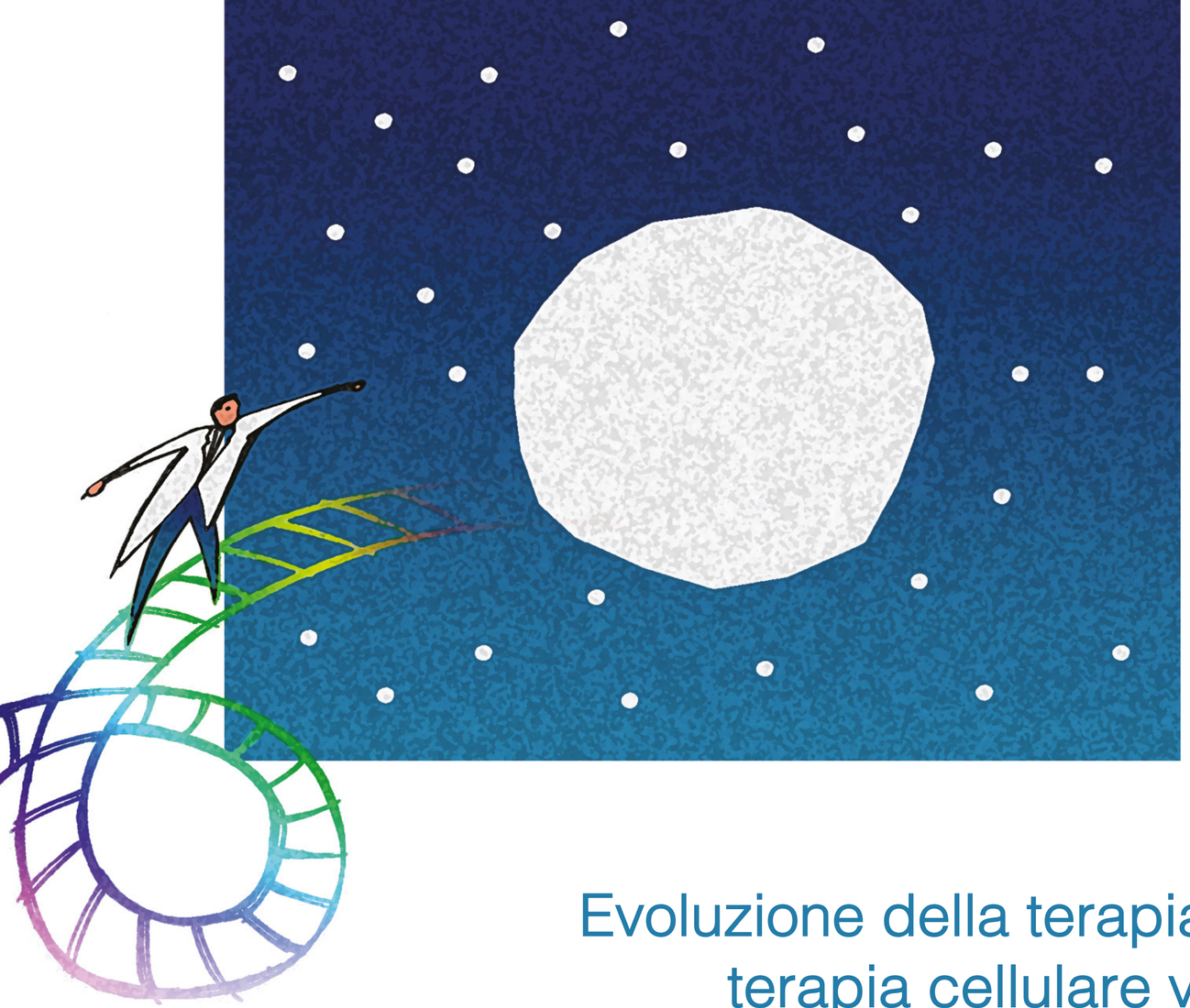


The young side of LYMPHOMA

gli under 40 a confronto

Milano, 14-15 aprile 2023

Evoluzione della terapia di II linea nei DLBCL: terapia cellulare vs immunoterapia

Mattia Novo
AOU Città della Salute e della Scienza di Torino

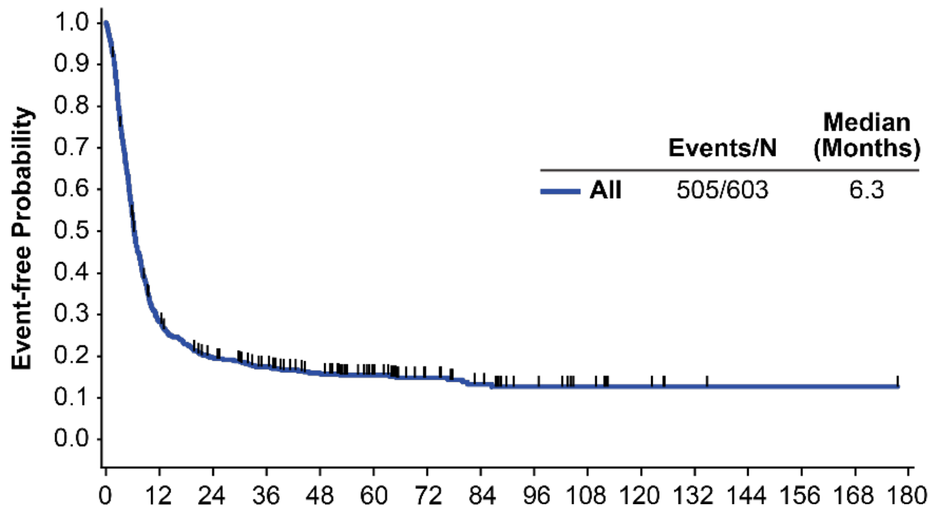
Disclosures of Mattia Novo

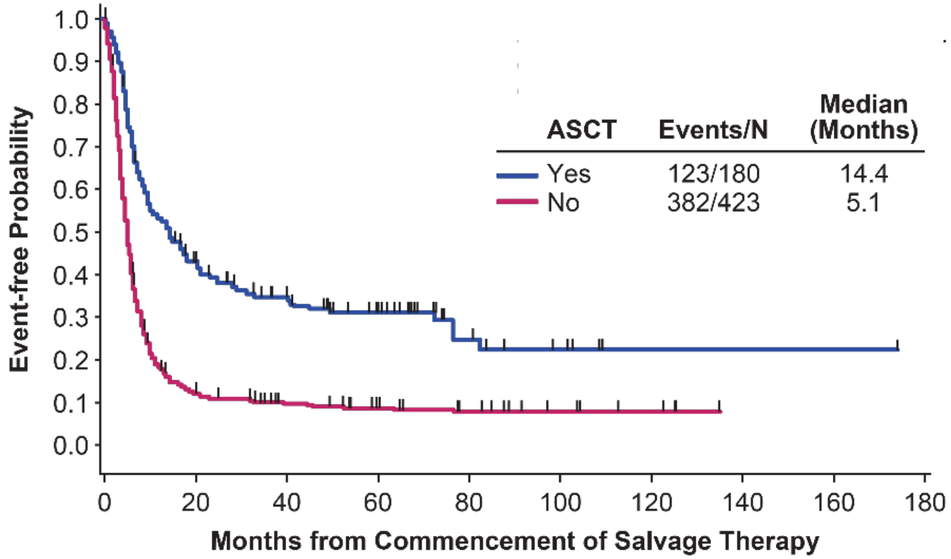
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

No disclosures

Relapsed/refractory DLBCL

- DLBCL is curable in around 60% with R-CHOP
- 35-40% is refractory or relapse - 5-years OS in Europe 55%
- Treatment for R/R DLBCL remains an unmet need:
  - 50% not eligible for ASCT
  - 10-15% can be salvaged with HDC+ASCT



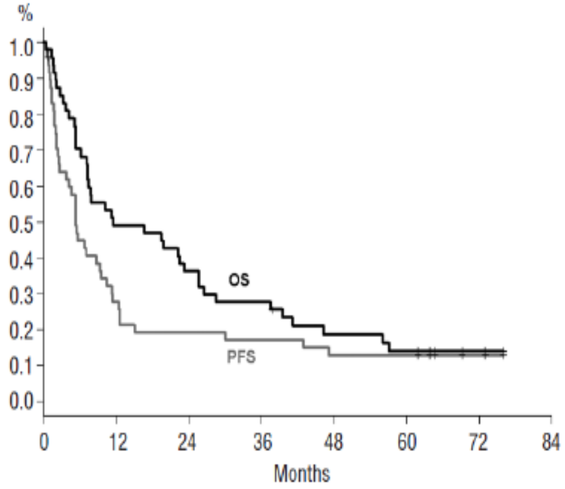


Sant M, et al. Lancet Oncol 2014; Coiffier B, et al. NEJM 2002; Gisselbrecht C, et al. JCO 2010; Crump M, et al, Blood 2017

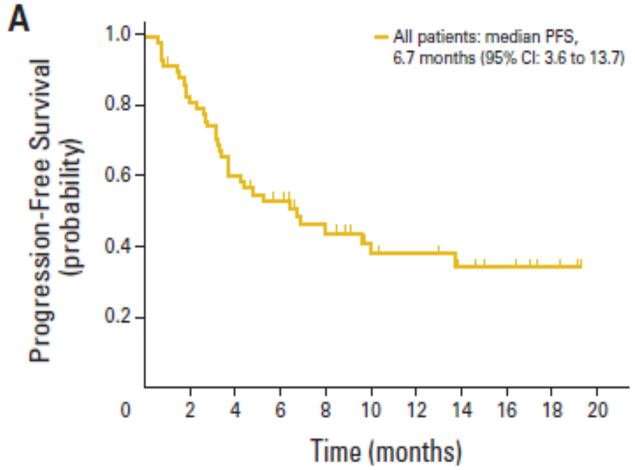
Treatment options for R/R DLBCL transplant-ineligible patients: yesterday…

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	49	69	46	38	5-yrs 12.8%	Mounier N, Haematol 2013
R-Bendamustine	59	67	63	37	Median 6.7 mo	Ohmachi K, L Clin Oncol 2013
	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymphoma 2015
	39	71	33	20	Median 2.0 mo	Sehn L, ePub JCO 2019 (standard arm)
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012
Lenalidomide	49	65	35	12	Median 4 mo	Wiernik PH, JCO 2008

