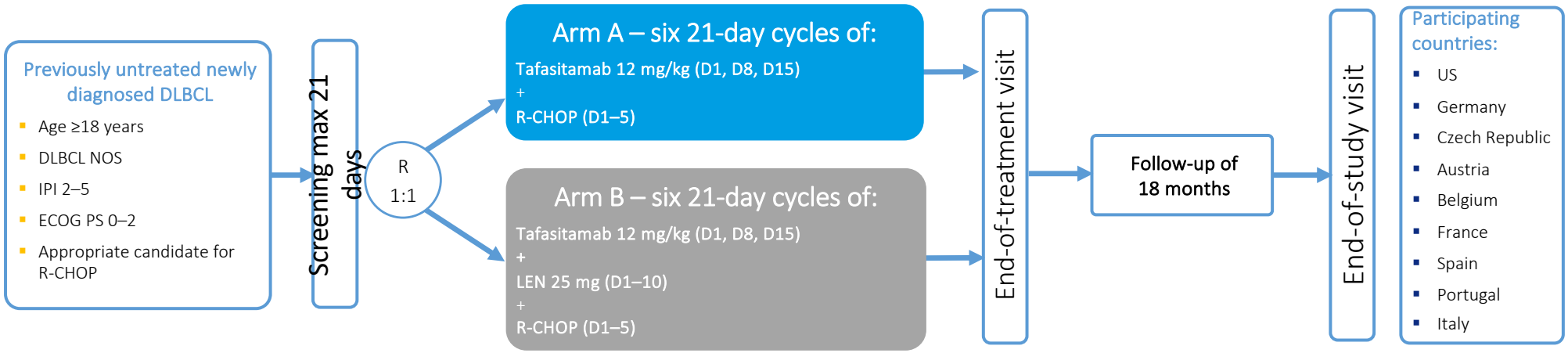
R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Belada D, et al. Poster presentation at Virtual ICML 2021; Abstract 237; Belada D, et al. Poster presentation at ASH 2020; Abstract 3028.

STUDY DESIGN

INTERNATIONAL, OPEN-LABEL, PROSPECTIVE, RANDOMISED PHASE 1B STUDY IN 1L DLBCL

- FIRST-MIND to confirm the safety and preliminary efficacy of **tafasitamab in addition to R-CHOP (Arm A)** *or* **tafasitamab + LEN in addition to R-CHOP (Arm B)** in patients with newly diagnosed DLBCL



Granulocyte-colony stimulating factor prophylaxis was mandatory in both treatment arms and venous thromboembolism prophylaxis was mandatory in Arm B.
1L, first-line; D, day(s); DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognosis Index; IRC, independent review committee; LEN, lenalidomide; max, maximum; NOS, not otherwise specified; ORR, overall response rate; PET-CR, complete response assessed by positron emission tomography; R, randomisation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; TEAE, treatment-emergent adverse event; US, United States.
Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04134936 (accessed 30 June 2021); Belada D, et al. Poster presentation at Virtual ICML 2021; Abstract 237; Belada D, et al. Poster presentation at ASH 2020; Abstract 3028.

PRELIMINARY EFFICACY (22 MAR 2021 DATA CUT-OFF)

- For the 60 patients with a tumour assessment at end of treatment across both treatment arms (response-evaluable population):
  - **ORR=83.3%** (n=50/60) [95% CI: 71.5–91.7]
  - CR=75.0 % (n=45/60) [95% CI: 62.1–85.3]

Data cut-off: 22 March 2021.
CI, confidence interval; CR, complete response; ORR, overall response rate.
Belada D, et al. Poster presentation at Virtual ICML 2021; Abstract 237.

CONCLUSIONS[1]

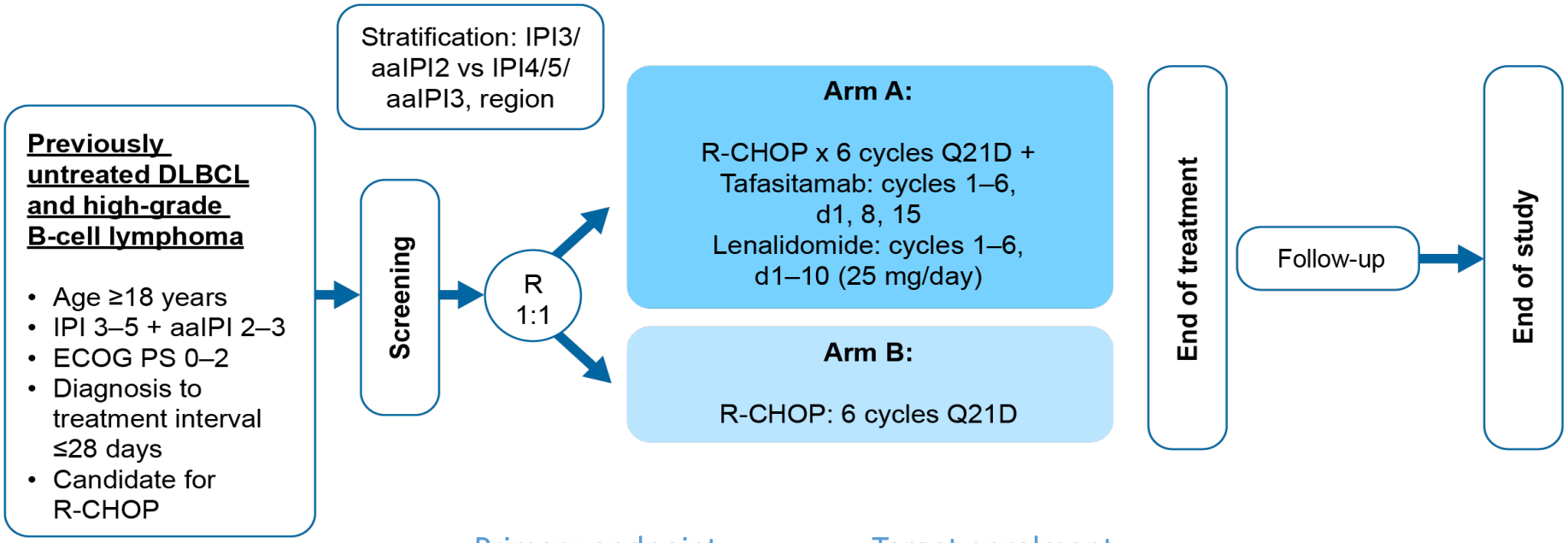
- Encouraging interim data suggest that the addition of tafasitamab or tafasitamab + LEN to R-CHOP is tolerable in patients with newly diagnosed DLBCL
- Incidence of TEAEs was generally comparable between treatment arms, including incidence of febrile neutropenia
- The safety profile was consistent with R-CHOP alone or in combination with LEN (R2-CHOP)[2–4]
- Grade ≥3 neutropenia and thrombocytopenia events were more frequent in the tafasitamab + LEN + R-CHOP arm (B) than in the tafasitamab + R-CHOP arm (A); events were manageable and the average relative dose intensity of R-CHOP was maintained
- At end of treatment, ORR in evaluable patients was 83.3% and the CR rate was 75.0%

CR, complete response; DLBCL, diffuse large B-cell lymphoma; LEN, lenalidomide; ORR, overall response rate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R2-CHOP, rituximab, lenalidomide, cyclophosphamide, doxorubicin, vincristine and prednisone; TEAE, treatment-emergent adverse event.

1. Belada D, et al. Poster presentation at Virtual ICML 2021; Abstract 237; 2. Sehn LH, et al. *Blood*. 2019;134(Suppl 1):4088; 3. Vitolo U, et al. *Hematol Oncol*. 2019;37:36–7; 4. Nowakowski GS, et al. Presented at ICML 2019. Article 006.

frontMIND: STUDY DESIGN (MORPHOSYS TRIAL)

