Linfoma de Células Grandes Tercera Línea

Paolo F. Caimi

Cleveland Clinic
Taussig Cancer Institute

Disclosures

- Conflict of interest
  - Research funding: ADC Therapeutics, Genentech, Genmab, Recordati, Kite
  - Scientific Board: Abcon, BMS, Novartis, Luminary
  - Consulting and advisory board: Abbvie, Arvinas, Sobi, Genmab

- I confuse company (and people's names)
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  - Equity: Abcon

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Most important disclosure

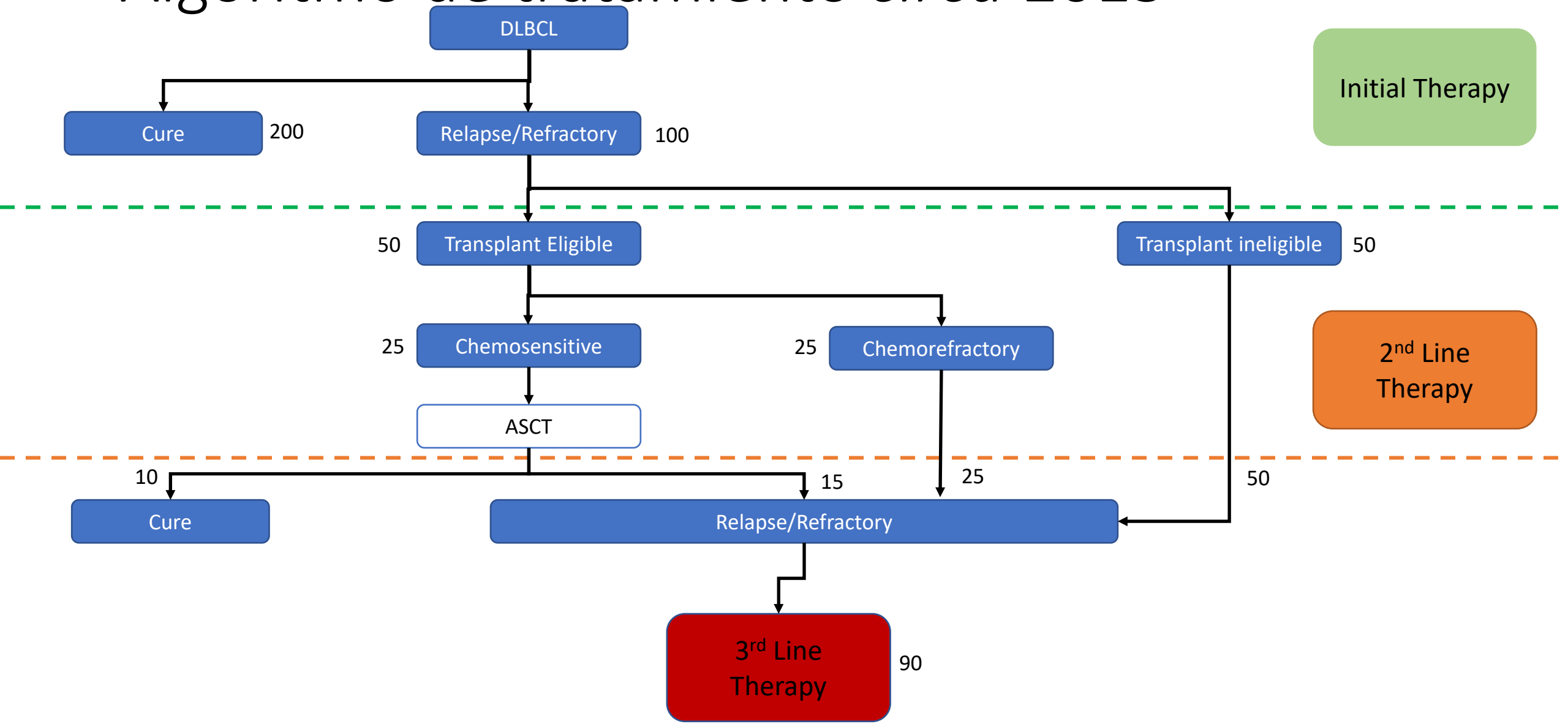
- Humans think they are good at predicting the future

> We are prone to overestimate how much we understand about the world and to underestimate the role of chance in events
>
> Daniel Kahneman. Thinking, Fast and Slow

Esquema

- ¿Se puede hablar todavía de líneas de tratamiento en DLBCL resistente?
- ¿Quimioterapia?
- Grandes cambios
  - Inmunoterapia y otros tratamientos basados en anticuerpos
- Cómo trato a mis pacientes hoy
- Que novedades espero ver en 6, 12, 24 meses

Algoritmo de tratamiento *circa* 2015



Adapted from Friedberg JW, Hematology Am Soc Hematol Educ Program. 2011;2011:498-505
and Pettengel R. ESMO E-Learning: Modern Management of DLBCL. http://oncologypro.esmo.org, May 2017.

DLBCL

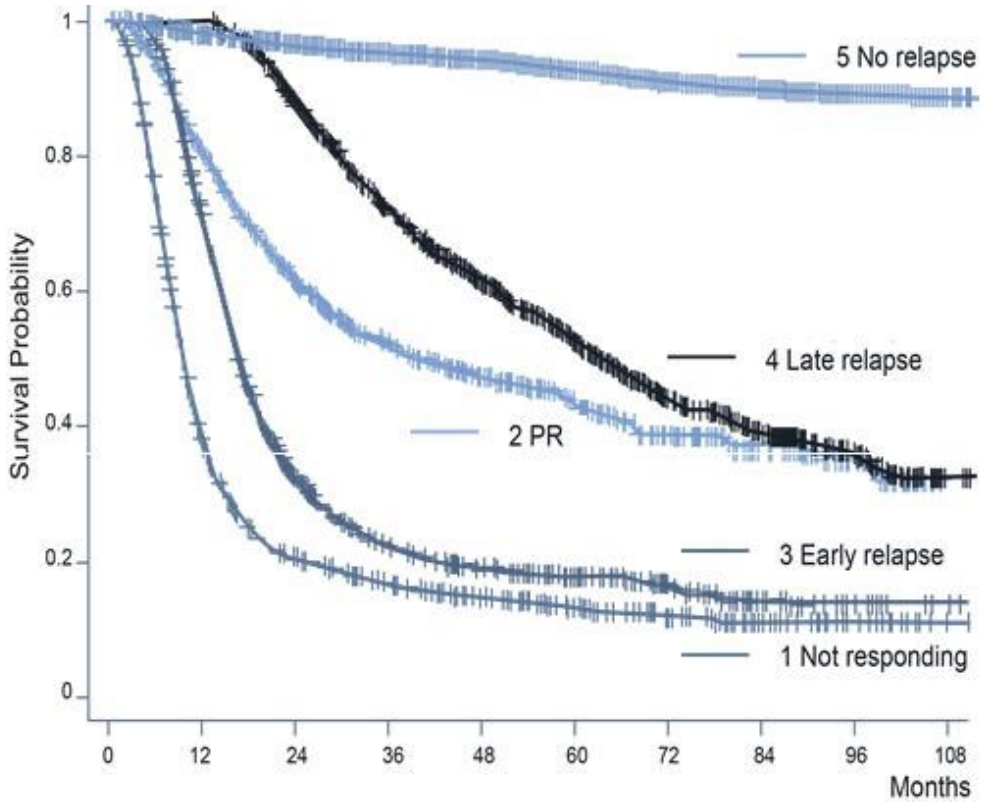
La realidad una vez que dominamos R-CHOP

Cured (60%)

Relapse after CR (20-25%)

PR (5%)

Refractory (15%)



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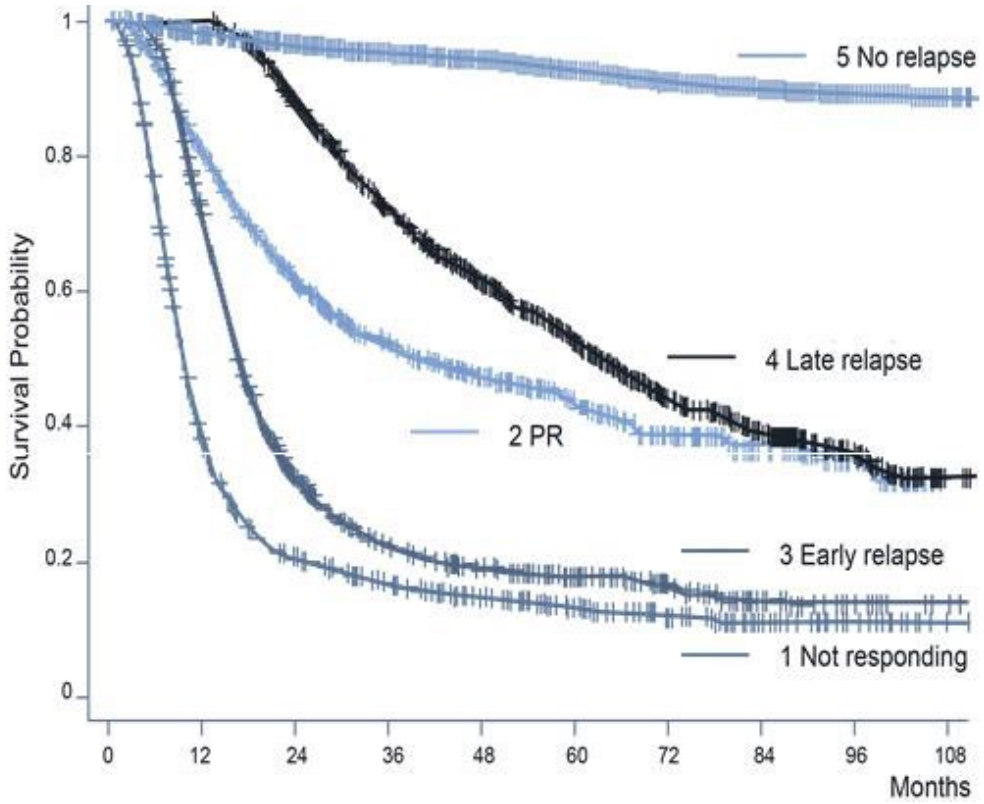

"Solved problem?"

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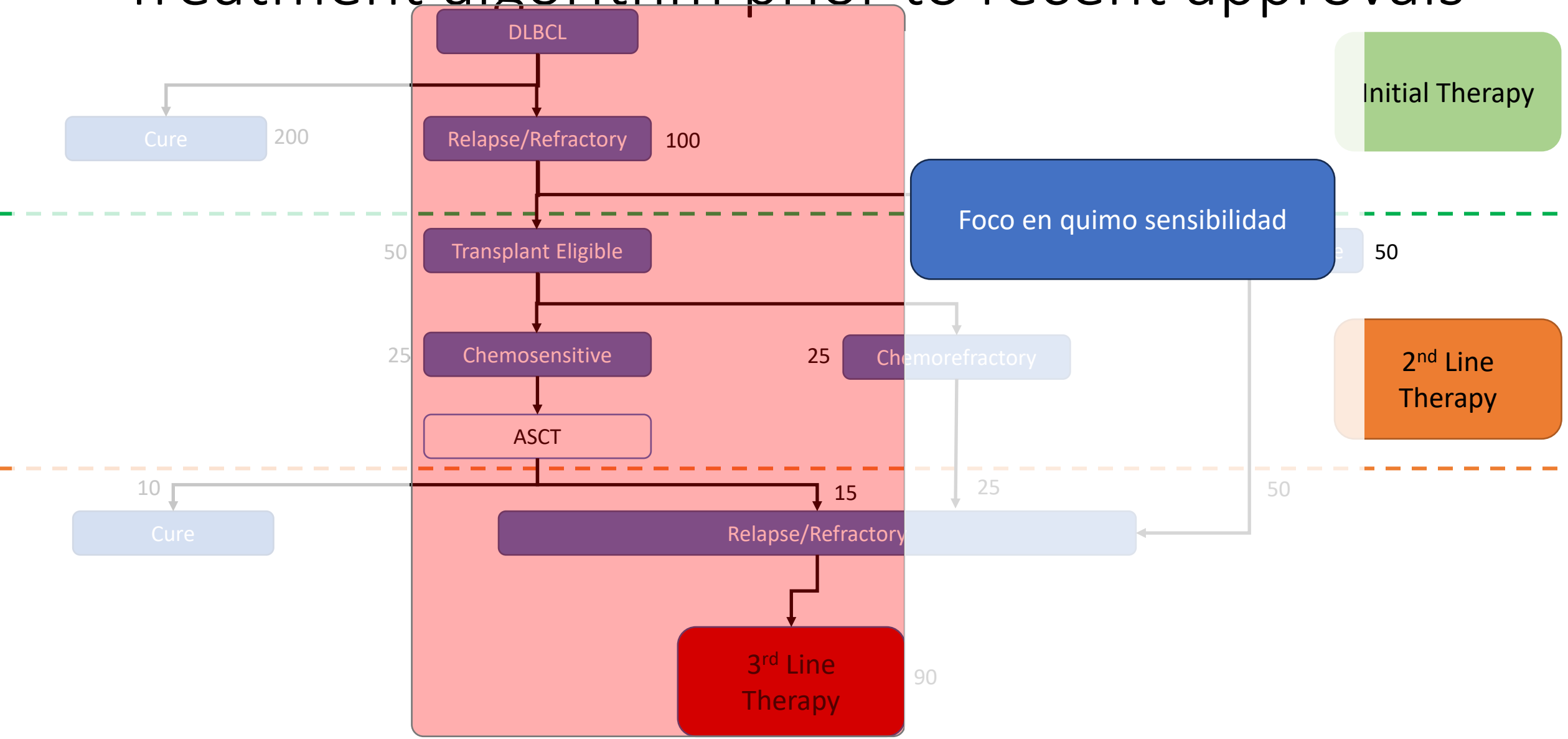
How good are these outcomes?

Treatment algorithm prior to recent approvals



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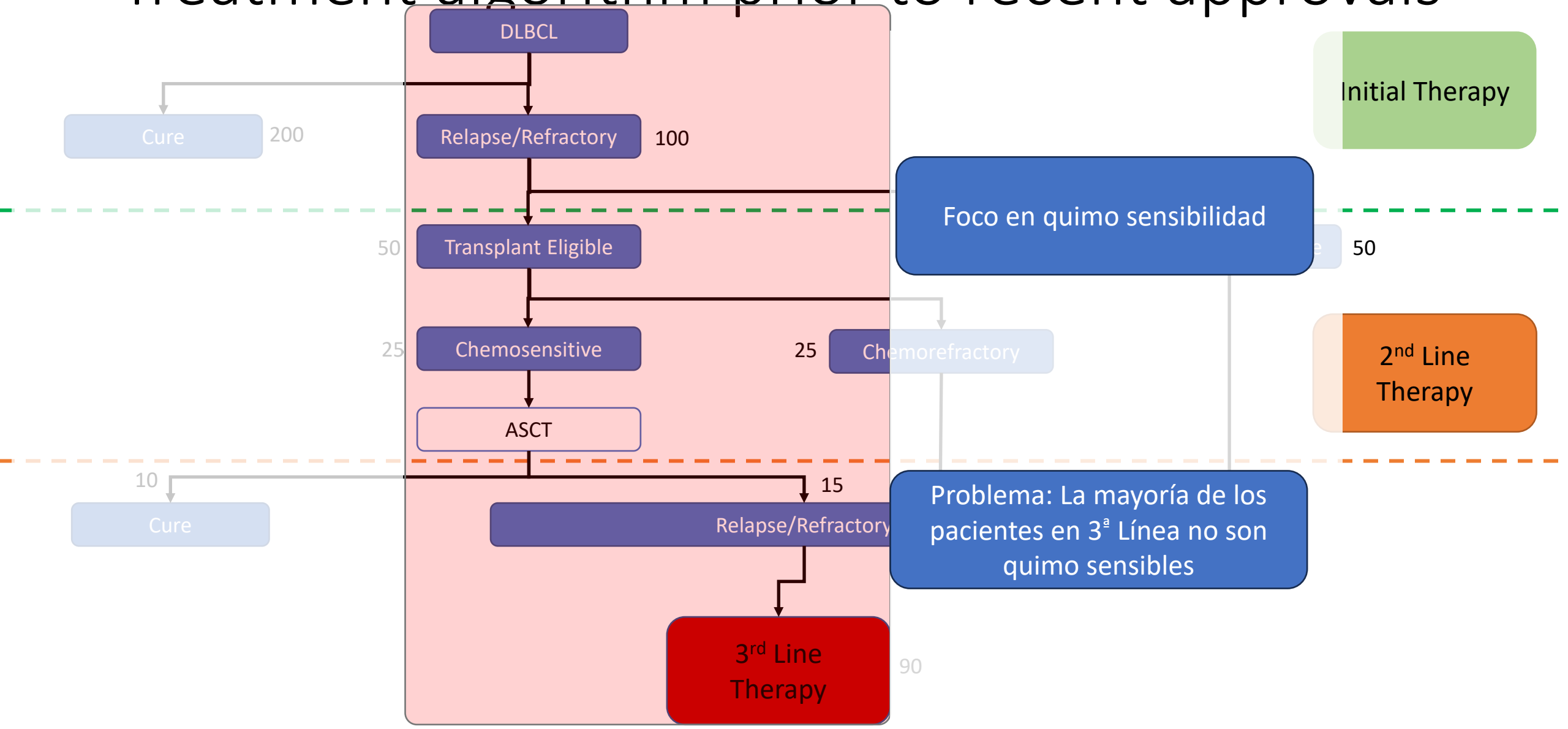

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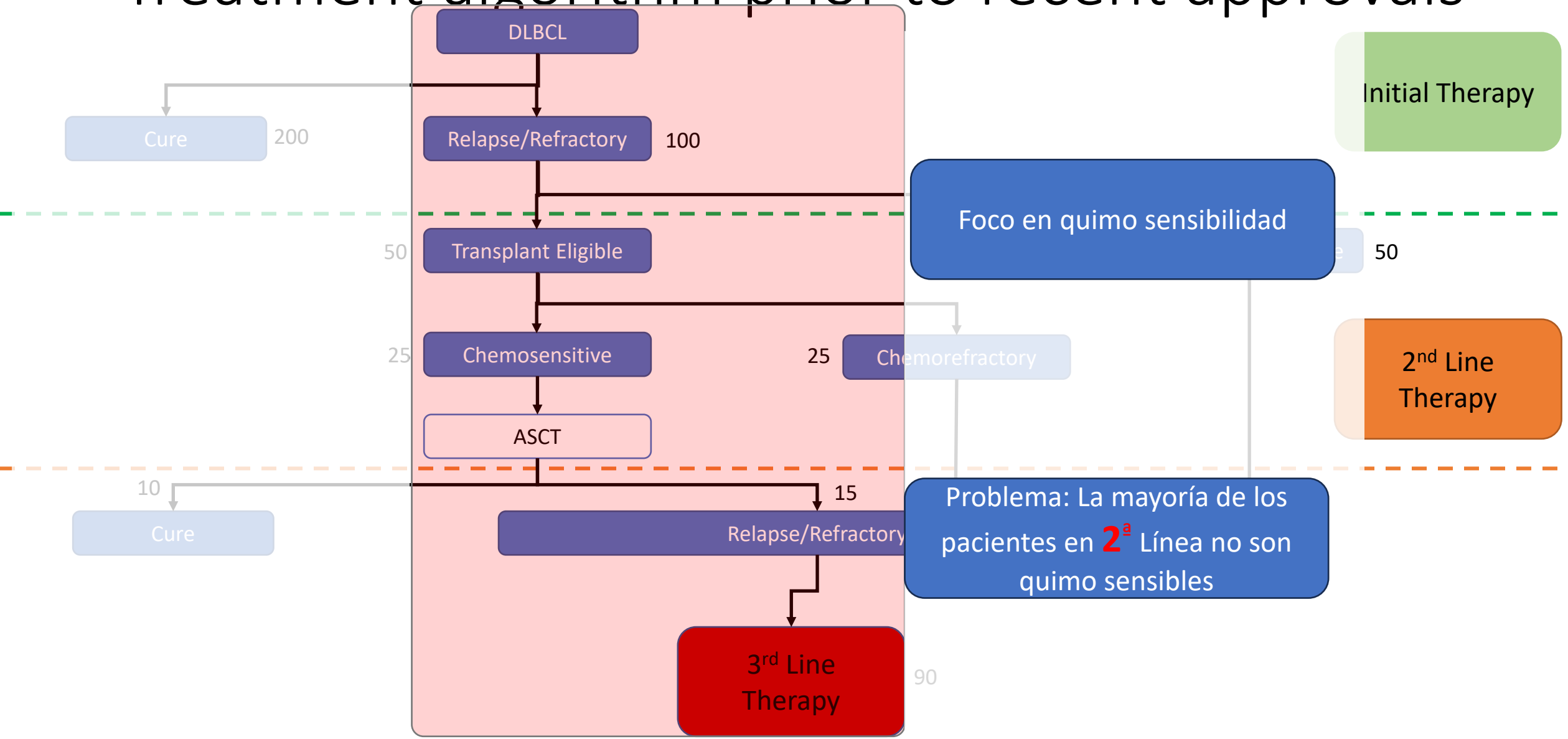

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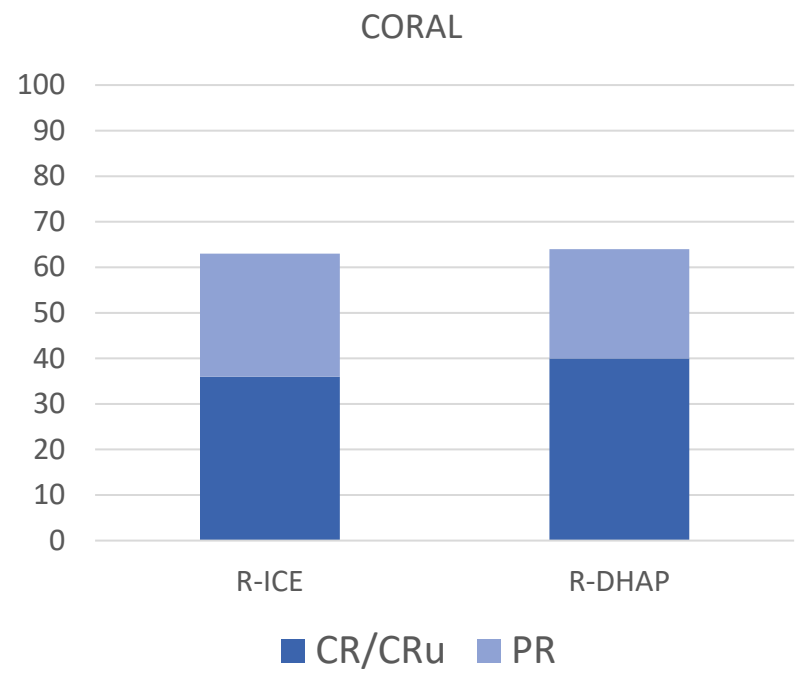
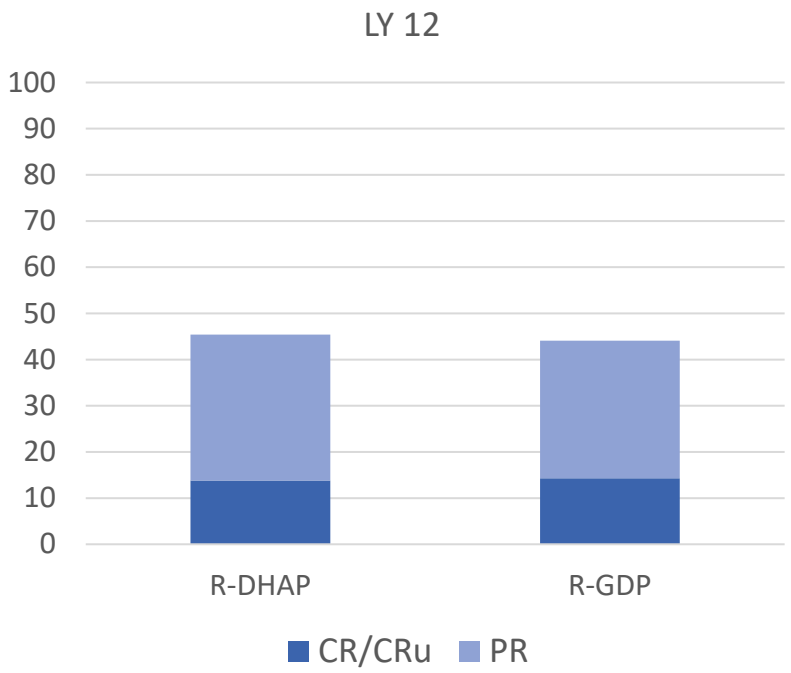
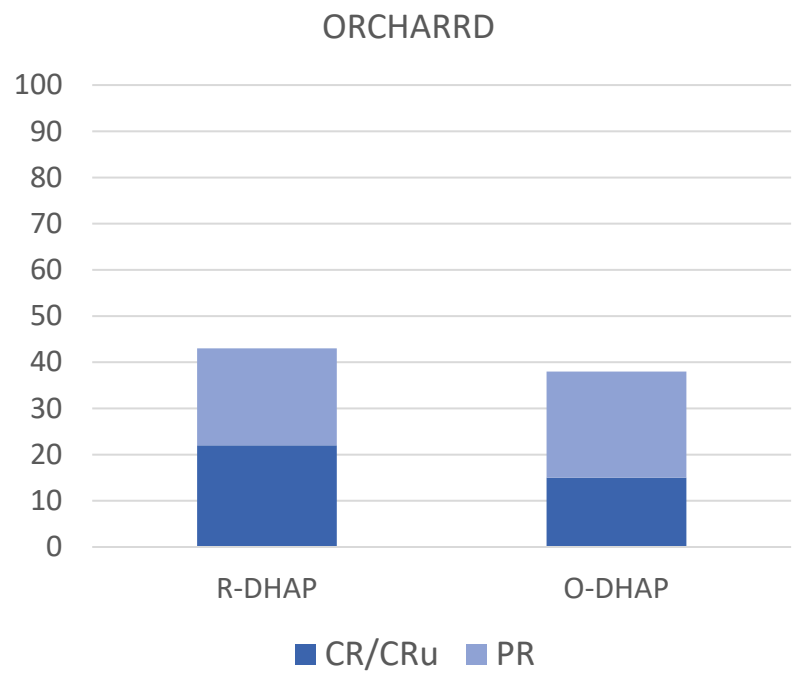
Quimo-inmunoterapia de Segunda Línea

- No single second line regimen of choice.
- Second line regimens achieve responses in 40 – 60% of cases.