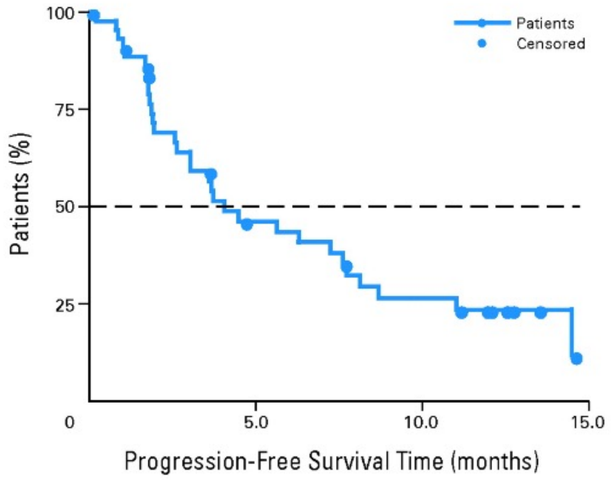
R-GEMOX



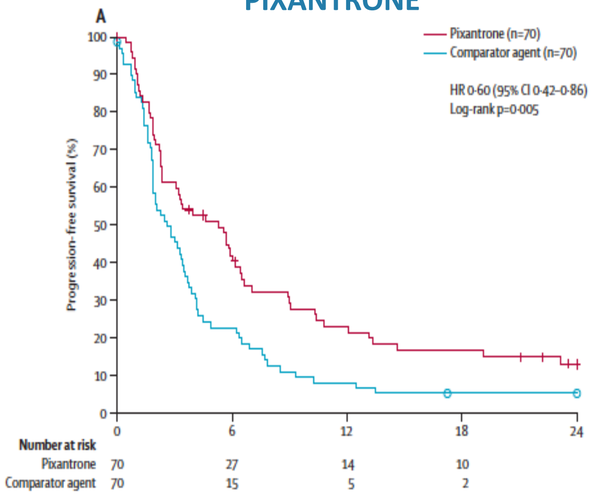
R-BENDAMUSTINE



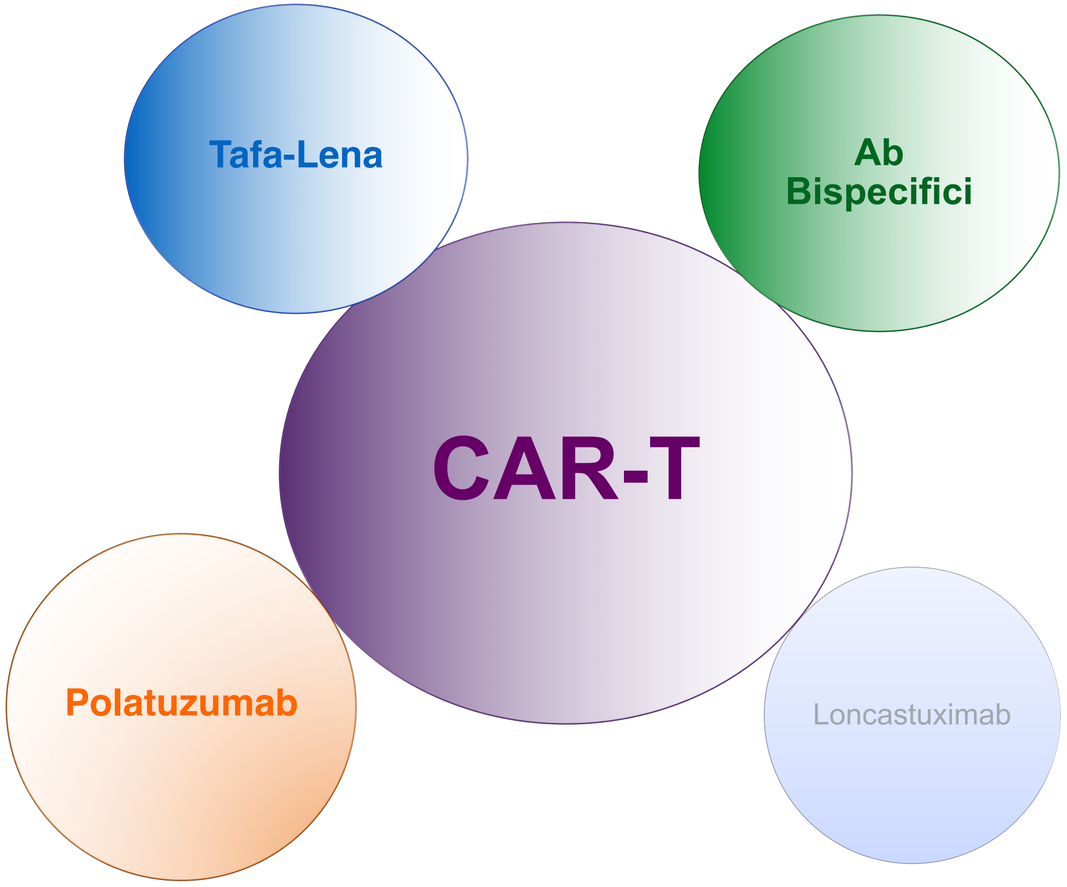
LENALIDOMIDE



PIXANTRONE



Treatment options for R/R DLBCL in 2023: a paradigm shift



Caso Clinico 1

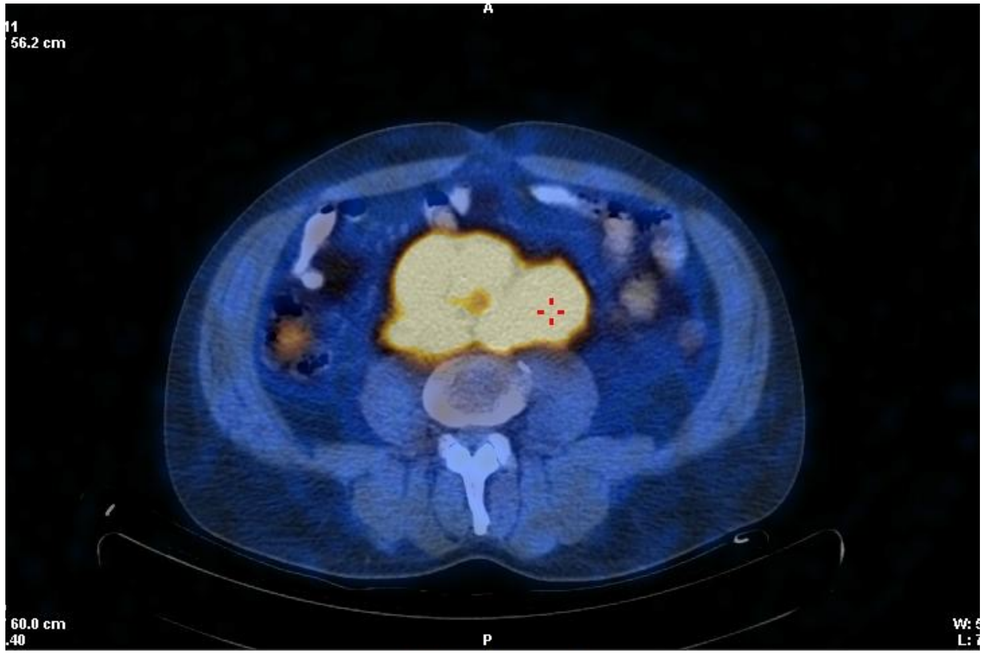
Marco, 68 anni

In Anamnesi:
-Ipertensione arteriora
-IPB

13 Gennaio 2021:
- Accesso in PS per edemi declivi.
- EE: GB 4500/mmc, N 2150/mmc, Hb 10.1 g/dl, PLTs 178000/mmc, **LDH 780 (ULN 450)**, **creat 1.5 mg/dl**

- TC torace-addome: **voluminosa neoformazione in sede periaortica (16 x 11 cm)** con estensione alla biforcazione aortica e lungo l'asse iliaco sx, infiltrazione della via escretrice sx con dilatazione calico-pielica. Dubbia formazione adenopatica mediastinica 27 mm

- Scintigrafia renale: fx renale significativamente ridotta in rene dx ipofunzionante e rene sx funzionalmente escluso
  → Posizionamento JJ bilaterale



- PET/TC: intensa captazione a livello della massa **addominale** (SUVmax 12), adenopatie a livello del mediastino posteriore (SUVmax 8.9), laterocervicale-retroclaveare sx (SUVmax 8.2), **scheletrici** (rachide lombare)

- 31/1/21 Biopsia escissionale linfonodo laterocervicale sx: *Linfoma diffuso a grandi cellule B, profilo GCB (CD20+, CD10+, BCL6+, BCL2+, MUM1+, Ki67 50%) (FISH MYC, BCL2, BCL6 neg)*

Linfoma DLBCL, profilo GCB, stadio IVA, IPI 4 (età, stadio, LDH, PS), CNS IPI4

- BOM: negativa
- Puntura lombare: negativa

Terapia di I linea:
- febbraio – luglio 2021: 6 cicli R-CHOP + 2 R

- 23/7/21 TC collo-torace-addome: riduzione del bulky addominale 12 x 8 cm (vs 16x11 cm), restanti adenopatie regredite
- 28/7/21 PET: significativa riduzione di intensità di captazione del tracciante in neoformazione lomboaortica (SUVmax 5.2 vs 12). Restanti reperti negativi. Quadro di **Risposta parziale (DS4)**

→ **14/9-8/10/21 RT di consolidamento su massa bulky 36 Gy/18 fr**

- 23/11/21 TC collo-torace-addome: quadro stabile
- 11/1/22 PET: **incremento di intensità di captazione in sede di massa addominale (SUVmax 8) (DS5)**

Programma terapeutico II linea: R-DHAOx + HDC + ASCT

Febbraio 2022 (pre-avvio II linea) Ricovero per urosepsi + IRA.
Successivi plurimi episodi recidivanti di IVU con residua compromissione della fx renale:
creat 1.9-2 mg/dl (eGFR 35 ml/min) …

DOMANDA n 1

Paziente di 69 aa affetto da DLBCL refrattario a I linea RCHOP, con funzionalità renale compromessa (eGFR < 60 ml/min). Quale terapia di II linea adottare?

a. R-GEMOx

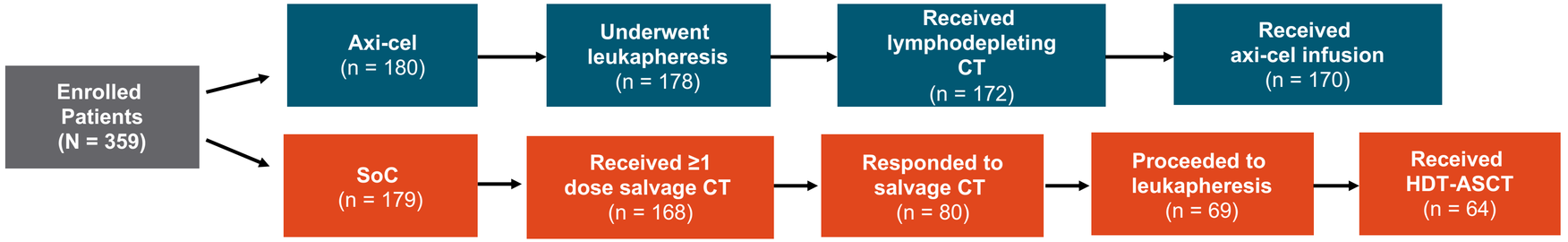
b. CAR-T

c. Tafasitamab-Lenalidomide

d. Pola-BR

CAR-T for R/R DLBCL in II line

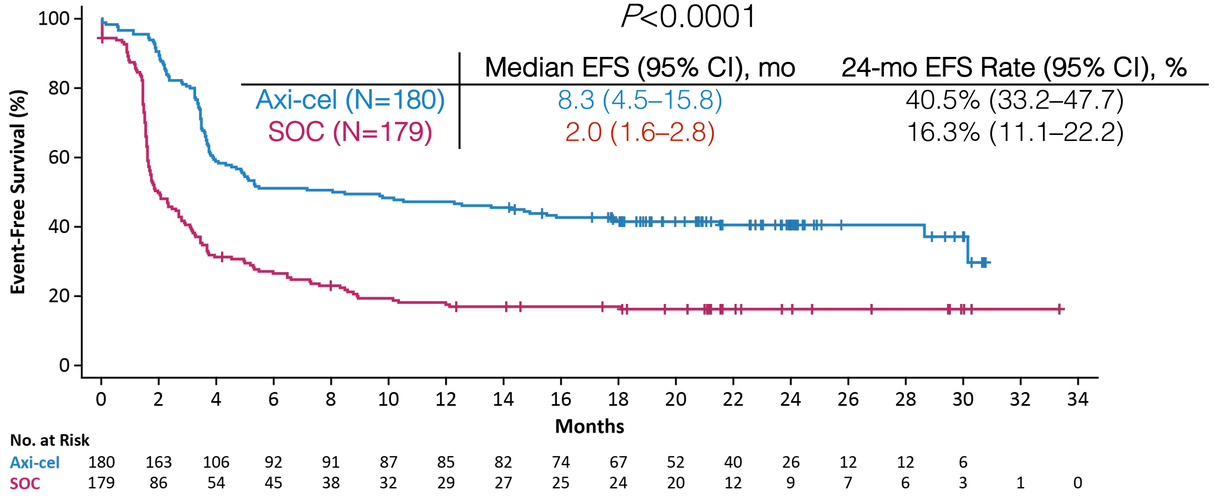
Axi-cel vs. SOC: ZUMA-7 trial



Axi-cel: ORR= 83%; CR=65%
SOC: ORR= 50%; CR=32%
OR, 5.31 (95% CI, 3.1–8.9); *P*<0.0001

Characteristic	Axi-cel (n = 180)	SoC (n = 179)	Overall (N = 359)
Median age, yr (range)	58 (21-80)	60 (26-81)	59 (21-81)
▪ ≥65 yr, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
2L age-adjusted IPI 2-3, n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy, n (%)			
▪ Primary refractory	133 (74)	131 (73)	264 (74)
▪ Relapse within 12 mo	47 (26)	48 (27)	95 (26)
Prognostic marker per central lab, 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, n (%)	101 (56)	94 (53)	195 (54)

HR 0.398 (95% CI, 0.308–0.514);
P<0.0001

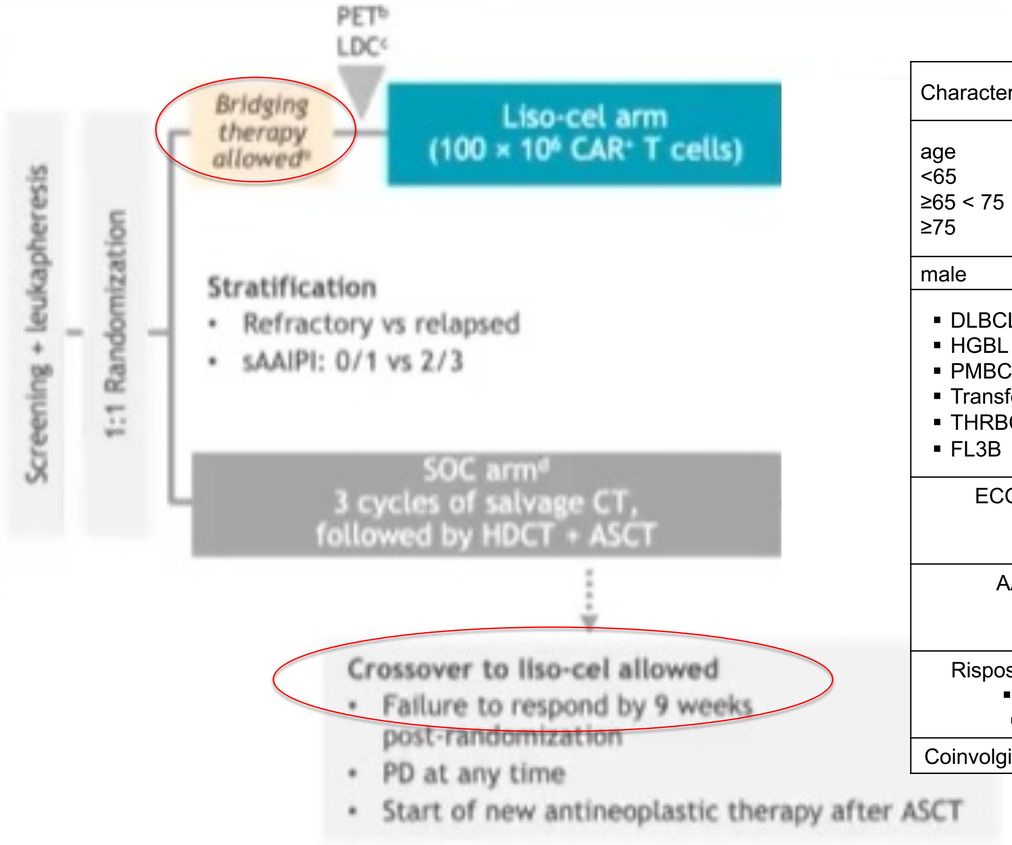


Axi-cel received regulatory approvals as II line for patients with DLBCL and HGBL R/R within 12 months from frontline therapy

Locke FL et al. New Eng J Med 2022

CAR-T for R/R DLBCL in II line

TRANSFORM trial: Liso-cel vs. SOC

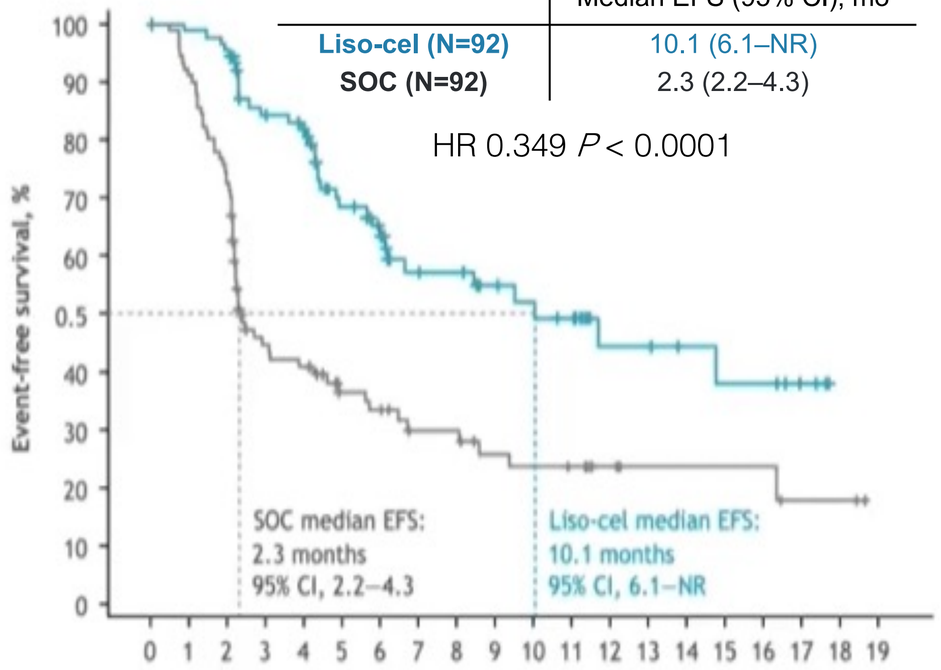


Characteristic, n (%)		SOC (n = 92)
age <65 ≥65 < 75 ≥75	60 (53.5-67.5) 56 (61) 36 (39) 0	58 (42-65) 67 (73) 23 (25) 2 (2)
male	44 (48)	61 (66)
▪ DLBCL-NOS ▪ HGBL double-triple hit ▪ PMBCL ▪ Transformed DLBCL ▪ THRBCL ▪ FL3B	53 (58) 22 (24) 8 (9) 7 (8) 1 (1) 1 (1)	49 (53) 21 (23) 10 (11) 8 (9) 4 (4) 0
ECOG PS, n (%) ▪ 0 ▪ 1	 48 (52) 44(48)	 57 (62) 35 (38)
AAIPI, n (%) ▪ 0-1 ▪ 2-3	 56 (61) 36 (39)	 55 (60) 37 (40)
Risposta alla 1L, n (5) ▪ Refrattari ▪ recidiva	 67 (73) 25 (27)	 68 (74) 24 (26)
Coinvolgimento SNC, n (%)	1 (1)	3 (3)

ORR: 86% vs. 48% $p < 0.0001$
CR: 66% vs. 39%, $p < 0.0001$

	Median EFS (95% CI), mo
Liso-cel (N=92)	10.1 (6.1–NR)
SOC (N=92)	2.3 (2.2–4.3)