INTERNATIONAL, PROSPECTIVE, OPEN-LABEL PHASE 3 STUDY IN 1L DLBCL AND HIGH-GRADE B-CELL LYMPHOMA



Primary endpoint

- EFS

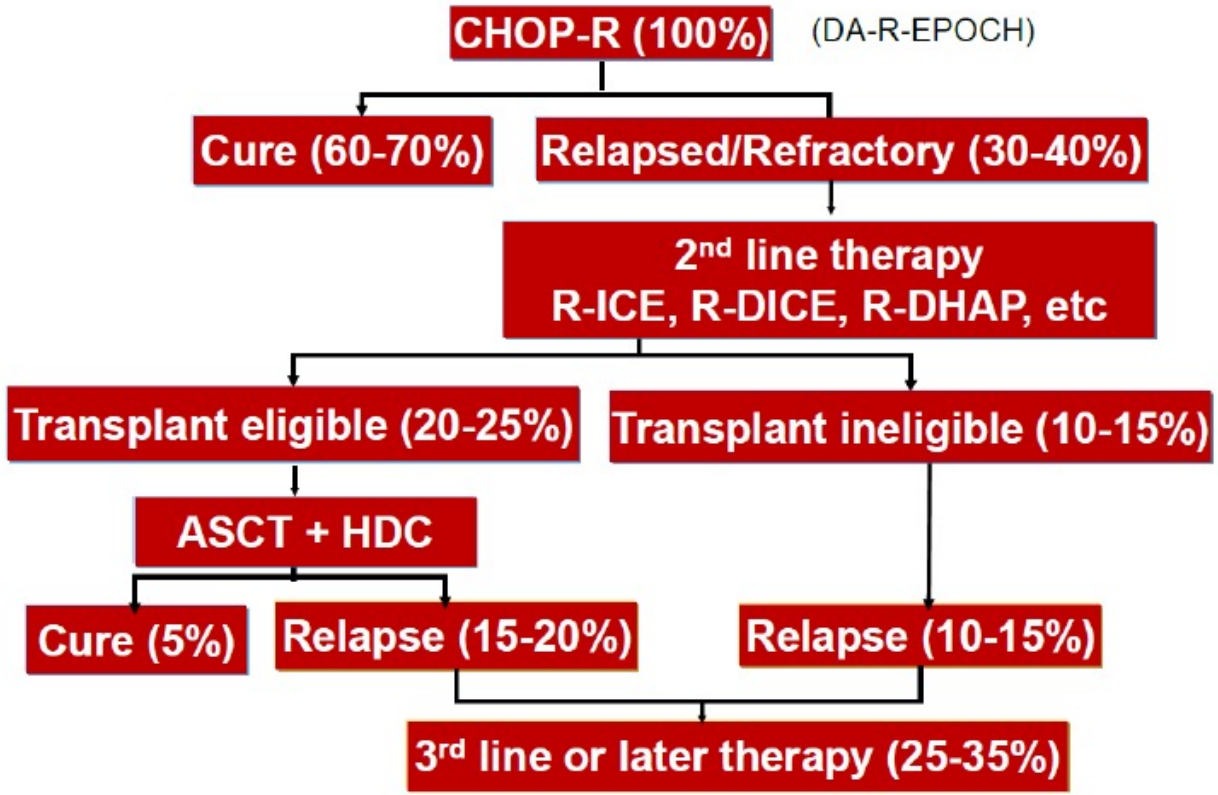
Target enrolment

- N=450

1L, first-line; aaIPI, age-adjusted International Prognostic Index; d, day(s); DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, International Prognostic Index; Q21D, every 21 days; R, randomisation; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone.

TERAPIA DI SECONDA LINEA

Common Treatment Algorithm for DLBCL

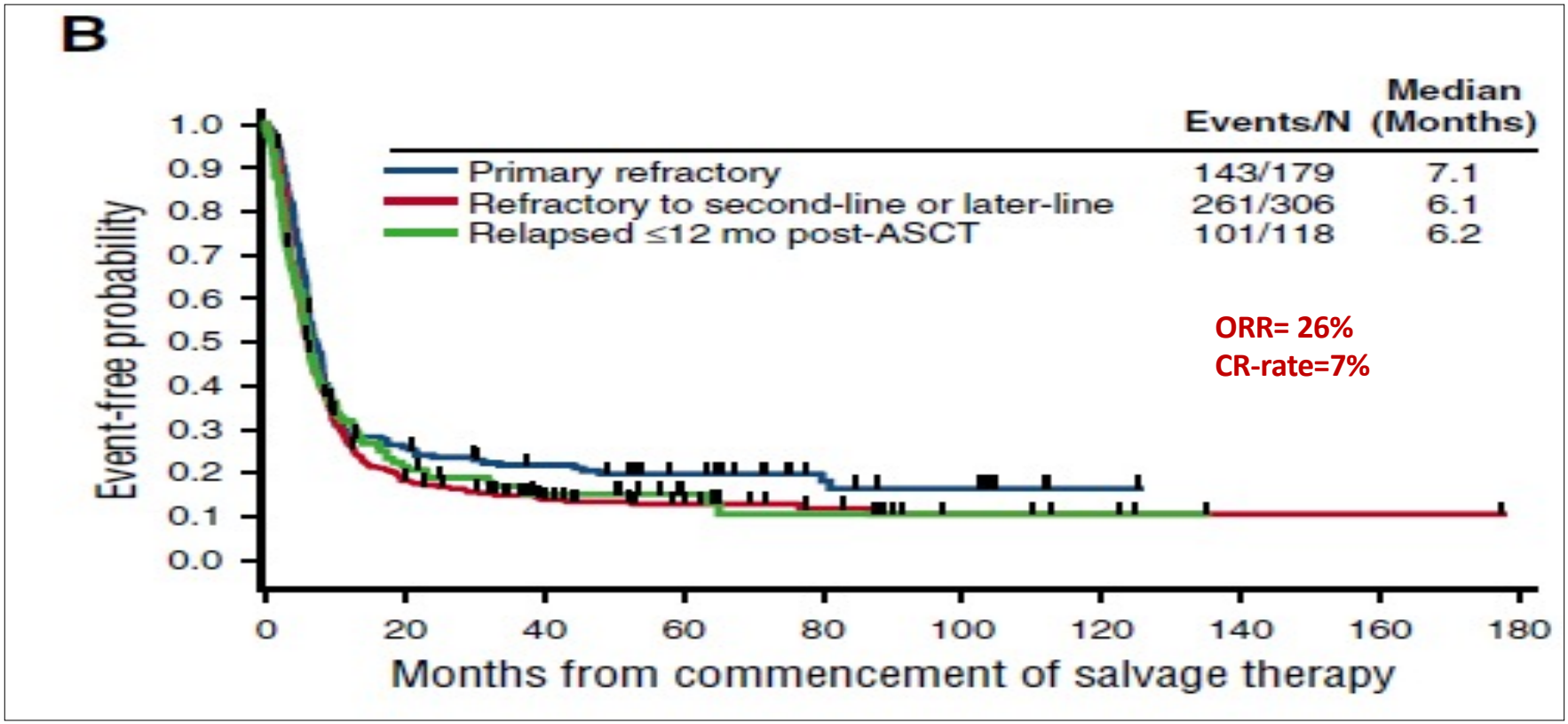


CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]

Crump M,et al Blood 2017;130:1800-8

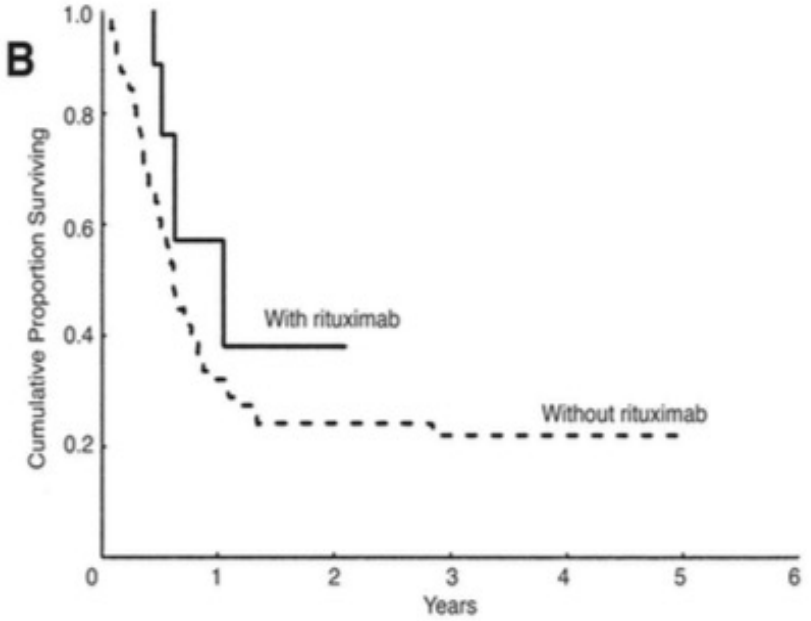


Main role of front line therapy in DLBCL nd low activity of salvage therapy

Outcome of patients not eligible to transplantation

Five -year FU of Coiffer trial (NEJM 2002)

- 399 RHOP vs CHOP
- Median age 69 year

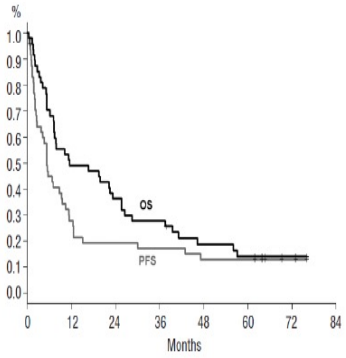


Feugier , JCO 2005

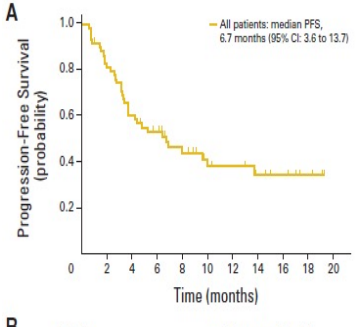
Unsatisfactory outcome among patients non-eligible to transplant

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	49	69	46	38	5-yrs 12.8%	Mounier N, Haematol 2013
R-Bendamustine	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymph2015
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Onc 2012
Lenalidomide	49	65	35	12	Median 4 mo	Wiernik PH, JCO 2008