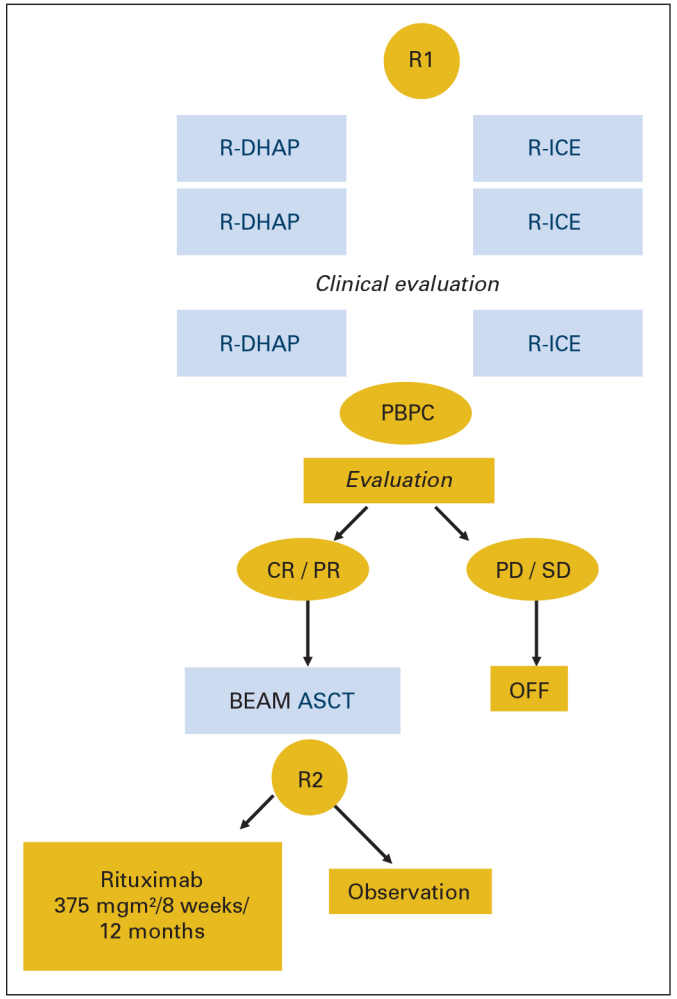


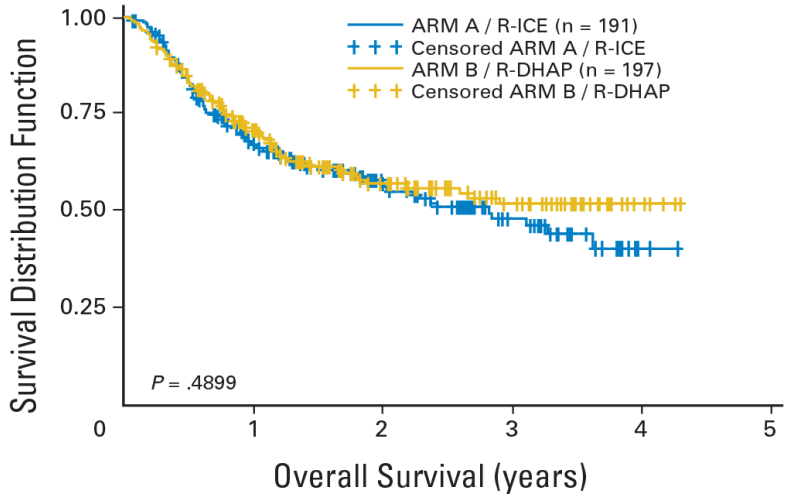


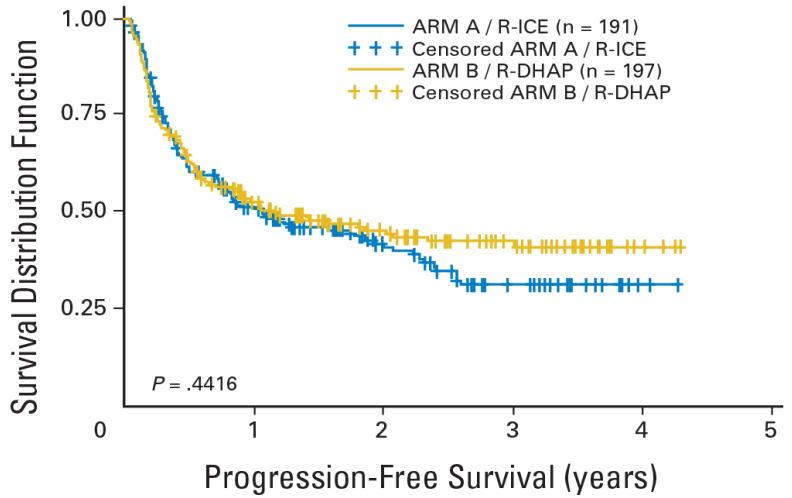


Gisselbrecht C, *et al*. J Clin Oncol, 2010.
Crump M, *et al*. J Clin Oncol 2014.
Van Imhoff GW, *et al*, J Clin Oncol 2017.

Second line regimens
CORAL Trial



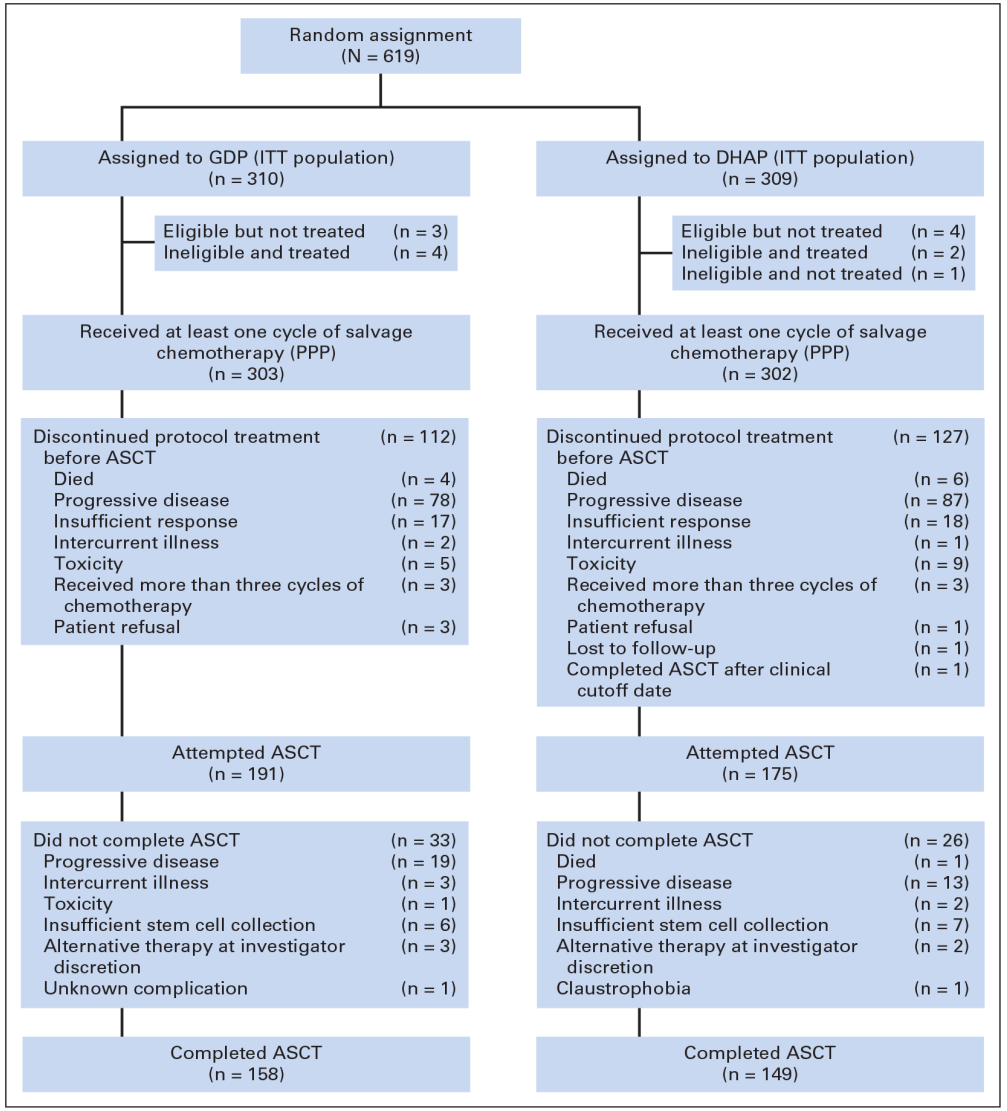


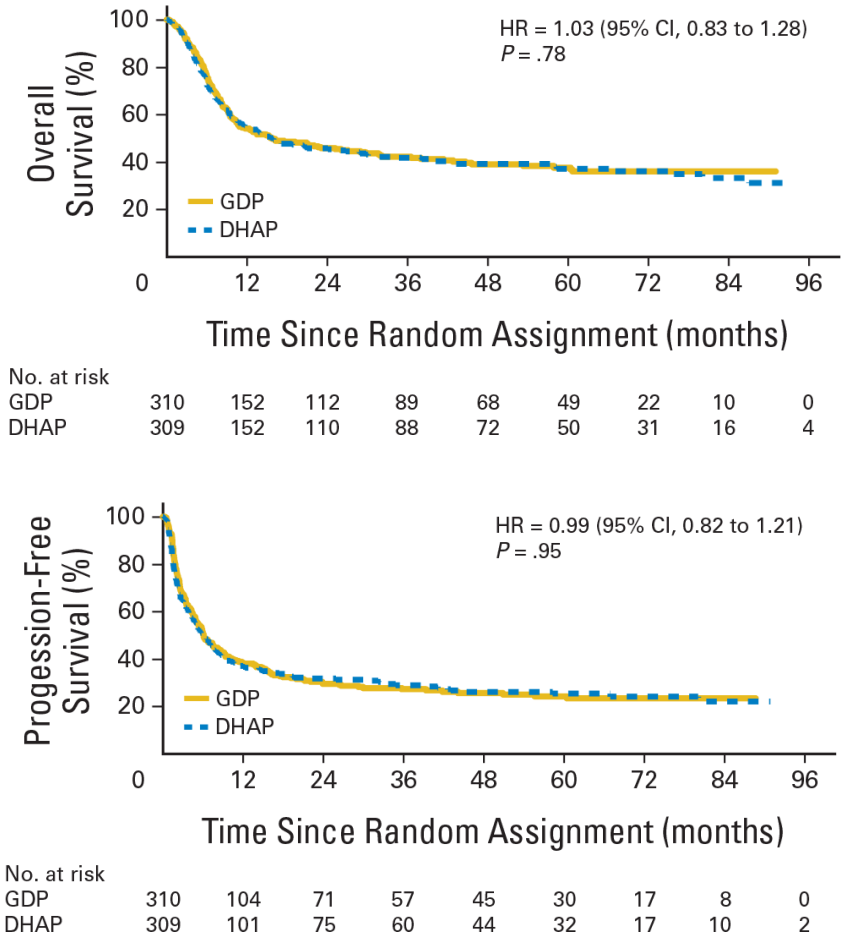


Gisselbrecht C, *et al*. J Clin Oncol, 2010.

Second line regimens

LY 12 Trial





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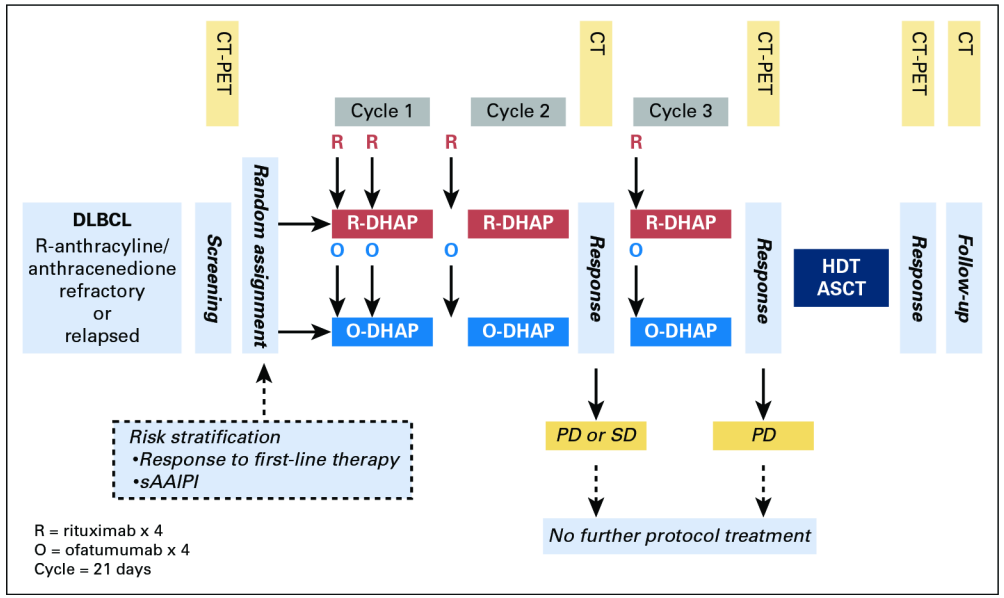
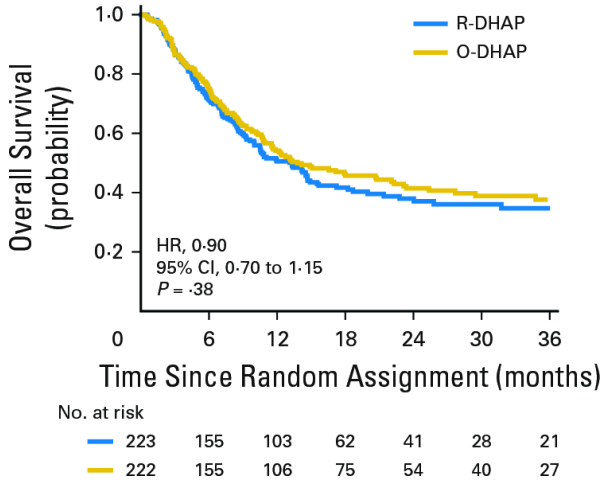
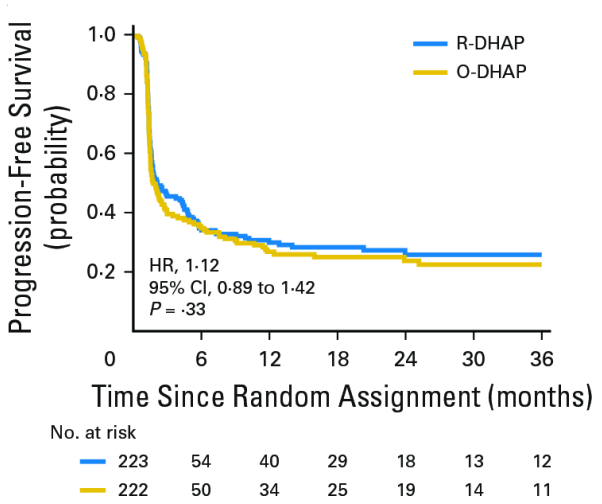
Second line regimens
ORCHARDD



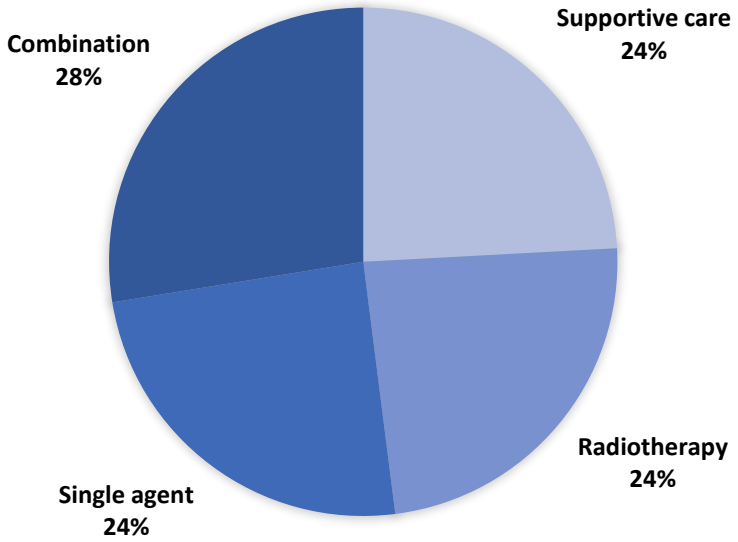


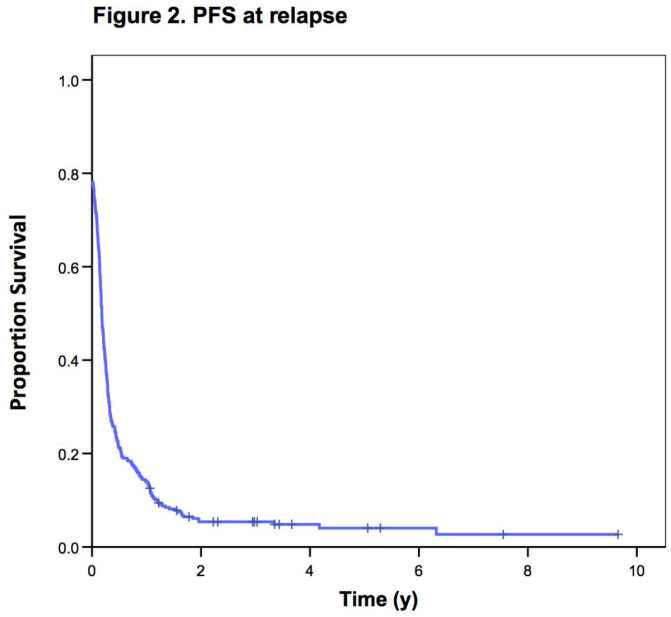


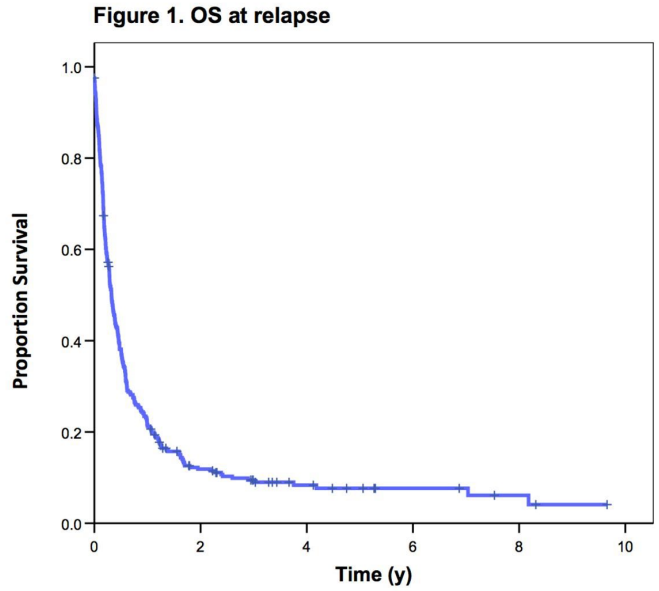
Van Imhoff GW, *et al*. J Clin Oncol, 2017.

Outcomes of Transplant Ineligible*

- British Columbia Cancer Agency
  - 326 patients
    - 274 ineligible / 52 refractory or toxicity after second line
  - Median age 70 years





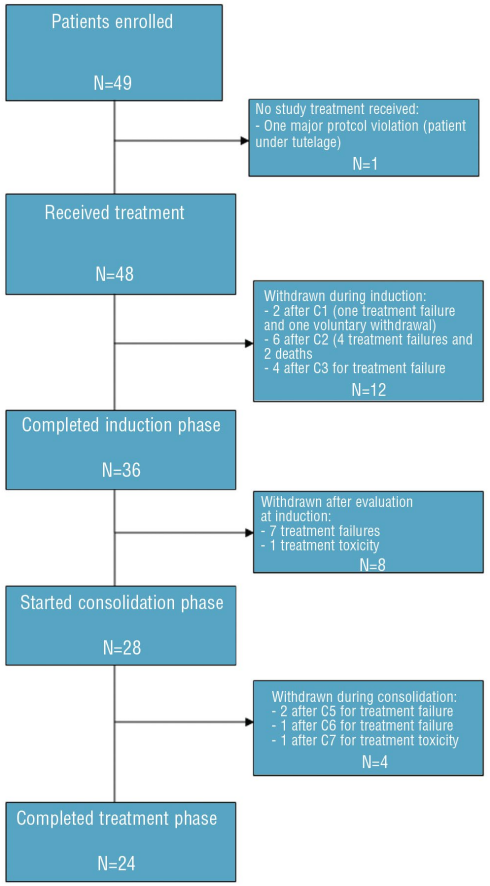


Kansara RR, et al. ASH Annual Meeting 2014

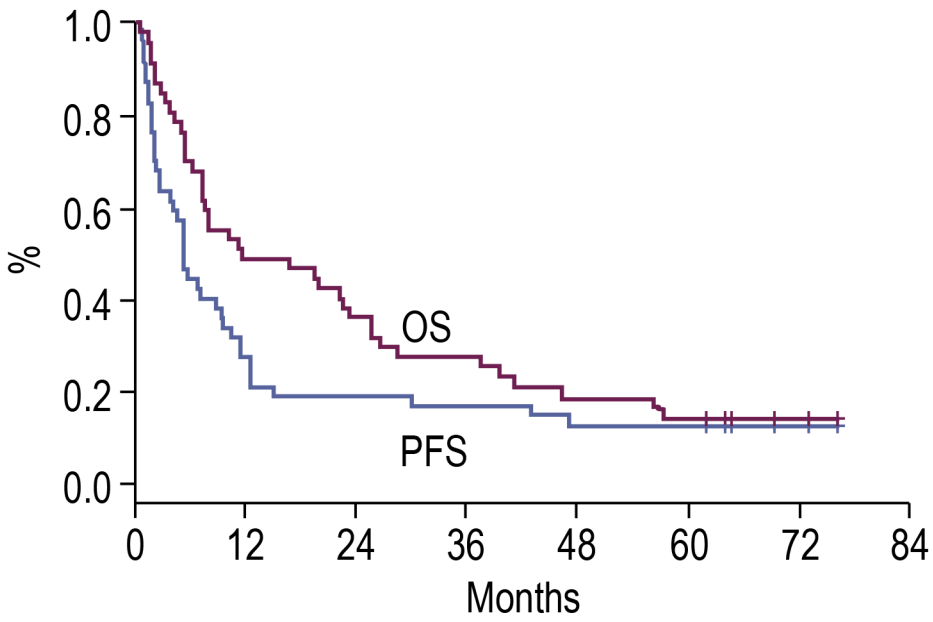
Second Line Regimens for Transplant Ineligible

R-GemOx

- No single second line regimen of choice.
- R-GemOx as option when tolerable



- 49 patients: 46 relapsed / 3 refractory
- Included relapse after ASCT
- Median age 69 years
- ORR: 61%
- 5 – year PFS: 12.8%
- 5 – year OS: 13.9%



Mounier N, et al. Haematologica. 2013

Salvage Regimens for Relapsed Refractory

Single agents

Regimen	N	Lines of Tx	ORR	CR/Cru	PFS (months)	
Lenalidomide	108	3	35	13	3.7	1
Ibrutinib						
DLBCL	80	3	25	10	1.6	2
ABC-DLBCL	38	3	37	16	2.0	
Pixantrone	70	3	37	20	5.3	3

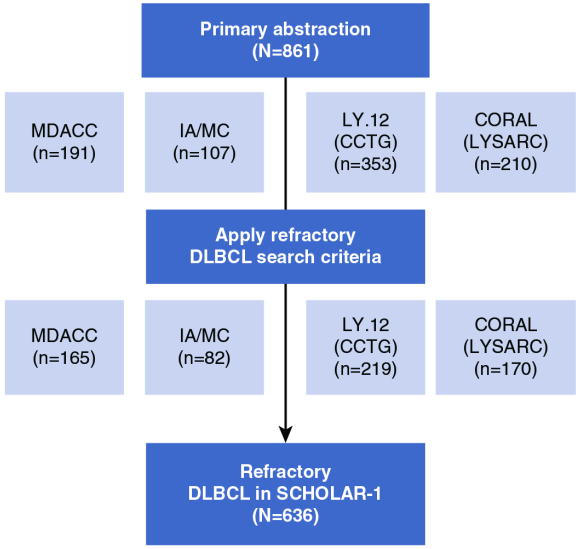
Combinations

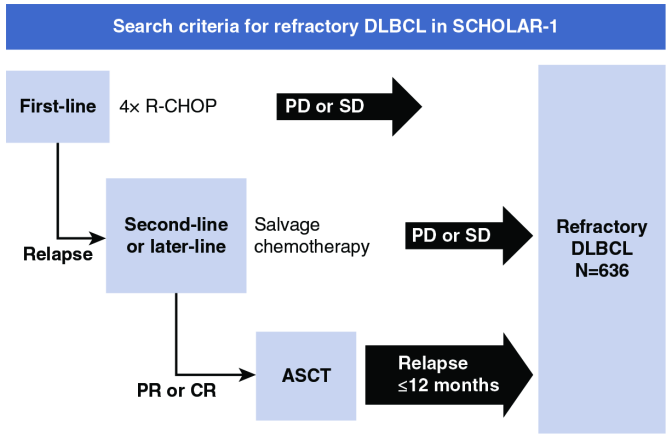
Regimen	N	Lines of Tx	ORR	CR/Cru	PFS (months)	
Lenalidomide + R	102	1 - >3	27.5	9.8	3.1	4
Bendamustine + R	59	1 - >3	45.8	15.3	3.6	5

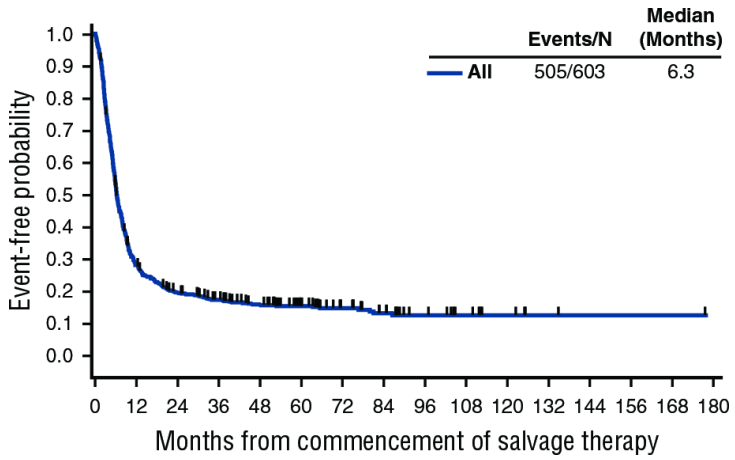
NCCN: R-CEPP, R-CEOP, Gemcitabine-vinorelbine-rituximab

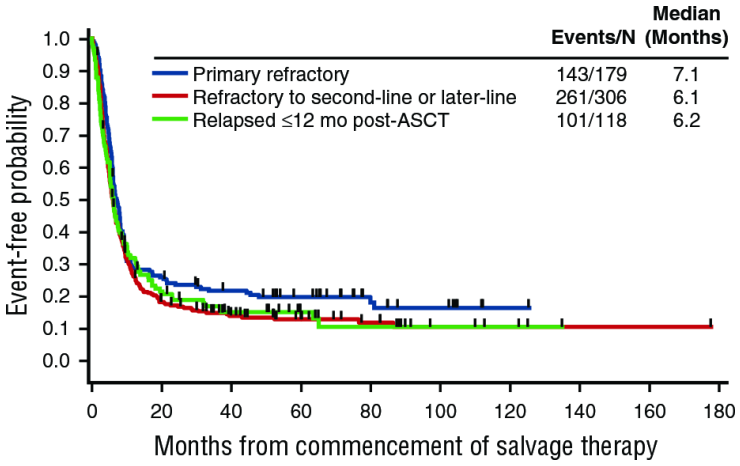
1. Witzig TE, et al. Ann Oncol 2011; 2. Wilson WH, et al Nat Med 2015; 3. Petengell R, et al. Lancet Oncol 2012. 4. Czuczman MS, et al. Clin Cancer Res, 2017; 5. Vacirca JL, et al. Ann Hematol 2014

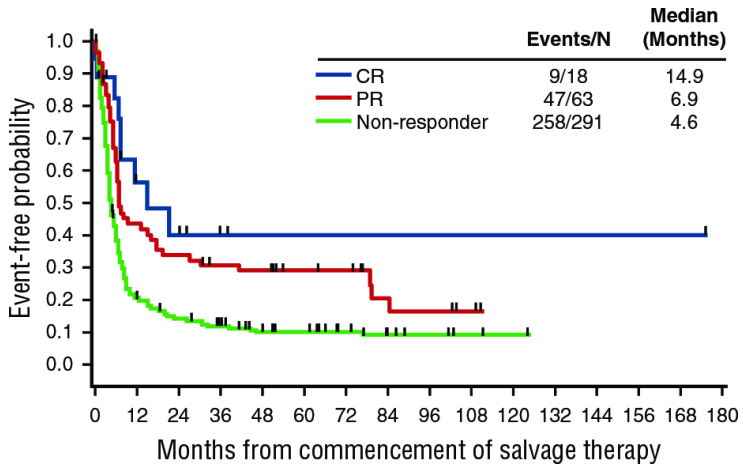
Outcomes of refractory patients
SCHOLAR-1

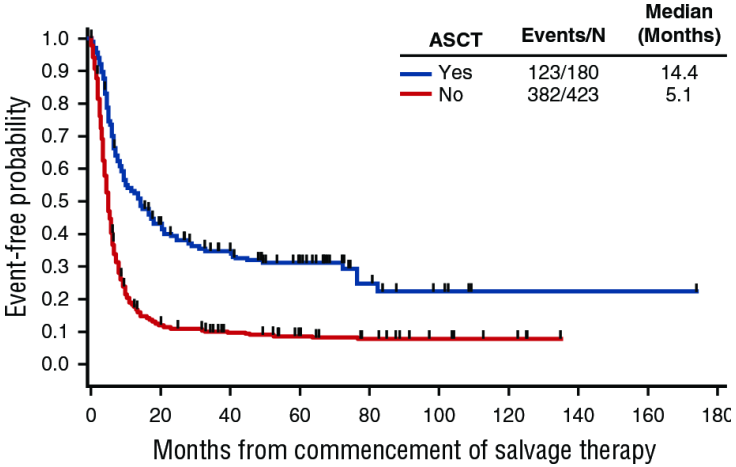












Crump M, et al. Blood 2017

How good are these outcomes?