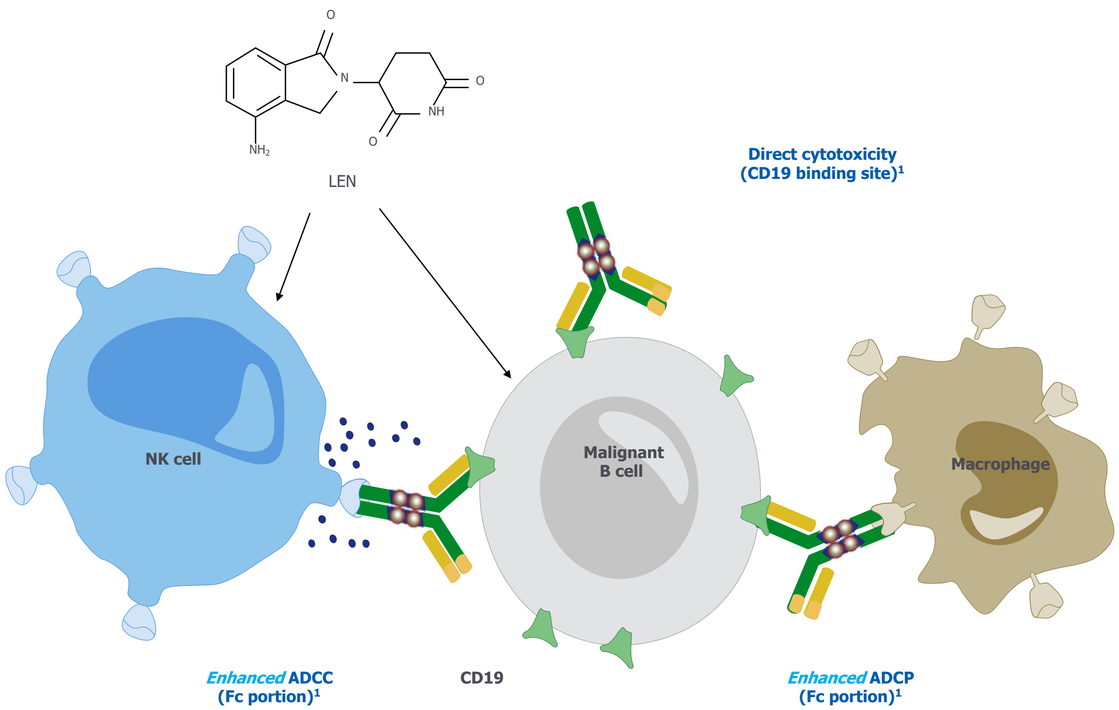
HR 0.349 $P < 0.0001$



Liso-cel received FDA approval as II line for patients with LGBL R/R within 12 months from frontline therapy or R/R transplant ineligible patients

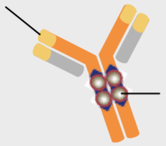
Kamdar M et al. The Lancet 2022

Tafasitamab and Lenalidomide



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

Affinity-matured
CD19 binding site



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

LEN[4,5]

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

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis

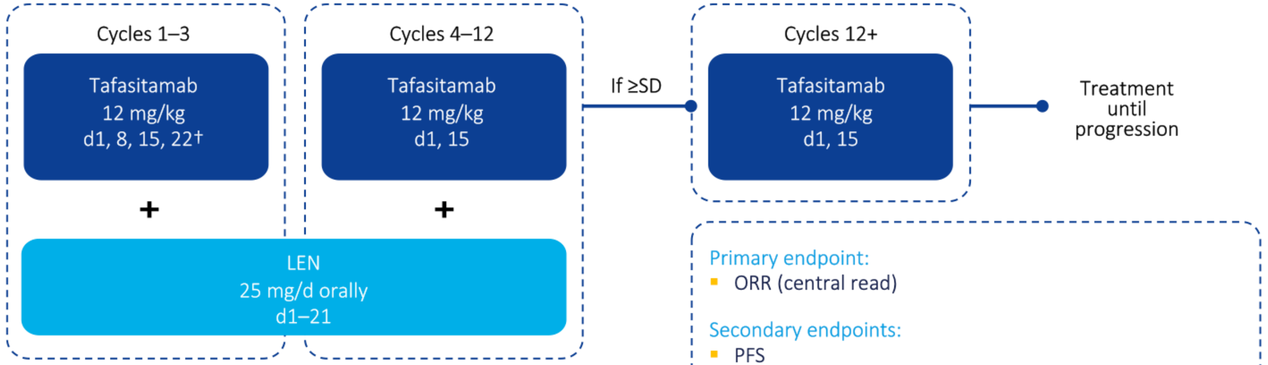
Horton HM, et al. Cancer Res. 2008; Woyach JA, et al. Blood. 2014; Jurczak W, et al. Ann Oncol. 2018; Czuczman MS, et al. Clin Cancer Res. 2017

Tafasitamab and Lenalidomide

L-MIND trial: Phase 2 single-arm, open-label, multicentre study

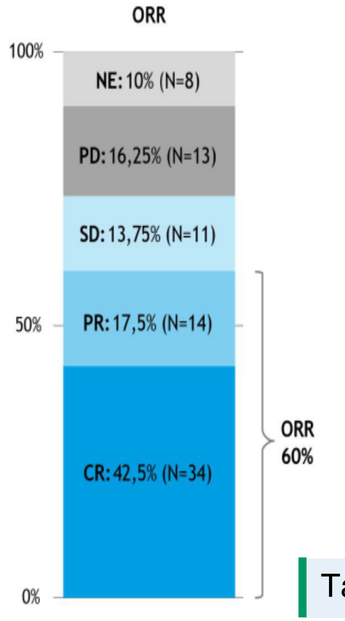
- R/R DLBCL
- Not eligible for HDCT plus ASCT
- 1–3 prior regimens
- Primary refractory patients were not eligible*
- ECOG PS 0–2

N=81



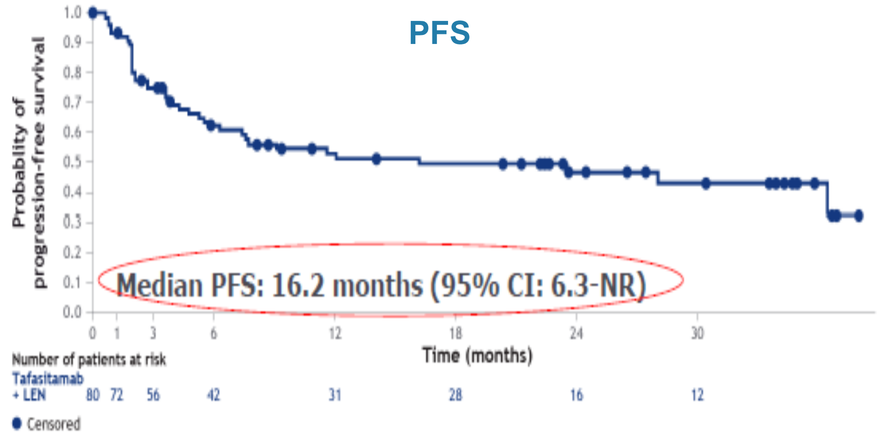
Primary endpoint:
- ORR (central read)

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

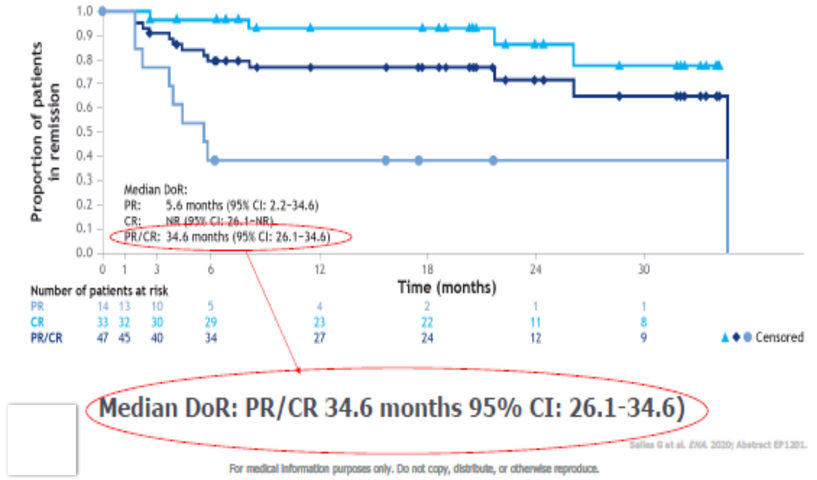


- ORR 60.0% (95% CI 48.4% - 70.8%)
- CR-rate 42.5%
  - 82% of CRs PET-confirmed
  - 18% of CRs based on CT only

PFS



DOR



Tafa-len received regulatory approvals for transplant ineligible R/R DLBCL

Salles G, et al. Lancet Oncol. 2020

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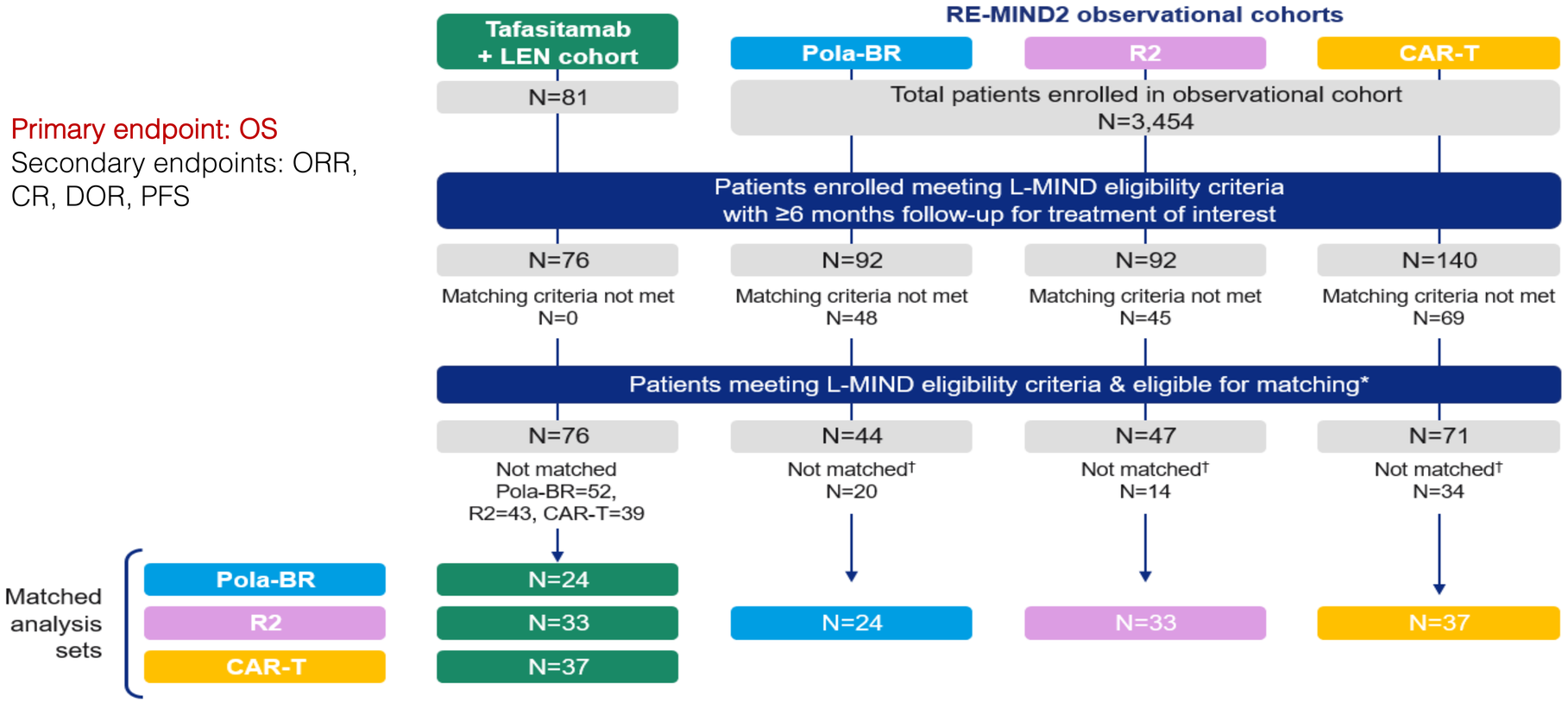
Tafasitamab and Lenalidomide

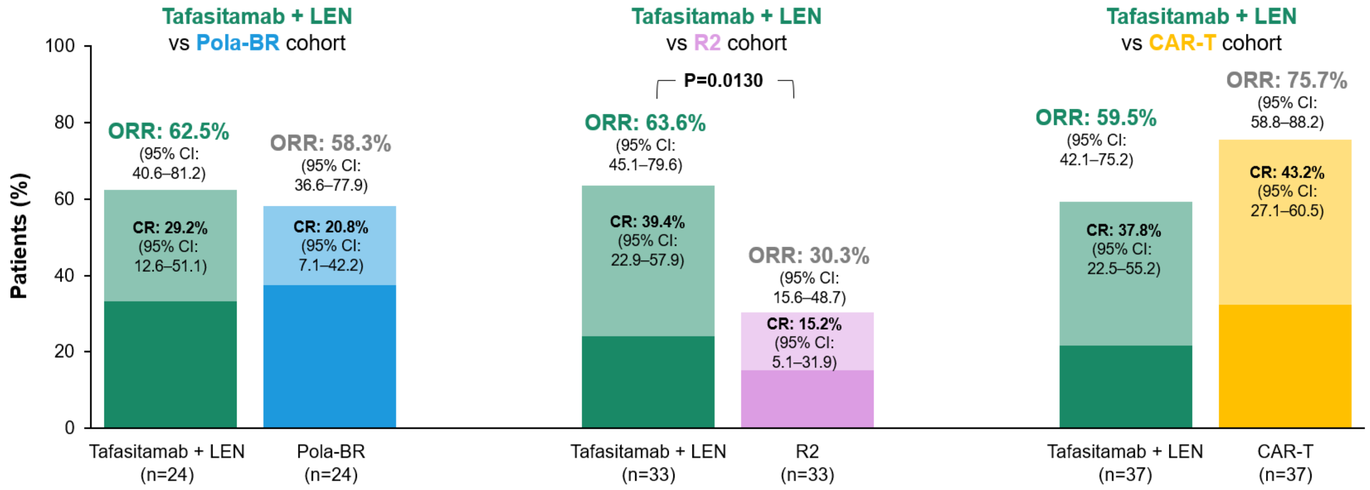
RE-MIND2 trial: Tafasitamab plus Lena versus Pola-BR, R2, and CAR-T
Observational, Retrospective Matched Cohort Study in R/R-DLBCL

Primary endpoint: OS
Secondary endpoints: ORR, CR, DOR, PFS

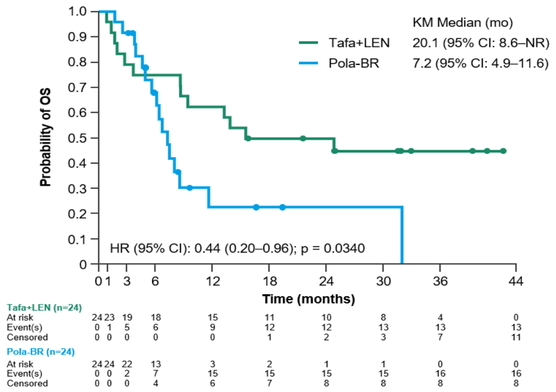


Nowakowski GS et al. Clin Cancer Res 2022.

