Quale terapia post CAR T-cells nei linfomi aggressivi

Roberta Di Blasi MD, PhD

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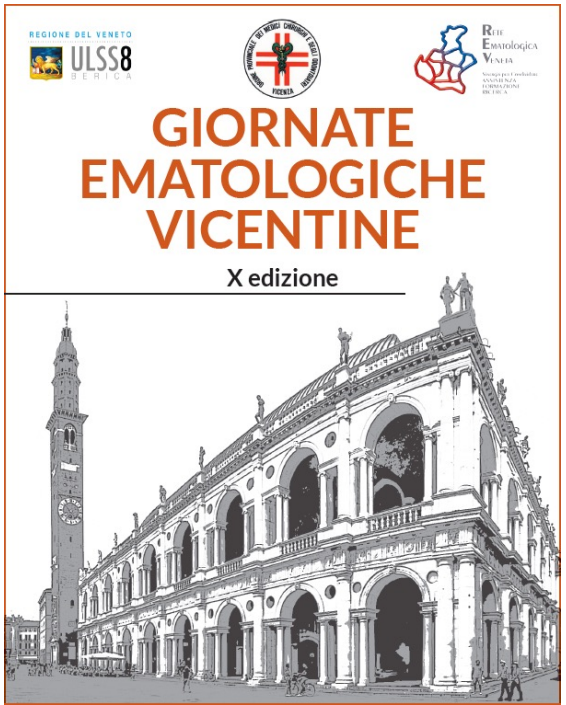

12 Ottobre 2023

DESCAR-T
Dispositif d'Enregistrement et de Suivi des CAR-T
French CAR-T registry

DISCLOSURES OF COMMERCIAL SUPPORT

- Novartis: Scientific Advisory Board and Conference speaker
- Kite/Gilead: Scientific Advisory Board, Conference speaker, Travel accommodation
- Janssen: Scientific Advisory Board
- Pfizer: Conference speaker
- BMS: Scientific Advisory Board
- Abbvie : Conference speaker
- Incyte : Conference speaker

Anti CD19 CAR T-cells in relapsed/refractory aggressive B-cell lymphomas

- Anti CD19 CAR T-cells allow the achievement of long lasting **response rates** in relapsed/refractory **(R/R)** aggressive B-cell lymphomas **(BCL)** with overall response rate **(ORR): 40-82%** in pivotal studies and real life settings (1-9)

- 2-year-Progression free survival (PFS) =33-42% (1-9)

1) Schuster SJ et al. NEJM 2019; 2) Nastoupil LJ, et al. J Clin Oncol. 2020; 3)Abramson JS et al. Lancet. 2020;
4) Pasquini MC et al. Blood Adv. 2020; 5) Iacoboni G et al. Cancer Med. 2021
6) Kuhnl A et al. Presented at EHA 2020;abstract S243; 7) Bethge WA et al. Presented at EBMT 2021;abstract AA2-2. 3.
8) Le Gouill S et al. EHA 2021 , abs 84, . 9) Kwon M, et al. Presented at EBMT 2021;abstract OS3-4. 5.;10:3214-23.

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- **58-66% of patients relapse**

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Failure after CAR T-cells: different mechanisms

- **Tumor intrinsic factors**
  - Loss of CD19 epitope that binds CAR T-cells
  - Upregulation of PD-1 pathway by T-cells during activation
  - HLA loss in antigen presentation : decreased tumor surveillance
  - High tumor burden

- **Host factors**
  - Incomplete T-cell depletion : role of PK/PD during lymphodepletion

- **Inadequacy of CAR T-cells**
  - « exhausted CAR t-cells »: role of prior chemotherapies?

Byrne M et al Biol Blood Marrow Transplant. 2019

Failure after CAR T-cells: US + Israel experience

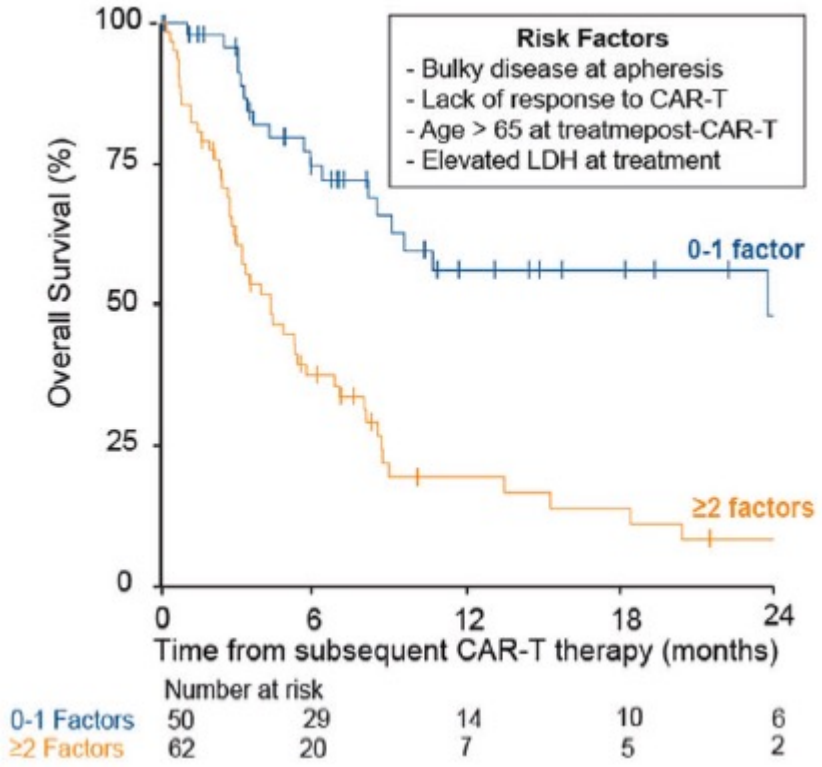
305 pts , 60% relapses = 182 pts

Predictors of EFS

- Non GC phenotype
- Primary refractory disease at apheresis
- High LDH
- Active disease at infusion
- Tisa cel