Outcomes of refractory patients
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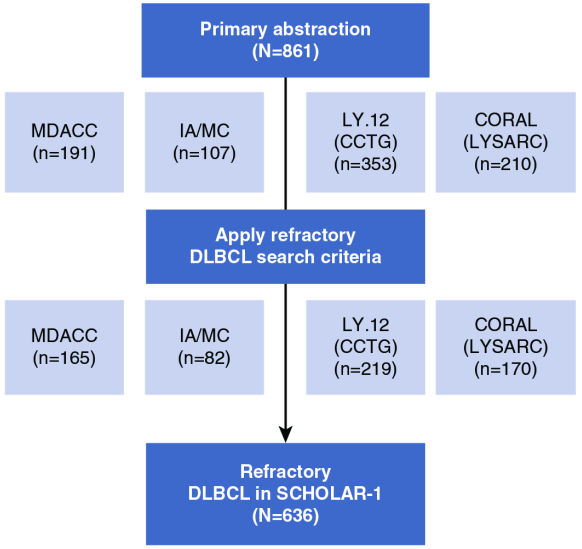

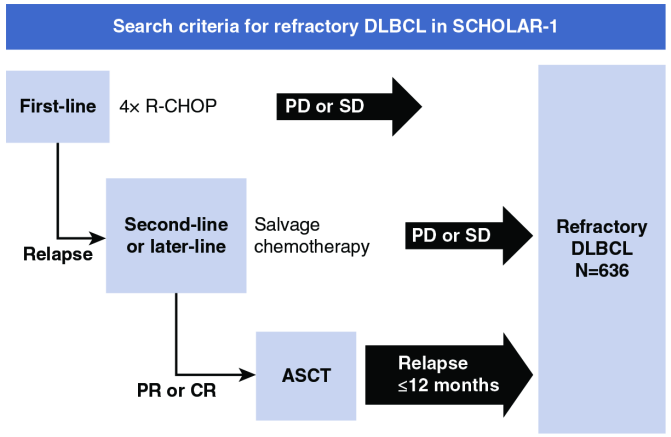

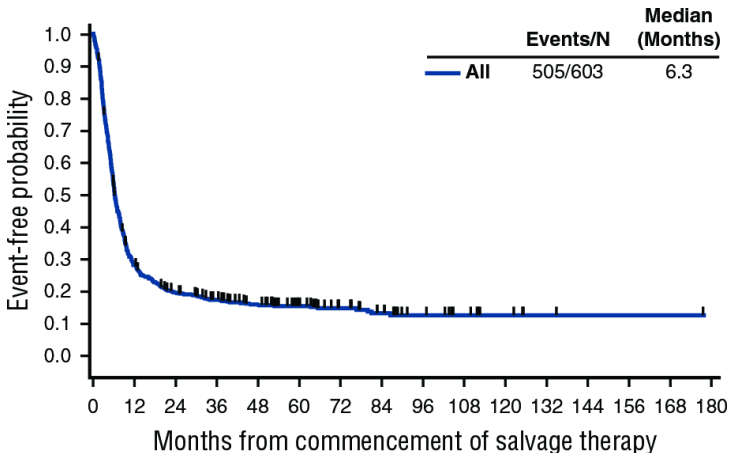

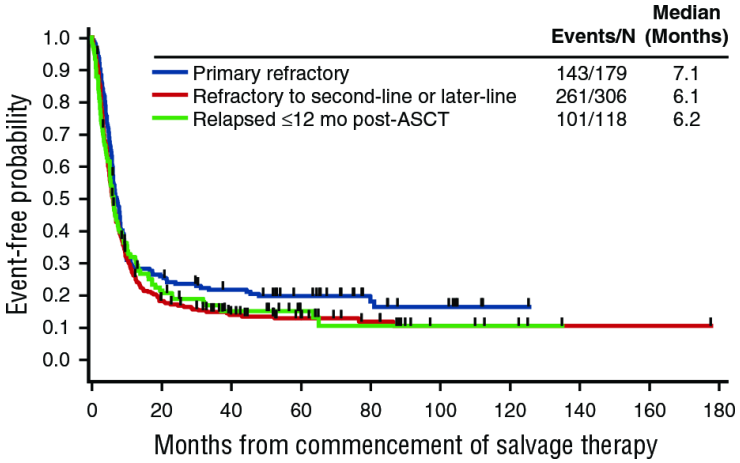

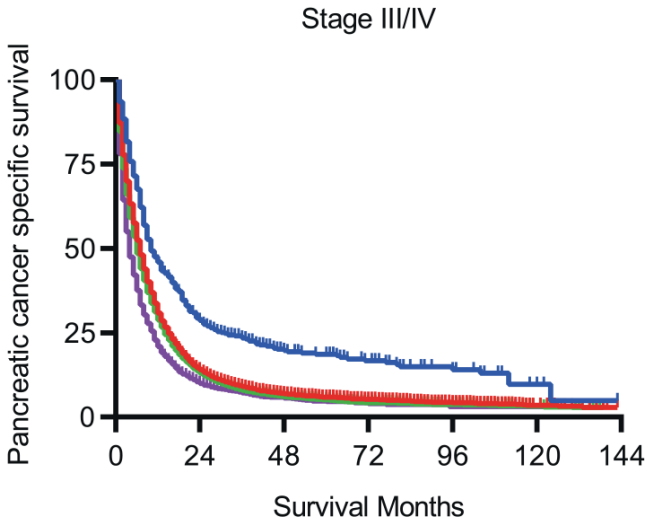

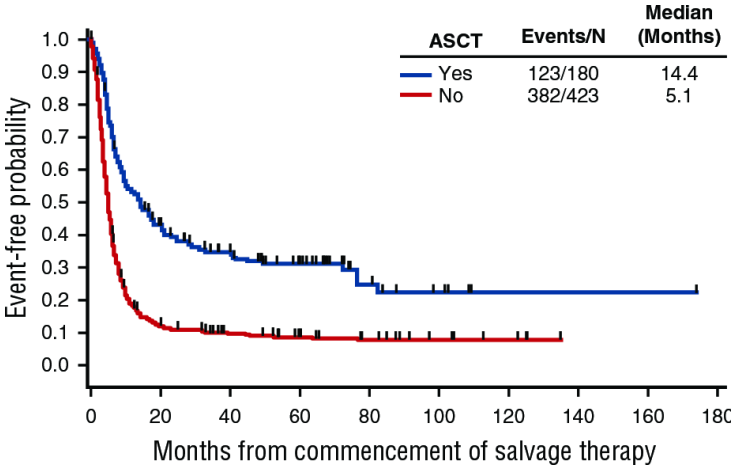

Crump M, et al. Blood 2017

Outcomes of refractory patients

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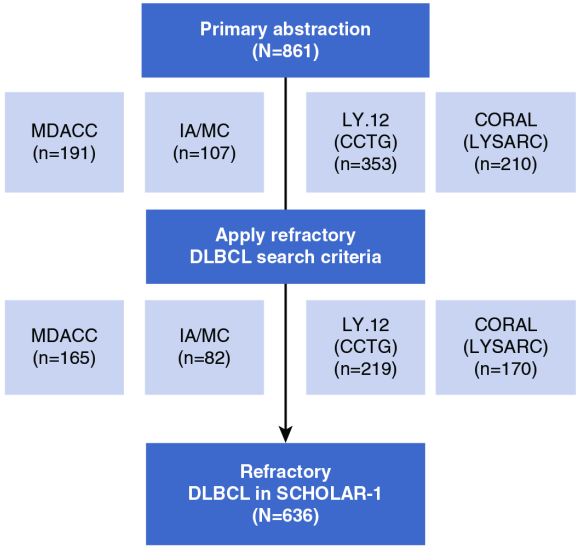

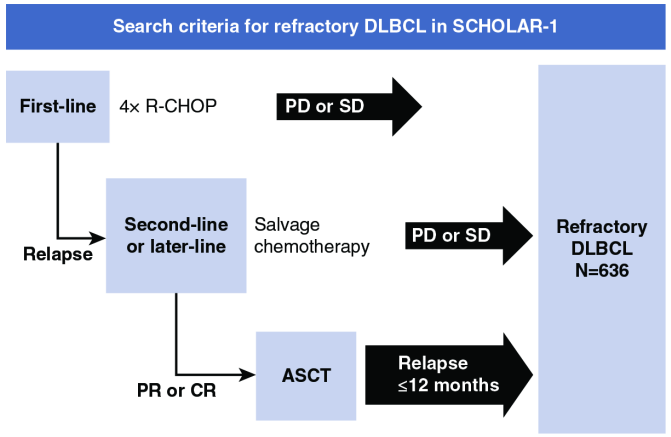

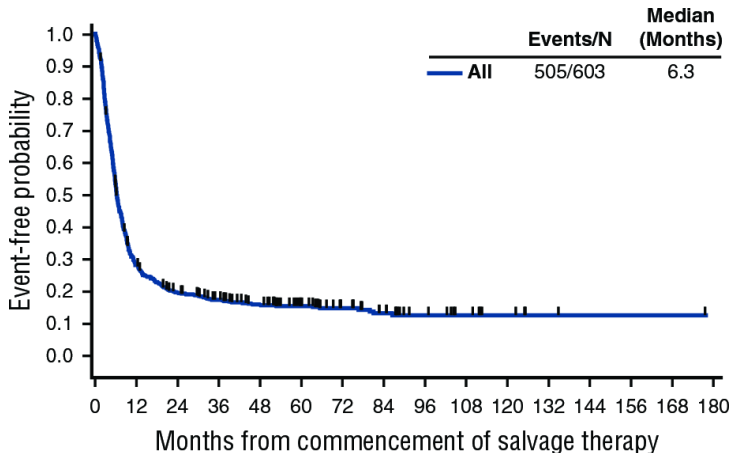

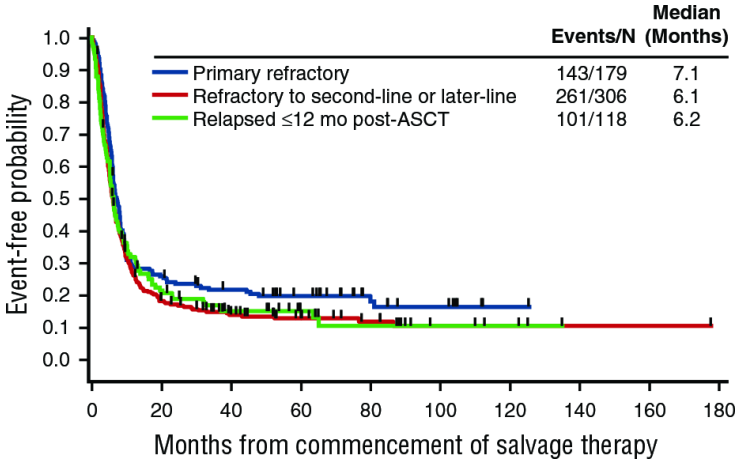

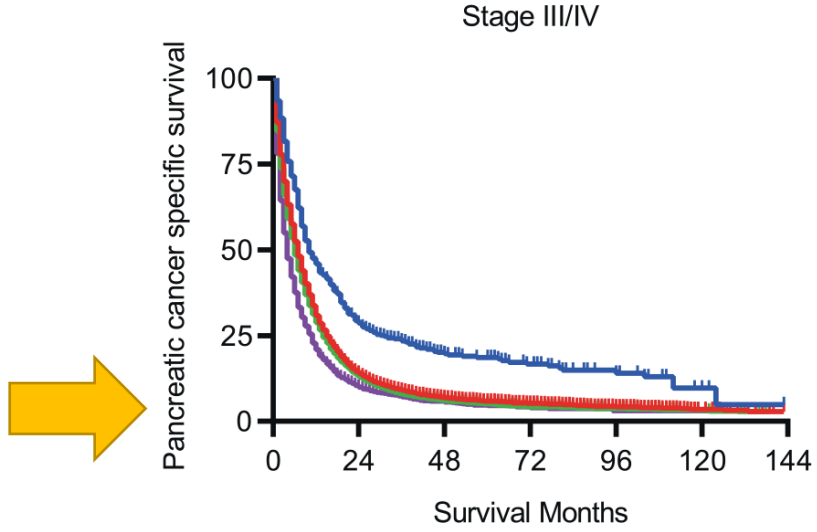

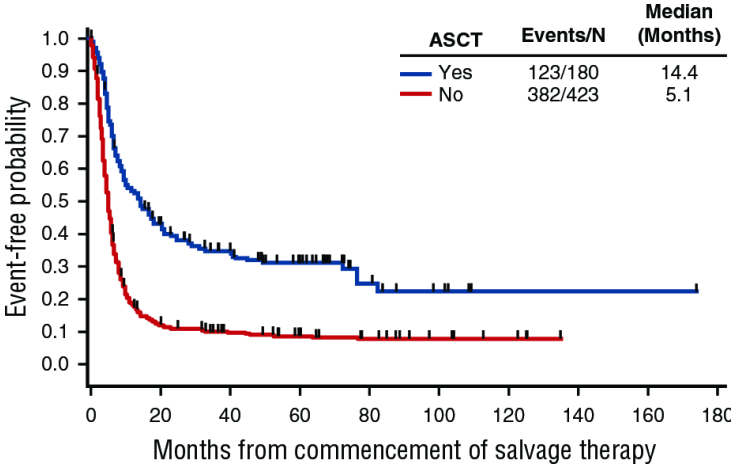

Crump M, et al. Blood 2017; Wang H, et al. Sci Rep 2020

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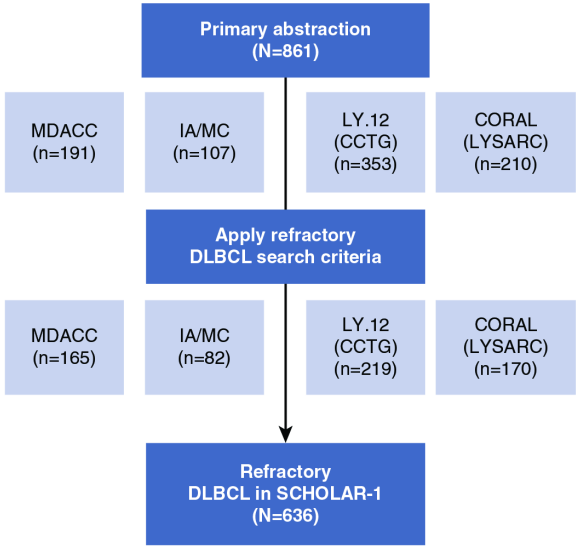
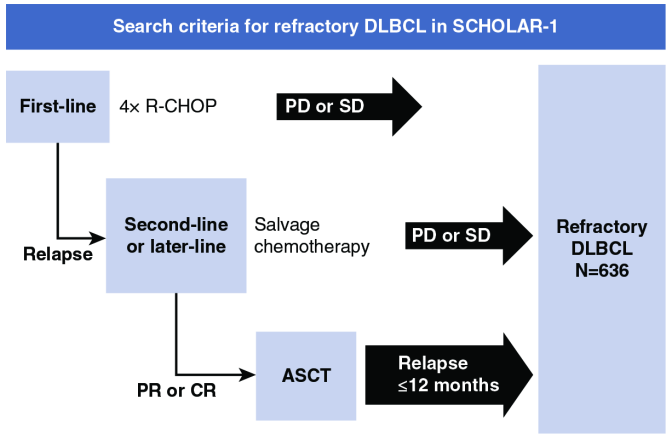
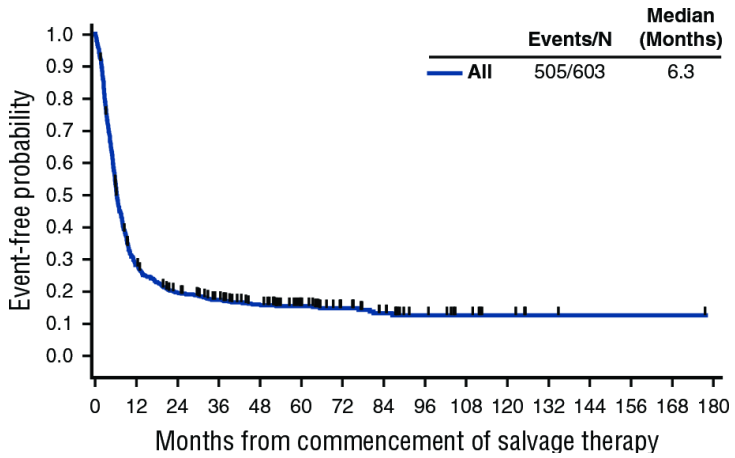
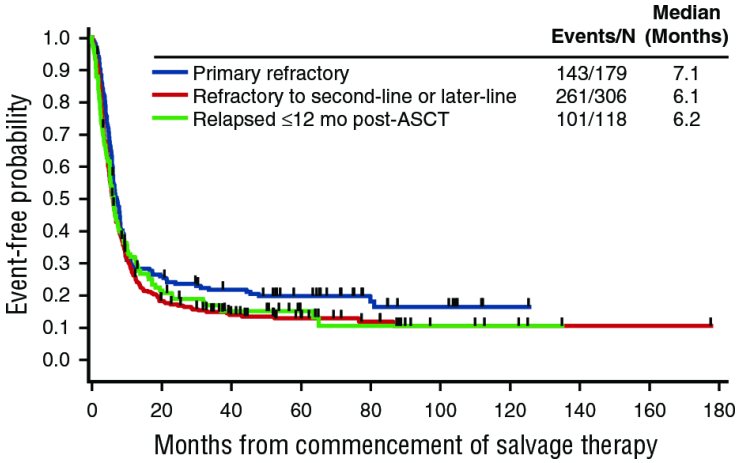
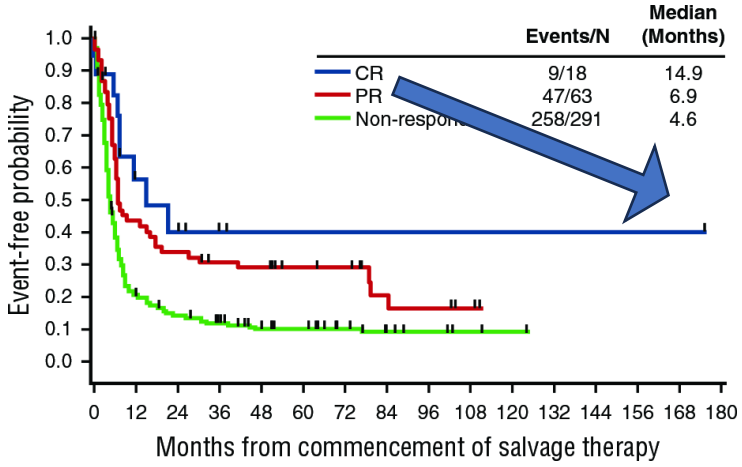
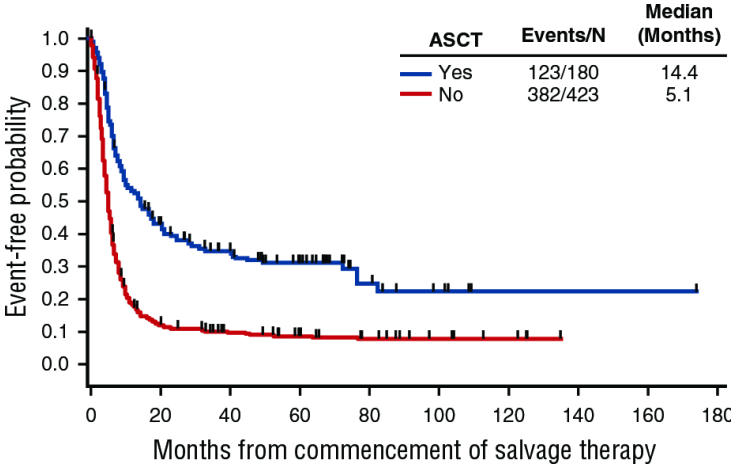












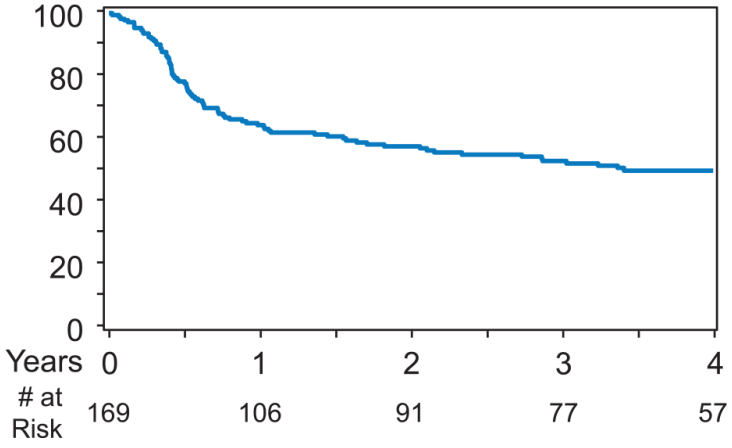
Crump M, et al. Blood 2017; Wang H, et al. Sci Rep 2020

ASCT for primary refractory DLBCL

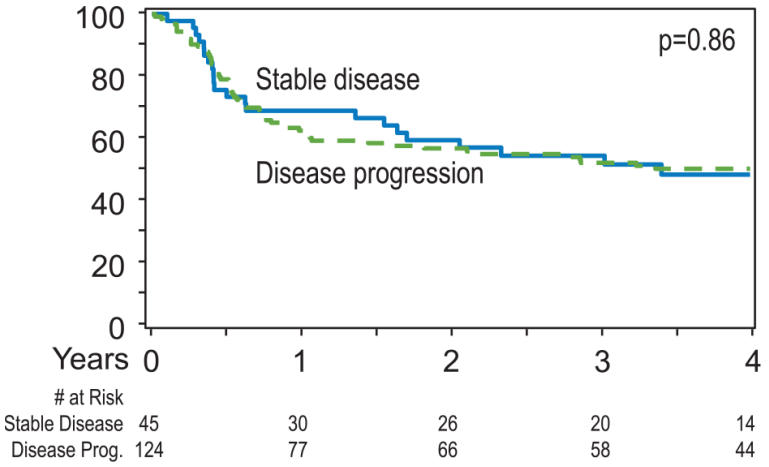
CIBMTR

- 169 patients with primary refractory DLBCL

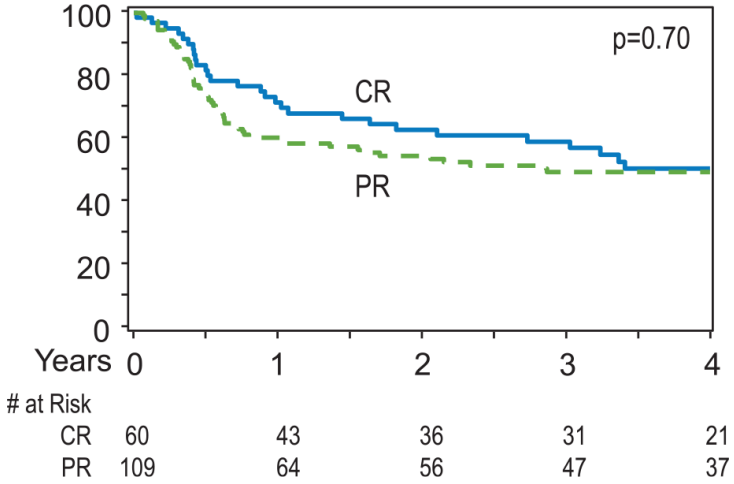
Overall survival



OS by response to 1st line therapy



OS by pre-transplant status



Bal S, et al. TCT 21:55e1-55e7

Nuevos agentes en DLBCL

Aprovados

- Non CD19 targeting antibody – drug conjugates
- CD19 – targeting therapies
- Bispecific antibodies

Investigación

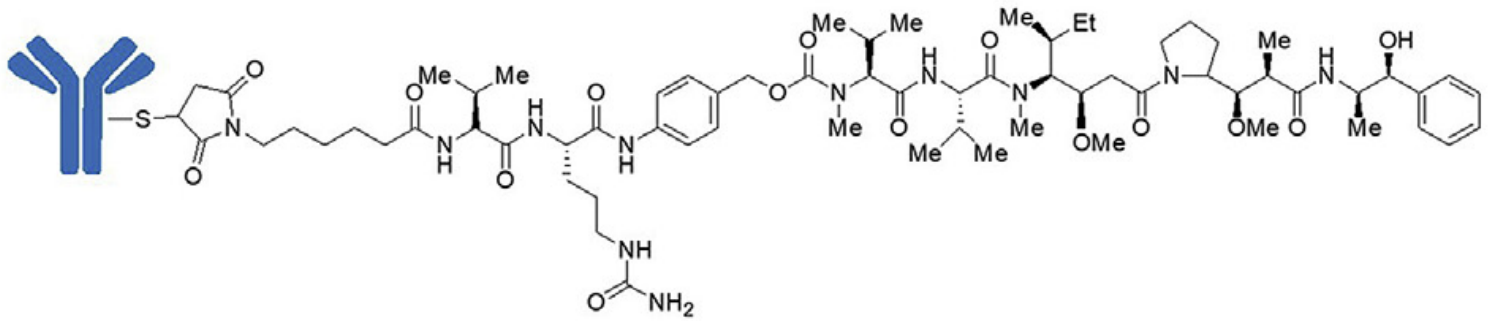
- Bispecific antibodies (4-1BB/CD19; CD28/19), trispecific
- Nuevas células inmunes efectoras:
  - CAR T, NK CAR, AlloCar, CAR macrophage.
  - aCD20, aCD19-20-22aBAFF-R, aBAFF-L,
- New immune targets (ROR1, CD47)
- BCL6