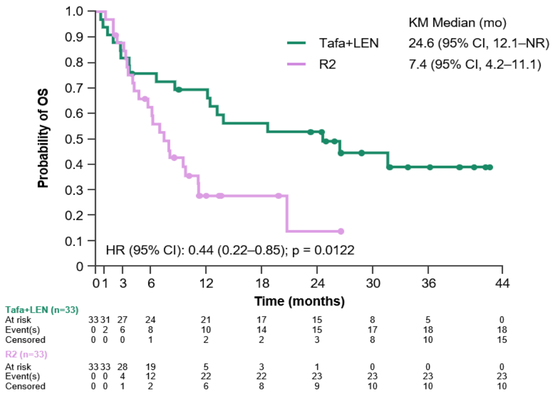
Tafasitamab and Lenalidomide



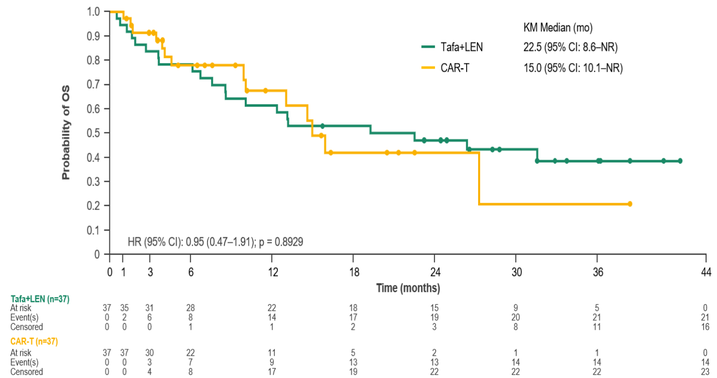
Tafa +Len vs Pola BR



Tafa +Len vs R2



Tafa +Len vs CART



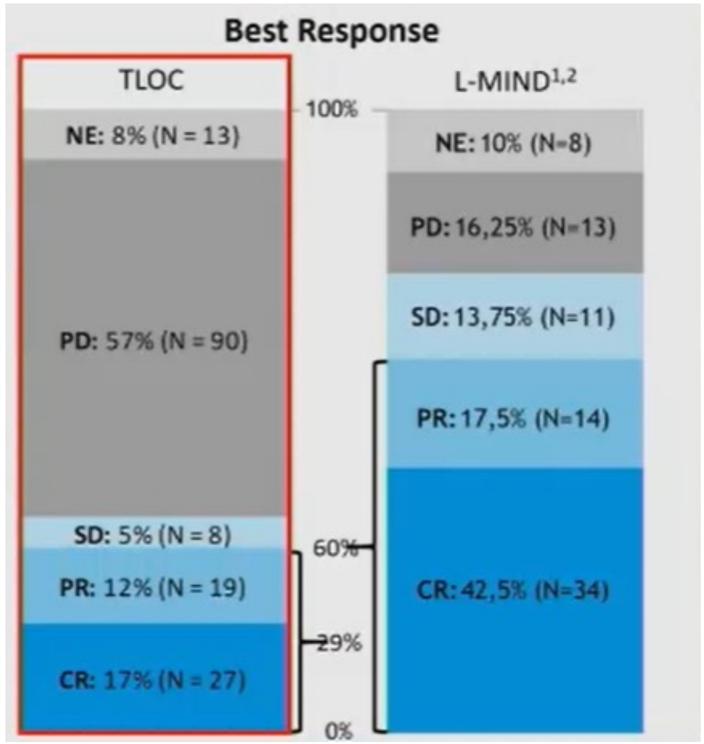
ORR: **62.5% for tafa + LEN vs 58.3% for pola-BR**, **63.6% vs 30.3% for R2**, and **59.5% vs 75.7% for CAR-T**

OS: significant benefit was associated with tafa + LEN vs pola-BR and vs R2 (HR: 0.44 in both matched comparisons)

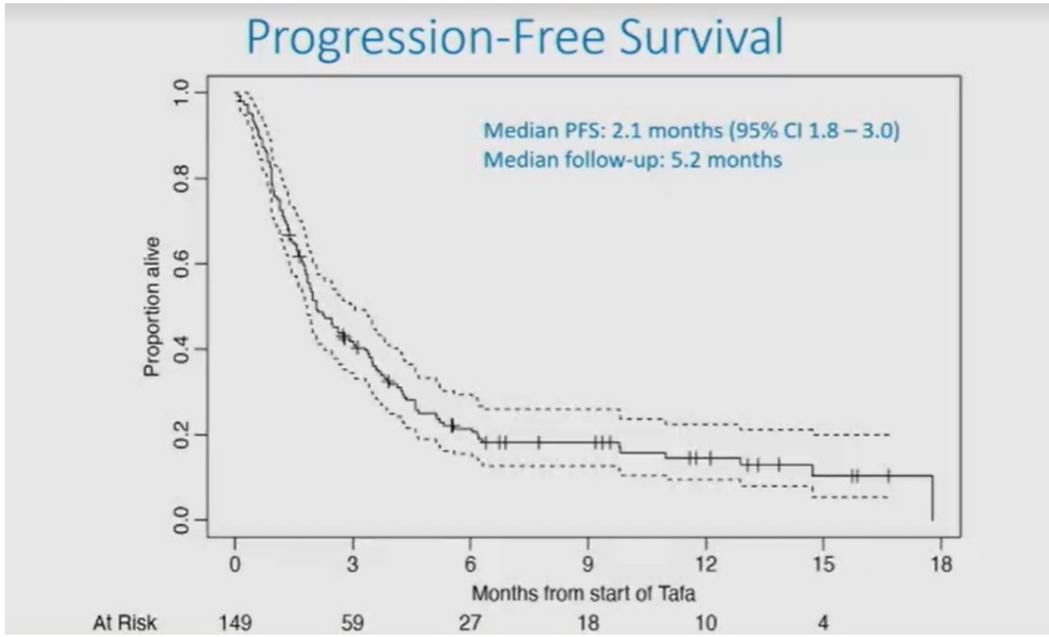
Nowakowski GS et al. Clin Cancer Res 2022.

Tafasitamab and Lenalidomide

Real-world Tafa-len treatment N = 157 (retrospective study)



- 42 patients (28%) had CAR-T before TL
- 4/19 CD19 not reported ,
- more prior lines of therapy
- more prior refractory



Worse PFS in patients with
- refractory disease,
- ≥ 3 lines of therapy,
- higher IPI

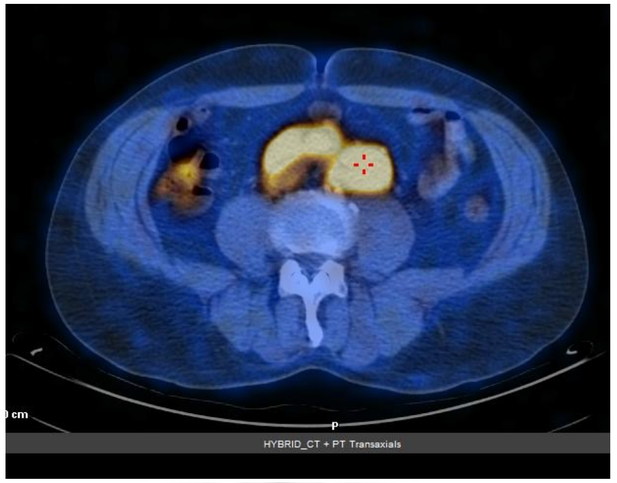
Quall D et al. Abs 323, ASH 2022.

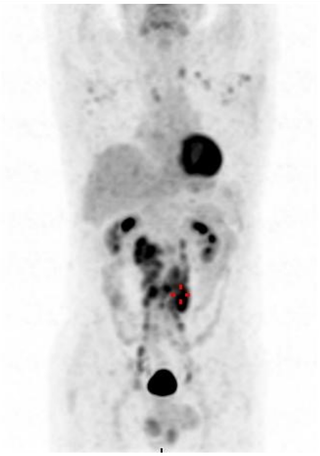
Caso Clinico 1

II linea: Tafasitamab + lenalidomide (Uso compassionevole)

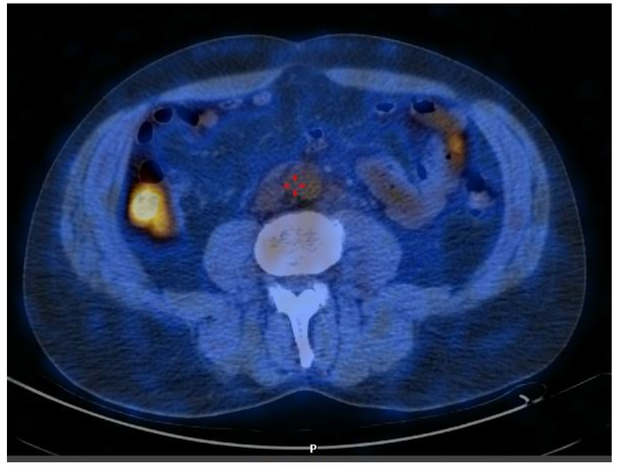
- 8/8/22 avvio di terapia (lenalidomide dose 10 mg)
- Ottobre 2022: peggioramento clearance renale (eGFR 24 ml/min) >> riduzione dose lenalidomide 5 mg
- Novembre 2022 rimborsabilità AIFA di Tafa-lena (Marco prosegue CUP per non eleggibilità sec. criteri definiti da AIFA)
- Aprile 2023: in corso 9° ciclo

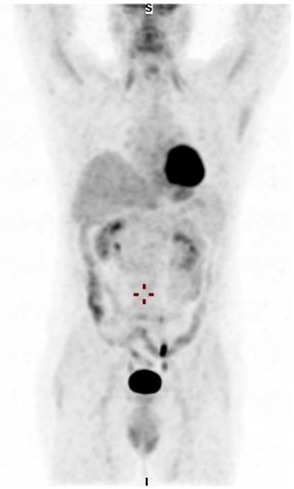
Giugno 2022
(pre-avvio Tafa-lena)





Ottobre 2022
(post 3° ciclo)





RC (DS2)

Aprile 2023

...

Caso Clinico 2

Giuliana, 57 anni

Anamnesi: safenectomia bilaterale

- A gennaio 2010 diagnosi di **linfoma DLBCL, stadio IIIA** (adenopata laterocervicale dx bulky, inguinale sx)

Febbraio – giugno 2010: 6 x R-CHOP → RC

- **Dicembre 2015 I recidiva**: plurime adenopatie sovra-sottodiaframmatiche con bulky addominale (12x20 cm), splenomegalia→ bx laparoscopica: linfoma DLBCL

febbraio-giugno 2016: 4 x R-DHAP →RC → FEAM + ASCT →Ottobre 2016 PET: RC

Gennaio 2022

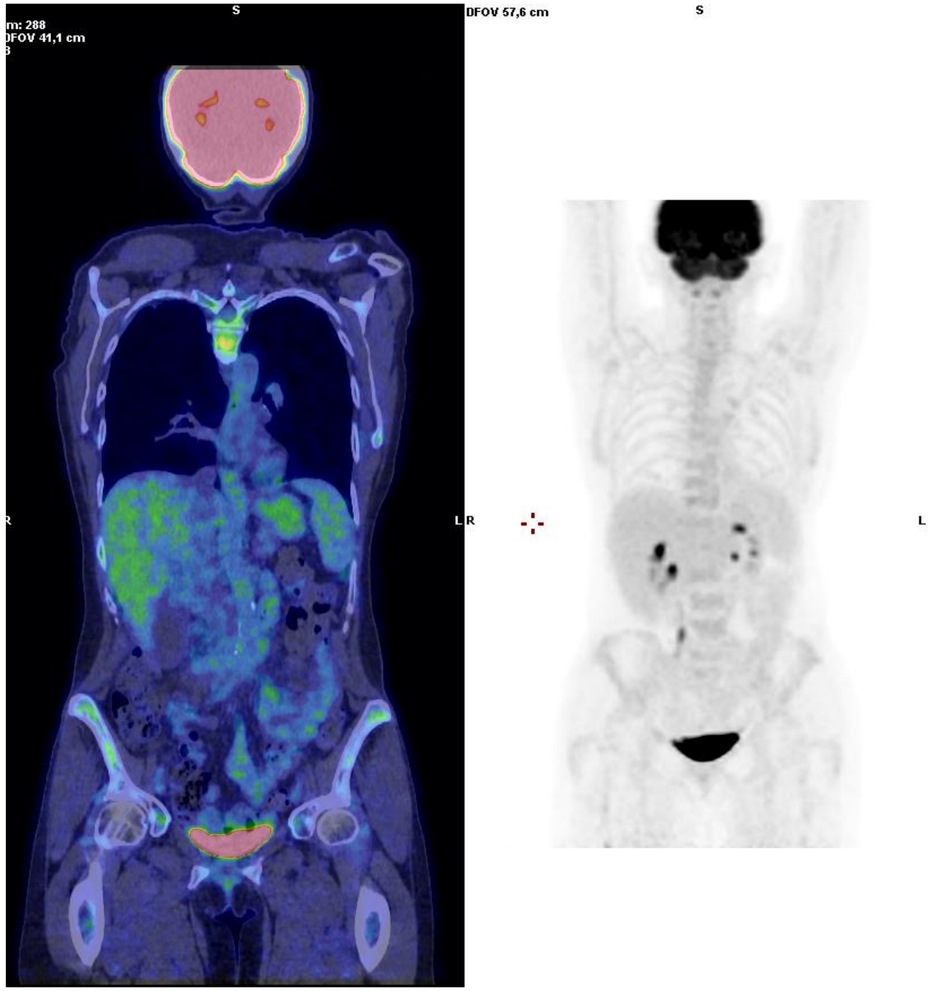
Febbricola serotina (TC max 38°C) e dolore in ipocondrio sx
- LDH 483 (ULN < 214)
- TC collo-torace-addome: **splenomegalia 17 cm, multiple adenopatie a colata** lungo piccola curvatura gastrica e tronco celiaco, in sede ilare epatica, inter-porto-cavale, interaortocavale, lomboaortica, mesenteriale, ilico bilaterale (max 4.8 x 2.7 cm)
- PET: captazione nelle sedi adenopatiche, milza, **plurime scheletriche** (rachide in toto, basicranio, bacino) (SUVmax 25)
- biopsia linfonodo laterocervicale sx: linfoma DLBCL CD20+ CD10- BCL6+ MUM1+ ki67 60%

III linea di terapia: CART

- 3/3/22 linfocitoaferesi
- 4/3/22 GDP (bridge)
-12/4/22 infusione CART (tisa-cel)