Predictors of OS

- Age
- High LDH
- Bulky disease at apheresis
- Refractoriness to CAR T-cells



19-56% overall survival with both 2 or less parameters

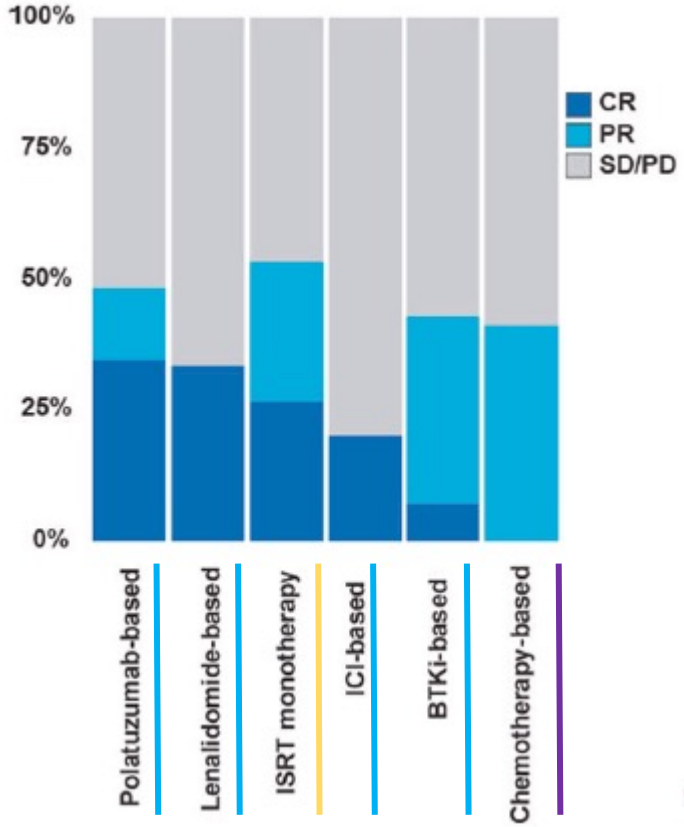
Alarcon Tomas A et al Leukemia. 2023

US + Israel experience: other strategies do better than chemotherapy

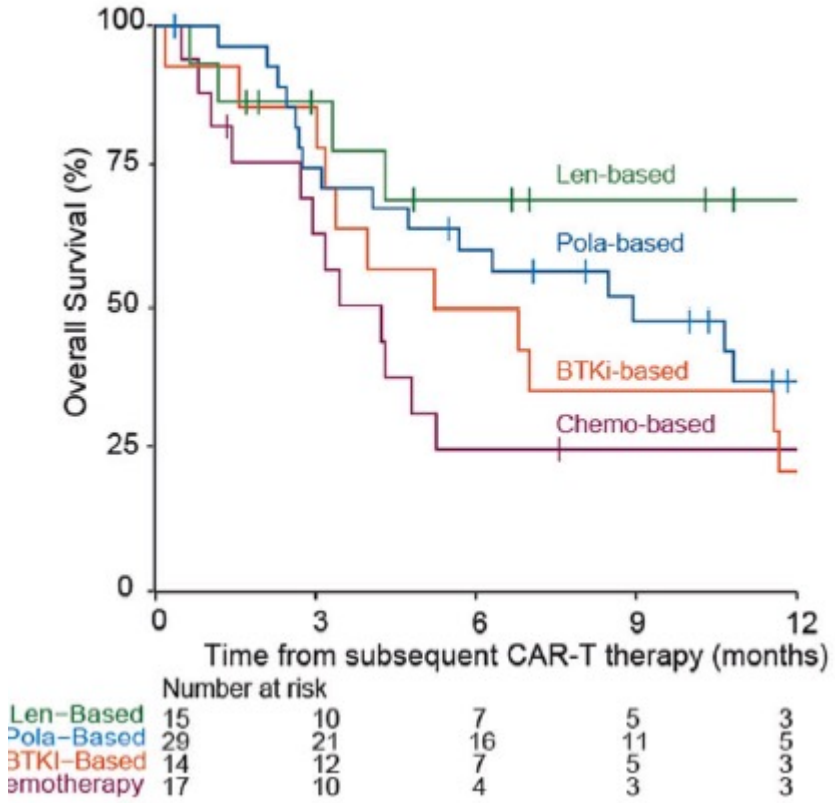
135 (74% of failure pts) received a treatment after CAR T-cells failure