Ignorados

- Selinexor

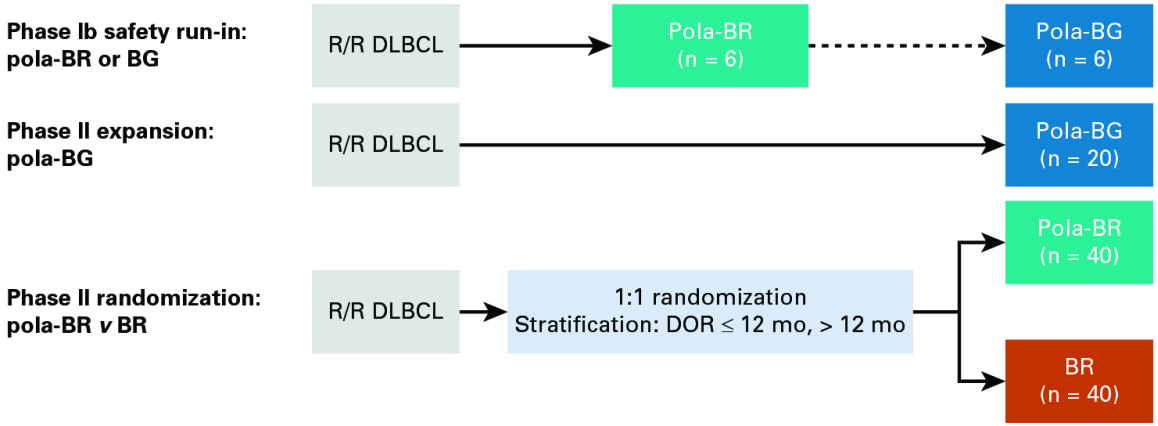
Polatuzumab vedotin

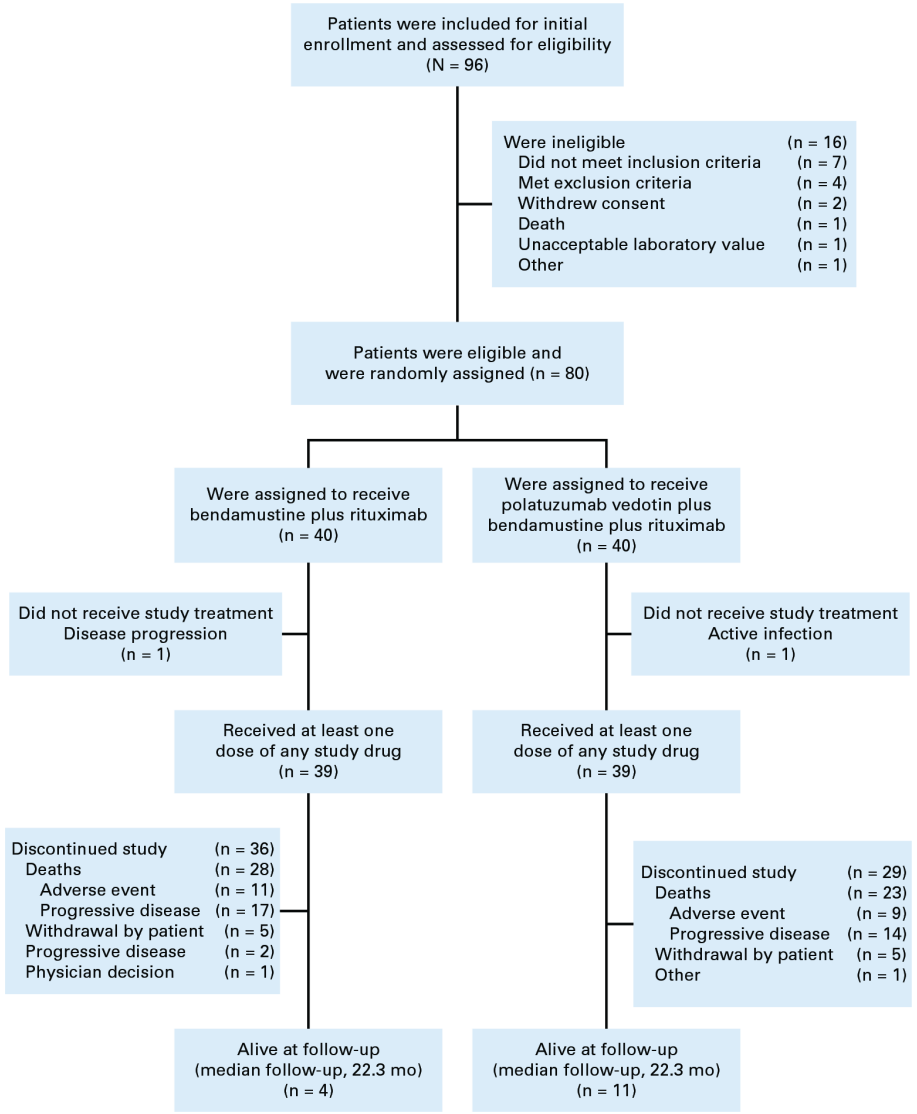
- CD79b targeting ADC
- Conjugated with MMAE (antimicrotubule)



Polatuzumab vedotin-piiq (Polivy®)

Polatuzumab + Bendamustine + Rituximab





Sehn L, et al. J Clin Oncol 2020

Polatuzumab + Bendamustine + Rituximab
Eligibility

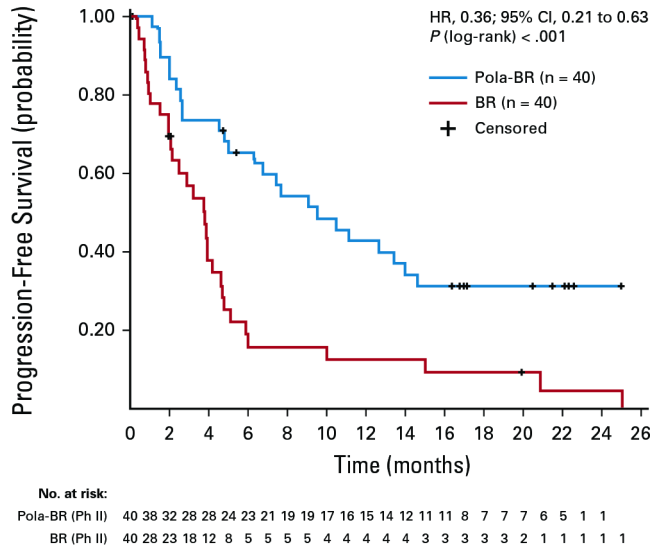
- Relapsed / Refractory DLBCL
  - No transformed lymphoma
- ≥ 1 prior line of therapy
- ECOG 0 – 2
- Neuropathy ≤ grade 1
- Transplant ineligible or relapse post ASCT

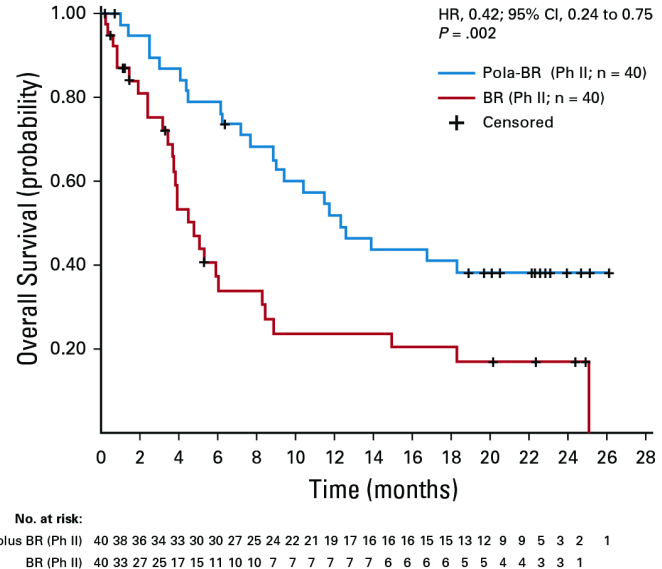
Sehn L, et al. J Clin Oncol 2020

Polatuzumab + Bendamustine + Rituximab

Efficacy

	Pola BR	BR
Overall response EOT	18 (45)	7 (17.5)
Complete response	16 (40)	7 (17.5)
Partial response	2 (5)	0
DoR, months (95% CI)	12.6 (7.2 – NE)	7.4 (4 – 18.9)
PFS, months (95% CI)	9.5 (6.2- 13.9)	3.7 (2.1 – 4.5)
DoR: Duration of response; EOT: end of treatment; PFS: progression free survival		





Sehn L, et al. J Clin Oncol 2020

Tafasitamab

- Monoclonal antibody directed against CD19
  - “Fc enhanced” – increased affinity for Fcγ receptor
  - Humanized
  - Mediates ADCC and AD cellular phagocytosis
  - Has direct cytotoxicity

Salles G, et al. Lancet Oncol, 2020.

Tafasitamab- Eligibility & Pt. Characteristics

L-MIND

- Phase 2 trial

Eligibility

- DLBCL
  - Including transformed indolent
  - Excluding double/triple hit
- Relapsed / refractory to 1 – 3 lines of therapy
  - Primary refractory (up to 3 months after initial therapy)
- Not candidates for ASCT
  - Older than 70 years
  - Organ dysfunction
  - Failed previous ASCT
  - No response to salvage therapy
  - Refused
  - Inability to collect CD34 cells

81 patients enrolled:

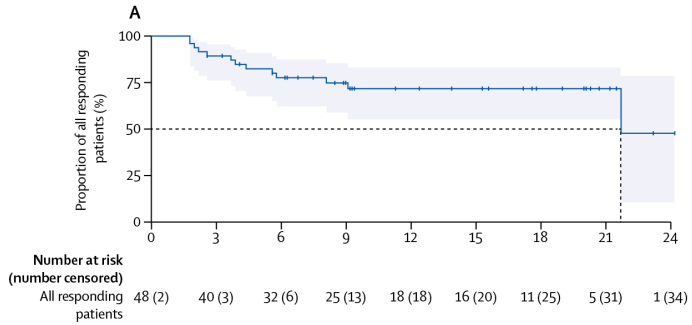
Median age:	72 years (62 – 76)
Transformed indolent	9%
Median previous therapies:	2 (1 – 4)
(50% had received 1 line)	
Refractory to last therapy:	42%
Bulky disease:	19%
ASCT ineligibility	
Age > 70 years	46%
Chemorefractory	23%
Refusal	16%
Comorbidities	14%
Other	1%

Salles G, et al. Lancet Oncol, 2020.

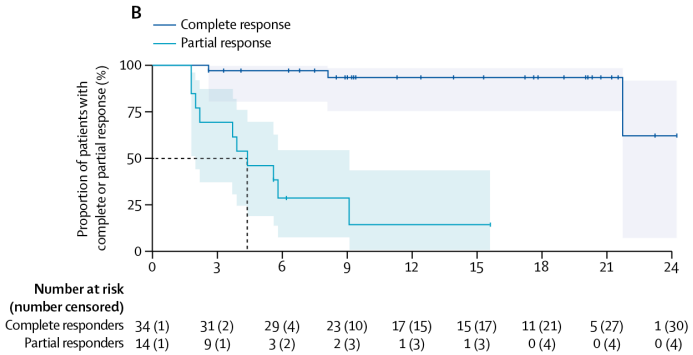
Tafasitamab
L-MIND trial results

	Patients treated with tafasitamab plus lenalidomide (n=80)*
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)
Disease control§	59 (74%; 63–83)

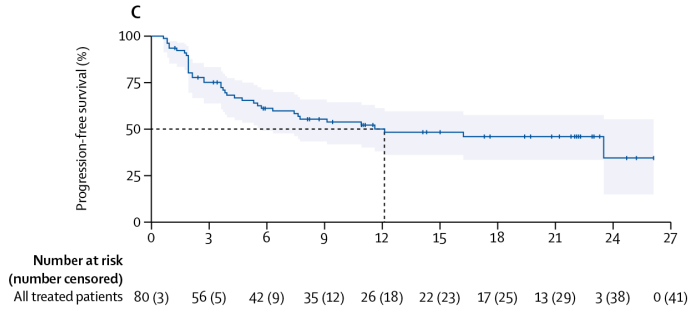
Data are n (%; 95% CI) or n/N (%). *One patient received tafasitamab only. †Patients had no valid postbaseline response assessments. ‡Complete response plus partial response. §Complete response plus partial response plus stable disease.



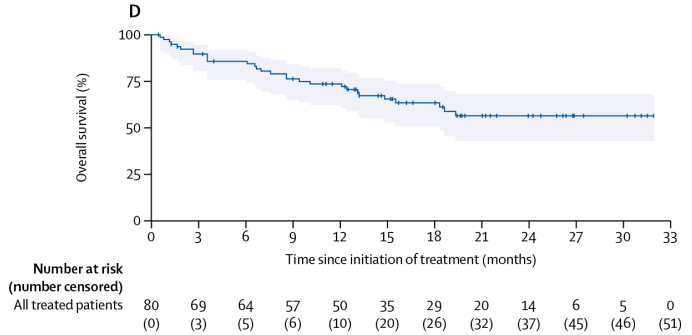
DoR



DoR by best response



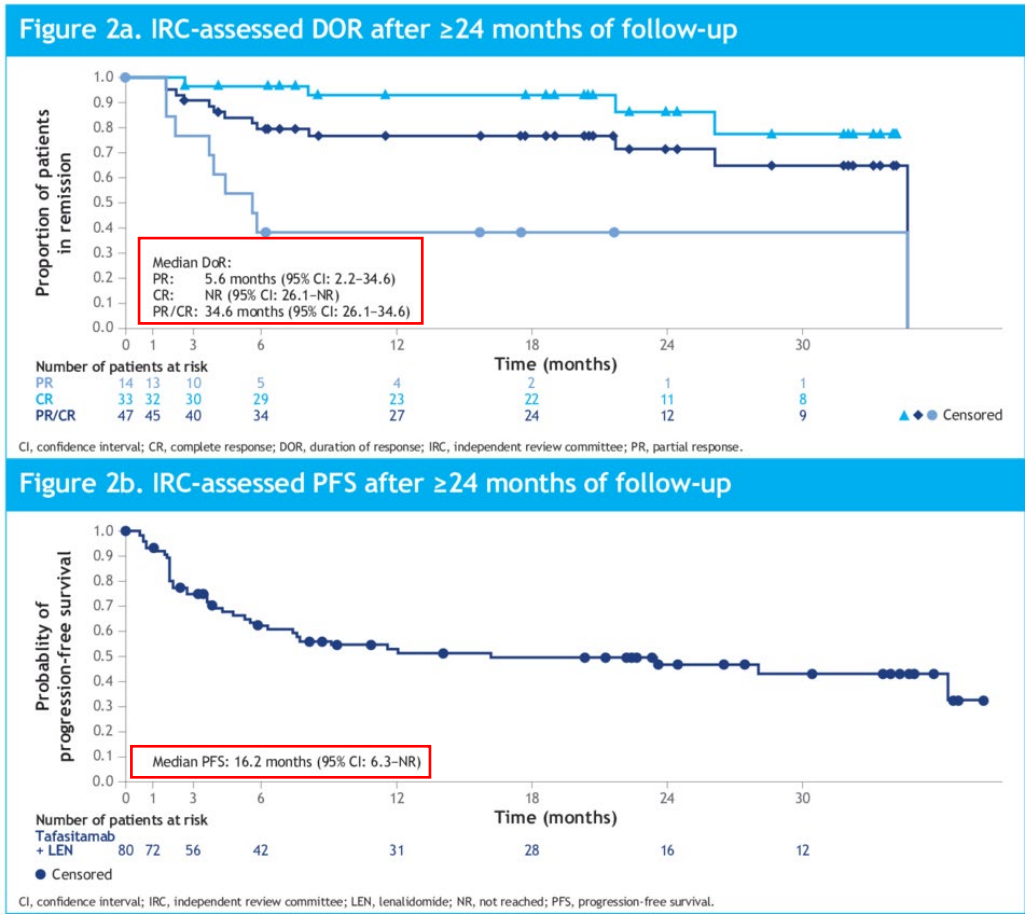
PFS



OS

Salles G, et al. Lancet Oncol, 2020.

L-MIND Longer Follow Up



Salles et al. EHA 2020 EP1201

Uso de tafasitamab en la práctica

- Pacientes >2ª linea
- Mucha peor PFS
- En un pequeño grupo es efectivo

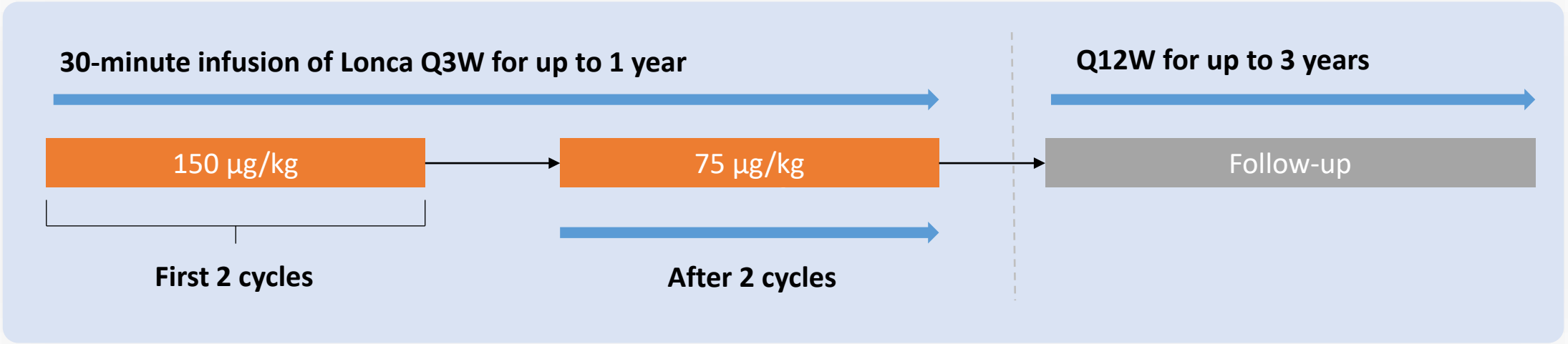
Qualls D, et al. Blood 2023.

Loncastuximab tesirine

- Antibody drug conjugate
  - AntiCD19
  - Payload is pyrrolobenzodiazepine (PBD) toxin
    - DNA cross-linking

Kahl B, et al. Clin Cancer Res, 2019

Phase II trial (LOTIS-2)



Eligibility

DLBCL

- Including transformed indolent
- Including double/triple hit
- Including primary refractory

Relapsed/refractory to ≥ 2 lines of therapy

If prior CAR-T cell therapy, repeat biopsy with CD19+ required

Excluded:

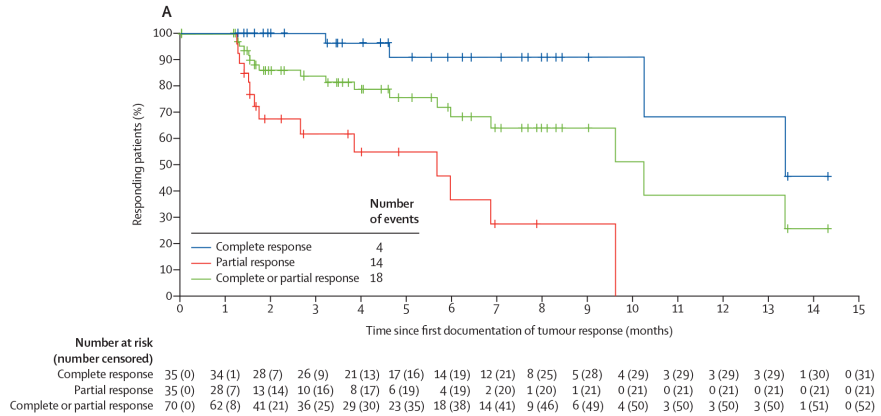
- Bulky disease (> 10 cm)
- ASCT within 30 days, AlloHCT within 60 days
- CNS disease

Phase II Results

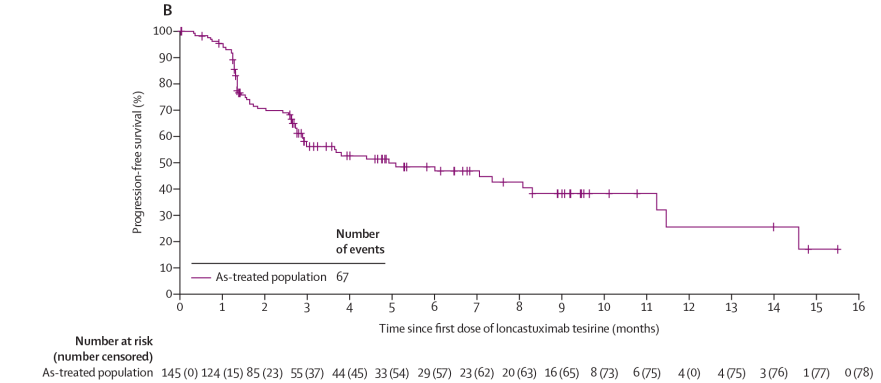
	As-treated population (n=145)
Overall response rate (complete or partial response)	70 (48·3% [39·9–56·7])
Complete response rate	35 (24·1% [17·4–31·9])
Complete response	35 (24%)
Partial response	35 (24%)
Stable disease	22 (15%)
Progressive disease	30 (21%)
Not evaluable*	23 (16%)

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.

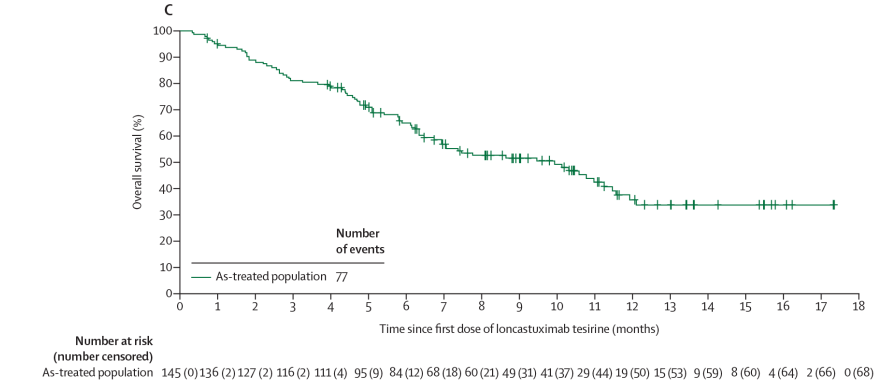
Table 2: **Best overall responses and overall response rate**



DoR:
10.3 months
(13.4 for CR)



PFS:
4.9 months



OS:
9.9 months

Caimi P, et al. Lancet Oncol, 2021.

Phase II Subgroup analysis

High-risk subgroup analysis of ORR

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
Age			
<65 years	32/65		49.2 (36.6, 61.9)
≥65 years	38/80		47.5 (36.2, 59.0)
Double/triple hit			
No	65/130		50.0 (41.1, 58.9)
Yes	5/15		33.3 (11.8, 61.6)
Transformed disease			
Transformed	13/29		44.8 (26.4, 64.3)
De novo	57/116		49.1 (39.7, 58.6)
Cell-of-origin			
GCB	26/48		54.2 (39.2, 68.6)
ABC	11/23		47.8 (26.8, 69.4)
Double/triple expressor			
No	60/125		48.0 (39.0, 57.1)
Yes	10/20		50.0 (27.2, 72.8)
WHO classification			
DLBCL NOS	64/127		50.4 (41.4, 59.4)
PMBCL	1/7		14.3 (0.4, 57.9)
HGBCL	5/11		45.5 (16.7, 76.6)

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
First-line response*			
Relapse	53/99		53.5 (43.2, 63.6)
Refractory†	11/29		37.9 (20.7, 57.7)
Last-line response*			
Relapse	29/43		67.4 (51.5, 80.9)
Refractory†	31/84		36.9 (26.6, 48.1)
Response to any prior line*			
Relapse	60/115		52.2 (42.7, 61.6)
Refractory†	9/25		36.0 (18.0, 57.5)
Prior stem cell transplant			
Yes	14/24		58.3 (36.6, 77.9)
No	56/121		46.3 (37.2, 55.6)
Prior CAR-T therapy			
Yes	6/13		46.2 (19.2, 74.9)
No	64/132		48.5 (39.7, 57.3)
Prior systemic therapies			
2 prior lines	30/63		47.6 (34.9, 60.6)
3 prior lines	17/35		48.6 (31.4, 66.0)
>3 prior lines	23/47		48.9 (34.1, 63.9)

Phase II Safety

TEAEs in ≥20% of the all-treated population

PREFERRED TERM	PATIENTS N (%)		
	<65 YEARS (N=65)	≥65 (N=80)	TOTAL (N=145)
Patients with any TEAE	65 (100)	78 (97.5)	143 (98.6)
GGT increased	33 (50.8)	27 (33.8)	60 (41.4)
Neutropenia	34 (52.3)	24 (30.0)	58 (40.0)
Thrombocytopenia	28 (43.1)	20 (25.0)	48 (33.1)
Fatigue	21 (32.3)	19 (23.8)	40 (27.6)
Anemia	23 (35.4)	15 (18.8)	38 (26.2)
Nausea	17 (26.2)	17 (21.3)	34 (23.4)
Cough	19 (29.2)	13 (16.3)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	11 (13.8)	29 (20.0)
Peripheral edema	11 (16.9)	18 (22.5)	29 (20.0)

Most common (≥10%) grade ≥3 TEAEs were:

- Neutropenia (38 patients; 26.2%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (25 patients; 17.2%)
- Anemia (15 patients; 10.3%)

Treatment-related TEAEs leading to treatment discontinuation occurred in 26 (17.9%) patients, most commonly (≥2%):

- GGT increased (16 patients; 11.0%)
- Peripheral edema (4 patients; 2.8%)
- Localized edema (3 patients; 2.1%)

ANTICD19 CAR-T CELLS

3 Approved Products

Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
AXI-CEL	TISA-CEL	LISO-CEL

Gisselbrecht C, et al. J Clin Oncol, 2010.

AXICABTAGENE CILOLEUCEL

ZUMA-1

Results: (Follow up 15.4 months)

- Median age 58 years [23 – 76]
- 69% had received at least 3 lines
- 21% with post ASCT relapse
- 26% primary refractory
- Median time to response 1 month (0.8 – 6)
- Median duration of response 11.1 months (3.9 – NR)

	ORR	CR
Best response	82%	58%
Ongoing response	42%	40%

Neelapu SS et al. N Engl J Med 2017;377:2531-2544.