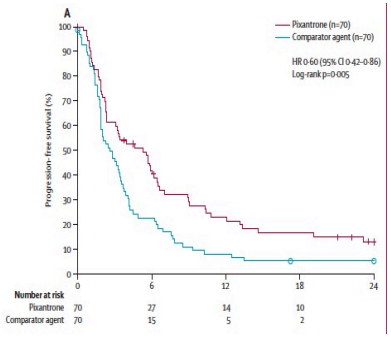
R-GemOx



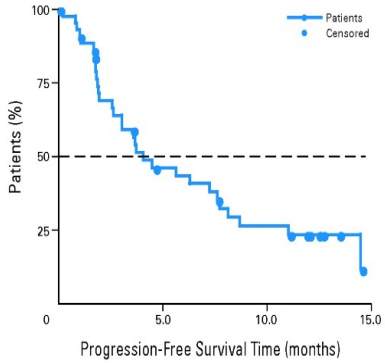
R-Bendamustine



Pixantrone

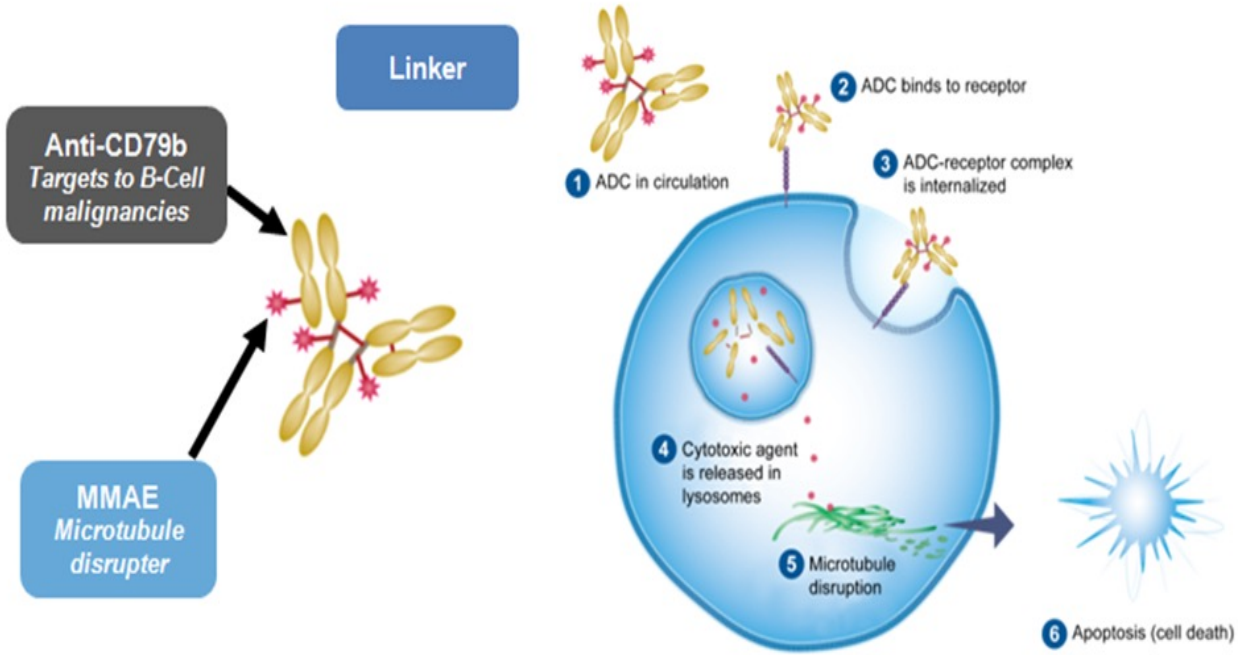


Lenalidomide



Polatuzumab Vedotin▼ (CD79b-ADC)

- ADC comprising potent microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



▼*Polatuzumab vedotin è sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 dell'RCP per informazioni sulle modalità di segnalazione delle reazioni avverse.*

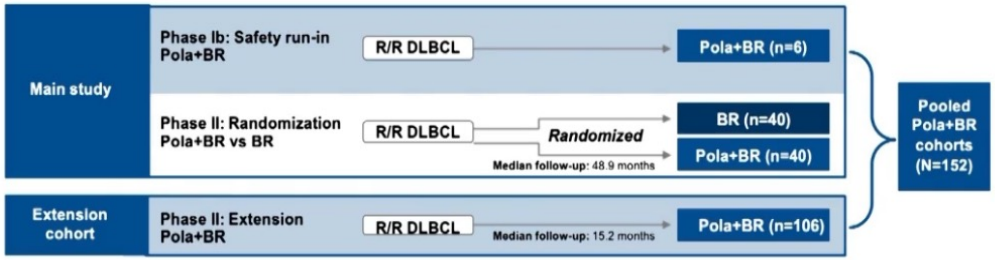
Pola + BR vs BR

Randomised Phase II study of pola-BR *versus* BR (GO29365): study design

Key eligibility criteria

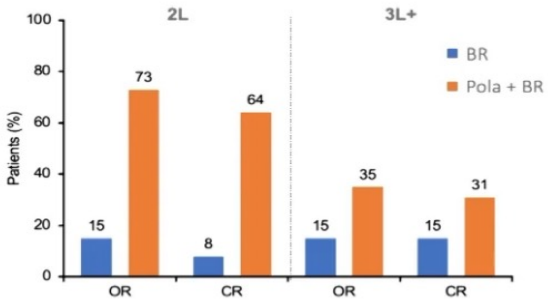
Inclusion: transplant-ineligible DLBCL, after at least 1 line of therapy

Exclusion: prior allogeneic SCT; history of transformation from indolent disease; current Grade >1 PN

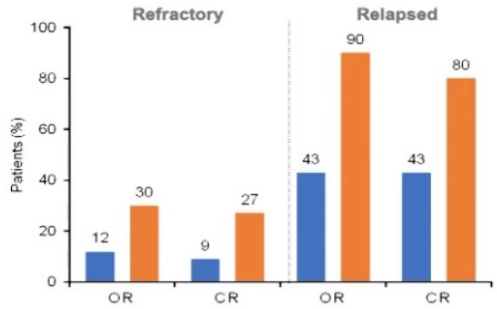


GO29365: Pola-BR improved response rates versus BR independent of patients' prior treatment experience