ORR= 39%

Therapeutic strategies



OS



Alarcon Tomas A et al Leukemia. 2023

Failure after CAR T-cells: 18 US academic medical centers

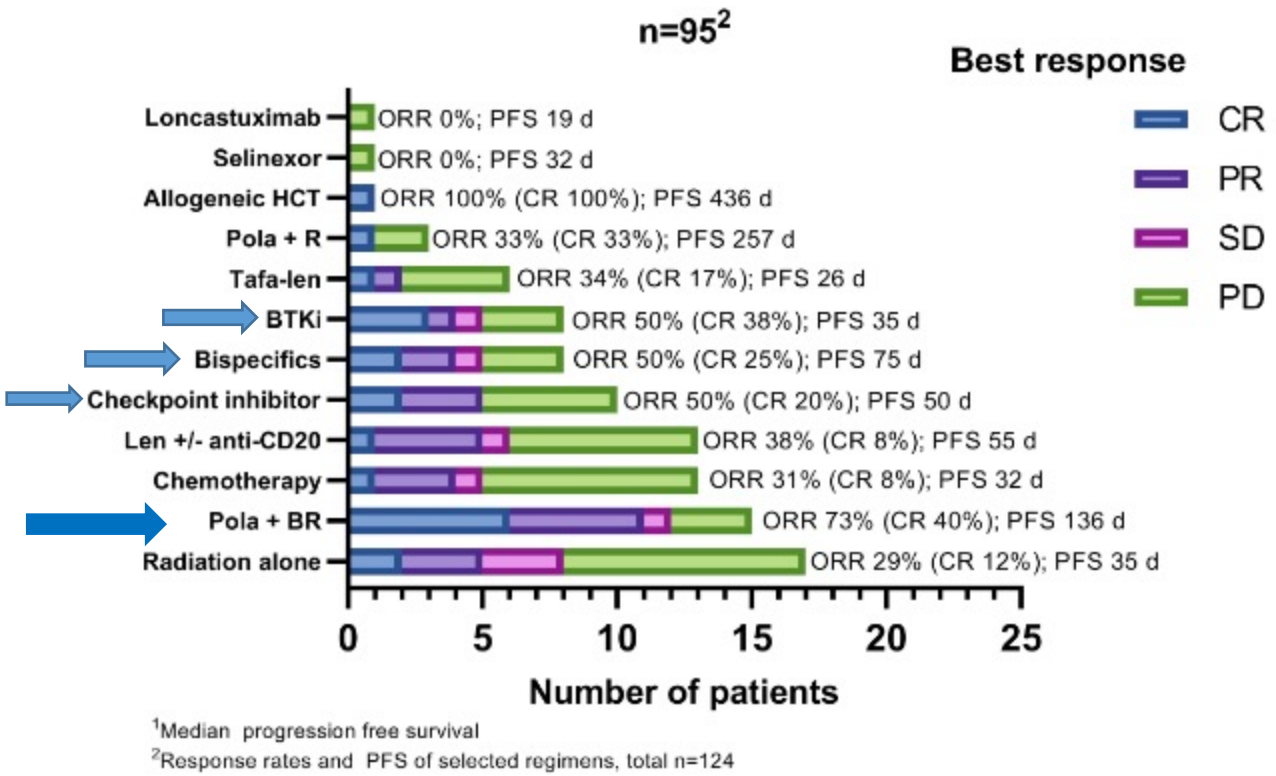
400 pts , <u>48 % PD</u> = 190 pts

125 (65.5%) received further therapies after CAR T-cells failure

Median OS= 5,7 mo, Median PFS= 2,7 mo

- 16% CD19- relapses

ORR and PFS



[1]Median progression free survival
[2]Response rates and PFS of selected regimens, total n=124

Zurko J et al. ASH 2021

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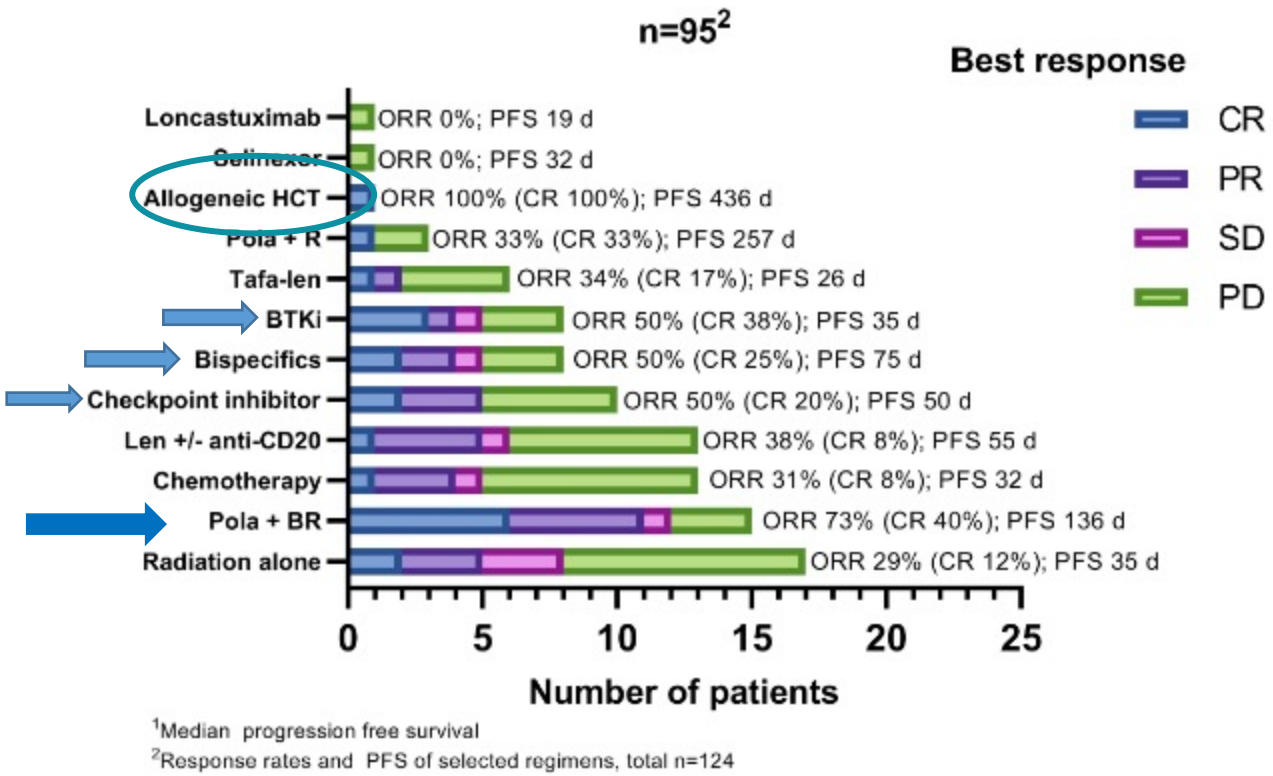