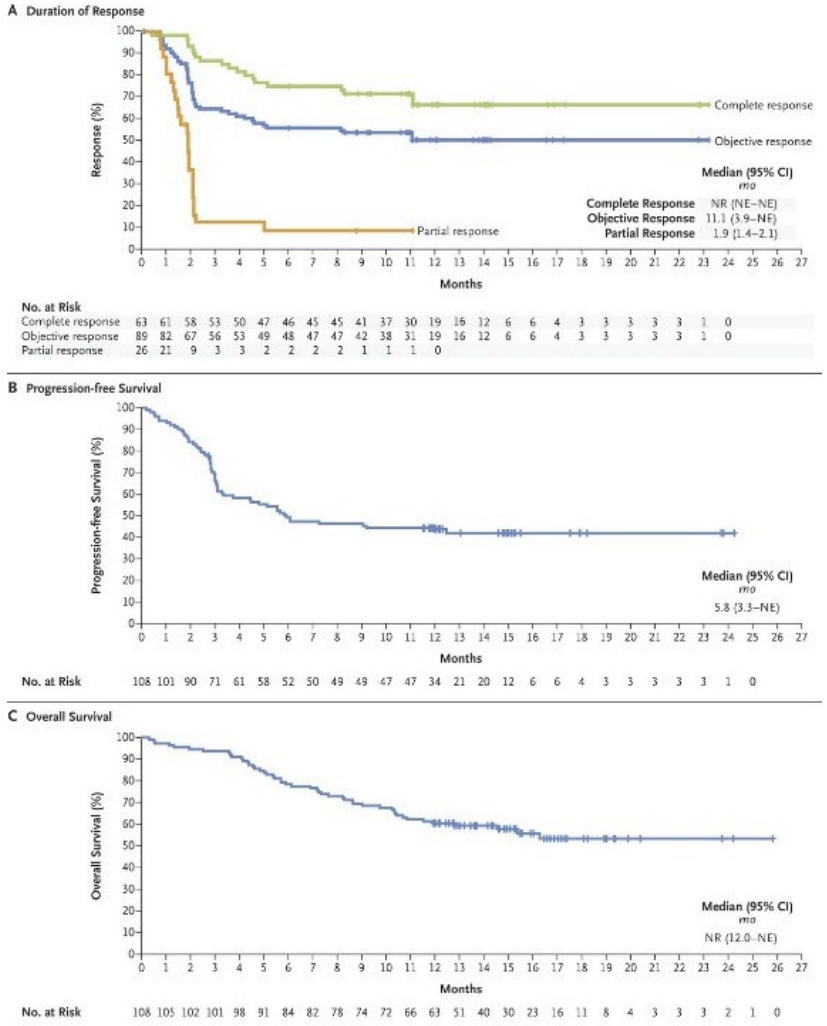
AXICABTAGENE CILOLEUCEL

ZUMA-1

Results:

12-month PFS: 44% (95% CI 34 – 53)

12-month OS: 59% (95% CI 49 – 68)

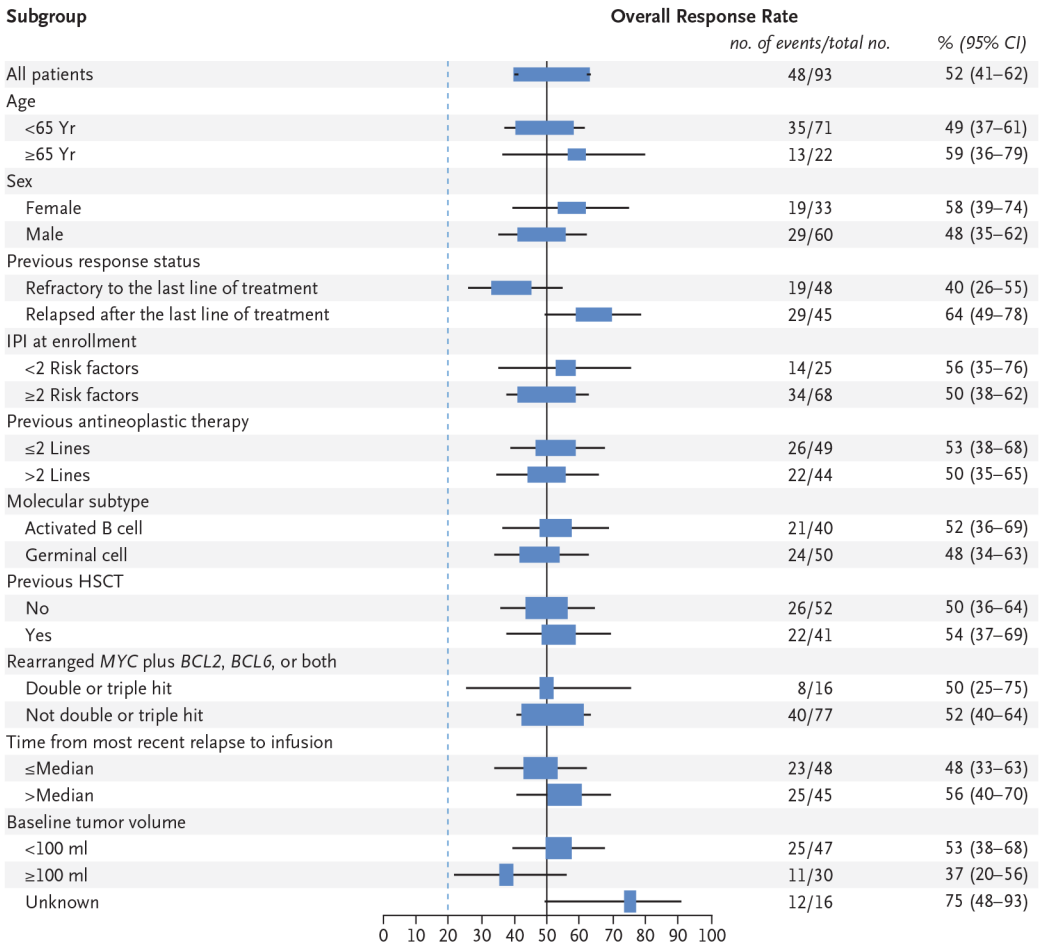


Neelapu SS et al. N Engl J Med 2017;377:2531-2544.

TISAGENLECLEUCEL

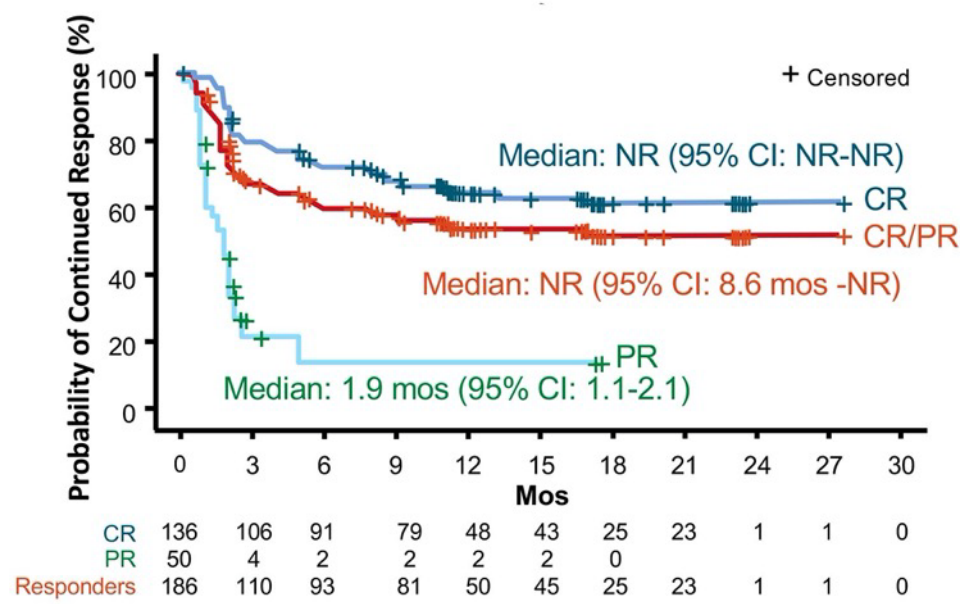
JULIET Trial

	ORR	CR
Best response	52%	40%



Schuster S et al. N Eng J Med 2019

Lisocabtagene maraleucel



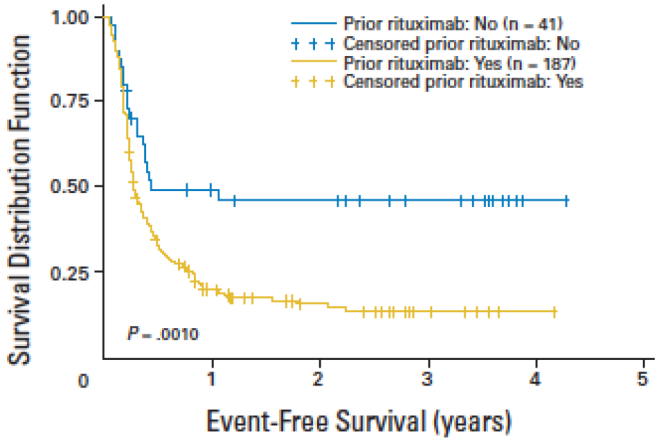
Characteristic	Liso – cel (n = 256)
ORR, % (95% CI)	73 (67 – 78)
CR rate, % (95% CI)	53 (47 – 69)
Secondary CNS, n (%)	7 (3)
Time to first response, median, mos (range)	1.0 (0.7 – 8.9)
DoR at 6 months, %, (95% CI)	60.4 (52.6 - 67.3)
DoR at 12 months, %, (95% CI)	54.7 (46.7 – 62.0)

Abramson J, et al. Lancet, 2020

How about CAR-Ts in second line?

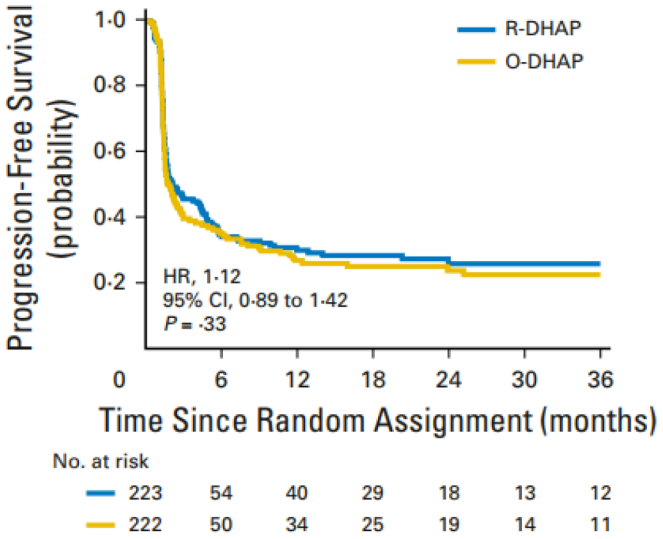
Poor performance of second line therapy

CORAL



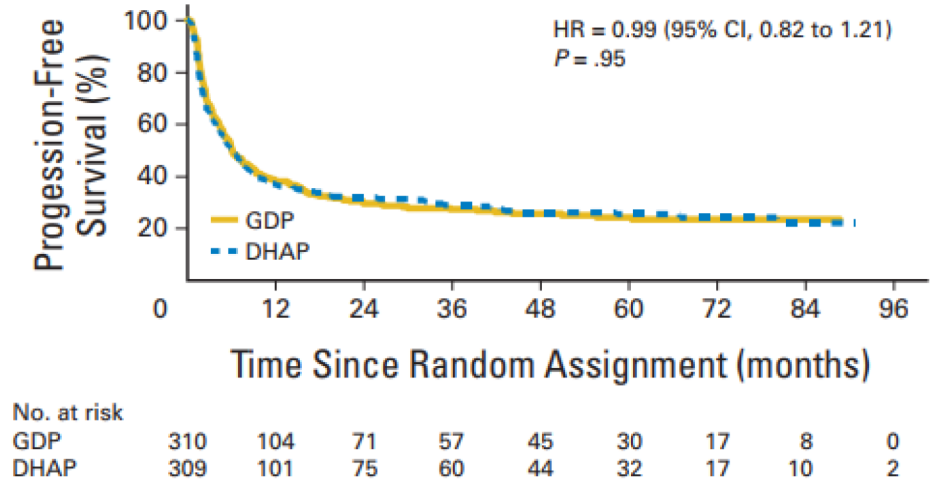
Gisselbrecht, et al. JCO 2010

ORCHAARD



van Imhoff, et al. JCO 2017

NCIC-CTG LY.12



Crump, et al. JCO 2014

Three RCTs of CAR-T vs. “standard” 2nd line therapy

Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD

TRANSFORM Study: Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase 3 TRANSFORM Study

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami

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

Michael R. Bishop,[1] Michael Dickinson[2], Duncan Purtill[3], Pere Barba[4], Armando Santoro[5], Nada Hamad[6], Koji Kato[7], Anna Sureda[8], Richard Greil[9],

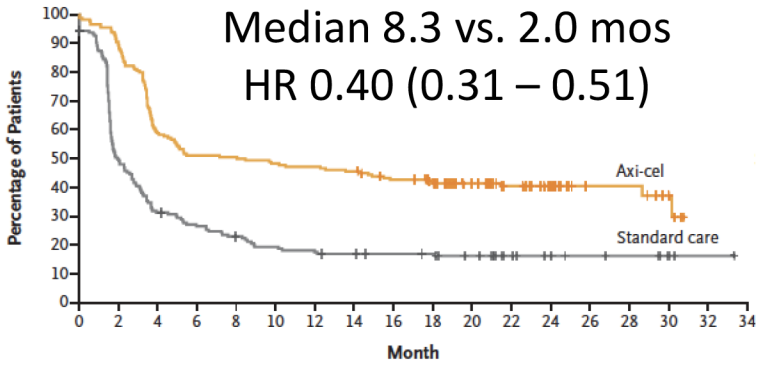
Axi - cel

N = 359
75% refractory
Double hit = 16%

ORR: 83% vs. 50%
CRR: 65% vs. 32%

EFS

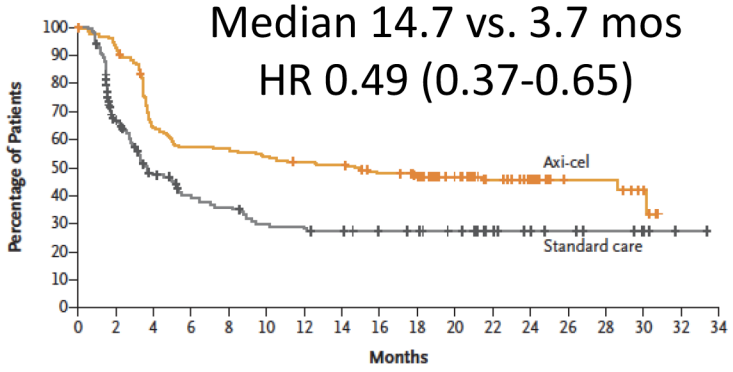
Median 8.3 vs. 2.0 mos
HR 0.40 (0.31 – 0.51)



No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

PFS

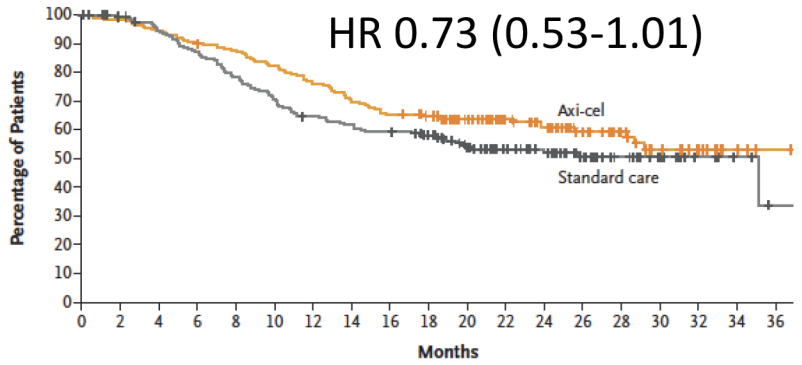
Median 14.7 vs. 3.7 mos
HR 0.49 (0.37-0.65)



No. at Risk																	
Axi-cel	180	166	112	100	99	94	90	88	80	73	56	43	28	12	12	6	
Standard care	179	94	61	47	43	35	33	31	28	27	24	15	11	9	7	4	1	0

OS

Median NR vs. 35.1 mos
HR 0.73 (0.53-1.01)



No. at Risk																		
Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2
Standard care	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1

Median follow up = 24.9 months

Locke F, et al. N Engl J Med 2022

Liso - cel

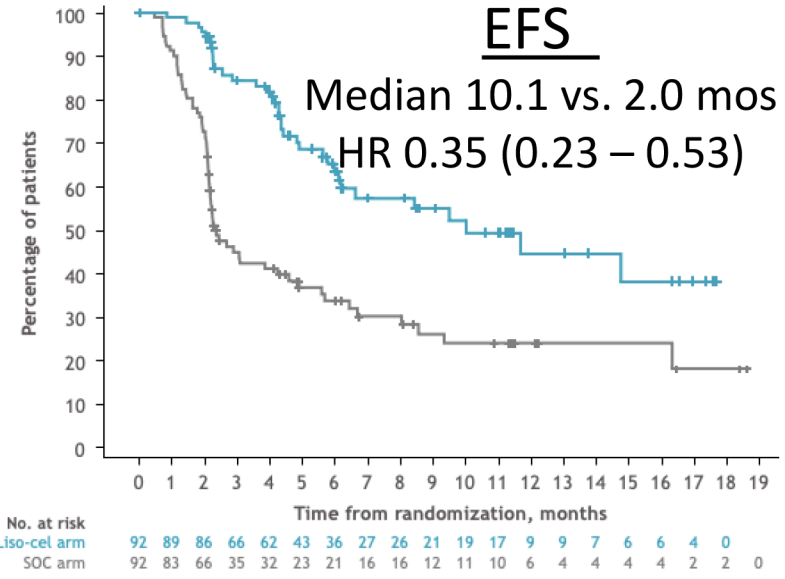
N = 184
75% refractory
Double hit = 24%

ORR: 86% vs. 48%
CRR: 66% vs. 39%

50% of SOC crossed - over

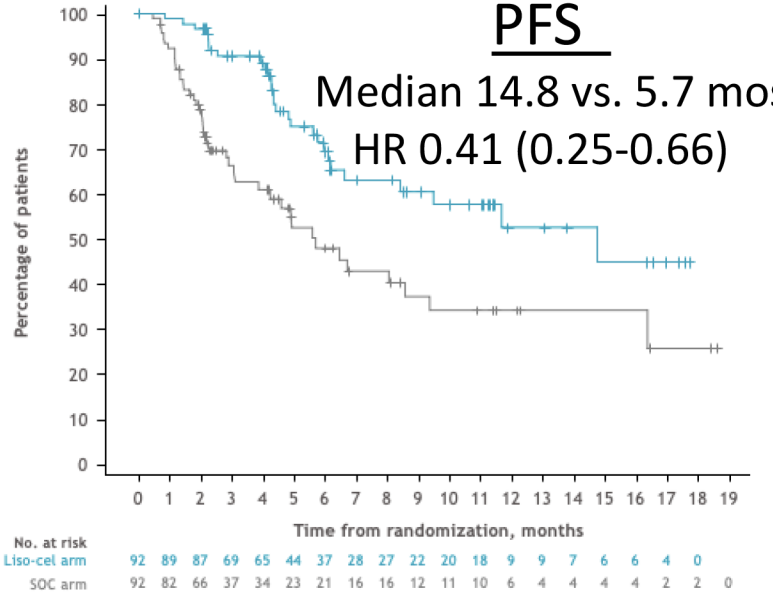
EFS

Median 10.1 vs. 2.0 mos
HR 0.35 (0.23 – 0.53)



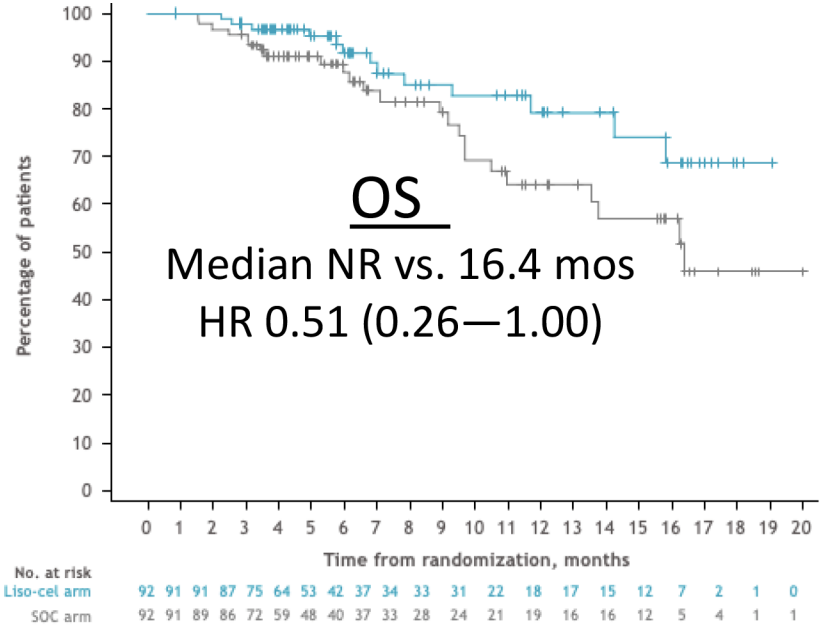
PFS

Median 14.8 vs. 5.7 mos
HR 0.41 (0.25-0.66)



OS

Median NR vs. 16.4 mos
HR 0.51 (0.26—1.00)

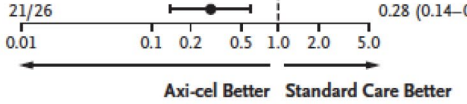


Median follow up = 6.3 months

Kamdar M, et al. Proc ASH 2021

Benefit of CAR-T present in all subgroups

Subgroup	Axi-cel (no. of patients with event/total no.)	Standard Care (no. of patients with event/total no.)	(95% CI)
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



Locke F, et al. N Engl J Med 2022

Subgroup		Stratified HR (95% CI)	Stratified HR
sAAIPI	0 or 1		0.298
	2 or 3		0.404
Prior response status	Refractory		0.350
	Relapse to last prior therapy		0.343
Age group, years	< 65		0.277
	≥ 65 to < 75		0.301
Sex	Male		0.331
	Female		0.346
ECOG PS (at screening)	0		0.420
	1		0.201
SPD	> 50 cm^2		0.099
	≤ 50 cm^2		0.366
Lactate dehydrogenase	< 500 U/L		0.350
	≥ 500 U/L		0.460
Prior CT response status	Chemorefractory (PD, SD)		0.338
	Chemosensitive (PR, CR)		0.320
NHL type	DLBCL		0.357
	HGBCL		0.413
DLBCL subtype	DLBCL NOS de novo		0.395
	DLBCL transformed from indolent NHL		0.218
DLBCL subtype based on cell of origin	GCB		0.348
	ABC, non-GCB		0.477

Kamdar M, et al. Proc ASH 2021

PILOT study

Age, median (range), years	74 (53-84)
ECOG PS 2	26%
CrCl <60	25%

Sehgal A, et al. ASH 2023. #105

PILOT study population

- Age ≥ 18
- DLBCL
- 1 prior line with anthracycline and antiCD20

- Age ≥ 70
- ECOG PS of 2
- DLCO ≤ 60%
- LVEF ≤ 50%
- CrCl ≤ 60%
- AST/ALT >2 x

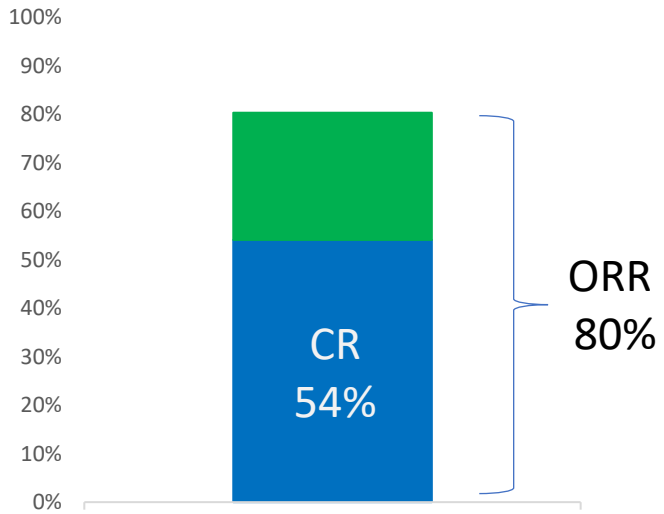
- 74 patients underwent apheresis
- 62 were infused liso-cel (1 non – conforming)
  - 61 patients included

Age, median (range), years	74 (53-84)
ECOG PS 2	26%
CrCl <60	25%

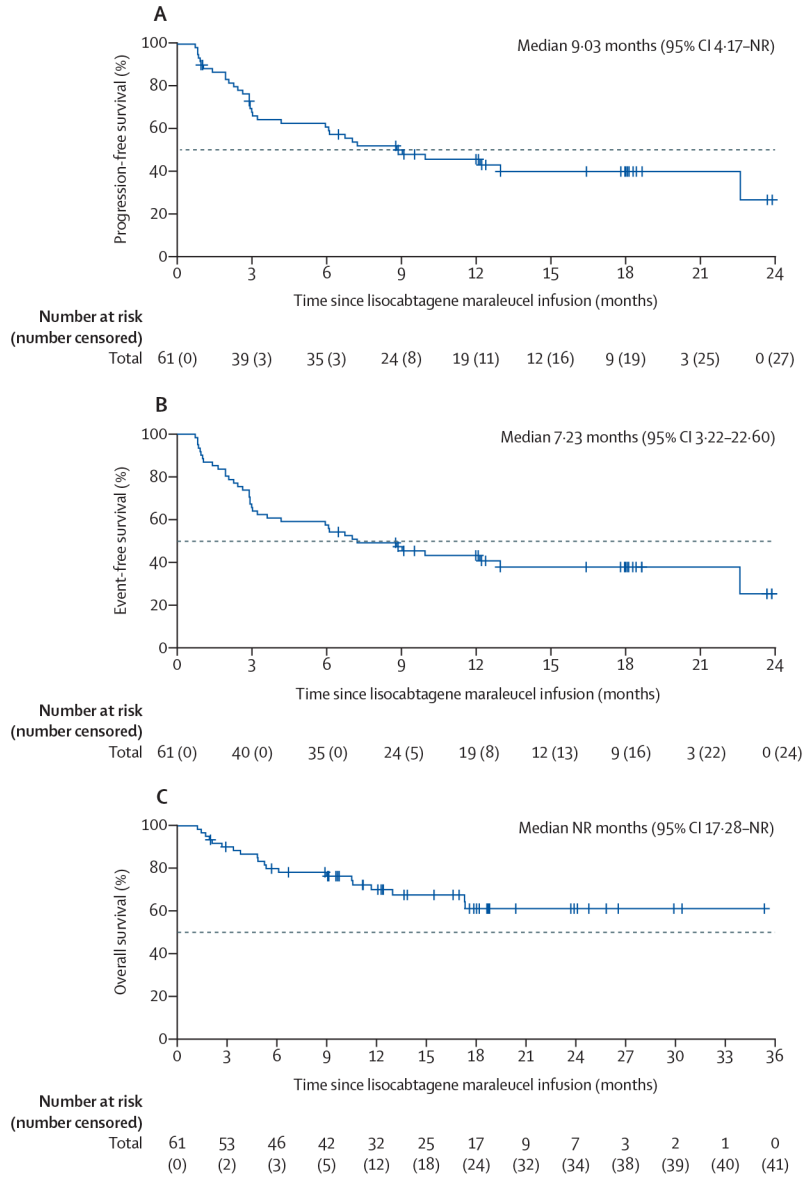
- Median follow up 24 months

Sehgal A, et al. ASH 2023. #105

PILOT study outcomes



- 18-month PFS rate 43%
- 18-month OS rate 59%
- Continued response at 18 months 53%