OR and PET-CR rates by prior line of therapy

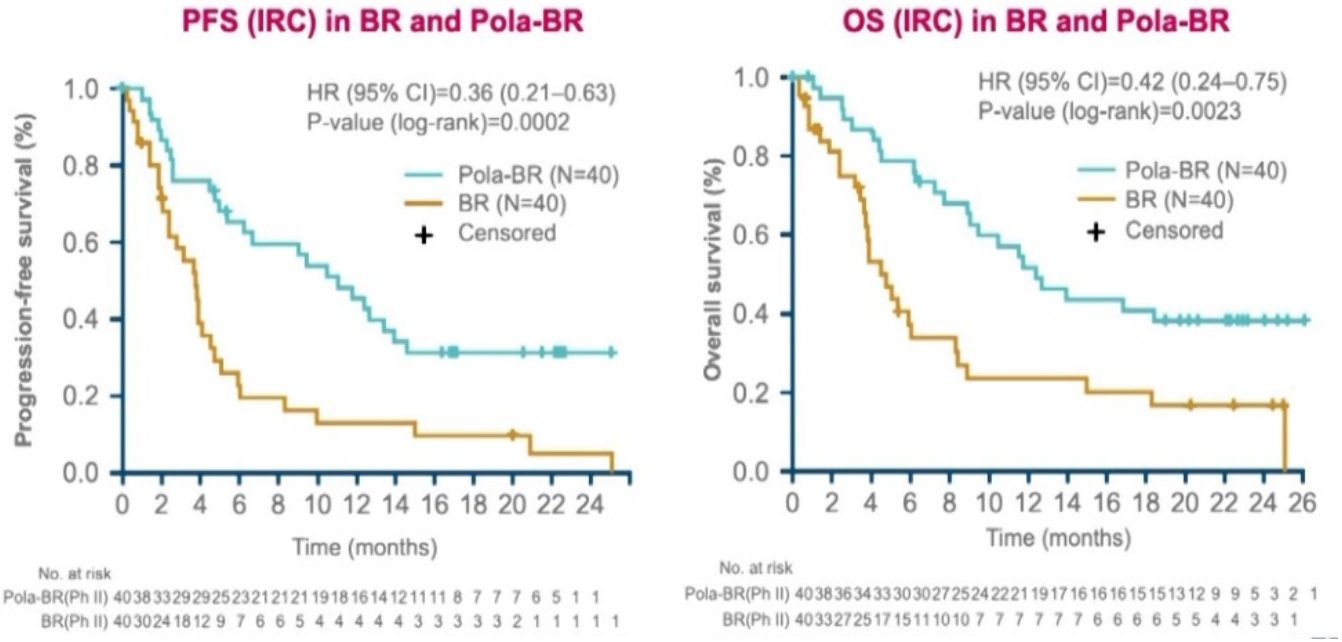


OR and PET-CR rates by refractory status



Sehn L,et al J. Clin Oncol 2019

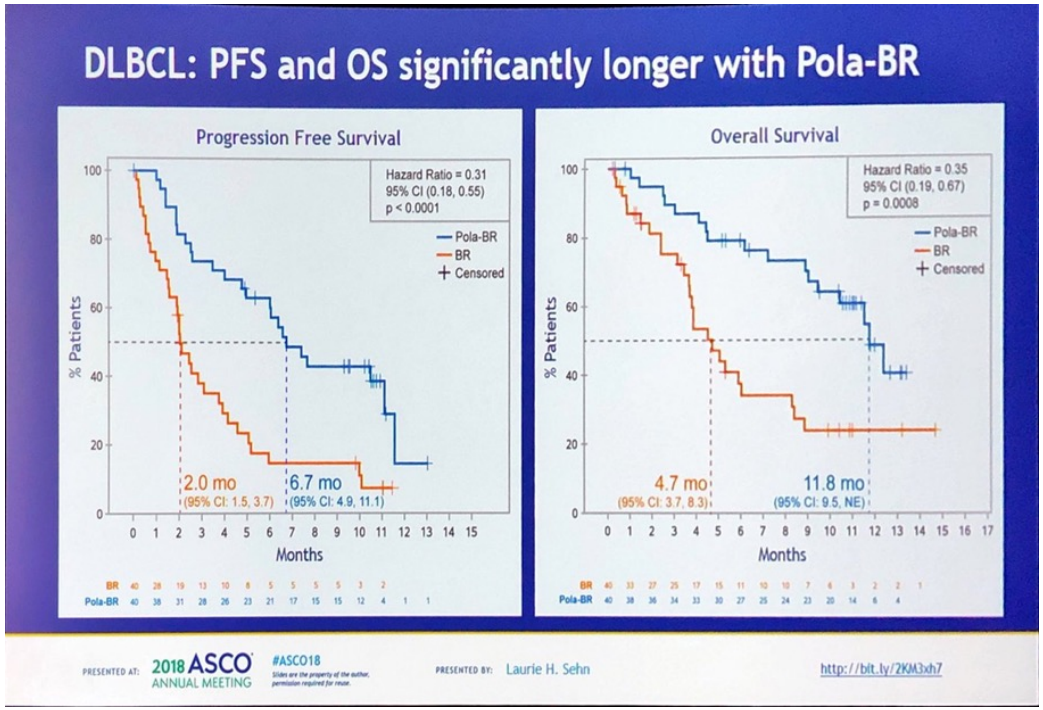
GO29365: PFS and OS was significantly longer with pola + BR versus BR



Pola + BR vs BR: median OS 12.4 vs 4.7 months

Sehn L,et al J. Clin Oncol 2019

R BENDA + POLATUZUMAB VEDOTIN



Studio di fase II

Pola-R Benda vs R Benda in r/r DLBCL
RC 40% vs 18%
prolungamento della PFS e anche della OS (fino a 12 mesi)

Concluso programma di uso compassionevole
Approvato da FDA dalla 3°linea e da EMA dalla 2°

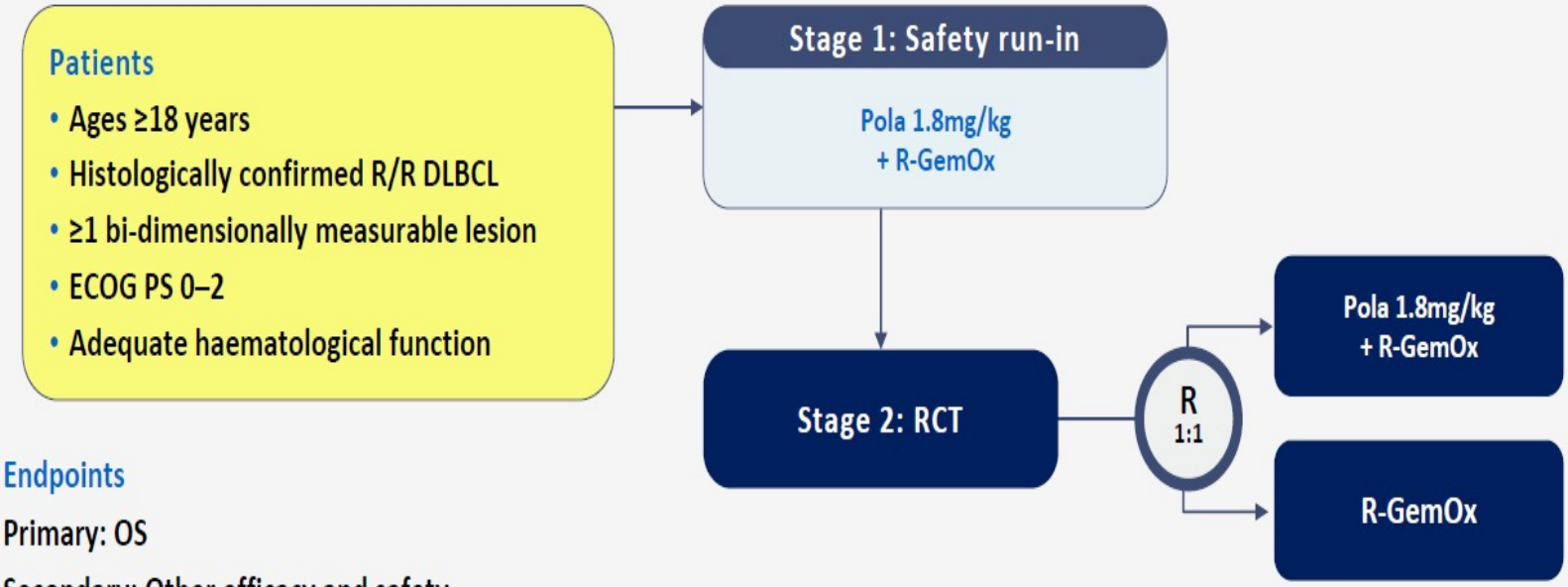
	Ph Ib safety run-in	Randomized Ph II		Ph Ib/II expansion
	Pola-BR (N=6)	Pola-BR (N=40)	BR (N=40)	Pola-BG (N=27)
PET-CR at EOT (IRC) n (%)	3 (50)	16 (40)	7 (18)	8 (30)
ORR, n (%)	3 (50)	18 (45)	7 (18)	11 (41)
DoR Median, mo (95% CI)	NR (NR, NR)	10.3 (5.6, NR)	4.1 (2.6, 12.7)	28.4 (3.0, 31.9)
PFS Median, mo (95% CI)	NR (1.8, NR)	7.6 (6.0, 17.0)	2.0 (1.5, 3.7)	5.4 (2.8, 30.4)
OS Median, mo (95% CI)	NR (5.6, NR)	12.4 (9.0, NR)	4.7 (3.7, 8.3)	10.8 (5.8, 33.8)

Sehn L et al, ASCO 2018

POLARGO Phase III study : Pola in combination with R-GemOx in R/R DLBCL

Rationale

- Pola + BR had an acceptable safety profile and demonstrated benefit vs BR in the GO29365 study
- R-GemOx is another widely used combination in DLBCL