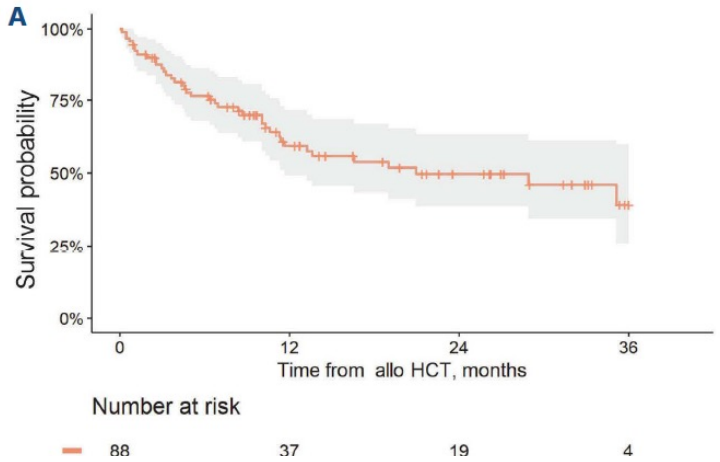
[1]Median progression free survival
[2]Response rates and PFS of selected regimens, total n=124

Zurko J et al. ASH 2021

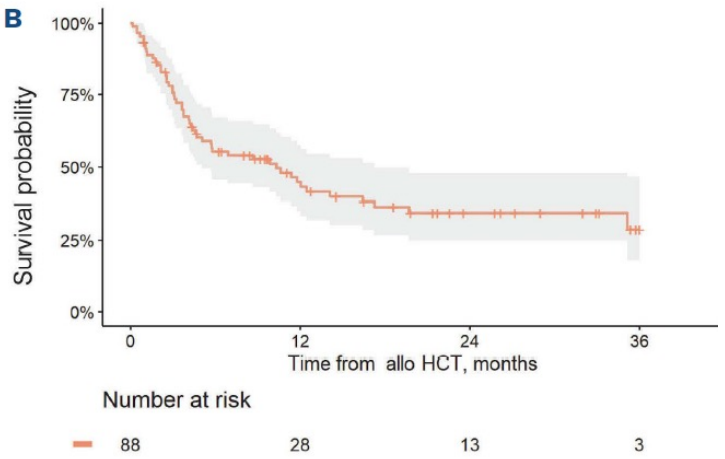
94 pts Allo HSCT

Median OS= 21mo, Median PFS= 10 mo

NRM=22%



OS at 1y= 59%

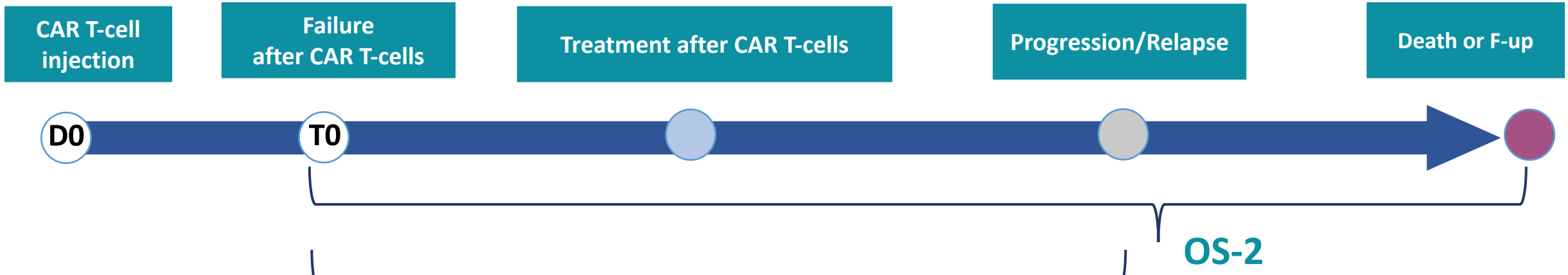


PFS at 1y= 45%

Zurko J et al Haematologica. 2023

French experience: DESCAR-T CAREL Study

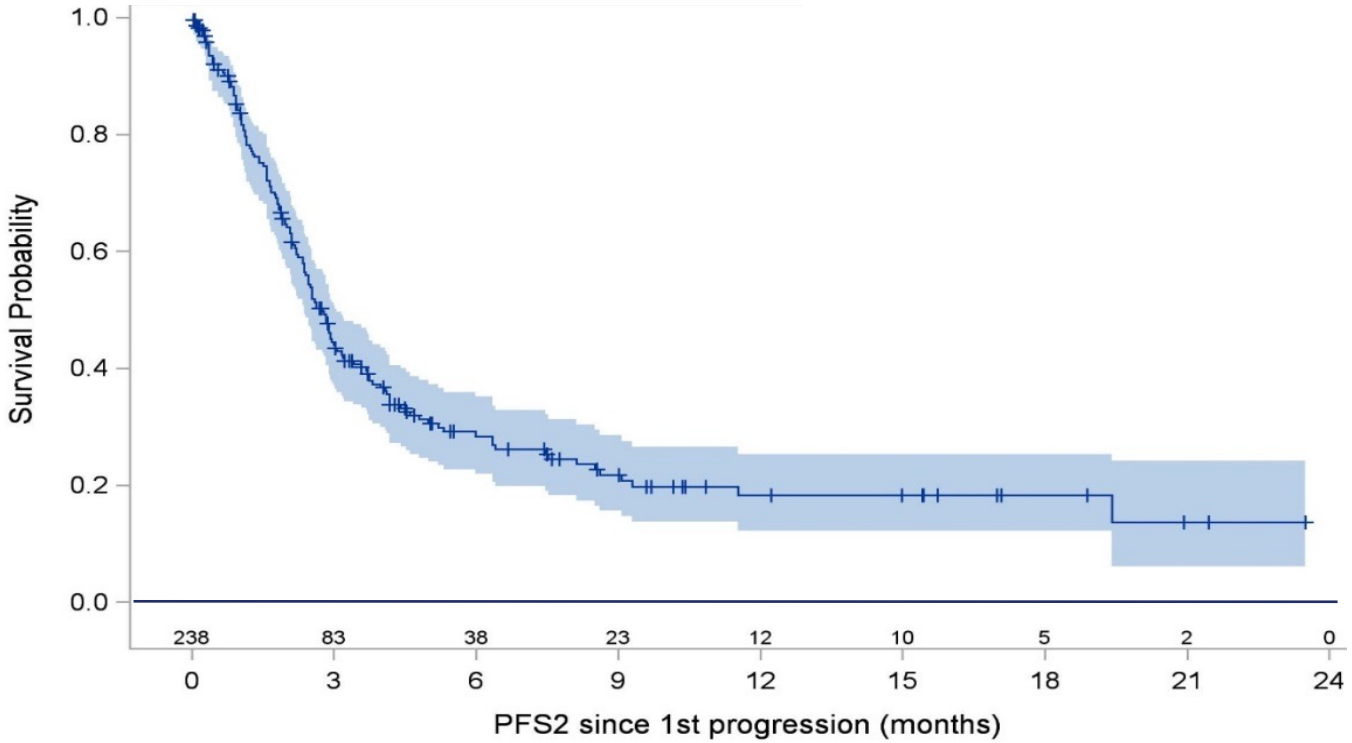