Sehgal A, et al. ASH 2023. #105

PILOT study safety

- 97% of patients had TEAE within 90 days of liso-cel
  - 38% CRS, 2% grade 3
  - 31% neurologic events, 5% grade 3
  - 8% hypogammaglobulinemia
  - 7% infections

- Later follow up safety events
  - Anemia and thrombocytopenia (5%)

Sehgal A, et al. ASH 2023. #105

Mosunetuzumab Showed Early Efficacy in R/R DLBCL[1]

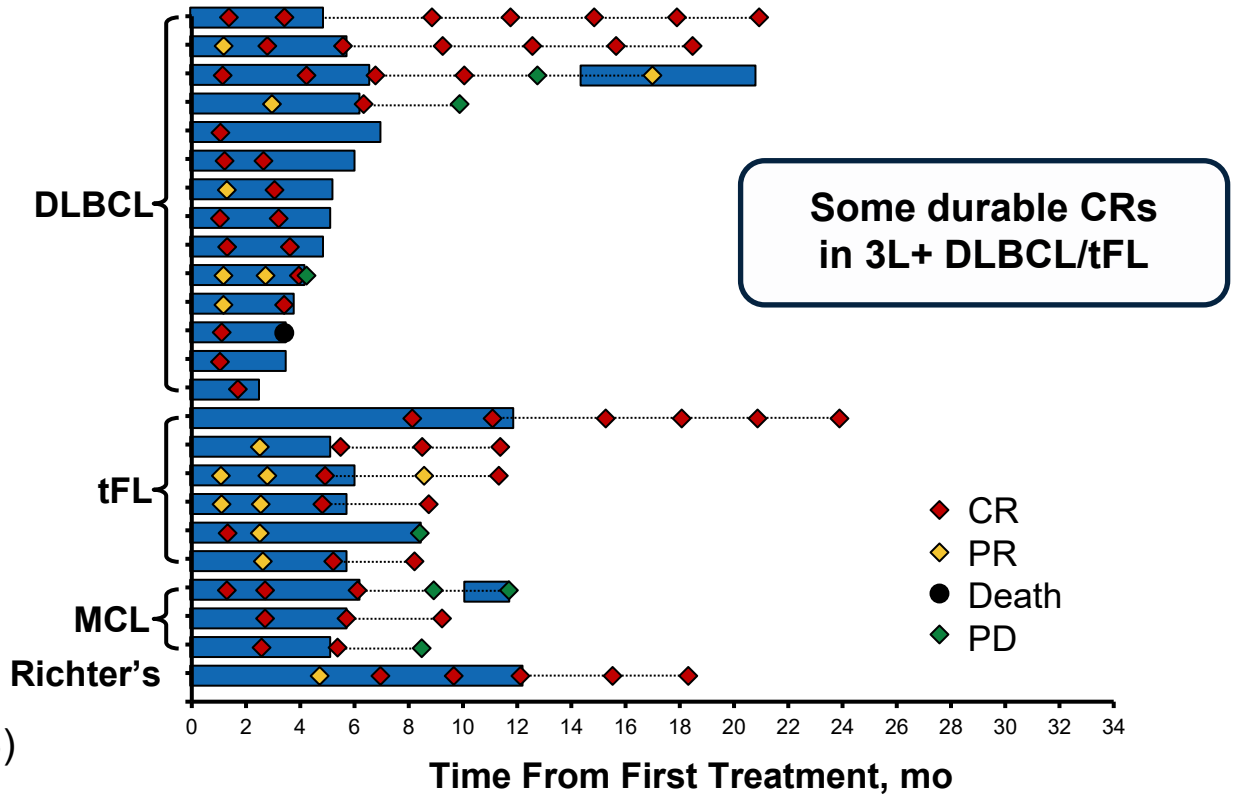
Response Rates and Duration in Aggressive NHL

Investigator-Assessed BOR (Pooled Data From 2.8-mg to 40.5-mg Cohorts)

	N[a]	ORR, n (%)	CR, n (%)
Aggressive NHL	124	46 (37.1)	24 (19.4)
All 3L+ DLBCL/tFL	**98**	**37 (37.8)**	**20 (20.4)**
Refractory to prior anti-CD20	88/98	32 (36.4)	18 (20.5)
With prior autoSCT	32/98	17 (53.1)	11 (34.3)

Increased efficacy in patients with higher exposure to mosunetuzumab, as measured by CD20 receptor occupancy (RO%)

Time on Treatment and DOR Among Aggressive NHL Complete Responders



17 CR patients (70.8%) remain in remission (up to 16 months off treatment)

[a] Efficacy-evaluable patients: patients who were enrolled for ≥3 months or had response data available at any time, or discontinued treatment for any cause.
CCOD: August 9, 2019.

1. Schuster S et al. ASH 2019. Abstract 6.

Updated Evidence Continues to Show Promising Efficacy and Safety of Mosunetuzumab in Aggressive NHL[1]

Mosunetuzumab, administered with step-up dosing, has a manageable safety profile and induces durable complete responses in R/R B-NHL, including in patients receiving prior CAR-T therapy

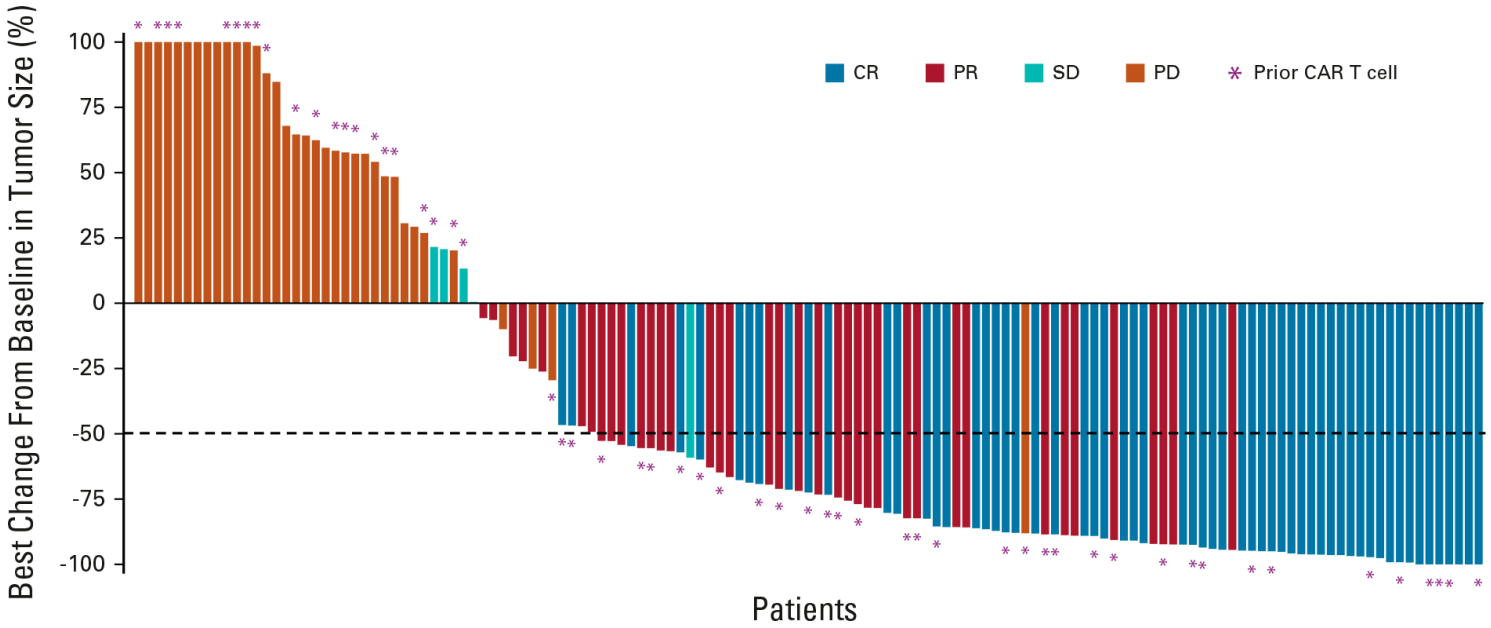
Best Objective Response[a]	Aggressive NHL[b] (n = 129)
ORR, No. (%) [95% CI]	45 (34.9) [26.7 to 43.8]
Complete response, No. (%) [95% CI]	25 (19.4) [13.0 to 27.3]
Partial response, No. (%) [95% CI]	20 (15.5) [9.7 to 22.9]
Stable disease, No. (%) [95% CI]	9 (7.0) [3.2 to 12.8]
Progressive disease, No. (%) [95% CI]	70 (54.3) [45.3 to 63.1]
Duration of response, median [95% CI], months	7.6 [5.6 to 22.8]
Duration of response in patients with complete response, median [95% CI], months	22.8 [7.6 to NE]

- ORR of 34.9% in patients with aggressive B-NHL
- Among patients with a complete response, the median DOR was 22.8 months
- **Safety**: 27% of patients overall experienced CRS; mostly low-grade (grade ≥3: 1%) and mainly confined to cycle 1

1. Budde EL et al. J Clin Oncol. 2022;40(5):481-491

Epcoritamab

Characteristic	Patients (N = 157)
Prior lines of antilymphoma therapy, No. (%)	
2	46 (29.3)
3	50 (31.8)
≥ 4	61 (38.9)
Primary refractory disease,[c] No. (%)	96 (61.1)
Refractory to last systemic therapy,[c] No. (%)	130 (82.8)
Refractory to ≥ 2 consecutive lines of therapy,[c] No. (%)	119 (75.8)
Prior autologous stem-cell transplant, No. (%)	31 (19.7)
Relapsed within 12 months after prior autologous stem-cell transplant, No./n (%)	18/31 (58.1)
Prior CAR T-cell therapy, No. (%)	61 (38.9)
Progressed within 6 months of CAR T-cell therapy, No./n (%)	46/61 (75.4)
Prior anthracycline therapy, No. (%)	154 (98.1)
First line	139 (88.5)
Second line	16 (10.2)



Thieblemont C, et al. J Clin Oncol 2023

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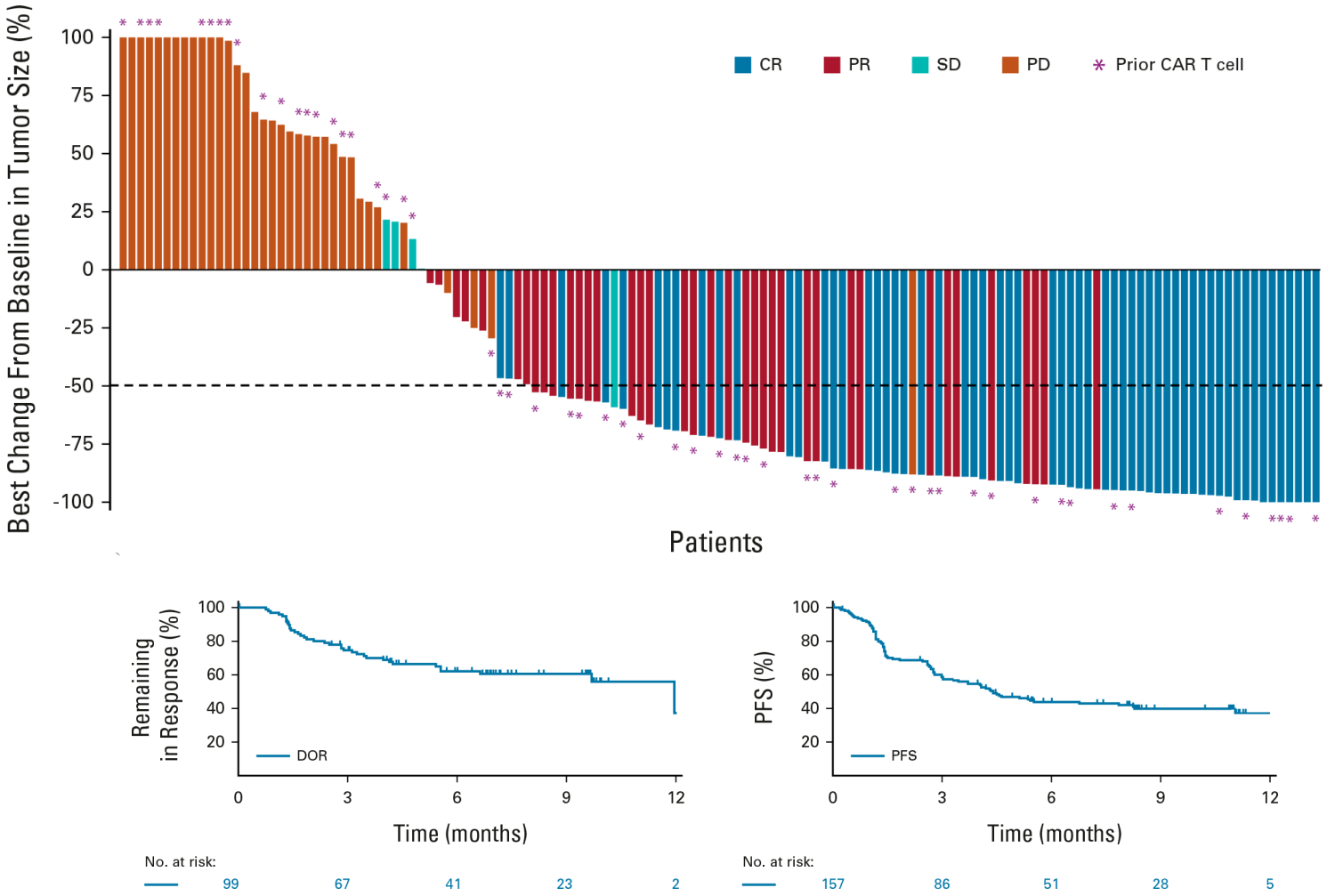


Thieblemont C, et al. J Clin Oncol 2023

Glofitamab Induced Robust Responses in R/R NHL Across Histological Subtypes, Including DLBCL and tFL[1]

Response, N (%)	All Histologies	DLBCL	tFL
All cohorts, N	171	73	29
ORR	92 (53.8)	30 (41.1)	16 (55.2)
CR	63 (36.8)	21 (28.8)	10 (34.5)
≥10-mg cohort, N	98	38	14
ORR	62 (63.3)	21 (55.3)	9 (64.3)
CR	51 (52.0)	16 (42.1)	9 (64.3)

Safety: CRS in 86 of 171 (50.3%) patients (grade 3 or 4: 3.5%); 2 (1.2%) patients experienced grade 3, transient immune effector cell-associated neurotoxicity syndrome-like symptoms

1. Hutchings M et al. *J Clin Oncol.* 2021;39:1959-1970.

Glofitamab Continues to Show Efficacy in R/R DLBCL…[1]

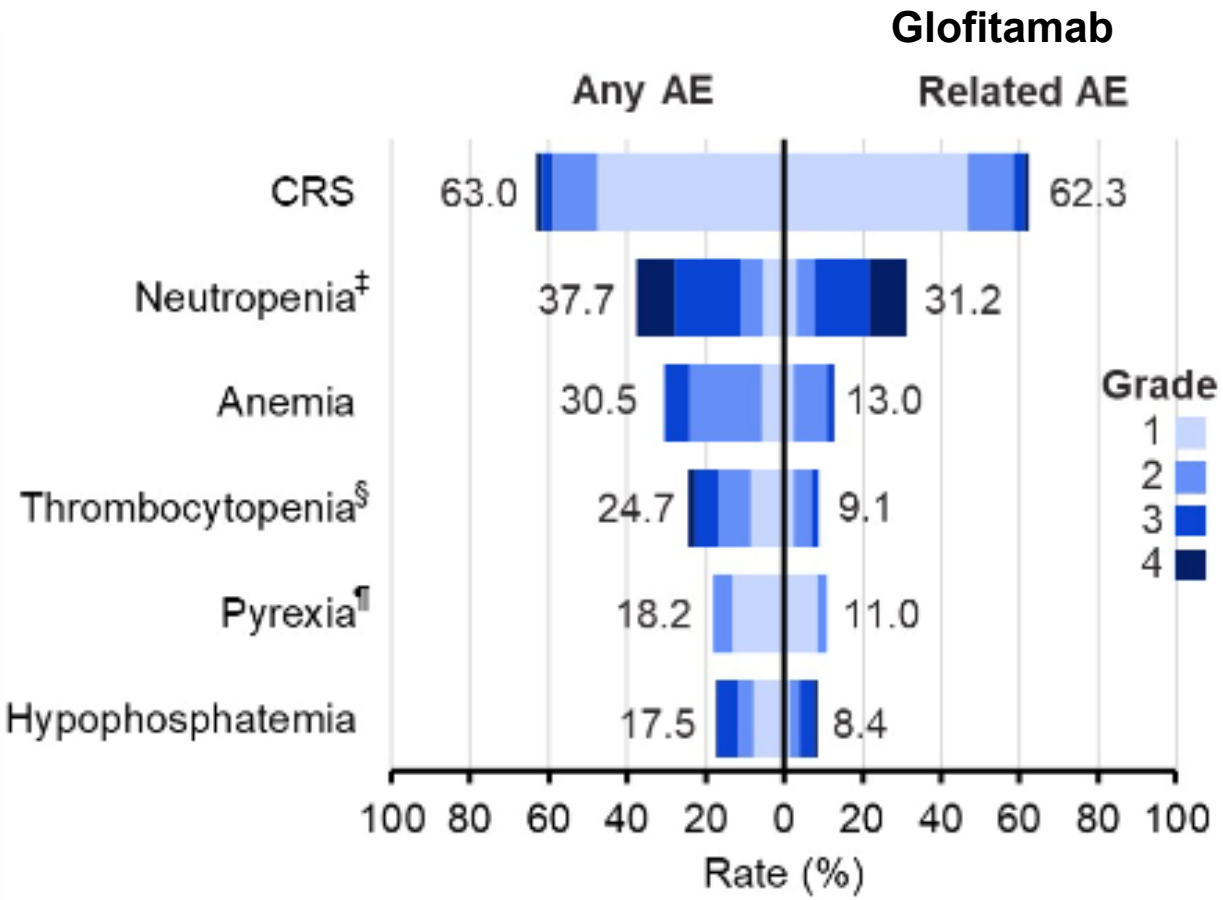
Response, N (%)	Glofitamab 2.5/10/30 mg)
All cohorts, N	61 / 155 (39.4)
ORR	80 / 155 (47.5
CR	61 / 155 (39.4)

- Median duration of follow-up: 12.6 months
- Early responses: median time to first CR was 42 days

1. Dickinson M, et al. ASCO 2022. Abstract 7500.

… With a Manageable Safety Profile[1]

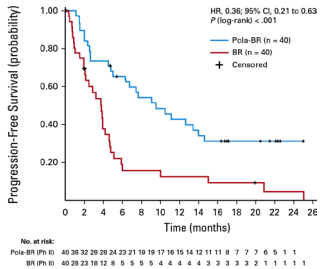
- Glofitamab was well-tolerated overall
- CRS was primarily associated with the initial doses, and was mostly grade 1 or 2
- Glofitamab-related AEs leading to discontinuation were uncommon



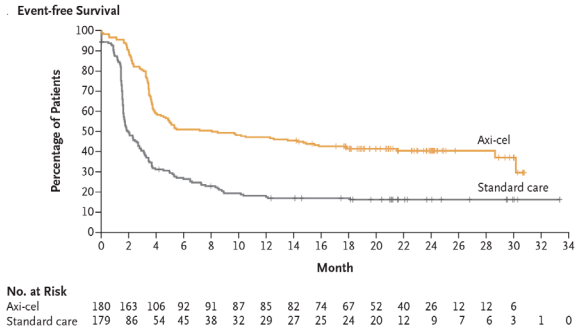
1. Dickinson M, et al. ASCO 2022. Abstract 7500.

¿Qué hacemos con todo esto?

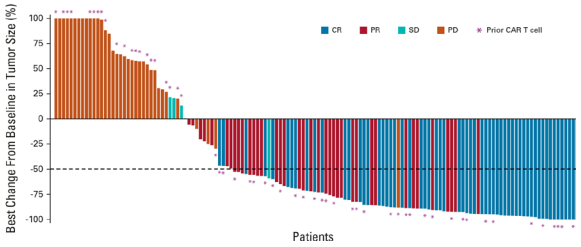
Pola - BR



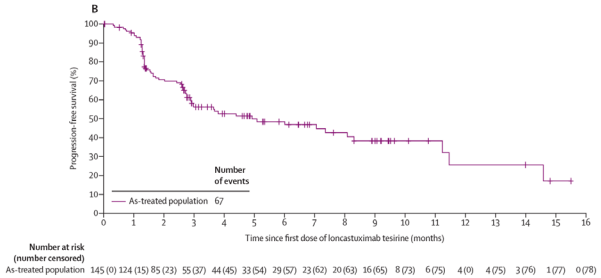
Axi-cel 2nd line



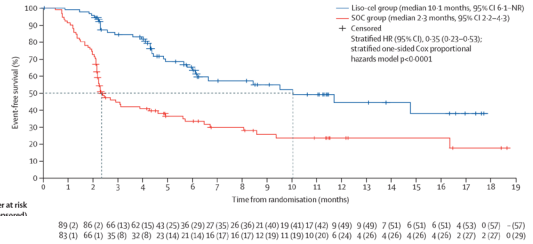
Epco Phase 1



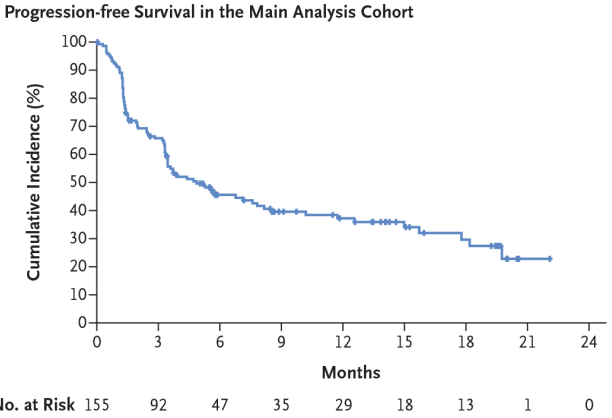
Lonca



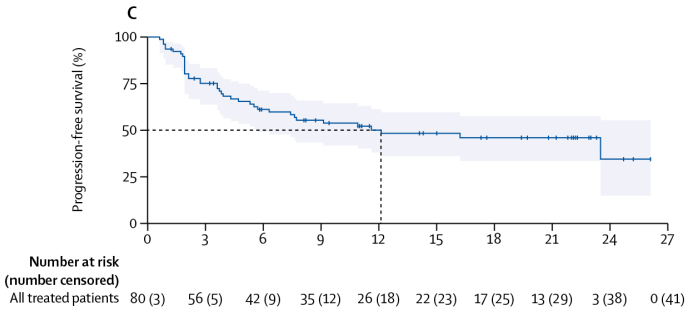
Liso-cel 2nd line



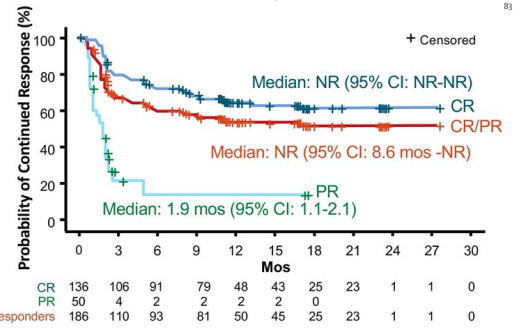
Glofit Phase 1



Tafa-Len

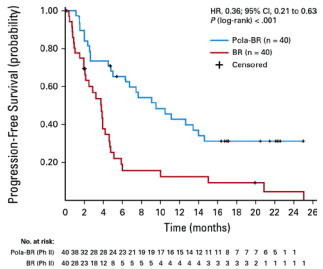


Liso-cel 3nd line

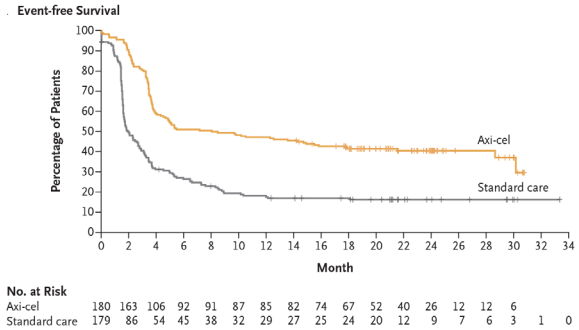


¿Qué hacemos con todo esto?