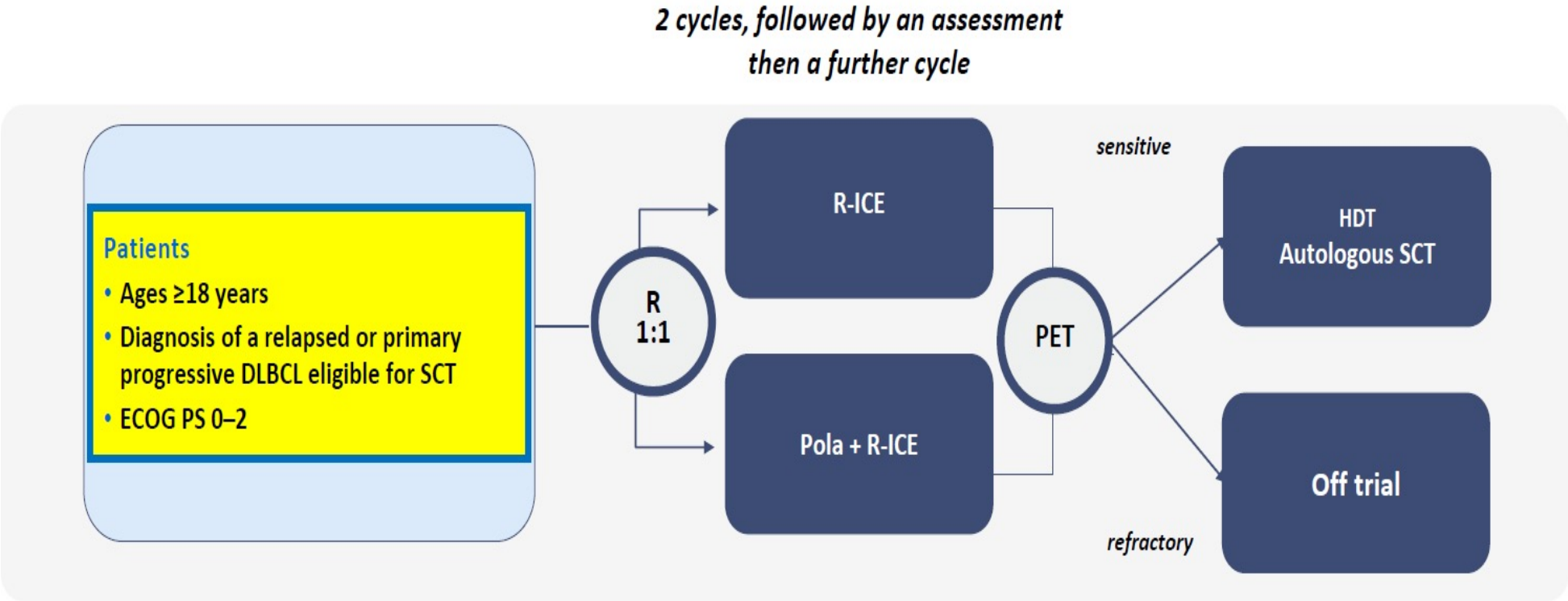
Endpoints

Primary: OS

Secondary: Other efficacy and safety

EUDRACT NUMBER: 2018-003727-10

R-ICE vs Pola R-ICE in a phase 3 study bridge to transplant

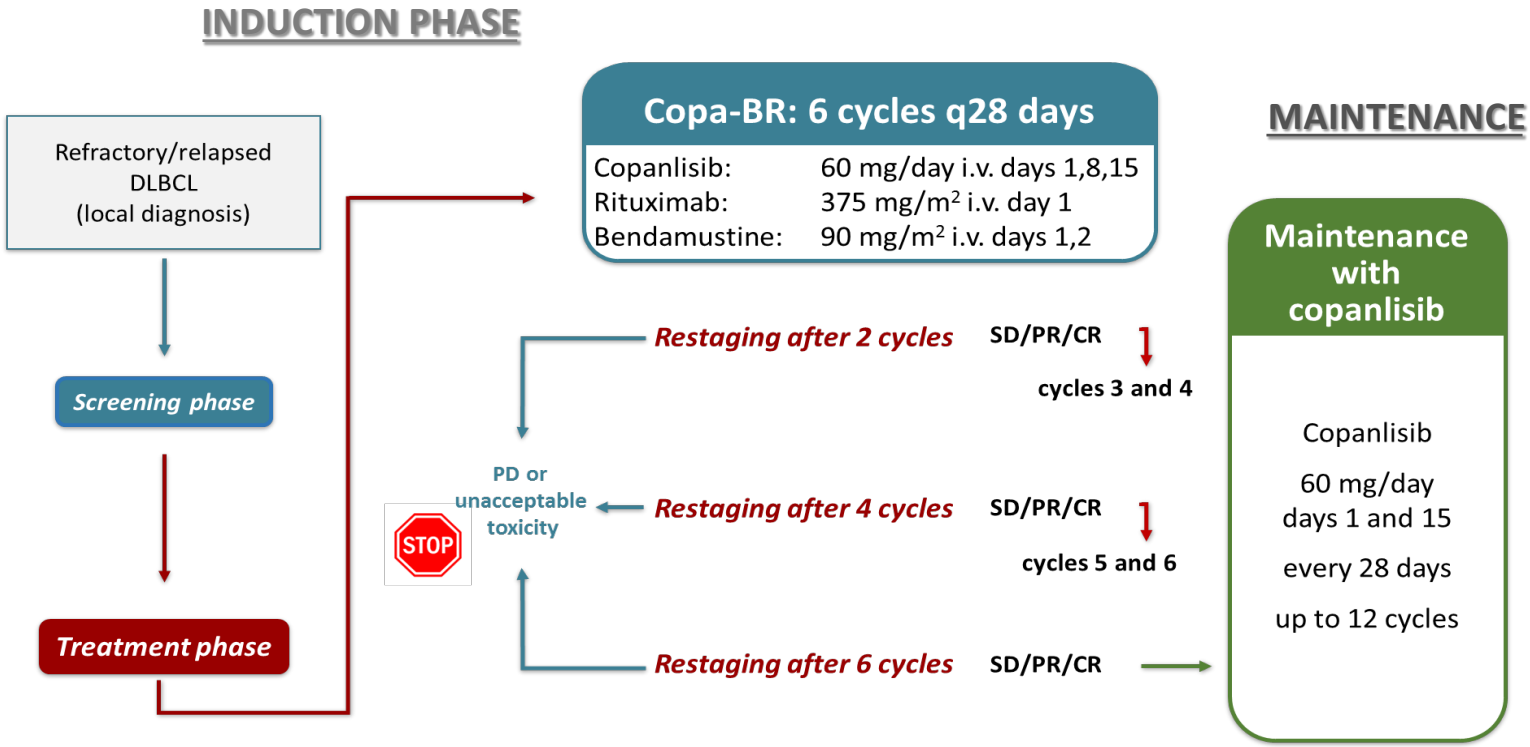


Primary Endpoint : 2-year EFS rate

EUDRACT NUMBER: 2019-002962-10

RB backbone and biological agents

CopaRB phase 2 trial



Descrizione

Studio sperimentale, multicentrico internazionale, in aperto, a braccio singolo, di fase II, che valuta l'efficacia di Copanlisib somministrato in combinazione alla terapia standard con Rituximab e Bendamustina in pazienti con linfoma diffuso a grandi cellule B (DLBCL), che hanno precedentemente effettuato almeno una ma non più di tre linee di terapia, non eleggibili a un trattamento di chemioterapia ad alte dosi e successivo trapianto di cellule staminali autologhe o a una terapia con CAR T-cell, o che hanno ripresentato la malattia dopo risposta completa o progressione dopo risposta parziale.

Possono partecipare a questo studio pazienti con età maggiore o uguale a 18 anni che rispettano i criteri di eleggibilità previsti dallo studio.

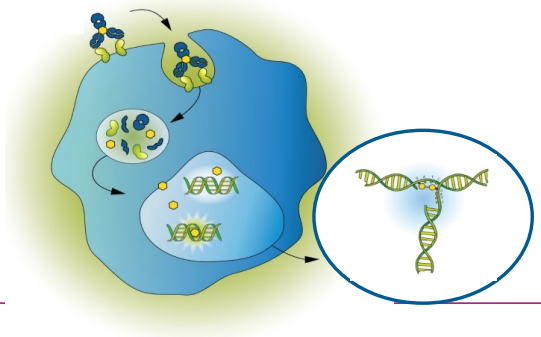
Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial

Paolo F Caimi, Weiyun Ai, Juan Pablo Alderuccio, Kirit M Ardeshna, Mehdi Hamadani, Brian Hess, Brad S Kahl, John Radford, Melhem Solh, Anastasios Stathis, Pier Luigi Zinzani, Karin Havenith, Jay Feingold, Shui He, Yajuan Qin, David Ungar, Xiaoyan Zhang, Carmelo Carlo-Stella

Despite recent advances in DLBCL treatment, outcomes for patients with R/R DLBCL remain poor

- Lonca is an ADC comprising a humanised anti-CD19 antibody conjugated to a potent PBD dimer[2]
- Lonca had encouraging antitumour activity and acceptable safety in R/R DLBCL in a Phase 1 first-in-human trial[3]

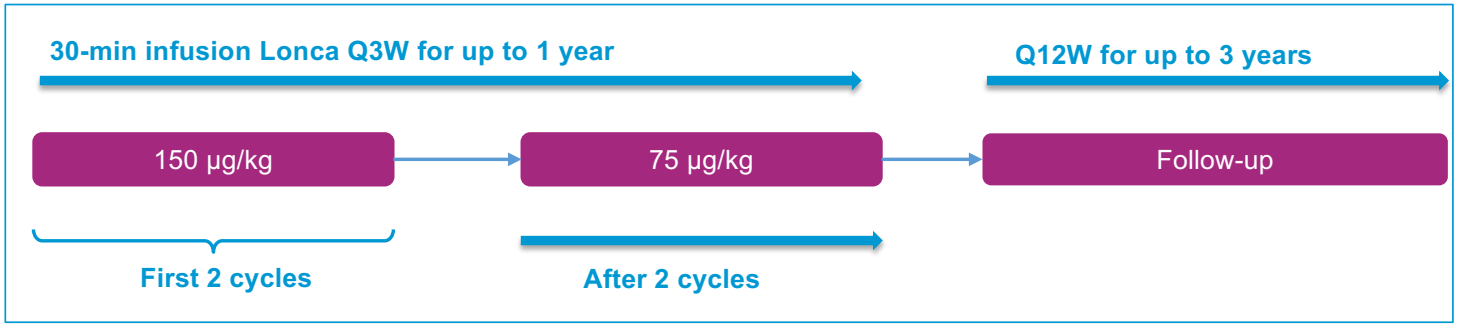
Lonca targets CD19, which is expressed in the majority of B-cell malignancies



internalised

2. The linker is cleaved and PBD dimers released
3. Cytotoxic DNA cross-links are formed
4. The DNA replication fork stalls
5. The cell goes into apoptosis

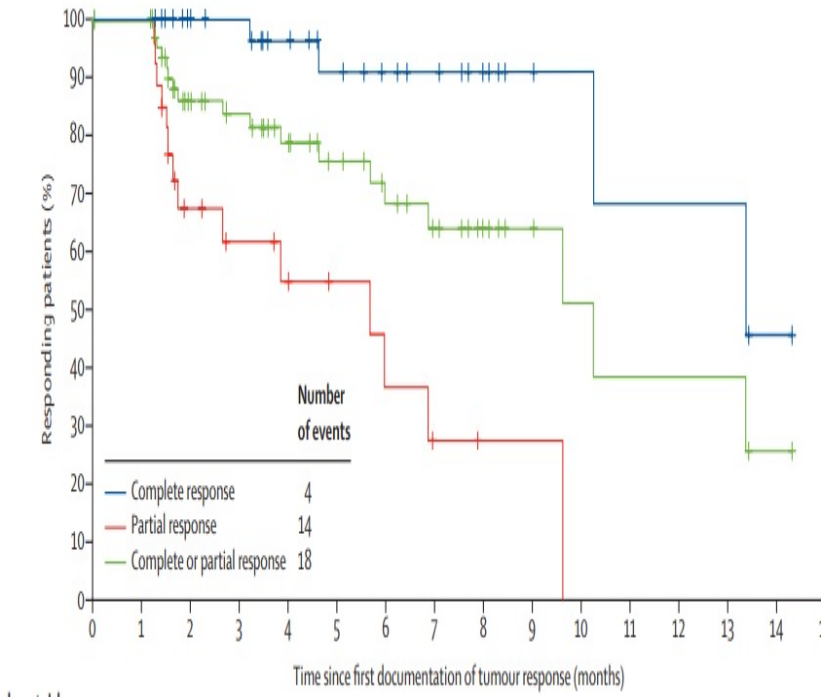
Lonca in R/R DLBCL



Patient treatment history		Total (N=145)
No. of previous systemic therapies,* median (range)		3 (2–7)
First-line systemic therapy response, n (%)	Relapse	99 (68.3)
	Refractory†	29 (20.0)
	Other‡	17 (11.7)
Last-line systemic therapy response,¶ n (%)	Relapse	43 (29.7)
	Refractory†	84 (57.9)
	Other‡	18 (12.4)
Refractory to all prior therapies, n (%)	Yes	25 (17.2)
	No	115 (79.3)
	Other‡	5 (3.4)
Prior stem cell transplant, n (%)	Allogeneic	2 (1.4)
	Autologous	21 (14.5)
	Both	1 (0.7)

et al. Lancet Oncology 2021

Loncastuximab: duration of response



	As-treated population (n=145)
Overall response rate (complete or partial response)	70 (48·3% [39·9–56·7])
Complete response rate	35 (24·1% [17·4–31·9])
Complete response	35 (24%)
Partial response	35 (24%)
Stable disease	22 (15%)
Progressive disease	30 (21%)
Not evaluable*	23 (16%)