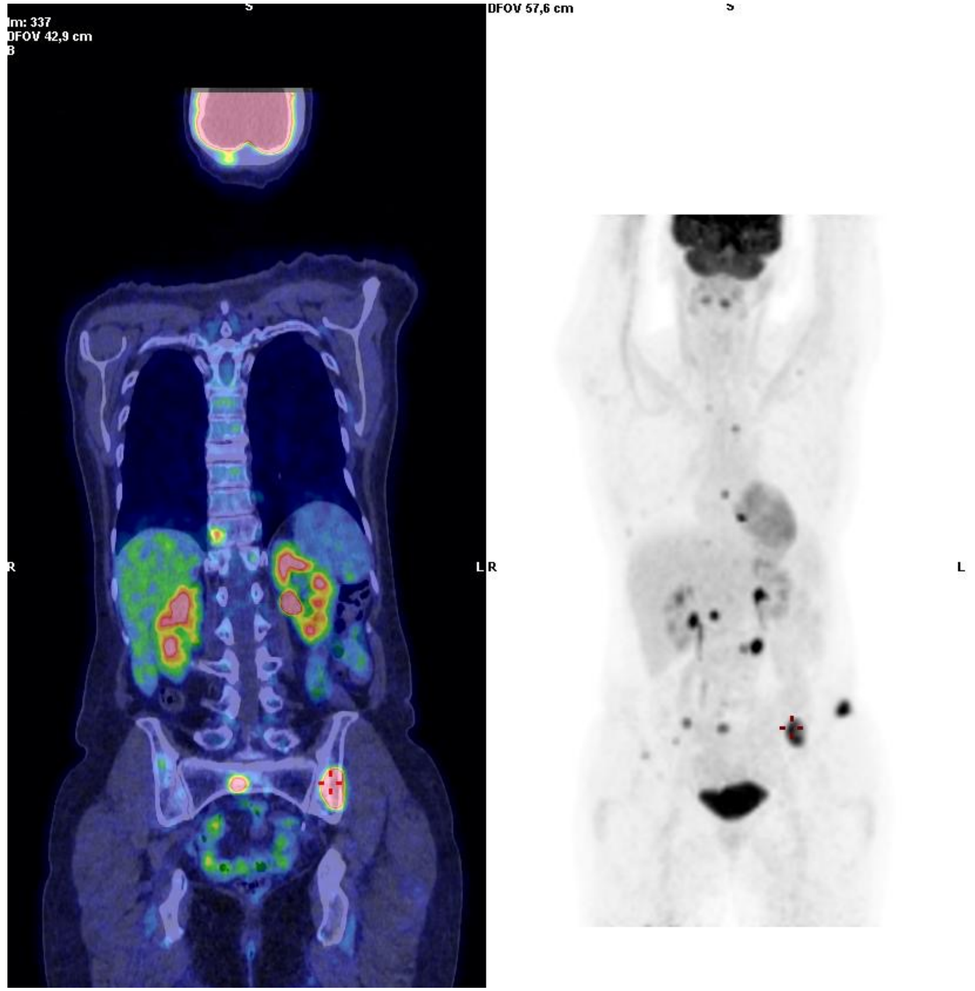
CRS G1, ICANS 0 (tocilizumab 1 dose x febbre persistente)

Maggio 2022 (+ 30 giorni)



RC (DS 3)

Luglio 2022 (+ 90 giorni)



Relapse (DS 5)

DOMANDA n 2

Pz di 57 aa affetta da DLBCL in recidiva dopo 3 linee di terapia: RCHOP, RDHAP+ASCT, CAR-T (recidiva a 3 mesi dall'infusione). Quale terapia adottare?

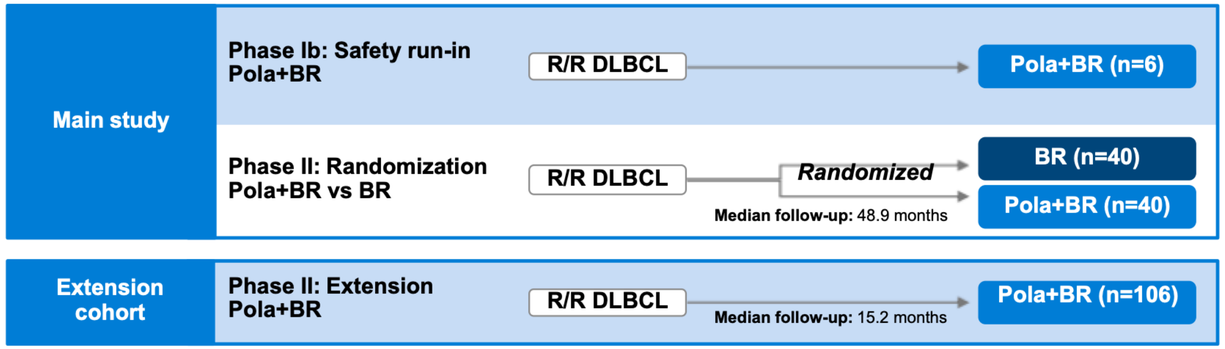
a. Glofitamab (CUP)

b. Tafasitamab-Lenalidomide

c. Pola-BR

d. R-GEMOx

Polatuzumab Vedotin + Bendamustine and Rituximab

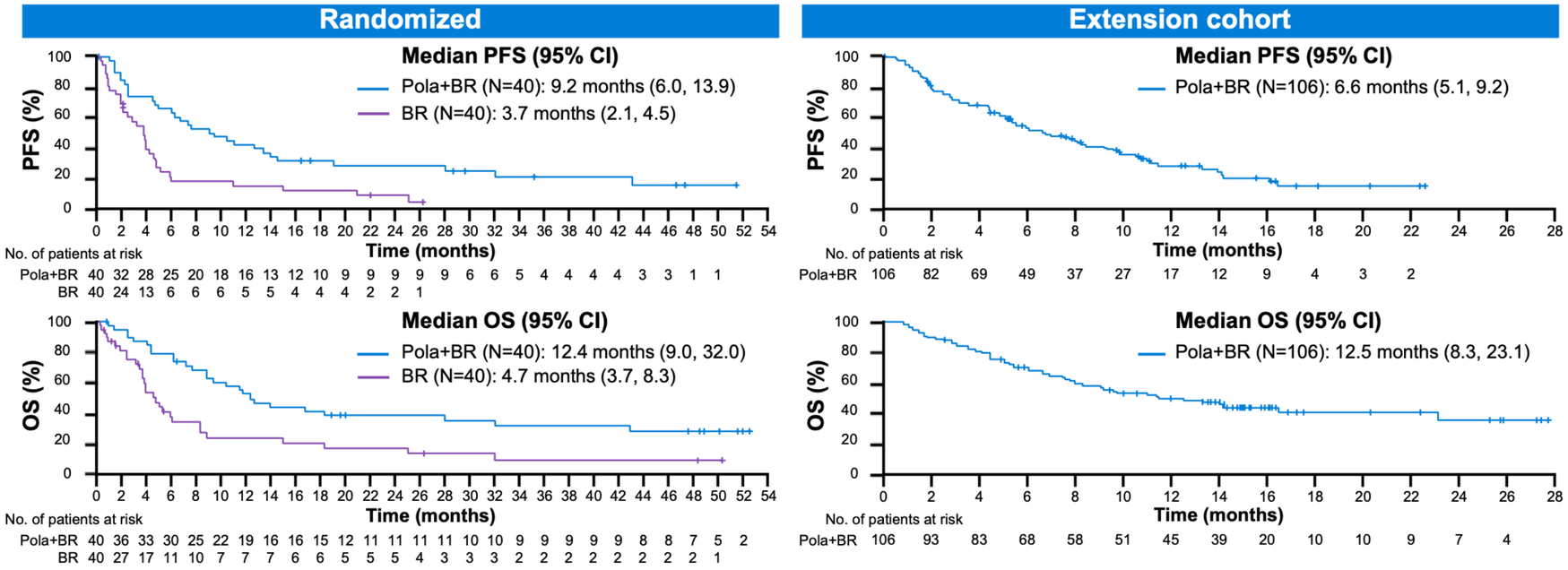


Key eligibility criteria

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

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

POLA-BR: ORR 45%; CR 40%



Based on the randomized comparison, Pola+BR received regulatory approvals for transplant-ineligible patients with R/R DLBCL

Sehn LH et al ASH 2020

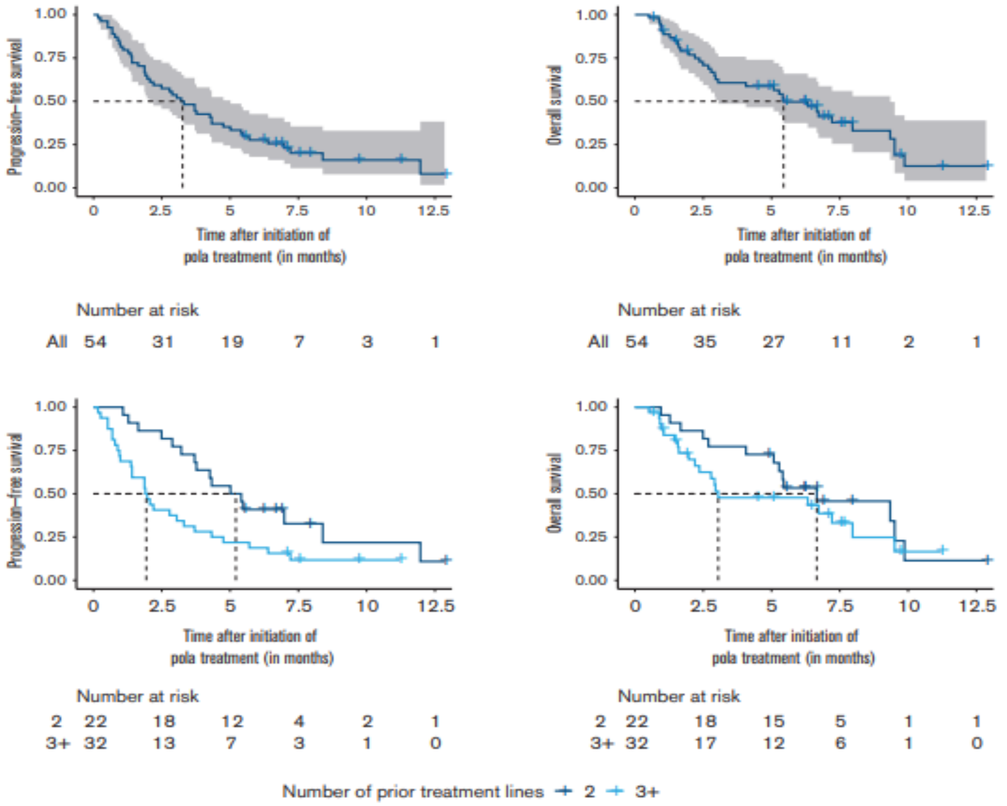
Polatuzumab Vedotin + Bendamustine and Rituximab

Real World Experience

Germany

Characteristic	Salvage cohort (n = 54)	Bridging cohort (n = 51)
Pola treatment		
Chemotherapy backbone		
pola-BR	32 (59.3%)	27 (52.9%)
pola-B	1 (1.85%)	1 (1.96%)
pola-R-CHP	0	1 (1.96%)
pola-R-gemcitabine	1 (1.85%)	0
No chemotherapy backbone		
pola-R	20 (37.0%)	19 (37.3%)
pola-monotherapy	0	3 (5.9%)
Median number of pola cycles (range)	4 (1-9)	2 (1-6)

- 105 pts with r/r DLBCL, age 22-87
- Most refractory to last treatment , 12 failed CART
- Pola containing regimen (mainly PolaBR)
- Median previous line: 3
- 54 salvage: ORR 48%
- 51 bridge to CART or to alloSCT



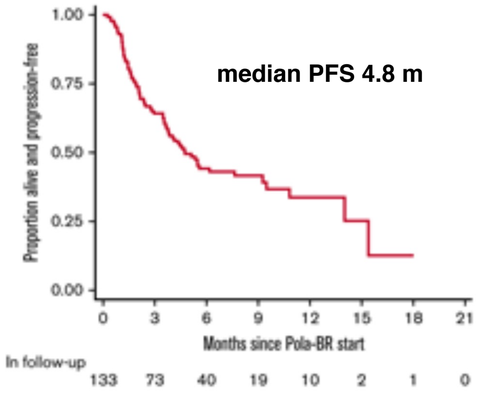
Adverse independent prognostic factors:
> 3 previous treatment lines; refractoriness to last treatment
7/12 pts failing CART responded to pola

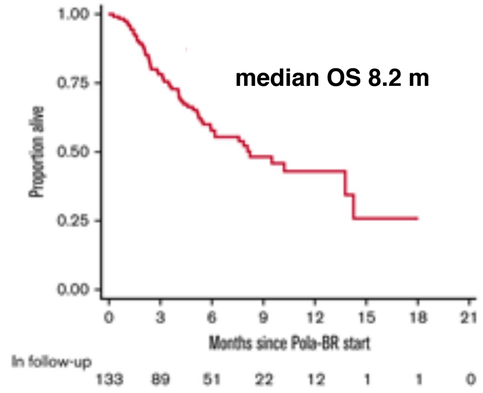
Liebers N et al. Blood Adv 2021

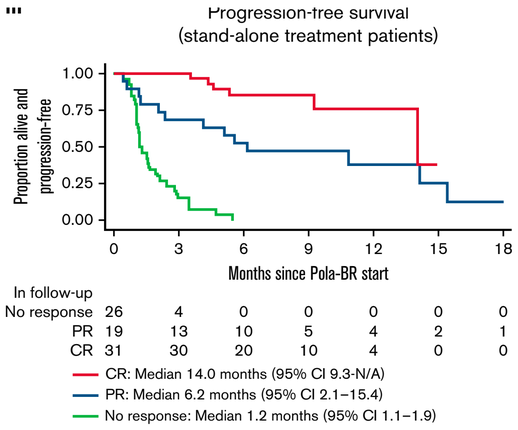
Polatuzumab Vedotin + Bendamustine and Rituximab

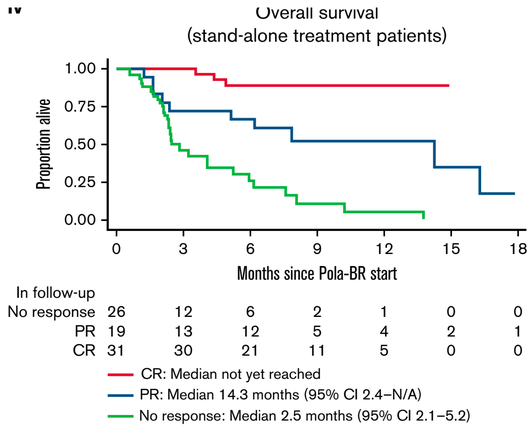
Real World Experience

UK









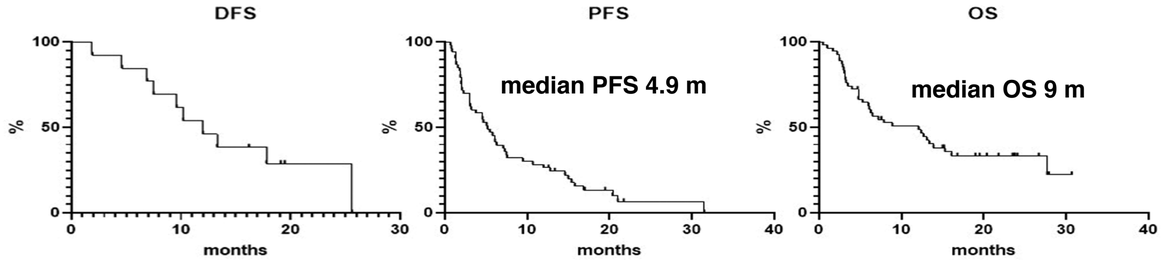
Stand alone cohort (n 78)
6/78 prior CART
0/78 prior ASCT