- 680 R/R BCL pts consecutively registered in DESCAR-T
- 550 treated, 238 Relapsed
- Median F-Up: 7.9 months
- Median time to relapse : 2.7 months (range 0.2; 21.5)



- **Treatments**
- **Response rate**
- **Events for patients that presented failure after CAR T-cells**
  - **Progression/Relapse**
  - **Death or Follow-up**

Progression-free survival-2 of all failure pts

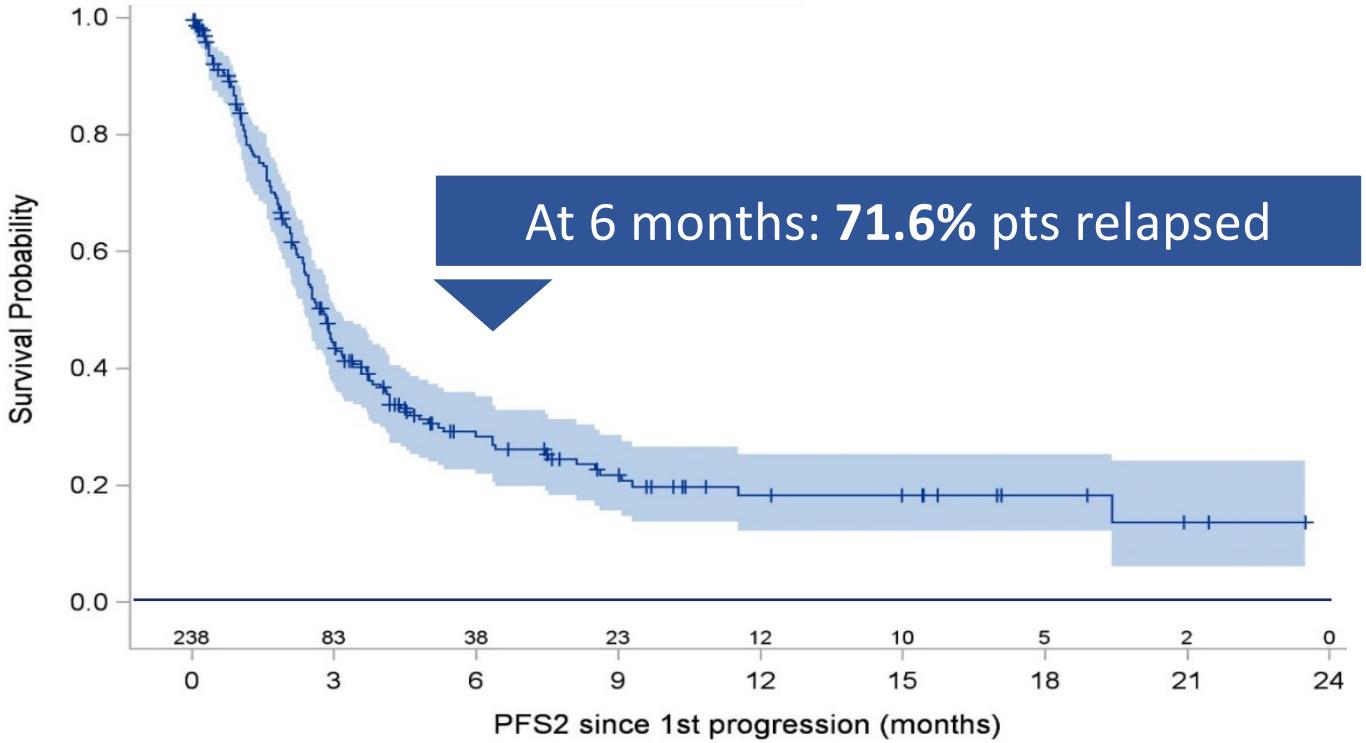
238 patients



Median **PFS-2=2.8 months** (95% CL, 2.4-3.1)