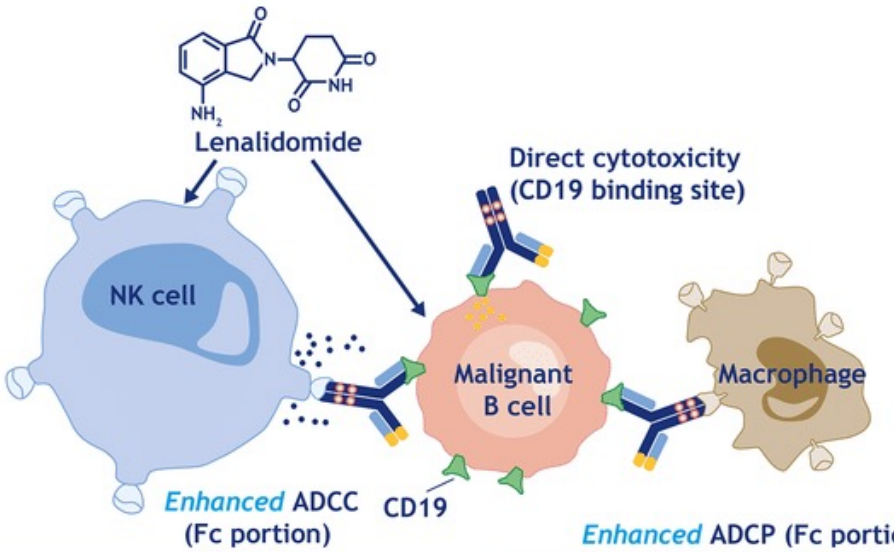
Data are n (% [95% CI]) or n (%). Response was assessed by central independent review. A best overall response of stable disease could only be achieved after the patient was on the study for a minimum of 35 days following the first dose of loncastuximab tesirine. Any disease assessment indicating stable disease before this timepoint was considered not evaluable for response if no assessment after this timepoint was available. *Patients without any scan available to the independent reviewer or patients whose scan was determined to be not evaluable by the independent reviewer.

Table 2: Best overall responses and overall response rate

Median DOR for the whole population 10.3 months
Median DOR for CR patients 13.4 months

Caimi et al. Lancet

MOR 208: an enhanced anti CD19



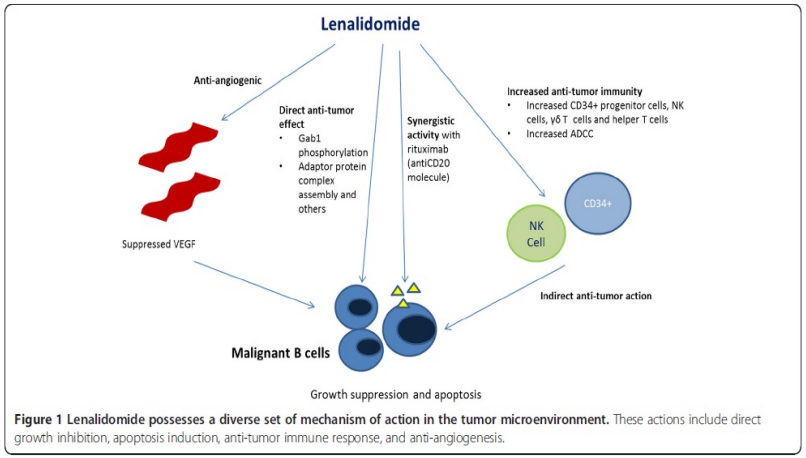


Figure 1 Lenalidomide possesses a diverse set of mechanism of action in the tumor microenvironment. These actions include direct growth inhibition, apoptosis induction, anti-tumor immune response, and anti-angiogenesis.

Tafasitamab (Fc-enhanced, anti-CD19 mAb)

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

Lenalidomide

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

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; DLBCL, diffuse large B-cell lymphoma; iNHL, indolent non-Hodgkin's lymphoma; mAb, monoclonal antibody; NK, natural killer; R/R, relapsed/refractory.

L MIND

- R/R DLBCL
- Not eligible for HDCT plus ASCT
- 1–3 prior regimens
- Primary refractory patients were not eligible*
- ECOG PS 0–2

N=81

Cycles 1–3
Tafasitamab 12 mg/kg d1, 8, 15, 22†
+
LEN 25 mg/d orally d1–21

Cycles 4–12
Tafasitamab 12 mg/kg d1, 15
+
LEN 25 mg/d orally d1–21

If ≥SD

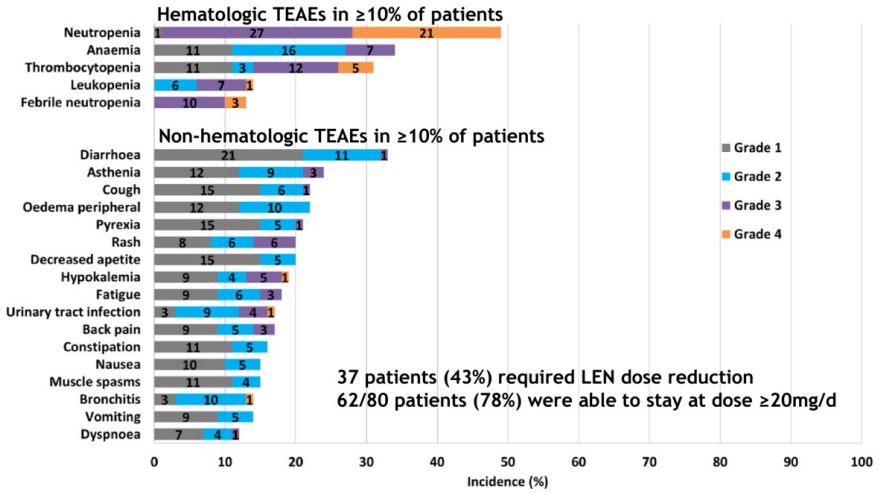
Cycles 12+
Tafasitamab 12 mg/kg d1, 15

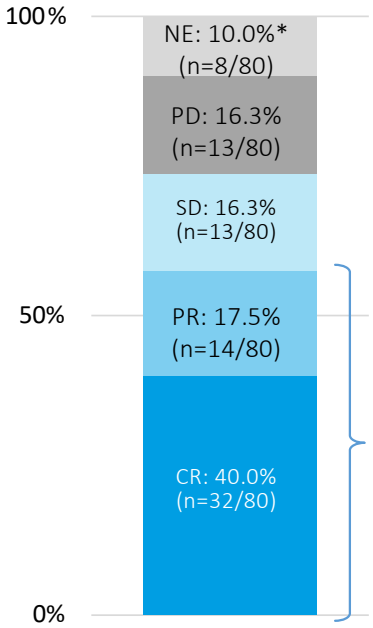
Treatment until progression

Primary endpoint:
- ORR (central read)

Secondary endpoints:
- PFS
- DoR
- OS
- Safety of the tafasitamab plus LEN combination
- Exploratory and biomarker-based assays

Safety Profile of Tafasitamab + LEN





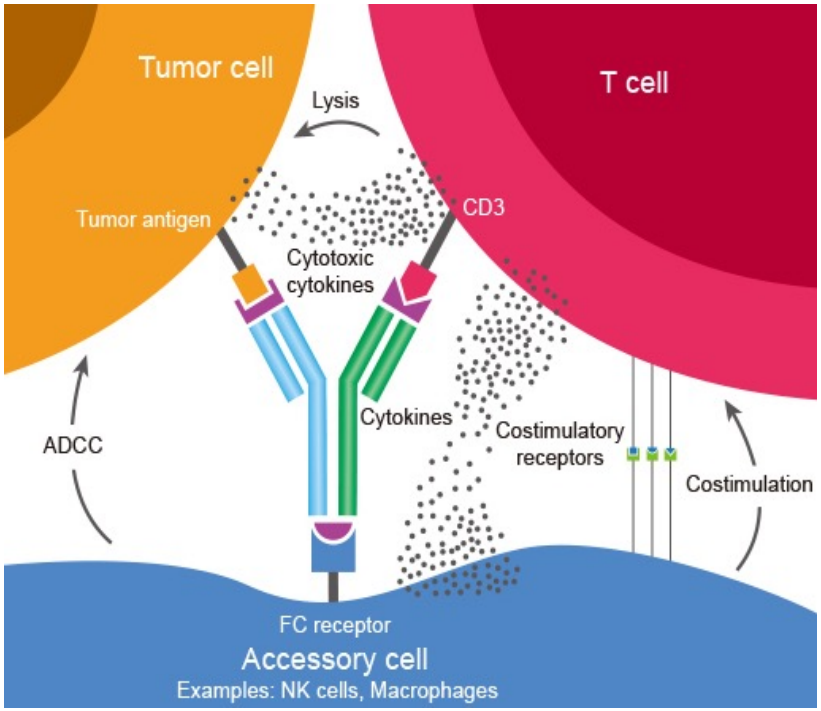
ORR: 57.5%
(95% CI: 45.9–68.5)

After follow up ≥ 35 m:

Median DoR 43.9 m
Median PFS 11.6 m
Median OS 33.5 m
No unexpected toxicities

Salles G et al Lancet Oncology 2020
Duell J, et al. Oral presentation at Virtual ICML 2021; Abstract 28.