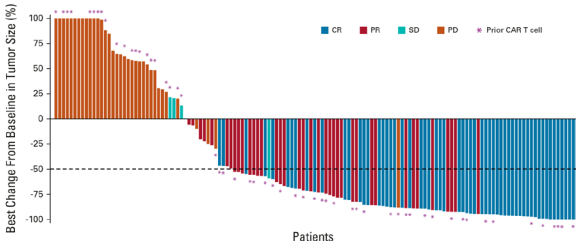
Pola - BR



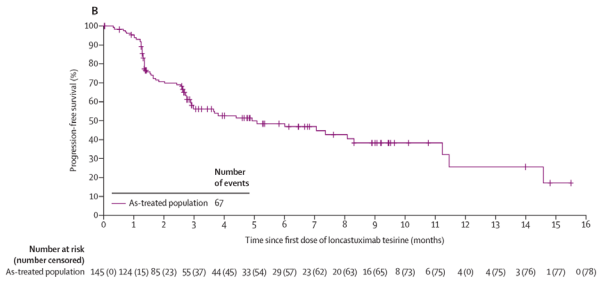
Axi-cel 2nd line



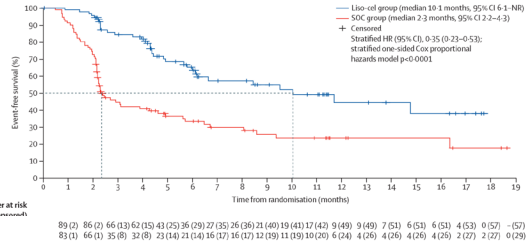
Epco Phase 1



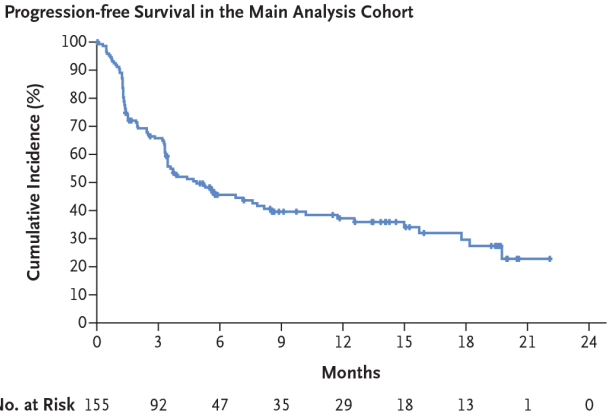
Lonca



Liso-cel 2nd line



Glofit Phase 1



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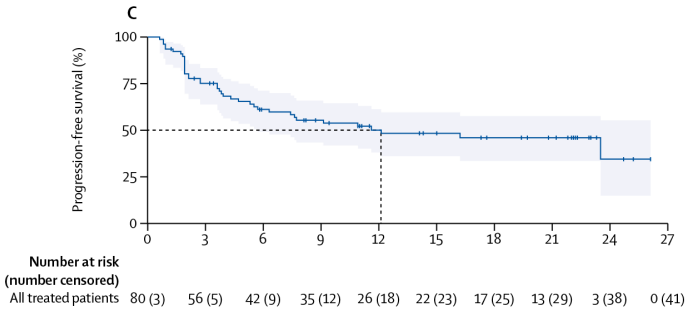

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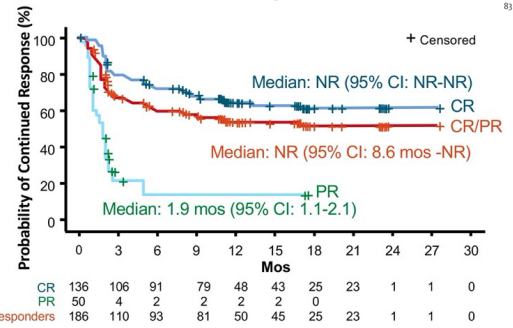
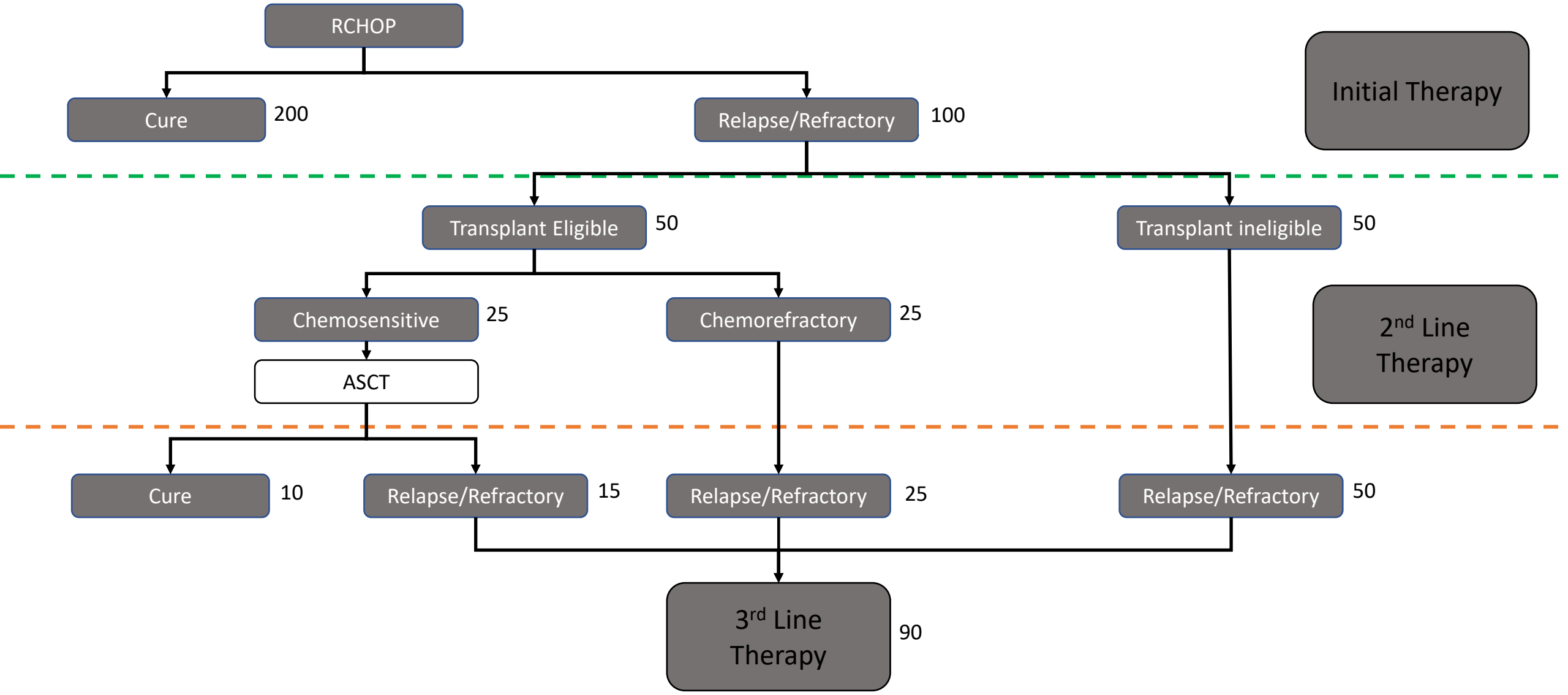


Desglosemos

- Se acaba la hegemonía de la eligibilidad para transplante
  - Comparte con eligibilidad para CAR T
- Las terapias no celulares para DLBCL recaído o refractario ahora tienen eficacia
  - Pero todavía pueden mejorar

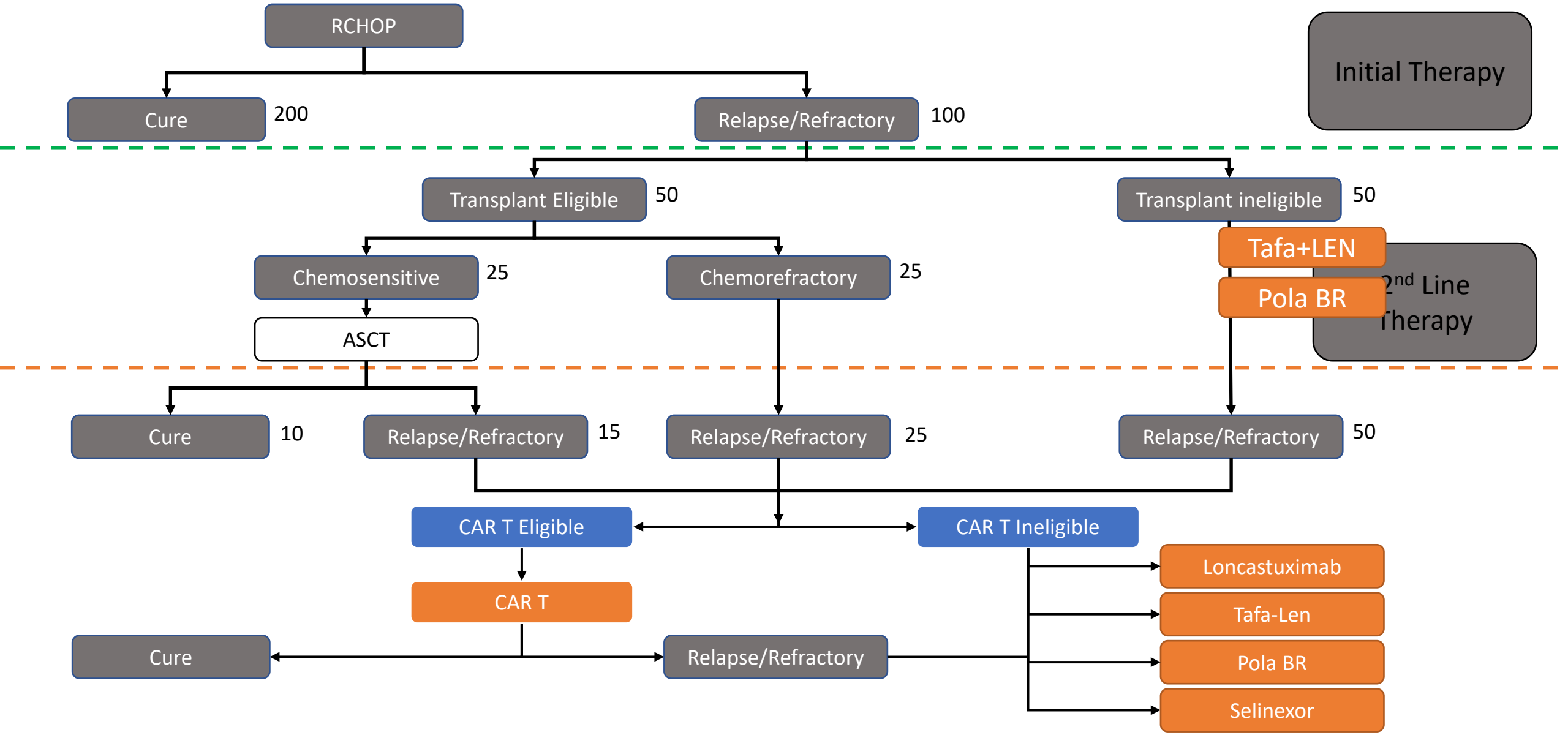
Como trato a mis pacientes hoy

El algoritmo antiguo

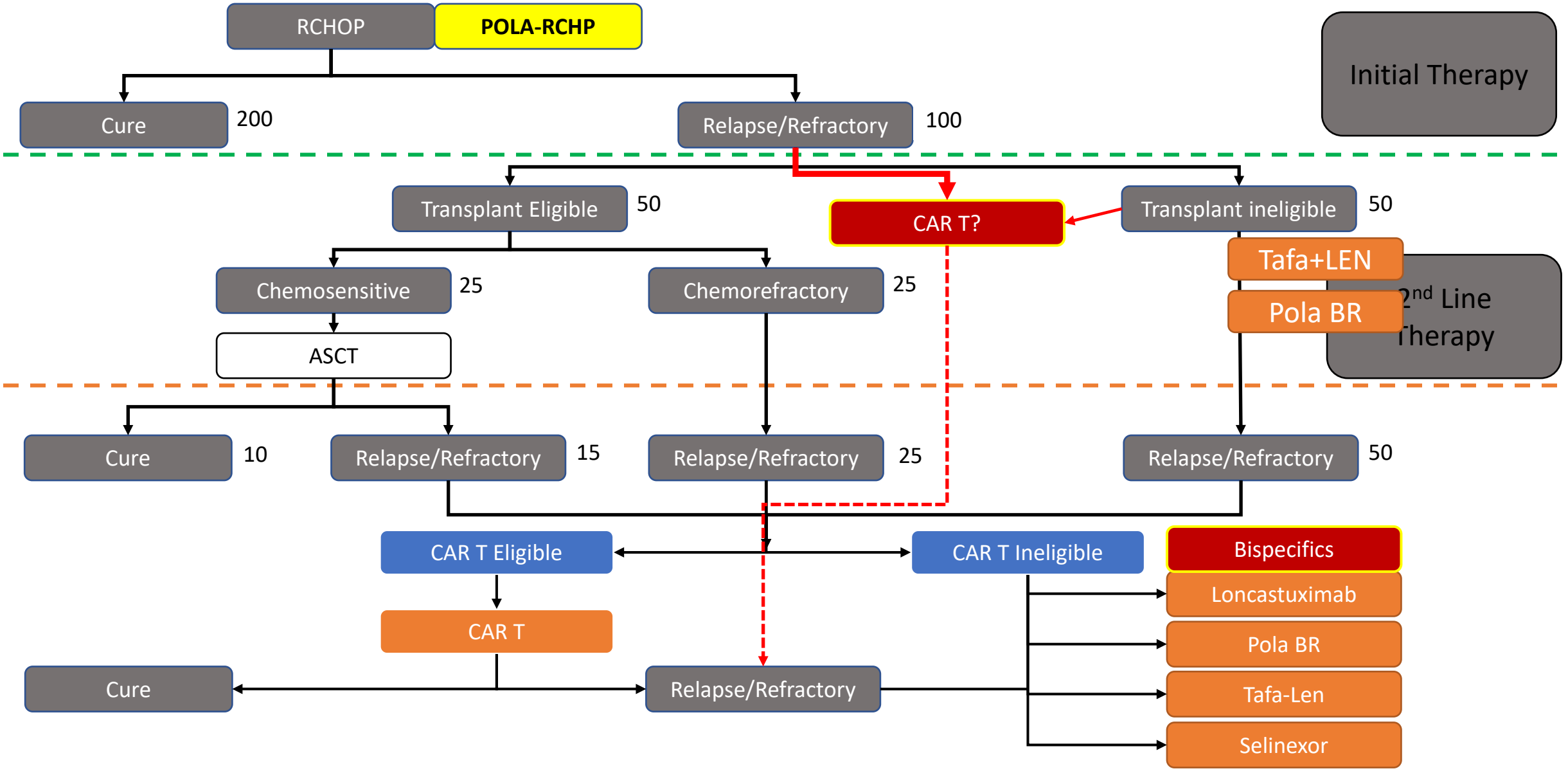


Adapted from Friedberg JW, Hematology Am Soc Hematol Educ Program. 2011;2011:498-505
and Pettengel R. ESMO E-Learning: Modern Management of DLBCL. http://oncologypro.esmo.org, May 2017.

The current algorithm



The future algorithm



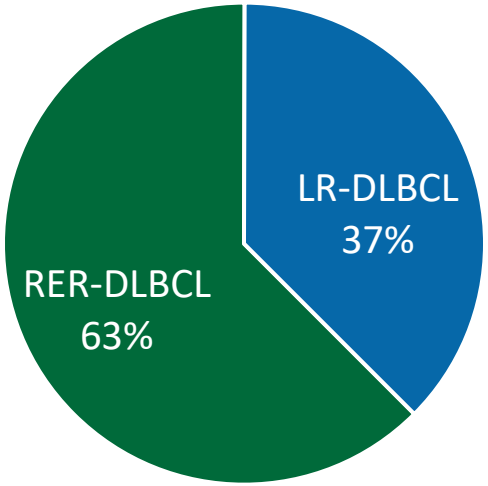
Let’s complicate it a little more

Methods

- Retrospective analysis, 3 centers (CCF, UH, Wash U)
- DLBCL patients treated with R-ICE (2010 – 2020).
  - RER-DLBCL: refractory or relapse ≤ 12 months after completing 1st line
  - LR-DLBCL: relapse > 12 months after completing 1st line
- Outcomes:
  - Disease response
  - Progression free survival
  - Overall survival
  - Cumulative incidence of relapse

Results

- 291 DLBCL treated with R-ICE
  - 182 (62.5%) had refractory disease or relapse <12 months after 1L(RER-DLBCL)
  - 109 (37.5%) had relapse >12 months after 1L (LR-DLBCL)



- Median follow up: 53 months (IQR 36-76)

Results

- Baseline characteristics

Characteristic	RER-DLBCL	LR-DLBCL	p value
Female gender	53 (29.1%)	43 (39.4%)	0.073
Age, median (IQR)	61.0 (52-67)	65 (56-70)	0.003
Transformed indolent	47 (25.8%)	34 (31.2%)	0.346
B symptoms	29 (17.3%)	23 (23.2%)	0.264
Elevated LDH	80 (49.1%)	57 (57.6%)	0.203
IPI ≥ 3	29 (15.9%)	25 (22.9%)	0.535
ECOG PS ≥ 2	16 (8.8%)	7 (6.4%)	0.305

Results

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Characteristic	RER-DLBCL	LR-DLBCL	p value
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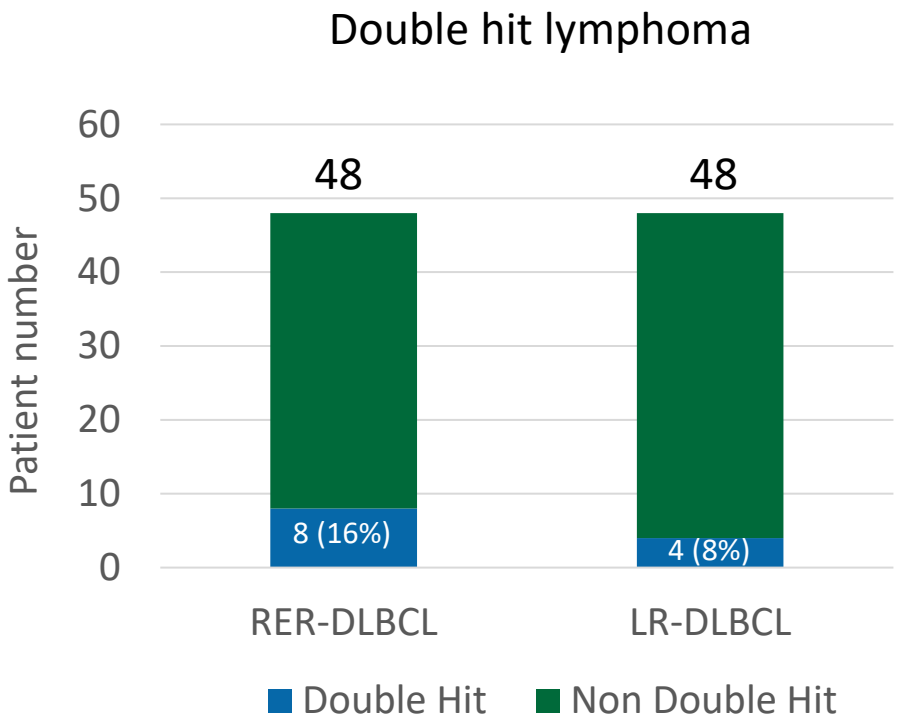
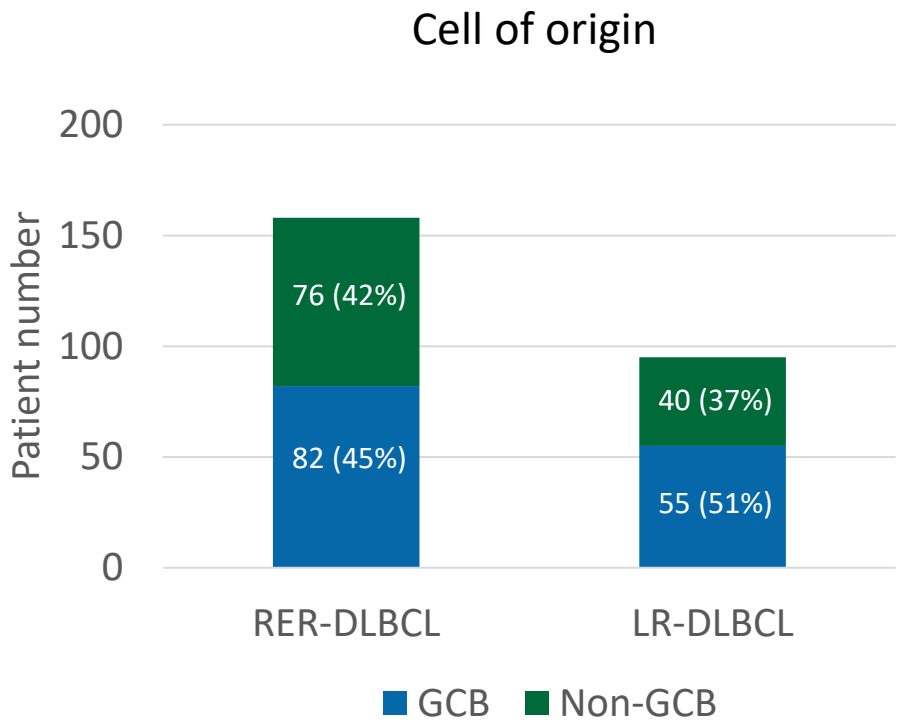
Results

- Biologic characteristics

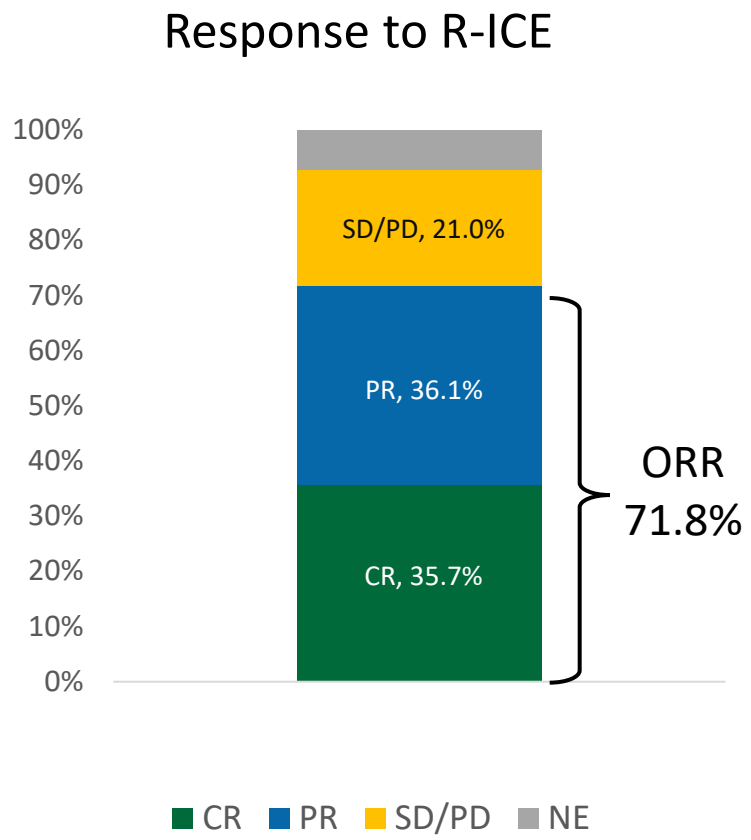




Results

- Response to R-ICE, all patients (n = 291)

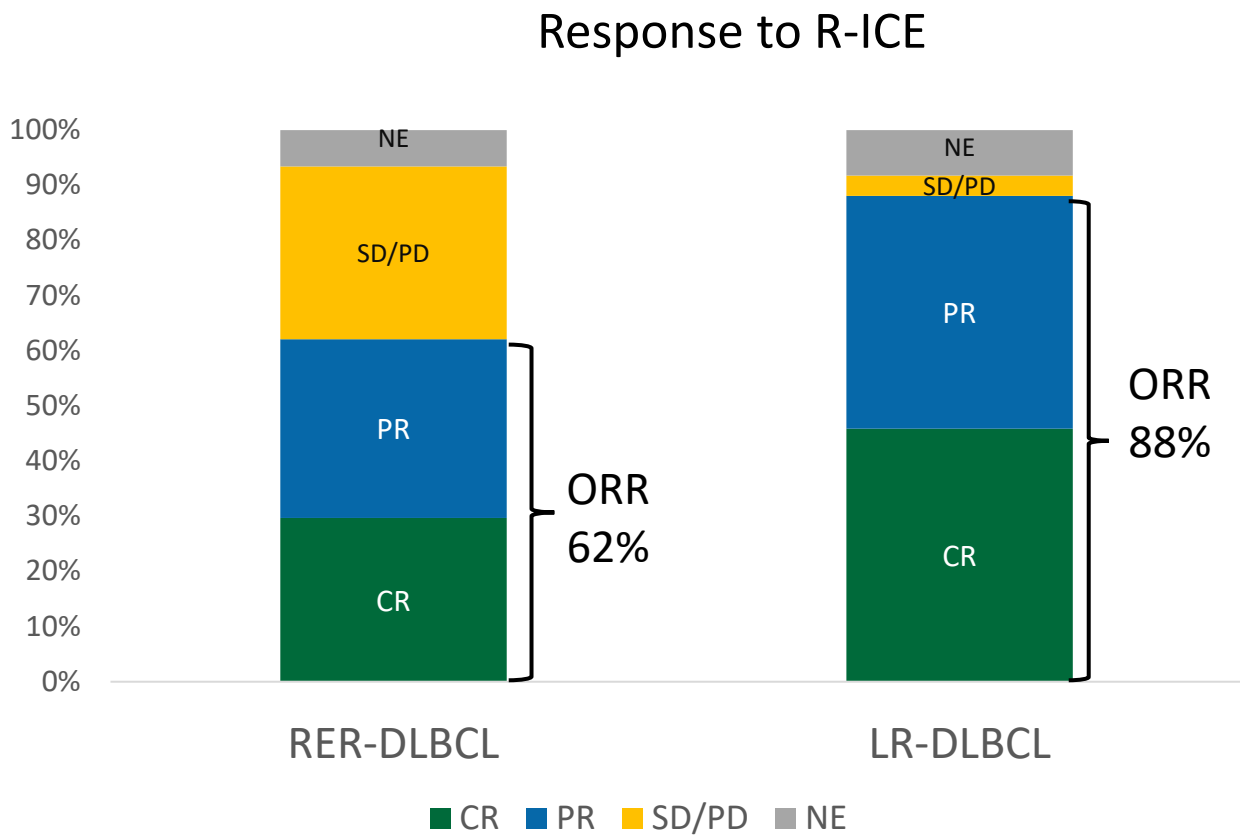
Best response	
CR	104 (35.7%)
PR	105 (36.1%)
SD/PD	61 (21.0%)
NE	21 (7.2%)



Results

- Response to R-ICE based on time from relapse to 1st line therapy

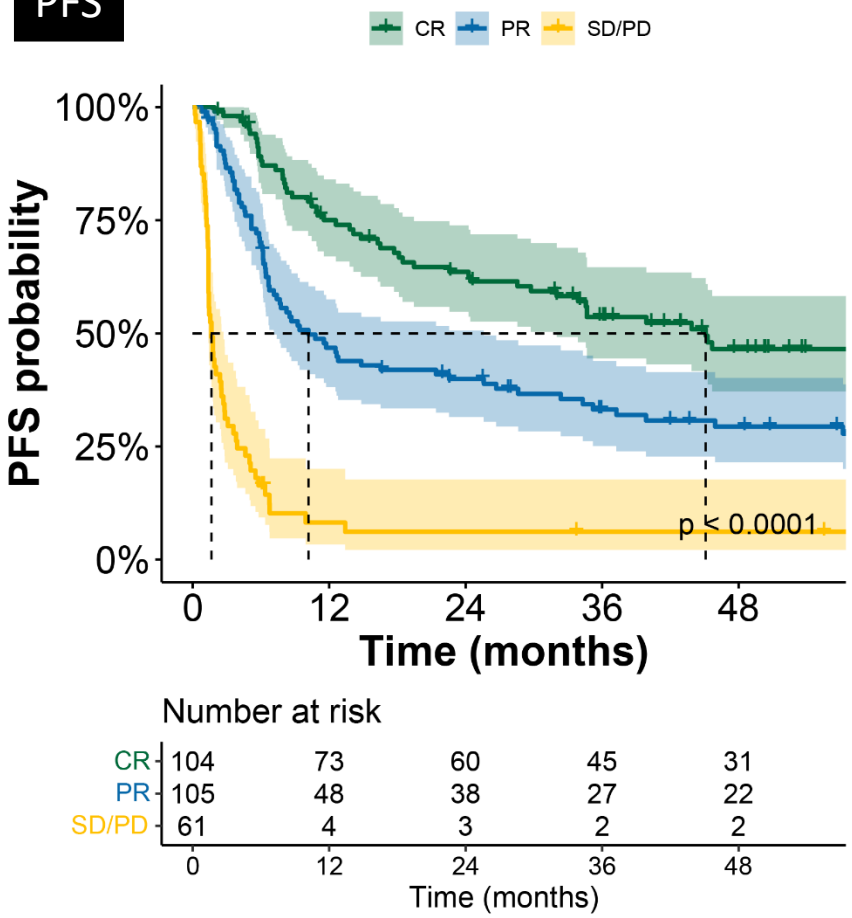
Best response	RER-DLBCL	LR-DLBCL	p value
CR	54 (29.7%)	50 (45.8%)	<0.0001
PR	58 (32.4%)	46 (42.2%)	
SD/PD	52 (31.3%)	4 (3.7%)	
NE	12 (6.6%)	9 (8.2%)	