Progression-free survival-2 of all failure pts

238 patients



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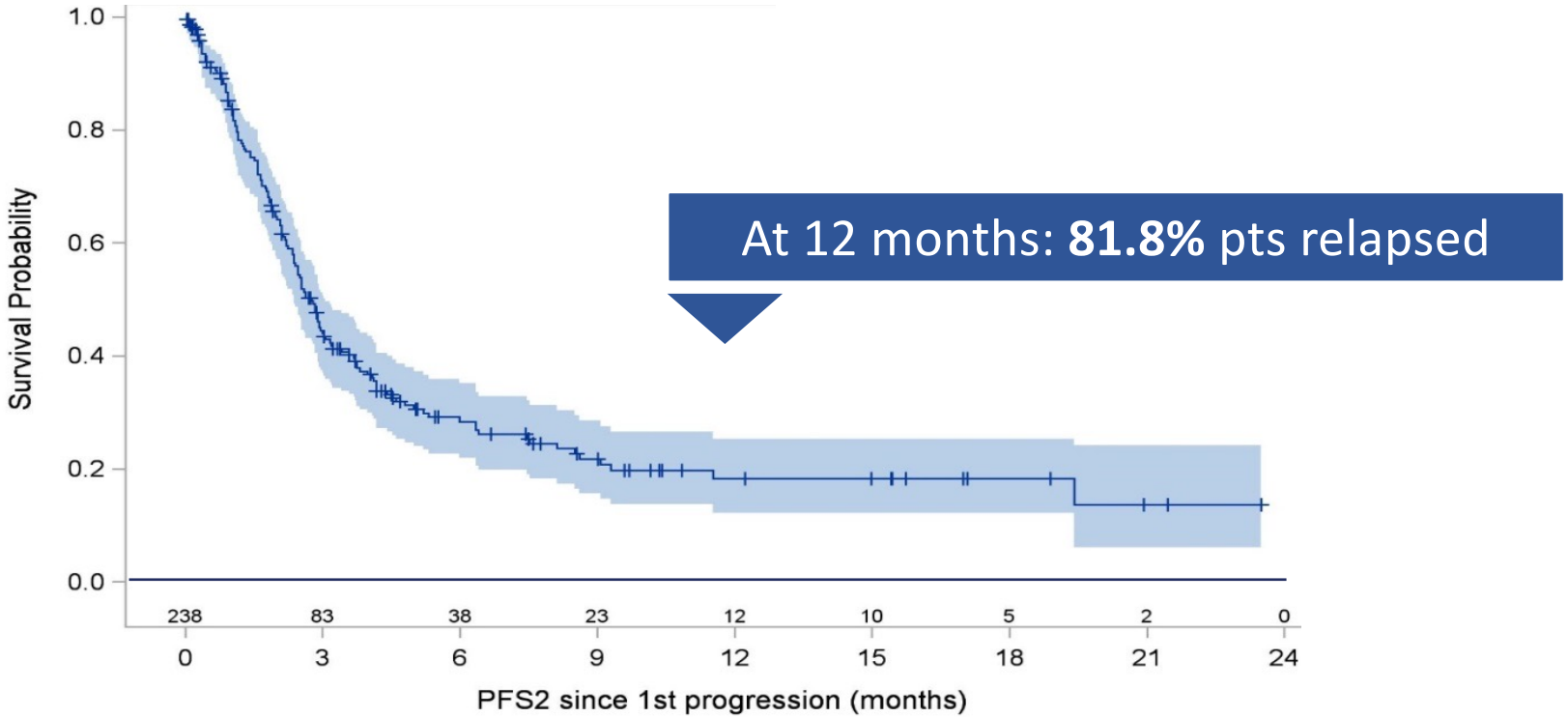


At 12 months: **81.8%** pts relapsed

Median **PFS-2=2.8 months** (95% CL, 2.4-3.1)

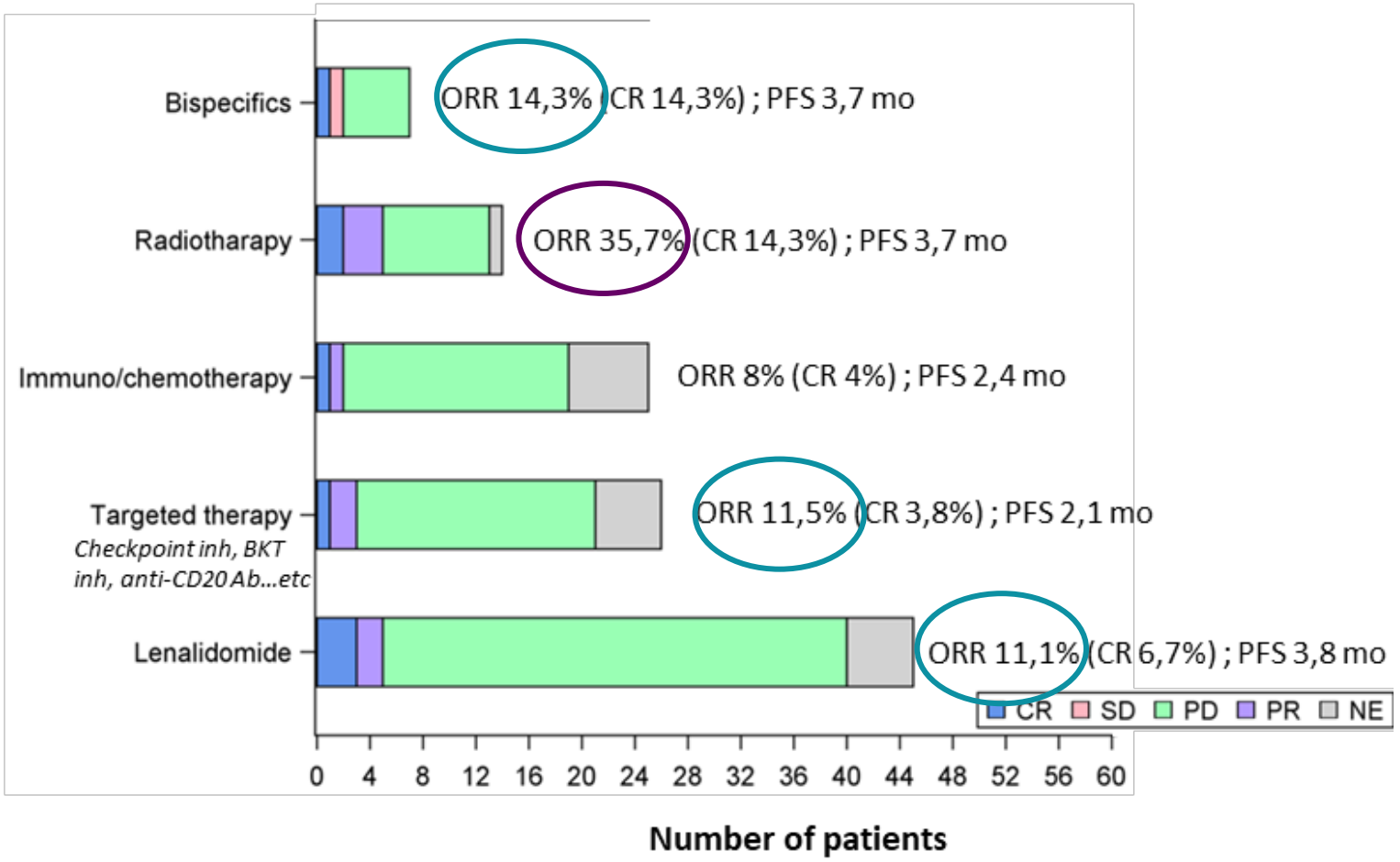
Response to treatment for failure after CAR T-cell