BISPECIFIC ANTIBODIES



- BsAbs redirect immune effector cells in close proximity to malignant cells
- T cells undergo activation due to CD3 cross-linking, which is associated with cytokine release (IFN-g, TNF-a, IL-2, -6, -10) and cytotoxic granule release (granzyme B)
- T-cell activation is MHC-unrestricted and no longer depends on the native TCR specificity of the activated T cell

BsAbs in Clinical Development

Bispecifics	Indications	Lymphoma type	ORR	CR	CRS	CRS Gd 3-4
Mosunetuzumab[1]	r/r NHLs	iNHL aNHL	63% (42/67) 37% (46/124)	44% 19%	29%	1%
Odranextamab[2]	r/r NHLs	FL DLBCL	96% 58%	77% 42%	59%	6.4%
Glofitamab*[3]	r/r NHLs	iNHL aNHL	67% (12/18) 49% (42/85)	52% 31%	56.4%	3.2%
Epocritamab[4]	r/r NHLs	FL DLBCL	100% (6/6) 56% (5/9)	0% 44%	59%	0%
Plamotamab[5]	r/r NHLs	FL DLBCL	75% 57%	38% 38%	55%	5%

* Pretreatment with Obinutuzumab 7 days prior to Glofitamab to debulk and mitigate CRS

[1]Schuster *et al*, ASH 2019; abstr 6; [2]Bannerji *et al*, ASH 2019; abstr 762; [3]Dickinson et al, EHA 2020, abstr 241; [4]Hutchings et al, EHA 2020, abstr 1218; [5]Patel et al, ASH 2019, abstr 4079

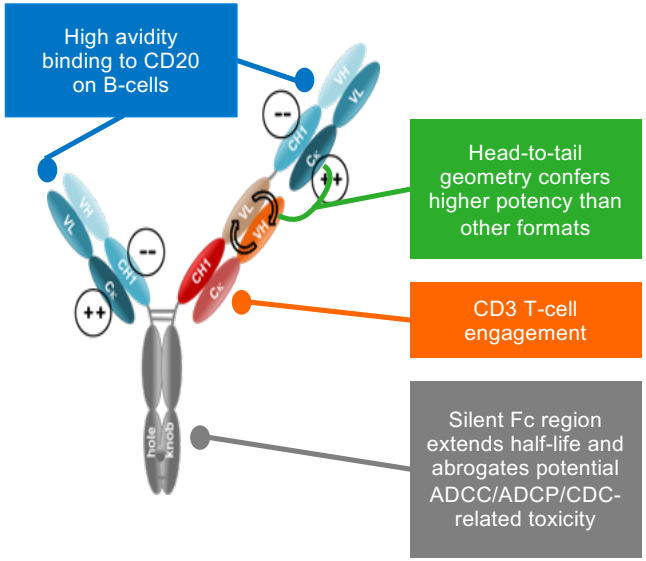
Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

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]

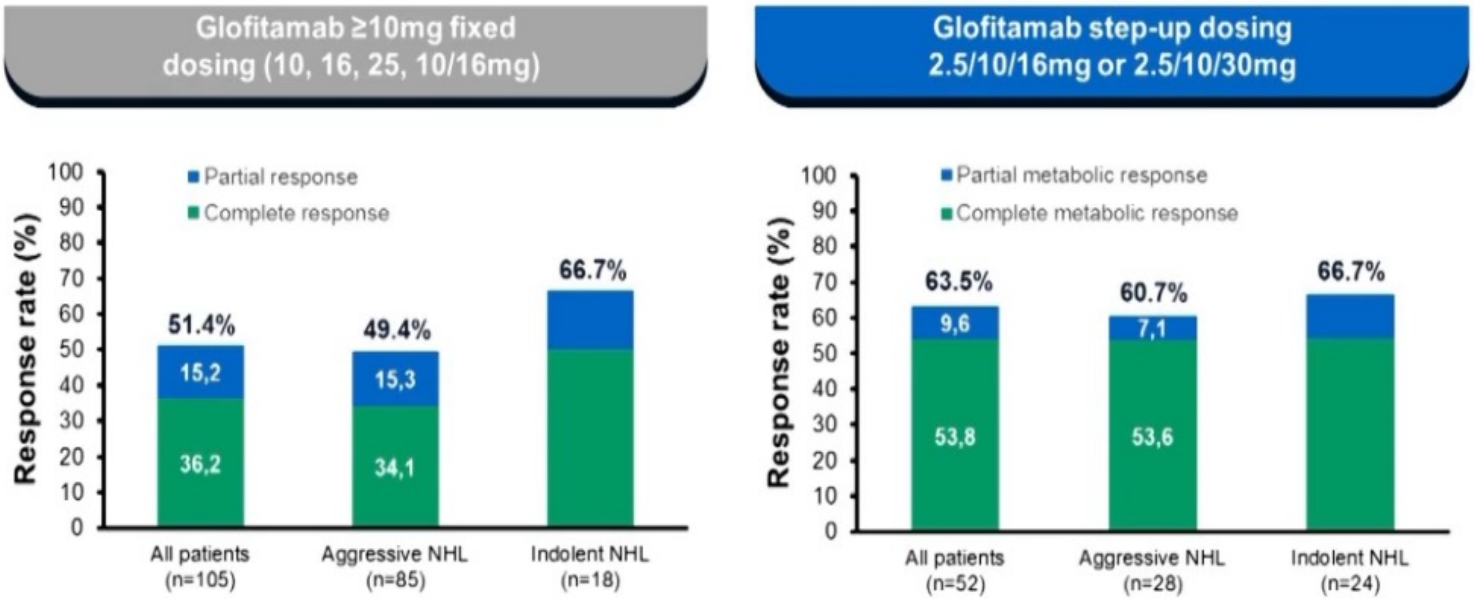
Glofitamab (CD20-TCB, RG6026, RO7082859) is a novel T-cell-engaging bispecific full-length antibody with a unique 2:1 molecular configuration

Glofitamab's molecular configuration is associated with superior potency under experimental conditions vs other CD20-CD3 bispecific antibodies with a 1:1 format, enabling concomitant treatment with other CD20 directed antibodies[3,4]

Induces rapid T-cell activation, proliferation and cytokine release, leading to target cell lysis