31/78 CR (39.7%):
- median PFS 14 mo
- median OS NR

Italy

Response Rates and Comparison Between the 2 Treatment Groups

	Total (n = 55)	PolaBR (n = 36)	PolaR (n = 19)	*P*
ORR, %	32.7	30.6	36.9	ns
CR, n (%)	10 (18.2)	7 (19.4)	3 (15.8)	
PR, n	8	4	4	
Best response rate, %	49.1	47.2	52.6	ns
CR, n (%)	15 (27.3)	10 (27.8)	5 (26.3)	
PR, n	12	7	5	



Adverse Events Occurrence in Study Population and Comparison Between the 2 Treatment Groups

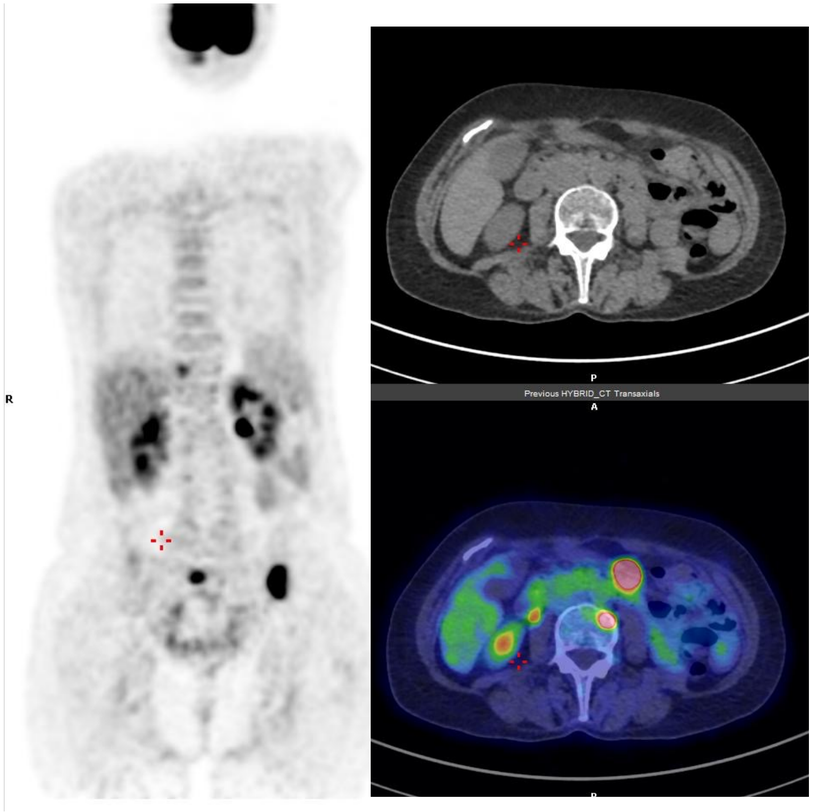
Number of Episodes	All	PolaBR (n = 36)	PolaR (n = 19)	*P*[a]
Any grade	66	38	27	ns
≥3	22	18	4	0.034
Serious adverse events	5	3	2	Ns

Northend M et al. Blood Adv 2022; Argnani L et al. Hemasphere 2022

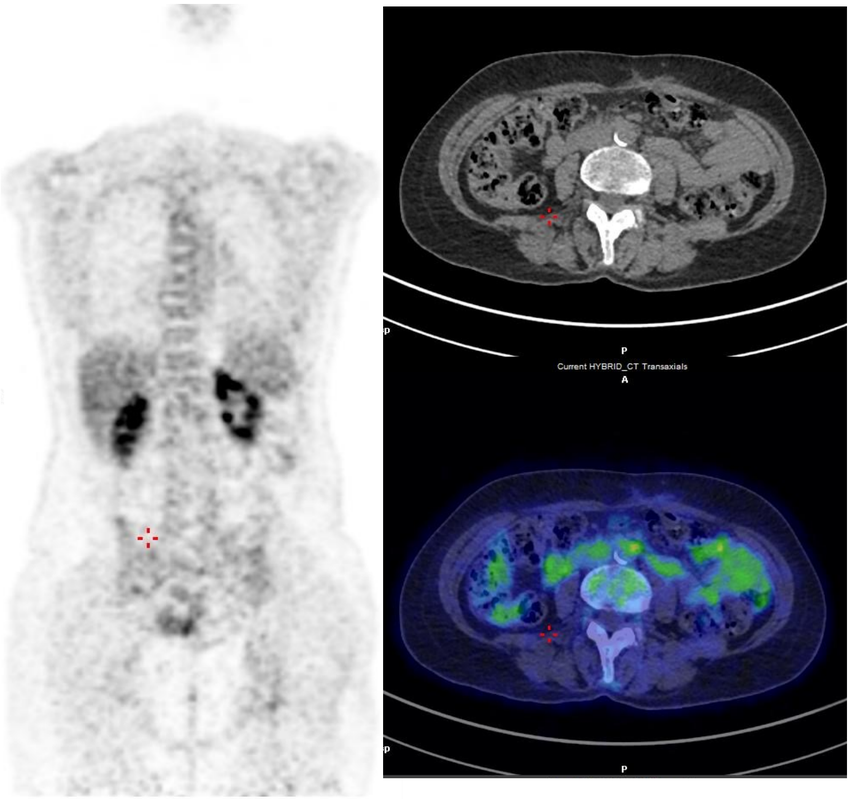
Caso Clinico 2

IV linea di terapia: Pola BR (6 cicli dal 22/7-28/12/22)

Luglio 2022

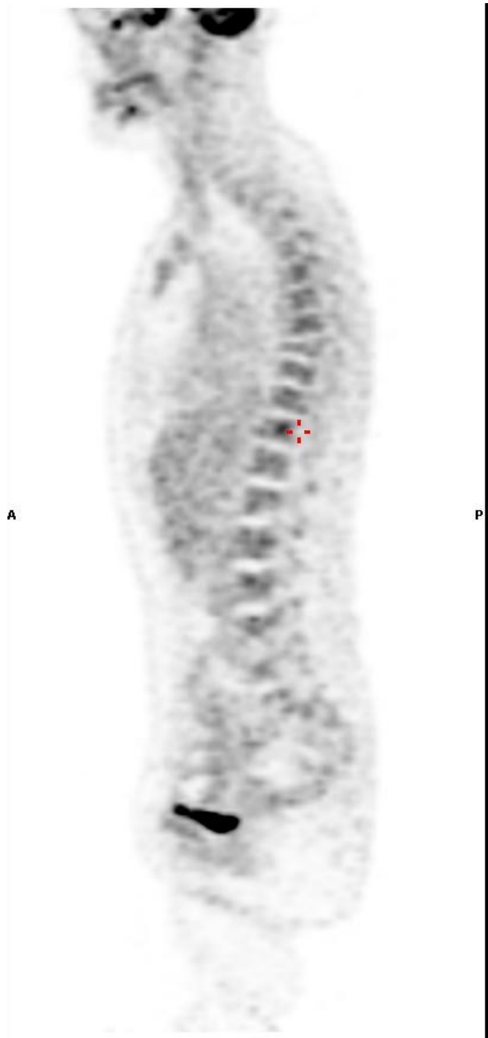


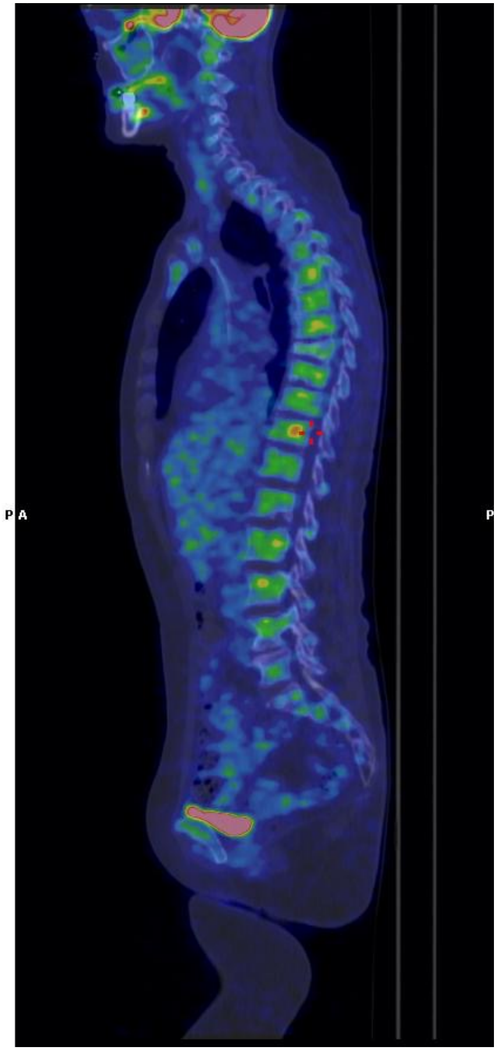
Ottobre 2022 (post 4° ciclo)

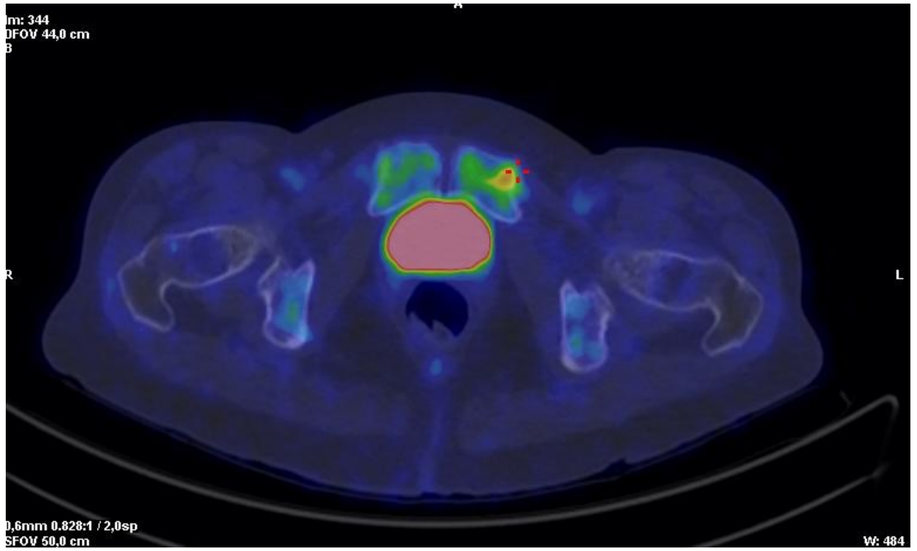


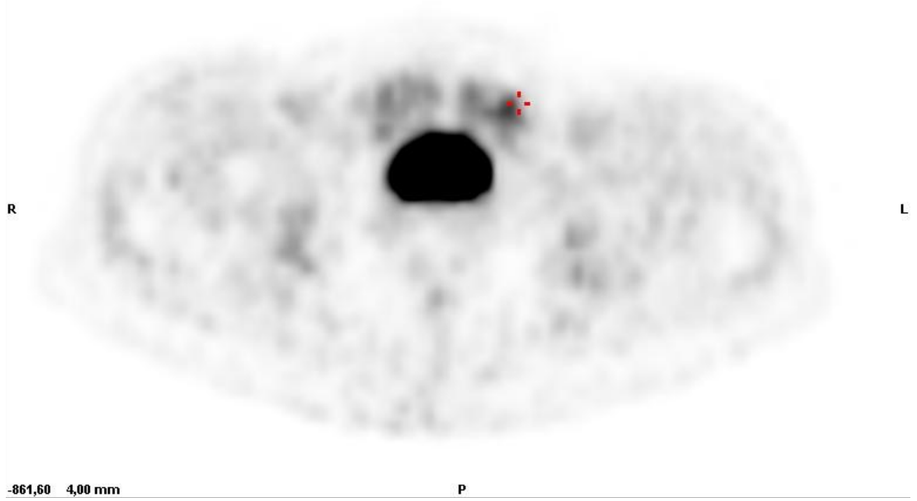
RC (DS 3)

Febbraio 2023









DOMANDA n 3

Paziente di 57 aa affetta da DLBCL in progressione dopo 4 linee di terapia: RCHOP, RDHAP+ASCT, CART, pola-BR. Quale terapia adottare?

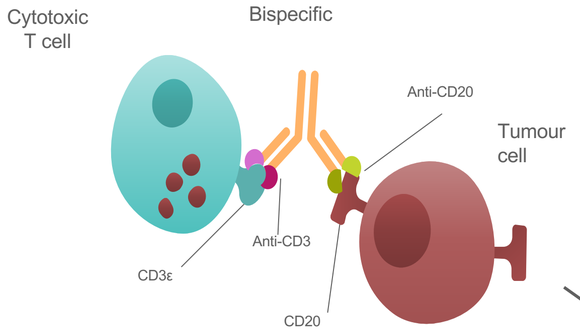
a. Pembrolizumab

b. R-GEMOx

c. Glofitamab (uso CUP)

d. Tafasitamab-Lenalidomide

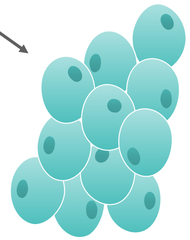
CD3xCD20 Bispecific Antibodies



Anti-CD20/CD3 bispecifics redirect endogenous non-specific T cells to engage and eliminate malignant B cells in NHL[1–3]

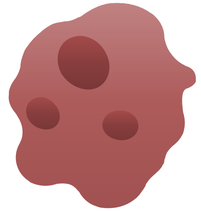
1. Local secretion of chemokines leading to the recruitment of T cells from the periphery