Relapsed patients	n=238
Relapsed patients receiving treatment	n=154
Available evaluation of response	n=120
Overall response *	**17 (14.1%)**
Complete response	8 (6.6%)
Partial response	9 (7.5%)
Stable response	1 (0.8%)
Progressive disease	85 (70,8%)

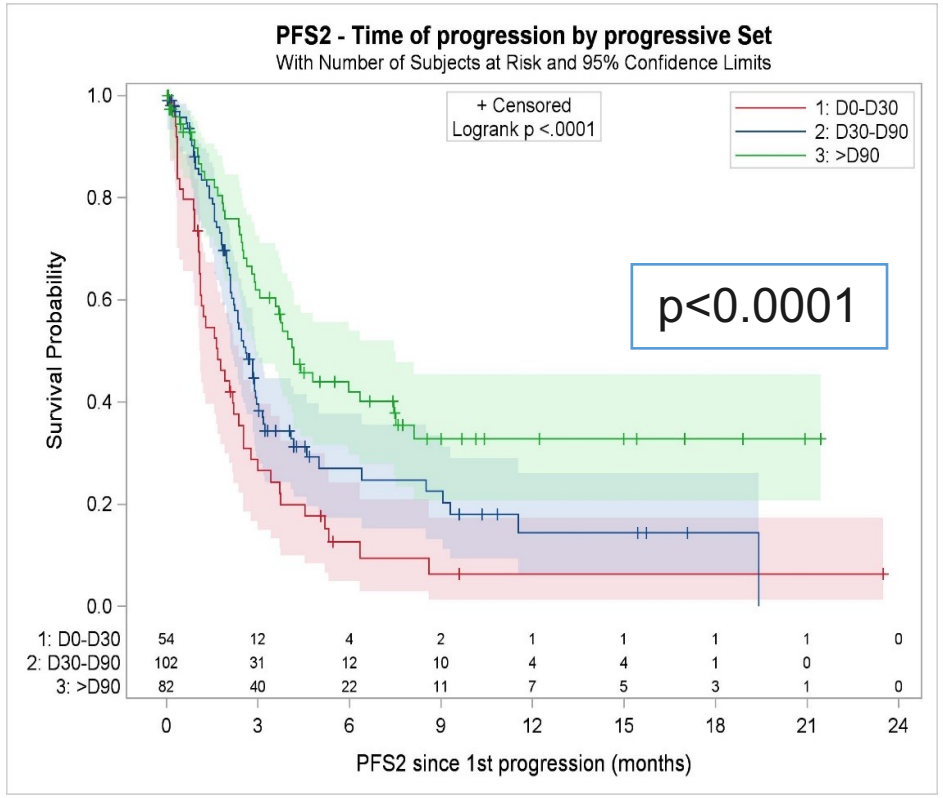
65%

** Cheson criteria 2014*

Salvage immunotherapy seem to offer better outcomes compared to standard immuno-chemotherapy