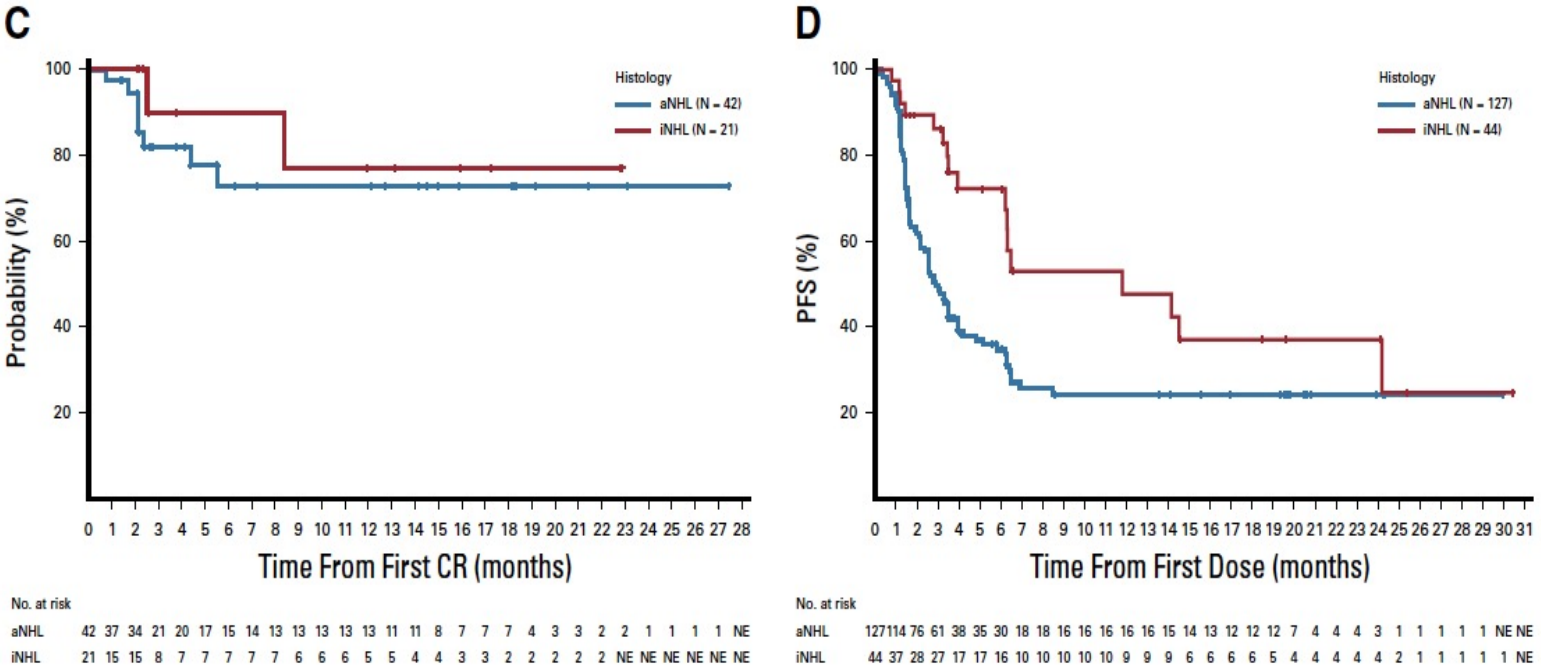


Glofitamab in heavily pretreated patients with non-Hodgkin lymphomas



Hurchings,2021

GLOFITAMAB OUTCOME: duration of CR and PFS

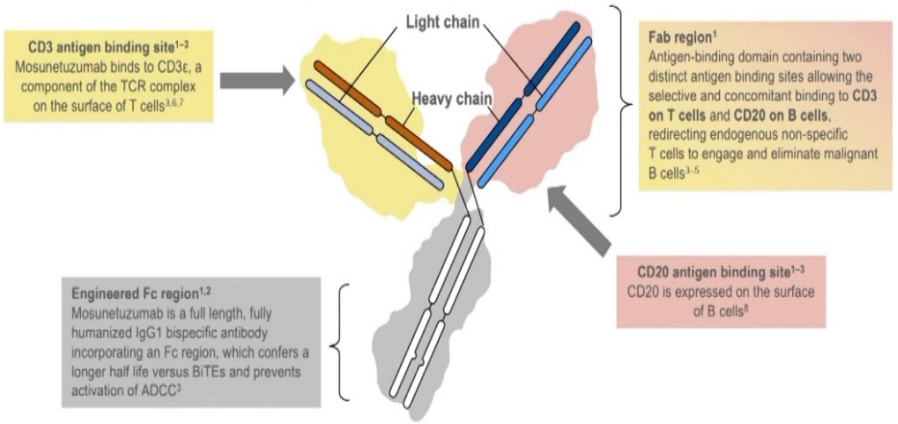


Median DOCR not reached
Of 63 patients with CR , 53 (84.1%) ongoing CR with a maximum observation of 27.4 mos

The median PFS was 2.9 months, with a plateau of approximately 24% from 8 months onward

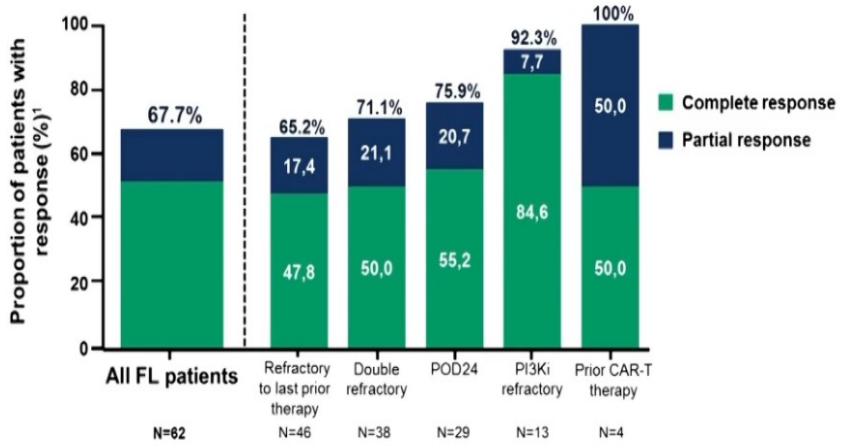
Hutchings , JCO 2021

Mosunetuzumab is a full length, fully humanized, IgG1 bispecific antibody that targets both CD3 and CD20



ADCC, antibody-dependent cell-mediated cytotoxicity; BiTE, bispecific T-cell engager; Fab, fragment antigen-binding; Fc, fragment crystallizable; IgG1, immunoglobulin G1; TCR, T-cell receptor

Mosunetuzumab in patients with relapsed/refractory follicular lymphoma



533 Mosunetuzumab Plus Polatuzumab Vedotin Has Promising Efficacy and a Favorable Safety Profile in Patients with Relapsed/Refractory Aggressive B-Cell Non-Hodgkin Lymphoma: Updated Results from a Phase Ib/II Study

Program: Oral and Poster Abstracts
Type: Oral
Session: 627. Aggressive Lymphomas: Clinical and Epidemiological: Real World evidence for CAR-T Management I
Hematology Disease Topics & Pathways:
Biological therapies, Lymphomas, non-Hodgkin lymphoma, Bispecific Antibody Therapy, Diseases, Therapies, Immunotherapy, Lymphoid Malignancies

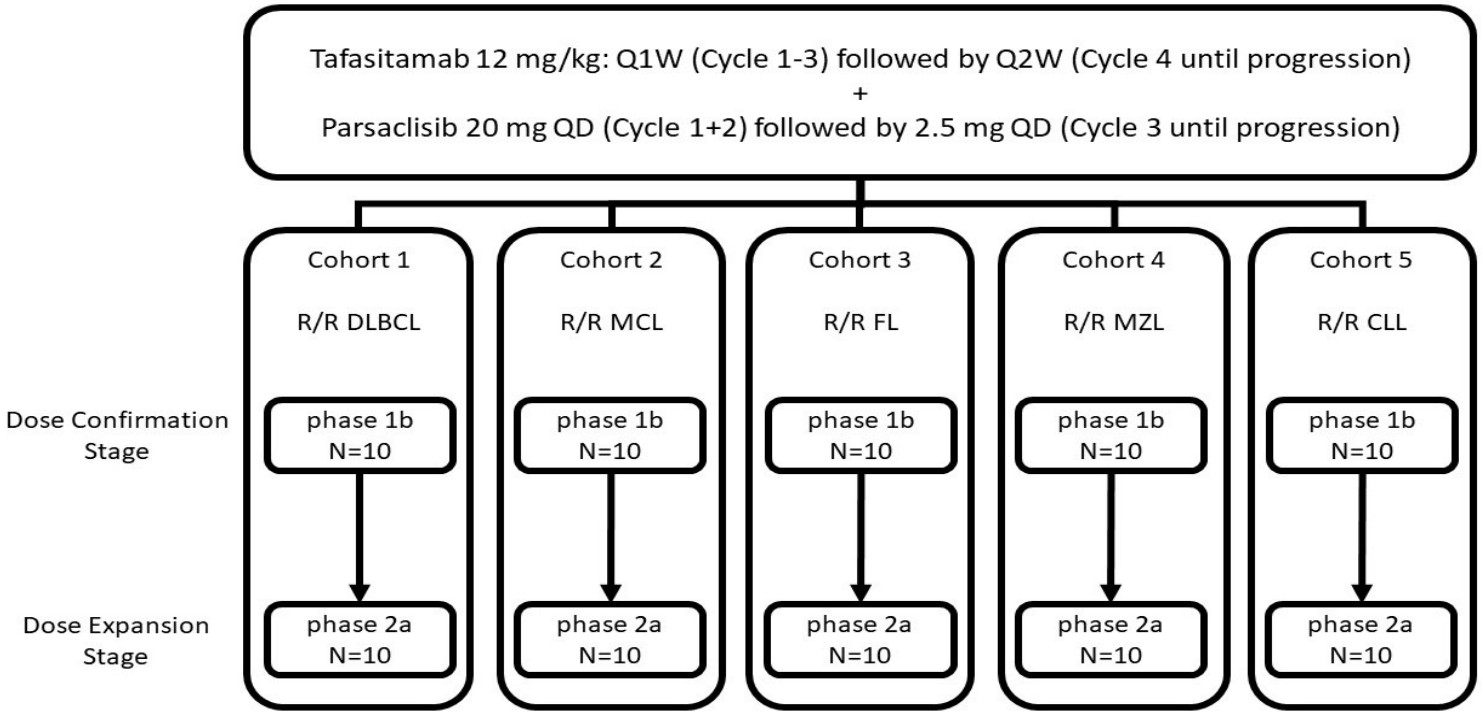
Conclusions: M-Pola shows promising efficacy and a favorable safety profile in pts with heavily pretreated R/R aggressive B-NHL, including those who have received prior CAR-T therapy. A low rate of CRS was observed, with the majority of events being Gr 1. The Phase II dose-expansion cohort continues to enroll pts with R/R aggressive B-NHL.

S. Assouline,2020

STUDY DESIGN

Tafasitamab e Parsaclisib

- **Clinical Phase**: 1b/2a
- **Study Design:** Single-arm, open-label, Phase 1b/2a, multicenter basket study that includes 5 disease-specific cohorts to which participants will be assigned based on the histology of their underlying disease



Conclusions

- DLBCL is a heterogenous disease, and a more accurate recognition of unfavourable DLBCL subsets is raccomanded to better tailor the treatment
- R-Chemotherapy is the backbone of treatment with novel drugs, but randomized trials with «X» + R-CHOP have failed
- New study designs potentially focused on mutational alterations with combination of multiple novel drugs may have a grater chance of success
- The addition of mAb anti CD19 could represent the keystone in the treatment of DLBCL