2. T cells undergo proliferation and expansion at the tumour site



3. T-cell activation occurs via downstream signalling events leading to the secretion of cytotoxic granules

5. Apoptosis

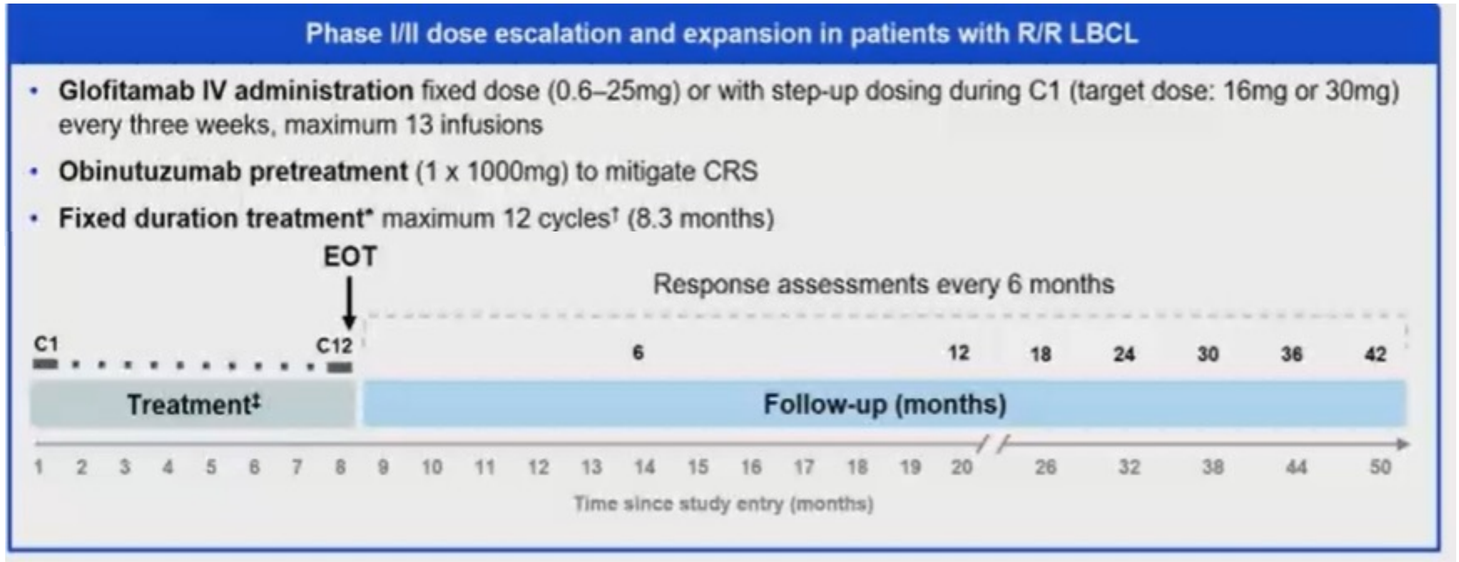


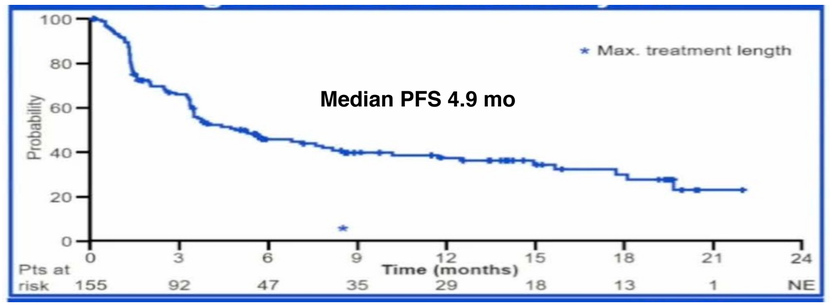
4. Potent lysis of tumour cells

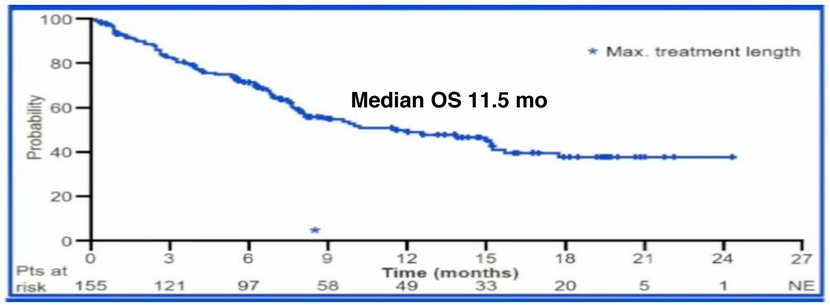
6. T cell–mediated tumour killing

Glofitamab

CD3xCD20 bispecific-monoclonal antibody with 2:1 format for increased potency



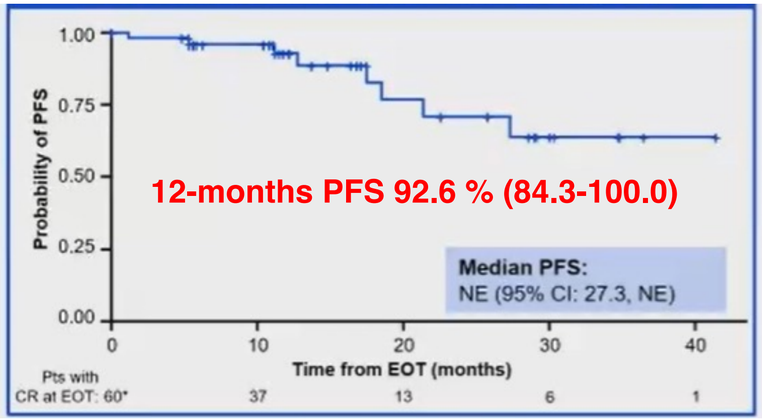




Phase 2, single arm

- n 155 R/R DLBCL (HGBL, DLBCL, TFL, PMBCL)
- 59.7% ≥ 3 prior lines
- 33.1% prior CAR-T
- ORR 51.6% (CR 39.4%)

PFS with landmark at EOT (N=61)



*Criteri d'inclusione CUP:
- numero di terapie precedenti: ≥3;
- non eleggibilità a SCT o CAR-T;
- esauriti i regimi platinum-based e bendamustine-based (con o senza polatuzumab)

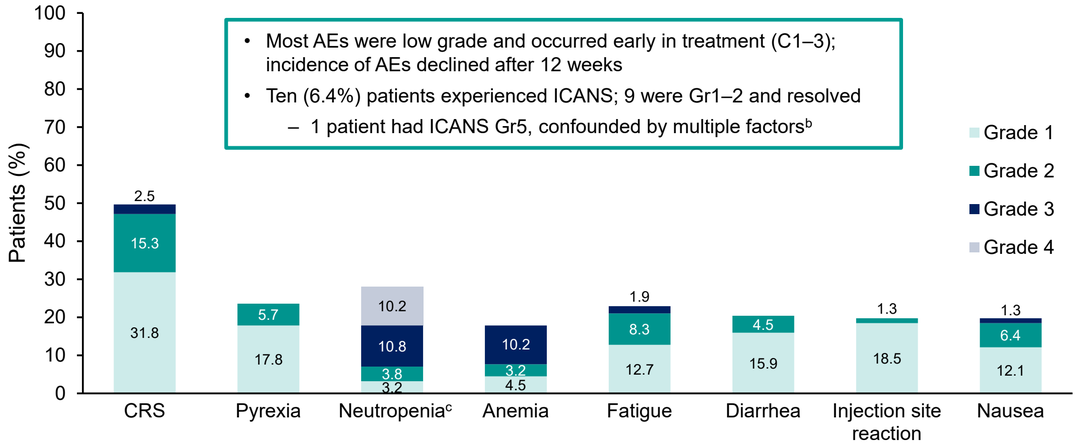
Dickinson M, et al. ASCO 2022; Hutchings et al. ASH 2022.

Epcoritamab

Subcutanoues Epcoritamab in R/R DLBCL: a phase 2 study in 157 patients

Adverse Events Were Primarily Low Grade

Treatment-Emergent Adverse Events[a] (≥15%) by Grade



[a]COVID incidence 4.5%. [b]Patient experienced ICANS after intermediate dose with multiple confounders, including extensive opioid use for Gr3 pancreatitis, hyperammonemia, multifocal cerebral infarcts in setting of possible microangiopathy, and tocilizumab administration. [c]Combined term includes neutropenia and decreased neutrophil count.

7

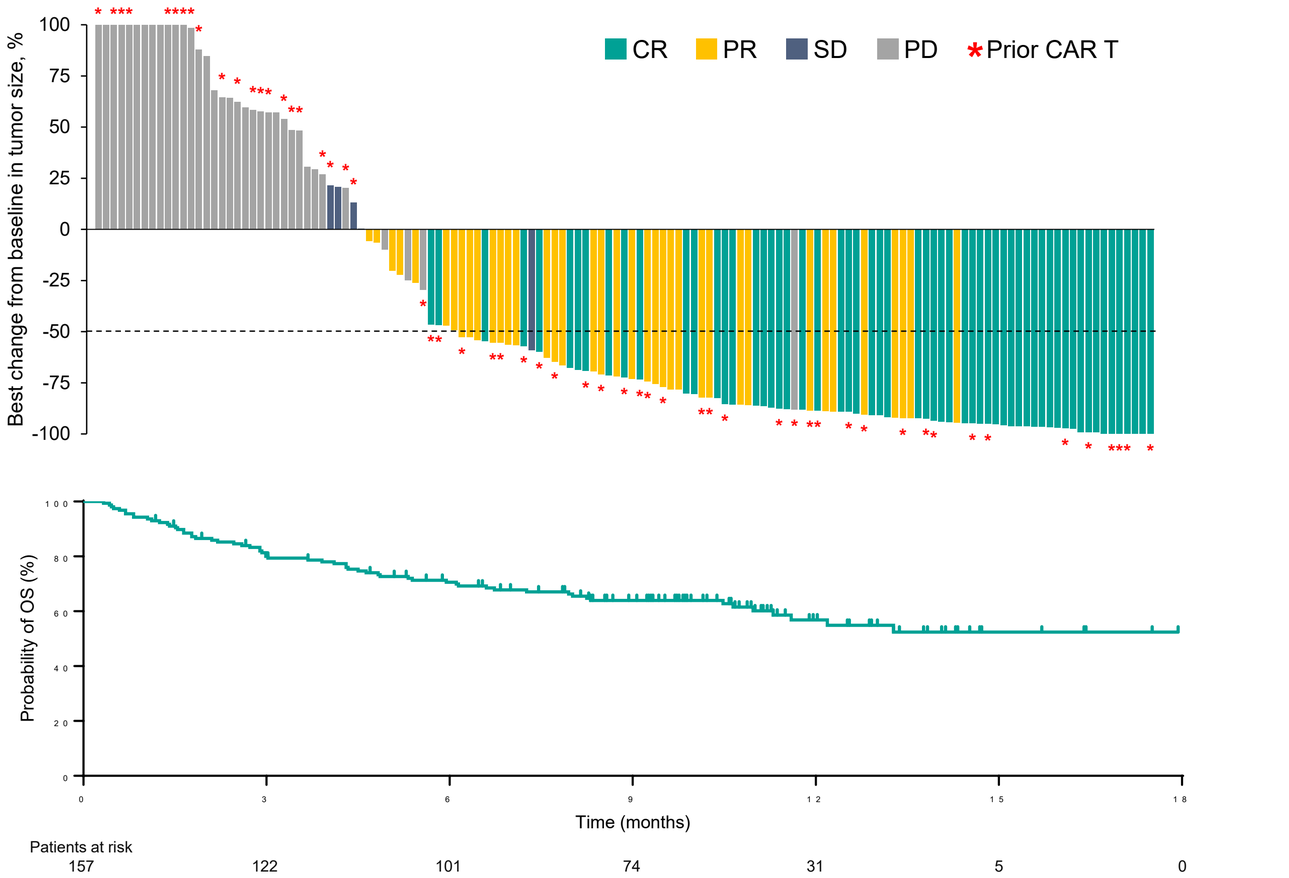
Response rate:

ORR 63%, CR 39%, prior CART 34%

Overall Survival:

Median not reached, 6 mo 71%, 12 mo 57%

Median duration of response 12 months

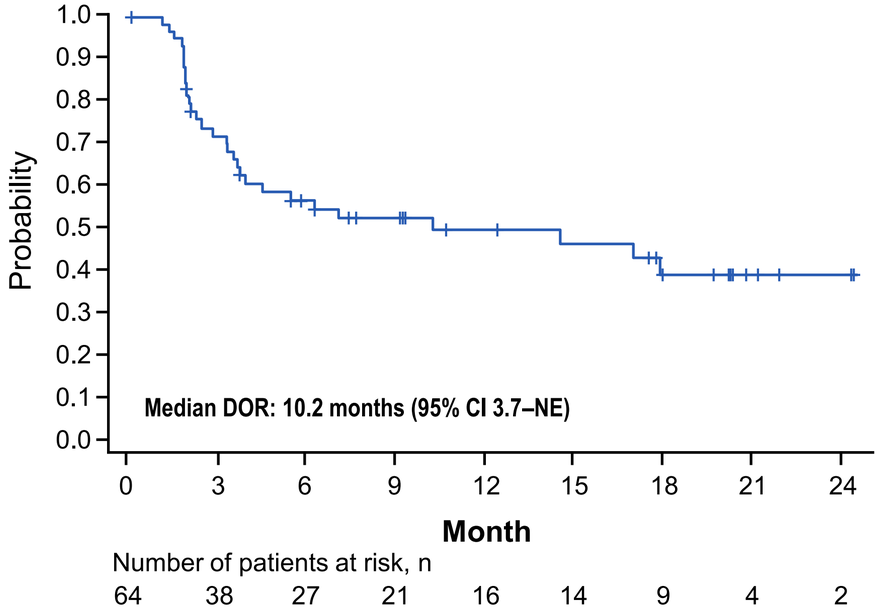


.Thieblemont C et al EHA 2022

Odronextamab

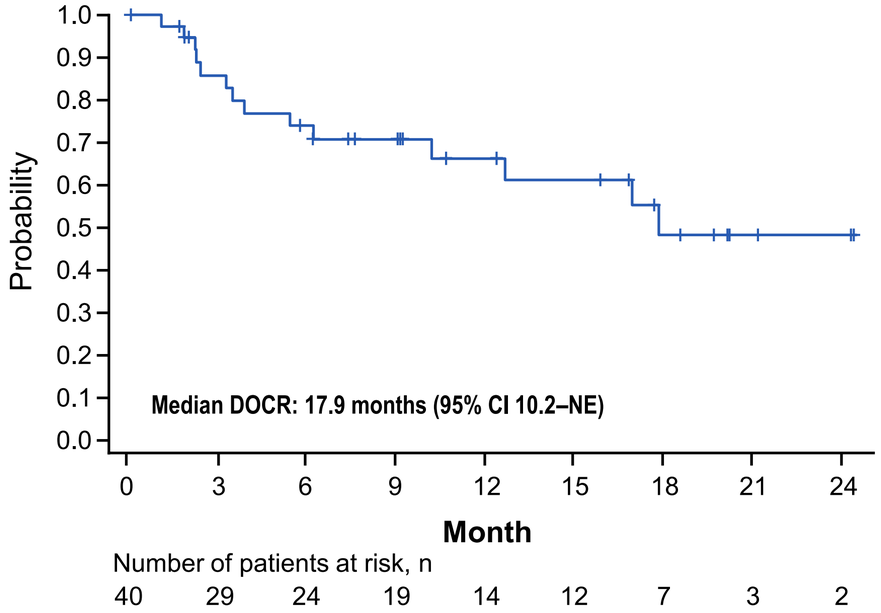
Odronextamab in patients with R/R Diffuse Large B-Cell Lymphoma (N= 140)

Duration of response – Independent central review



- 12-month DOR: 49.4% (95% CI: 35.0–62.2)
- 18-month DOR: 38.9% (95% CI: 23.9–53.6)

Duration of complete response – Independent central review



- 12-month DOCR: 66.4% (95% CI: 47.1–80.1)
- 18-month DOCR: 48.3% (95% CI: 26.1–67.4)

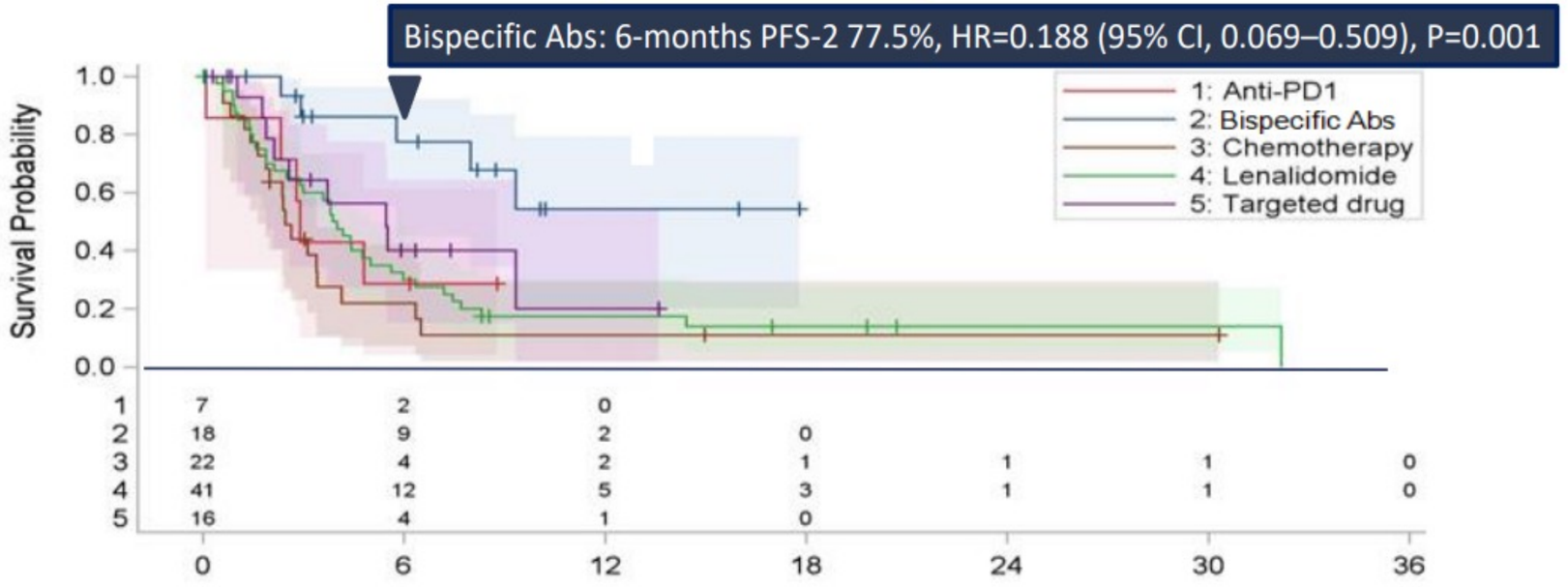
Data cut-off date: Sep 15, 2022.
CI, confidence interval; DOCR, duration of complete response; DOR, duration of response; NE, not evaluable.