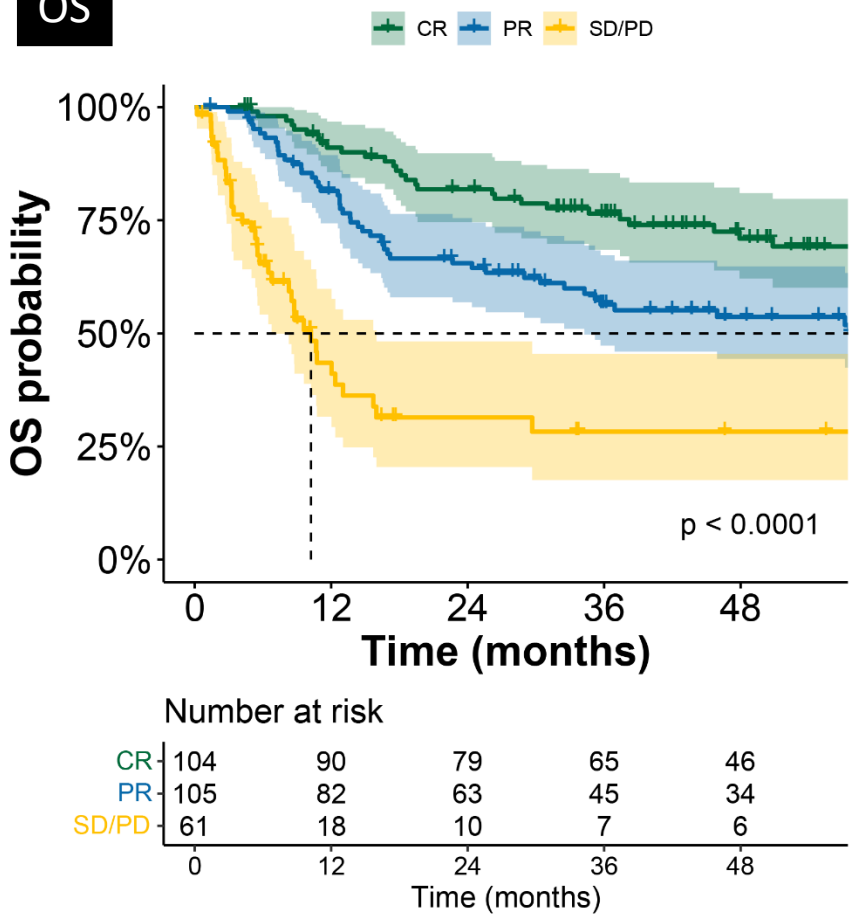
Results

- Outcomes according to response to R-ICE

PFS

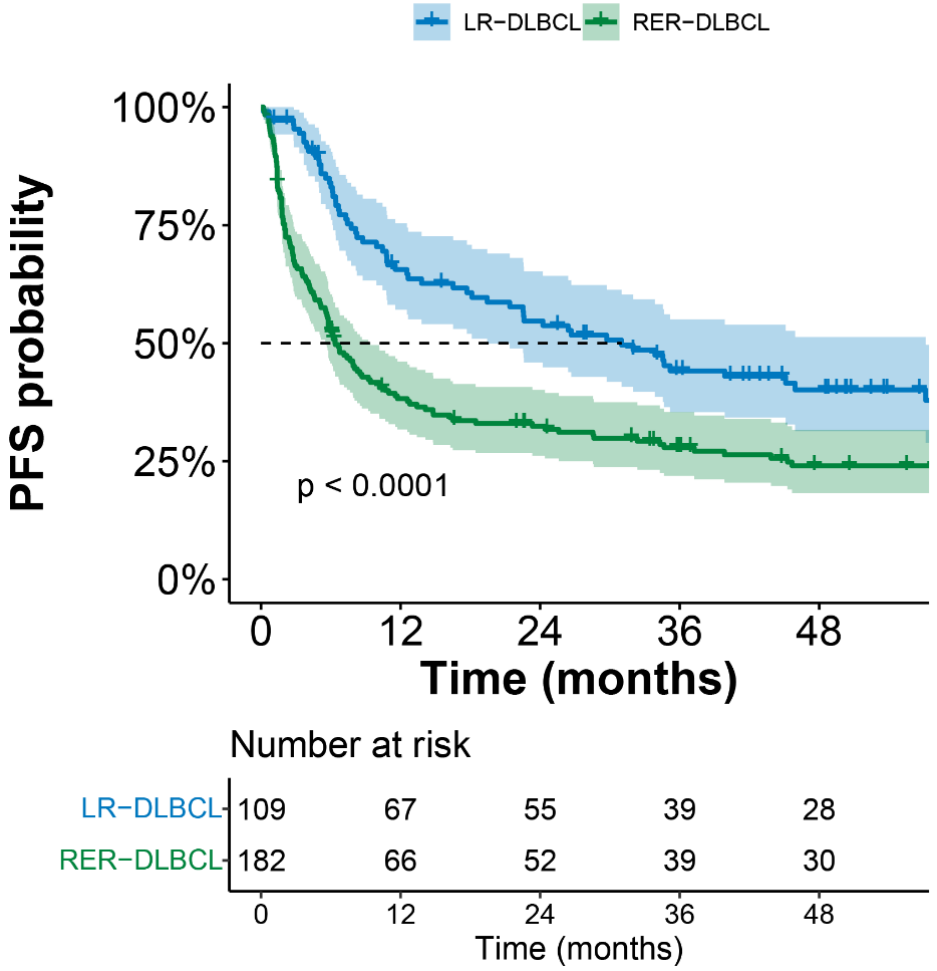


OS



Results

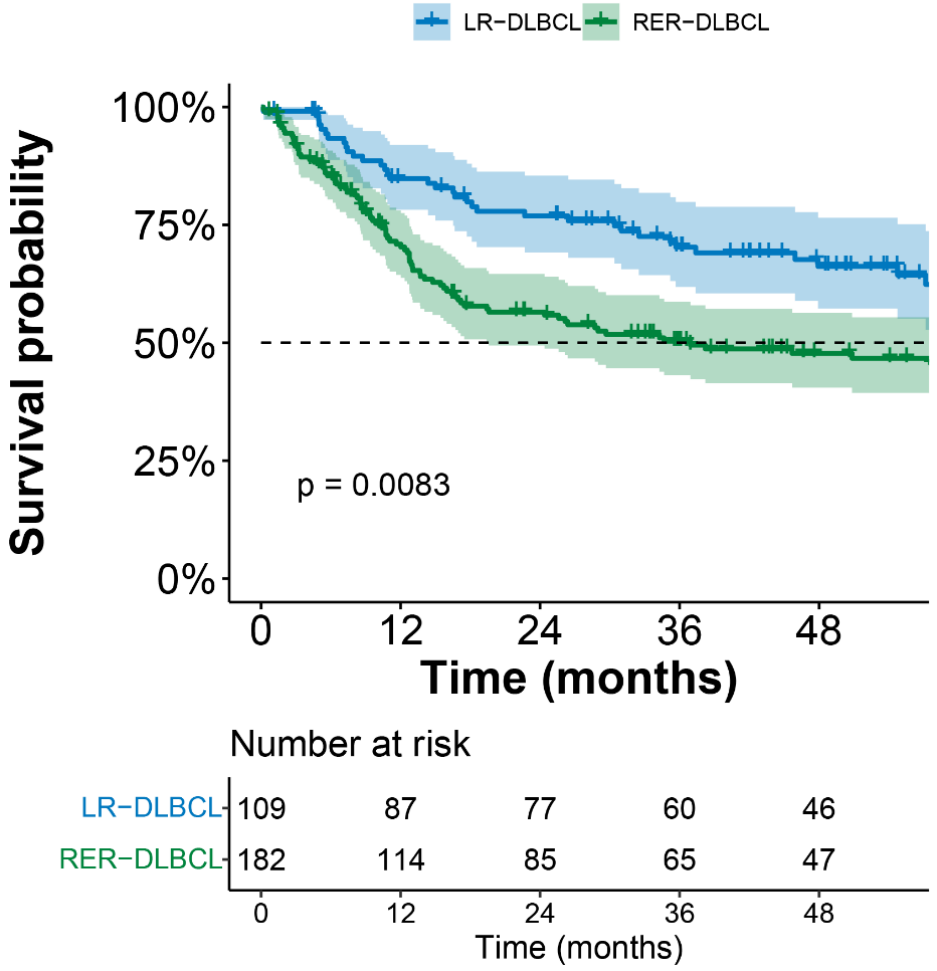
- Patients with RER-DLBCL had shorter median PFS than LR-DLBCL



	RER-DLBCL	LR-DLBCL	HR	p value
PFS, median	6 mos	31 mos	1.84	<0.001
4y PFS estimate	24%	40%		

Results

- Patients with RER-DLBCL had shorter median OS than LR-DLBCL

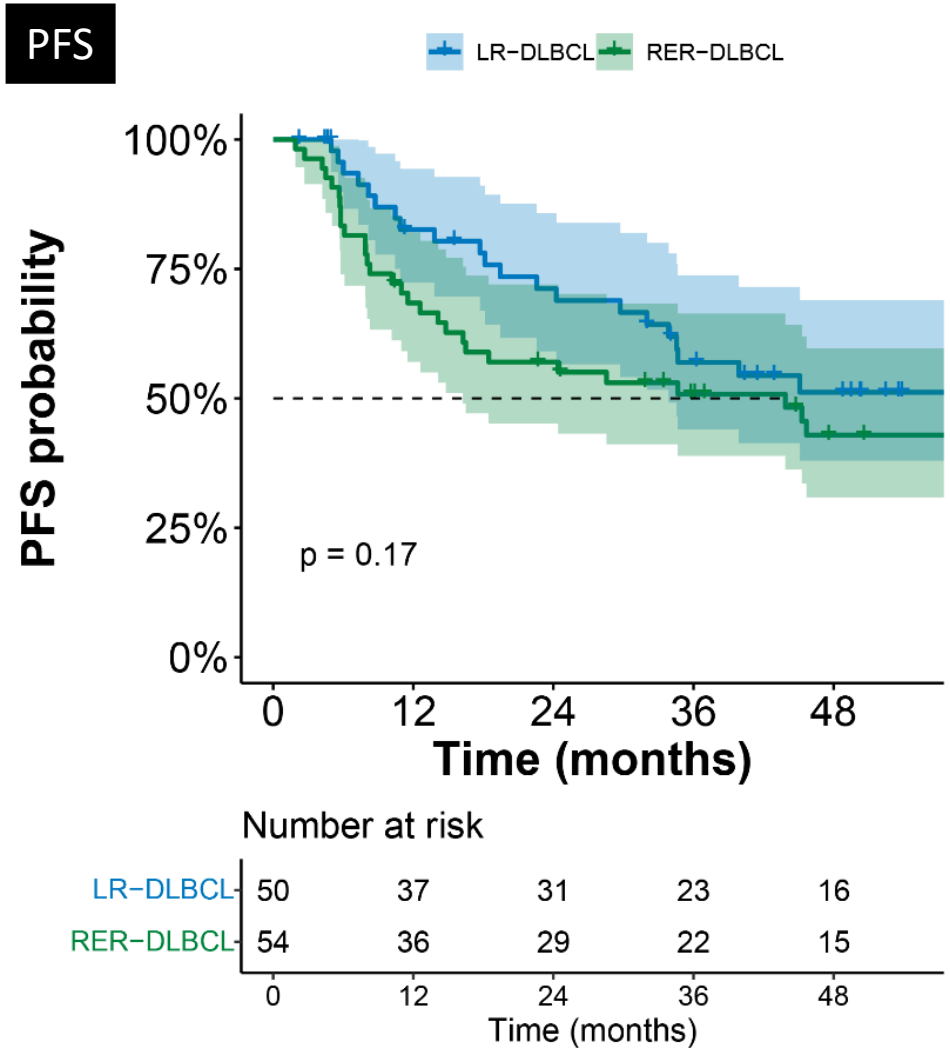


	RER-DLBCL	LR-DLBCL	HR	p value
OS, median	36 mos	68 mos	1.63	0.009
4y OS estimate	48%	66%		

Results

- Patients achieving CR after R-ICE had improved outcomes

	RER-DLBCL	LR-DLBCL	HR	p value
PFS, median	43 mos	NR	1.47	0.2
OS, median	85 mos	102 mos	0.98	> 0.9



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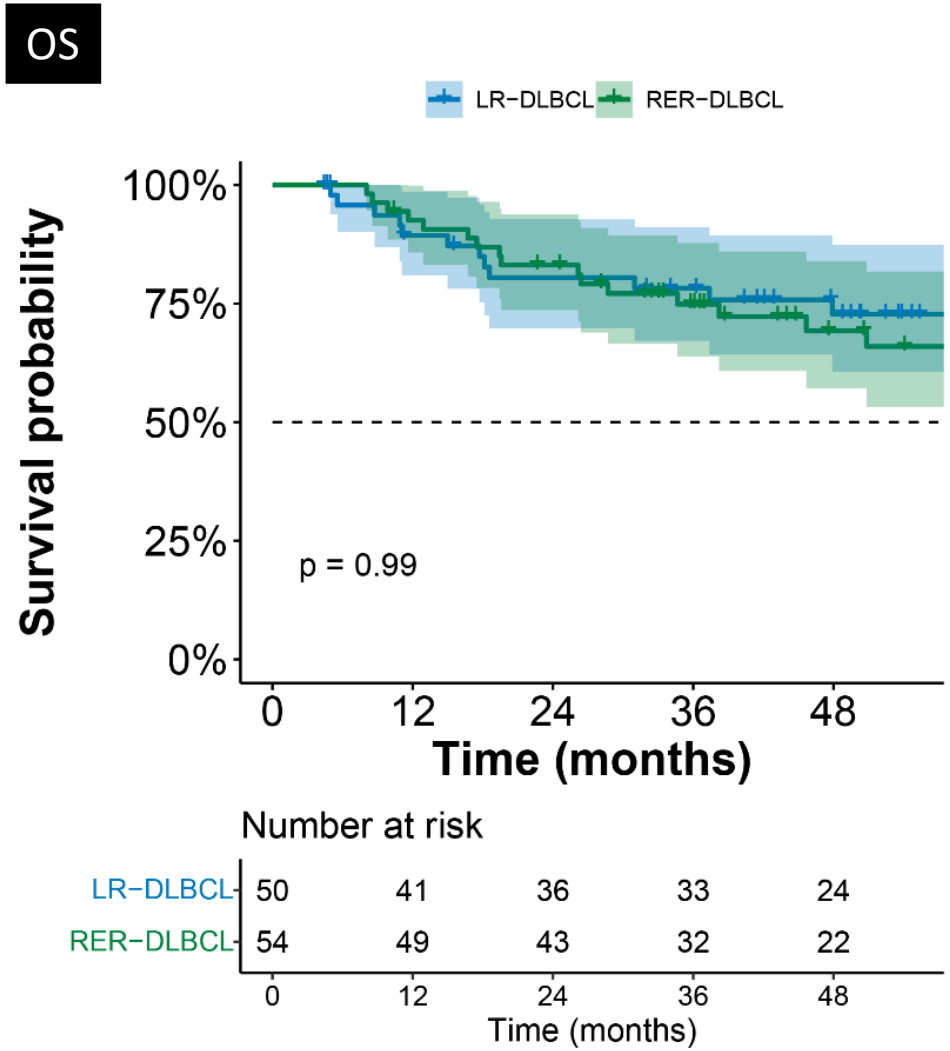
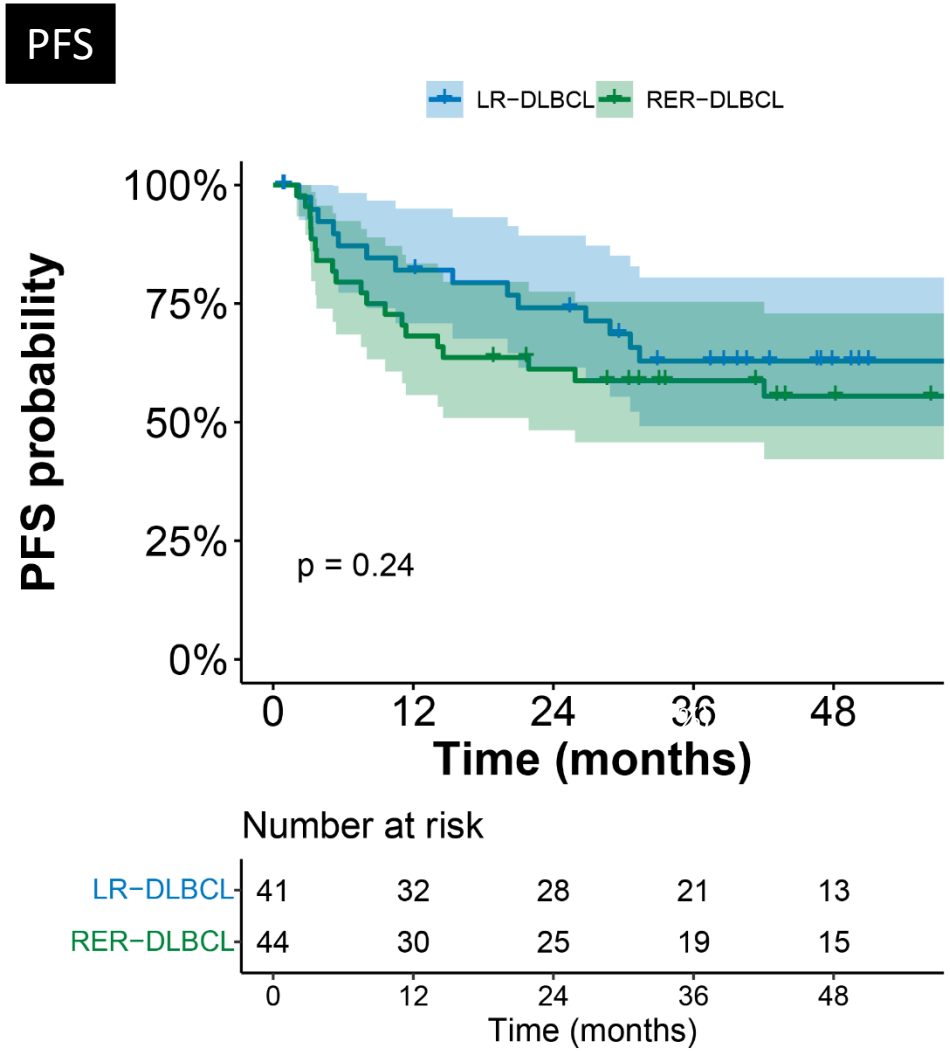


Results

- Patients undergoing ASCT in CR post R-ICE

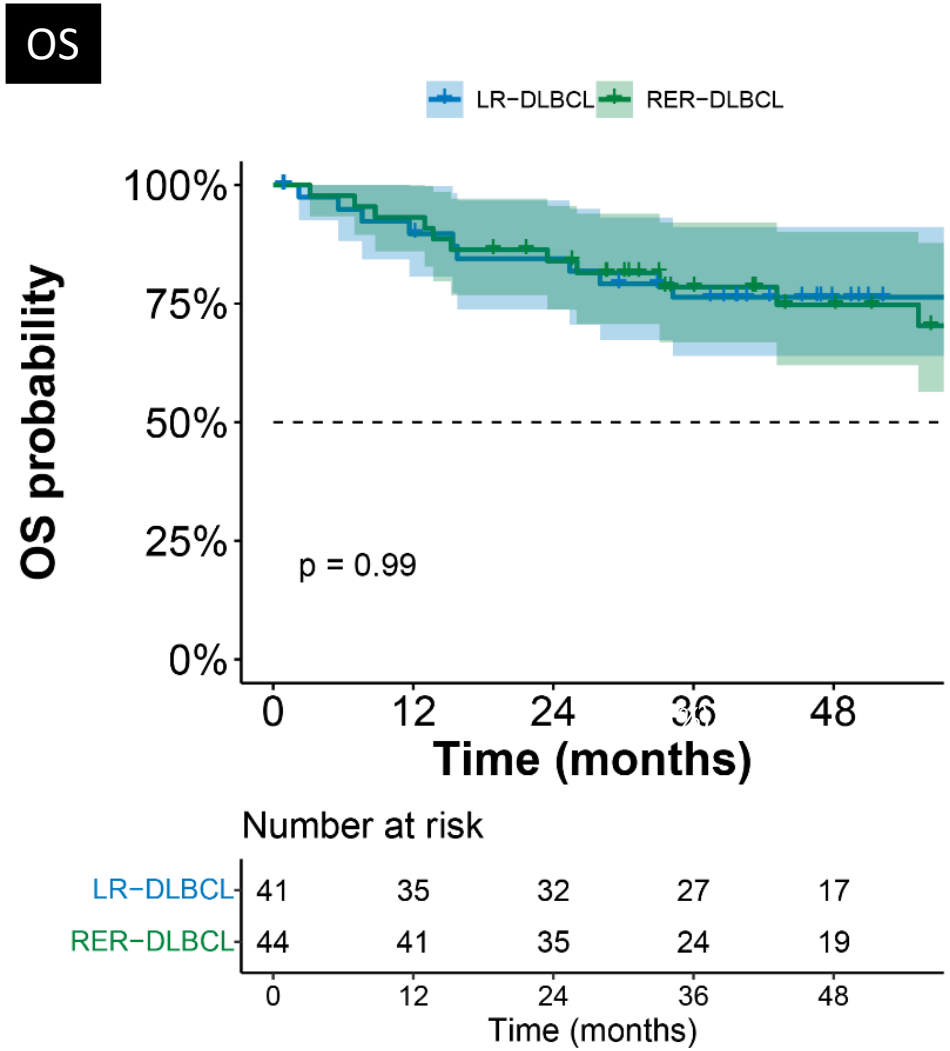
	RER-DLBCL	LR-DLBCL	HR	p value
4-year PFS	55%	63%	1.50	0.2
4-year OS	76%	75%	1.00	> 0.9



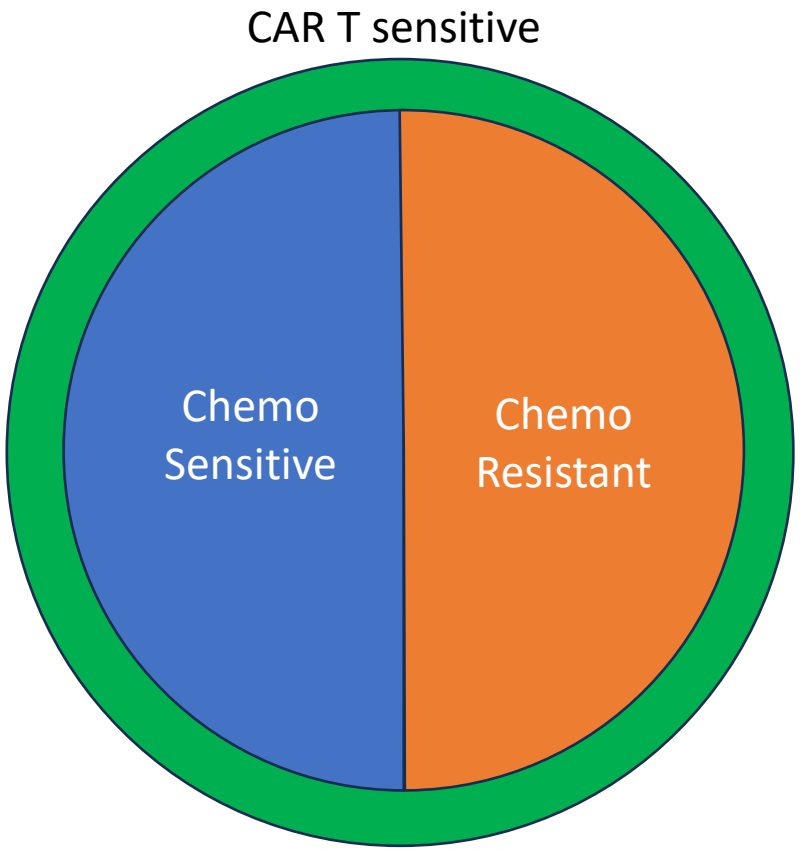
Results

- Patients undergoing ASCT in CR post R-ICE

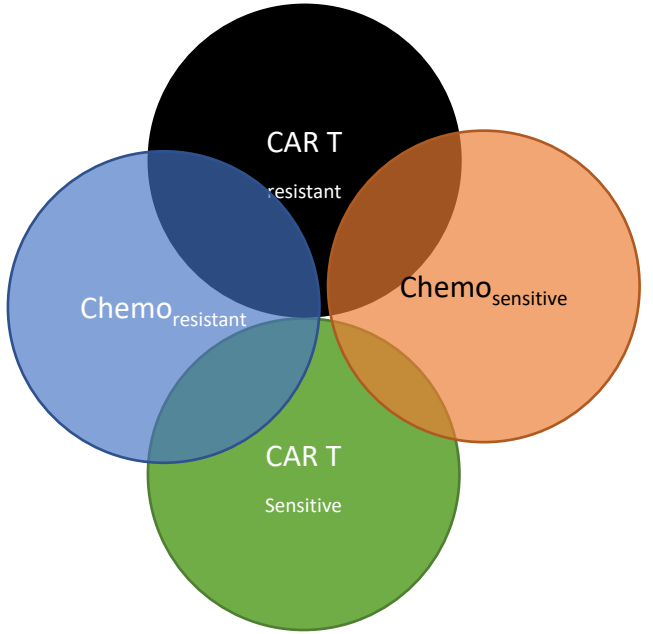
	RER-DLBCL	LR-DLBCL	HR	p value
4-year PFS	55%	63%	1.50	0.2
4-year OS	76%	75%	1.00	> 0.9



Flawed model

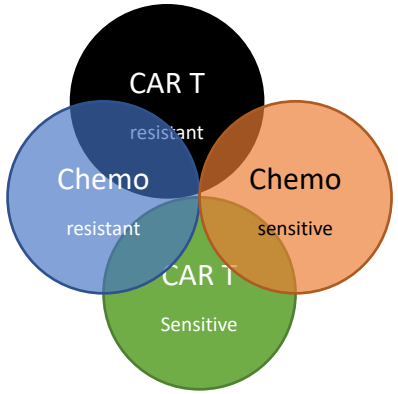


Alternative model



- Time to relapse is an imperfect surrogate of chemoresistance
- Chemosensitive patients with early relapse can have long term disease control

Primary refractory and early relapse DLBCL



Lista de novedades

- Combinaciones de bispecifics
- Tafa-Len-RCHOP en 1a línea
- Bispecificos en 1a línea
- Terapia basada en señales (primeros esbozos)

Final countdown

Cambio de paradigmas