Kim WS et al. ASH 2022.

Late Failure of Aggressive B-cell Lymphoma following CAR T-cell therapy: a Lysa study from the Descar-t registry

DESCAR-T

Late Failure set (≥M3)
145 pts (33.6%)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Anti-PD1	7	71.4 % (5)	28.6 % (2)	2.9 (0.1 ; NA)
Bispecific Abs	18	27.8 % (5)	72.2 % (13)	Not reached (5.8 ; NA)
Chemotherapy	22	81.8 % (18)	18.2 % (4)	2.5 (1.6 ; 3.4)
Lenalidomide	41	85.4 % (35)	14.6 % (6)	3.9 (2.5 ; 5)
Targeted drug *	16	56.3 % (9)	43.8 % (7)	5.5 (1.9 ; NA)

DESCAR-T - Titre - Confidentiel, ne pas diffuser

Erbella F et al. ASH 2022

Caso Clinico 2

V linea di terapia: Glofitamab (CUP)

29/3/23 C1D1 Obinutuzumab
5/4/23 C1D8 Glofitamab (2.5 mg)
12/4/23 C1D15 Glofitamab (10 mg)

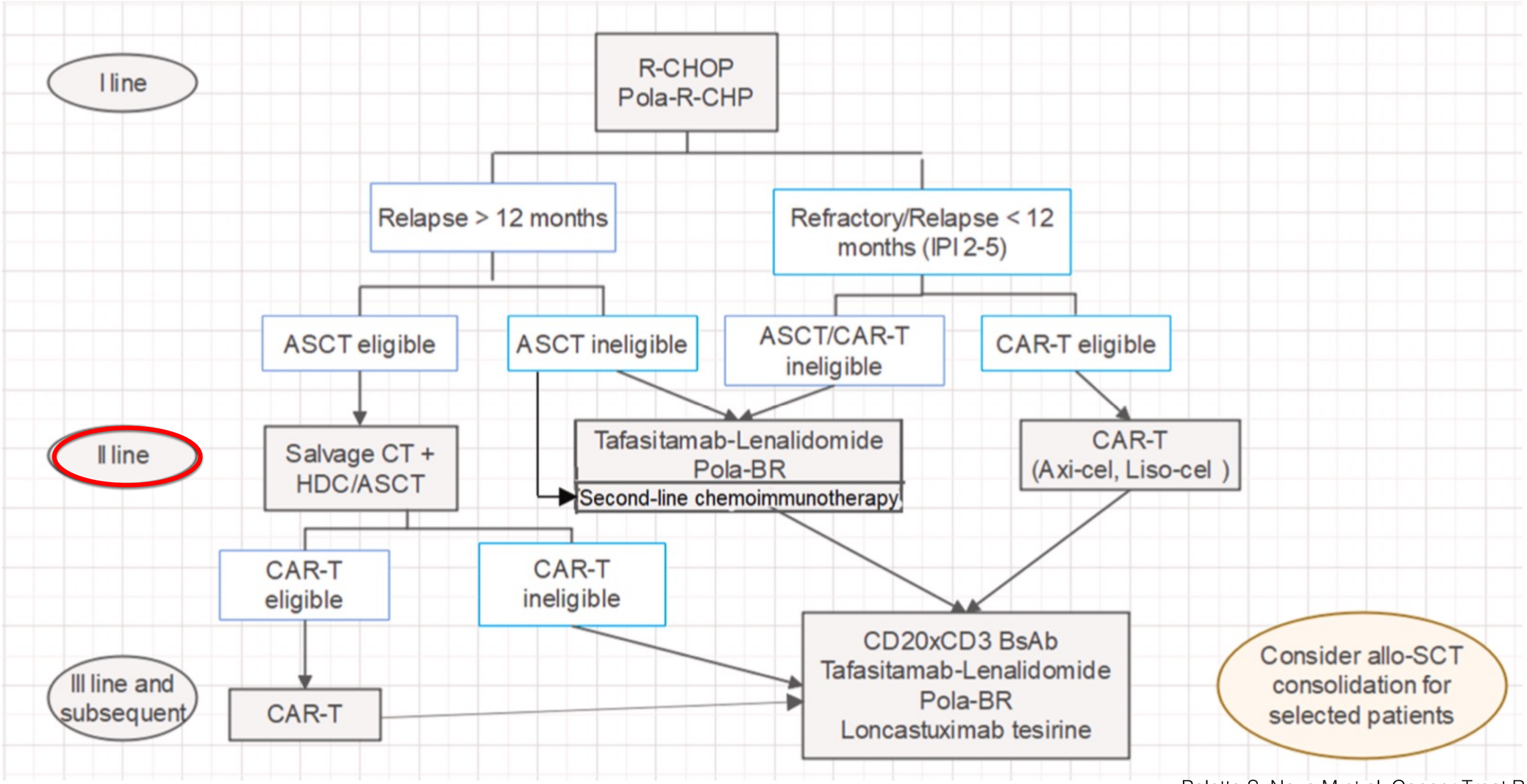
No CRS, No ICANS

Tipizzazione HLA famigliari: 2 fratelli HLA identici…

Conclusioni

- Il panorama delle opzioni terapeutiche per R/R DLBCL è stato fortemente implementato negli ultimi 2-3 anni.
- La scelta della II linea di trattamento dev'essere ponderata a seconda del timing di recidiva (refrattarietà/recidiva precoce vs recidiva tardiva) e caratteristiche del paziente.
- In II linea l'opzione terapeutica di prima scelta in caso di recidiva < 12 mesi sarà presto rappresentata da CART mentre in caso di recidiva > 12 mesi il trapianto autologo rimane lo SOC.
- La scelta terapeutica per pazienti non candidabili a CAR-T e trapianto oggi può variare tra Pola-BR, Tafa-Lena e chemioterapia a seconda delle caratteristiche del paziente, della malattia e tempo alla recidiva.
- Gli Ab Bispecifici rappresentano un'opzione terapeutica (trials o CUP) per pazienti pluritrattati ma in futuro il loro utilizzo potrebbe essere anticipato a linee più precoci.

Treatment algorythm for DLBCL in 2023



Poletto S, Novo M et al. Cancer Treat Rev 2022

Grazie per l'attenzione !

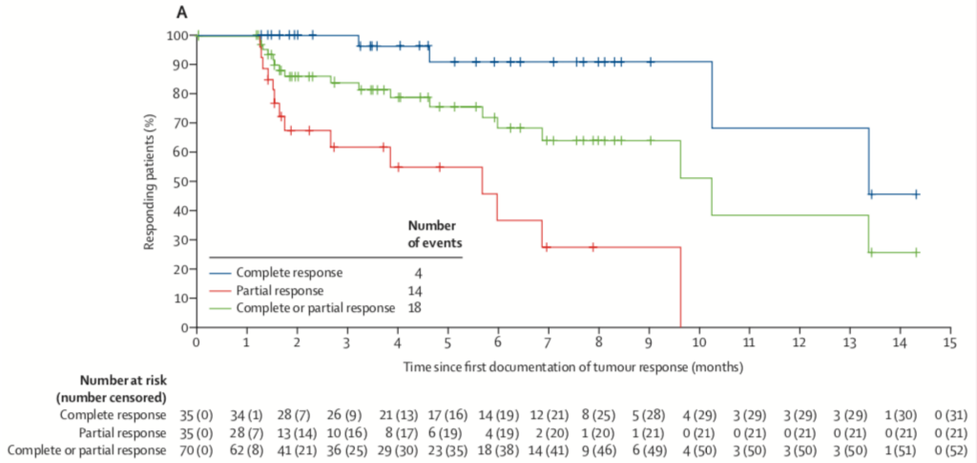
Loncastuximab for R/R DLBCL

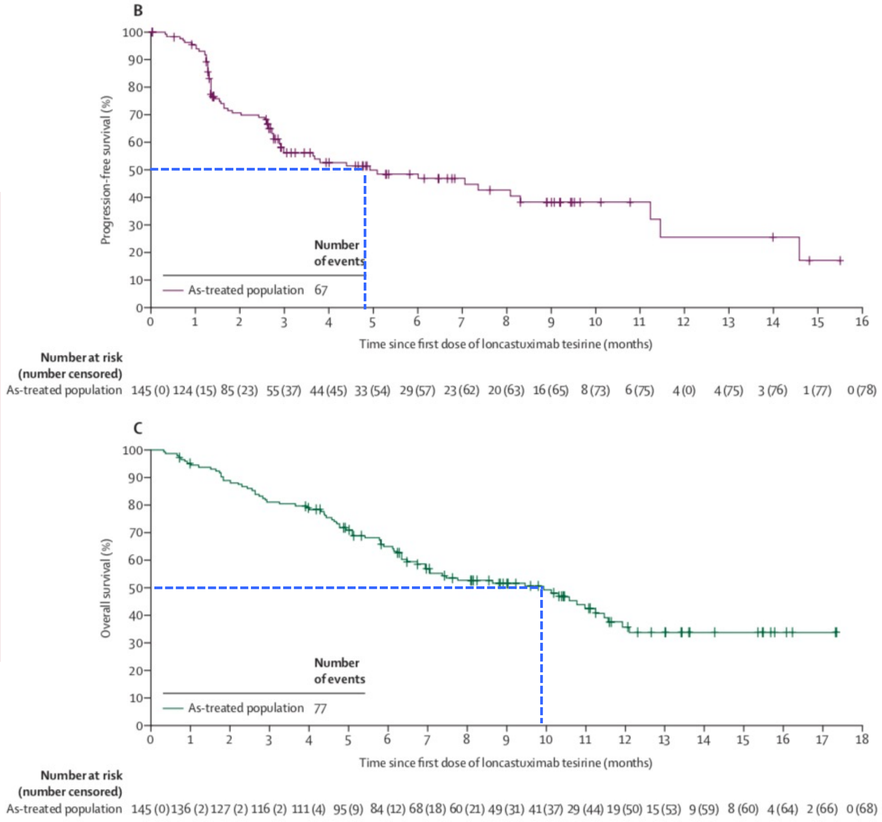
LOTIS-2 Trial: phase 2, single arm

N = 145 DLBCL,R/R ≥ 2 prior lines

n prior lines median 3 (2-4)

ORR 48.3% (CR 24.1%)





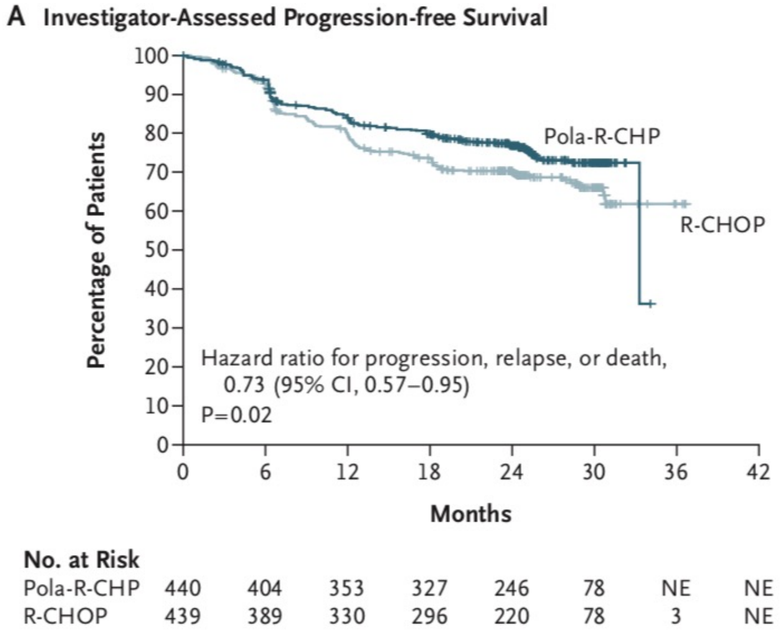
Pola-R-CHOP

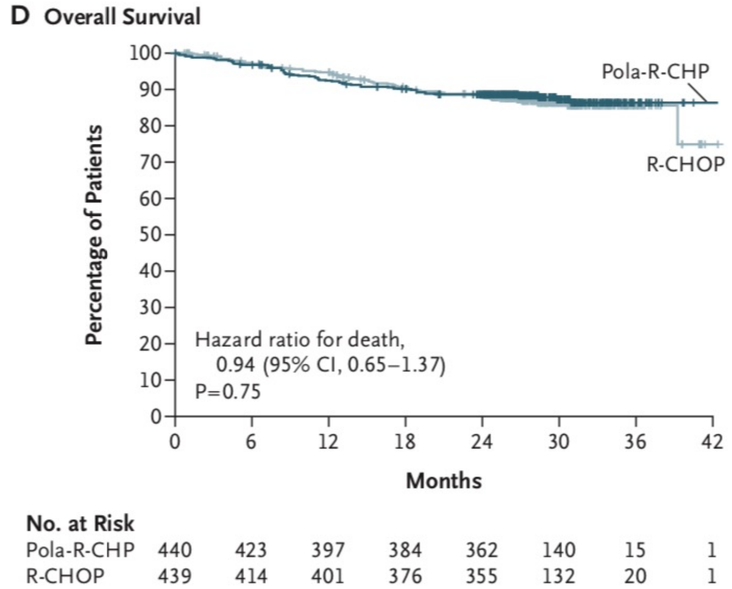
POLARIX trial: phase 3, randomized, double blind

Pola-R-CHP (n 440) vs R-CHOP (n 439)

Age 18-80 y

IPI 2-5





2-yers PFS **76.7%** [95% CI, 72.7 to 80.8] vs. **70.2%** [95% CI, 65.8 to 74.6]

No benefit:
- Age < 60y
- IPI low risk
- GCB profile