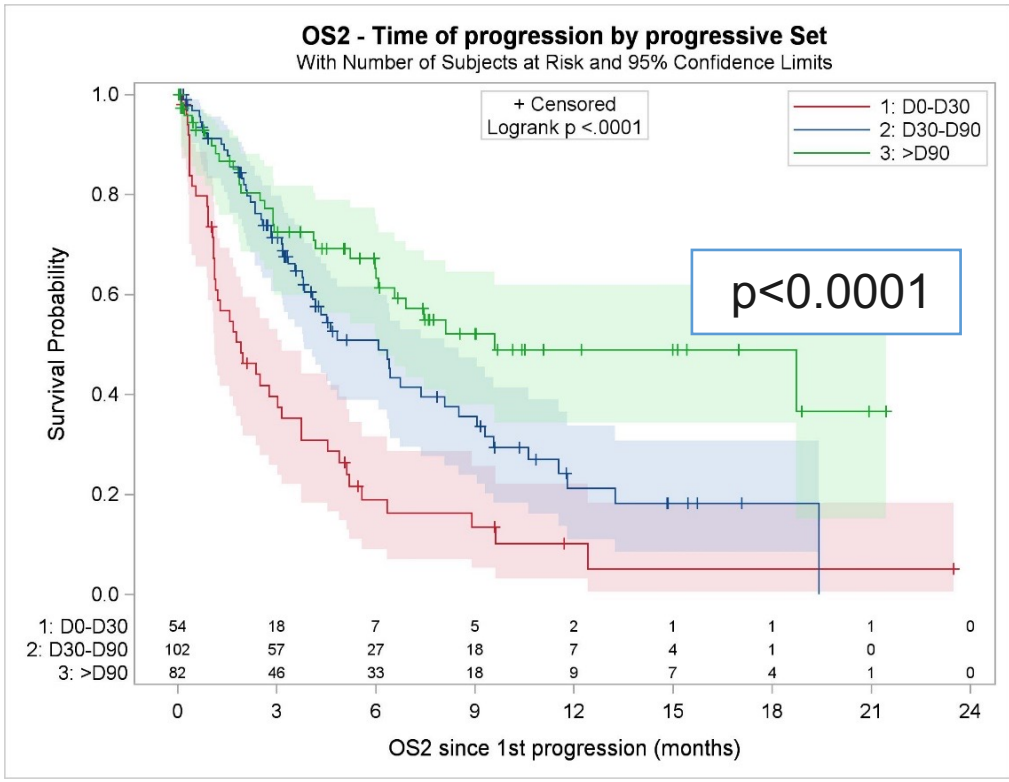


PFS-2 and OS-2 according to failure time



Median PFS-2

D0-30=1.7 months (95% CI, 1.1-2.4)
D30-D90=2.6 months (95% CI, 2.1-3.0)
>D90=4.2 months (95%CI, 2.9-7.5)



Median OS-2

D0-30= 1.9 months (95% CI, 1.1-3.2)
D30-D90=6.1 months (95% CI, 3.8-8.1)
>D90=9.6 months (95%CI, 6.0 – NR)

R Di Blasi et al, Blood 2022

Prognostic factors

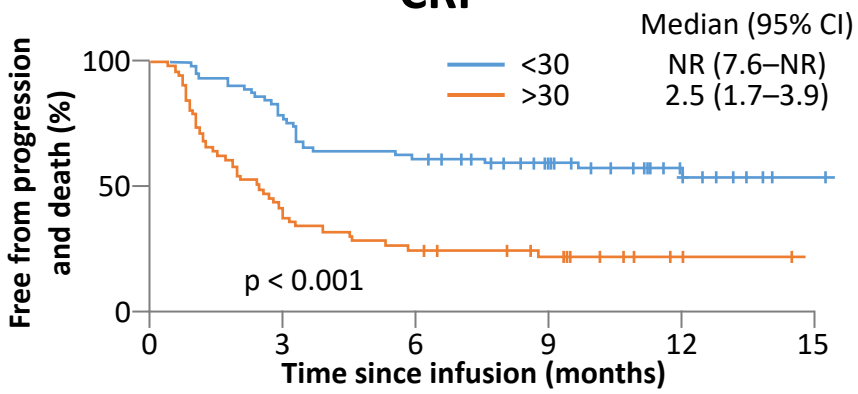
	HR, 95%CI	P-value
Progression-Free Survival		
LDH prior to infusion > UNL	**3.42 [1.93;6.05]**	**<.0001**
Progression/relapse D0-D30	1.74 [0.93;3.25]	0.0815
Bispecific antibodies	NA	0.9878
Lenalidomide	0.55 [0.29;1.07]	0.0789
Targeted therapy	0.69 [0.33;1.45]	0.3228
Ferritin prior to infusion > UNL	**1.02 [1.00;1.03]**	**0.0173**
Overall Survival		
LDH prior to infusion > UNL	**2.10 [1.16;3.78]**	**0.0136**
Progression/relapse D0-D30	**2.93 [1.56;5.50]**	**0.0009**
Bispecific antibodies	0.22 [0.03;1.80]	0.1566
CRP prior to infusion > UNL	**1.11 [1.04;1.19]**	**0.0027**
Targeted therapy	0.47 [0.21;1.07]	0.0729
Lenalidomide	**0.42 [0.21;0.82]**	**0.0116**

Solutions?

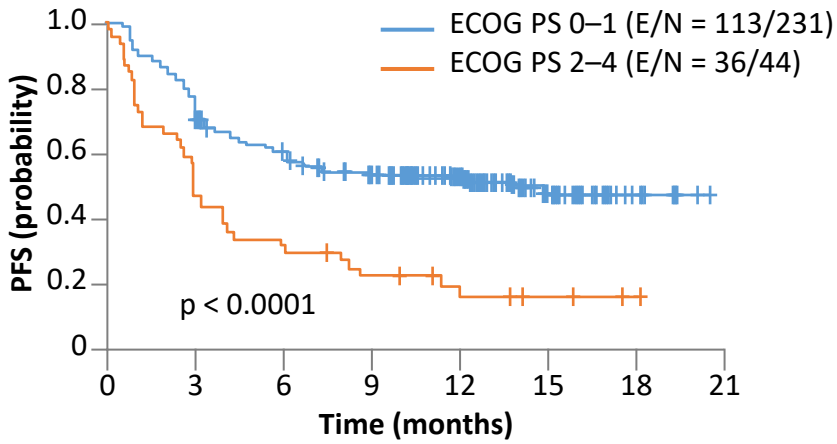
- Accurate evaluation of patients comparing biological and clinical parameters
- Earlier use of CAR T-cells in the therapeutic strategy (ZUMA-7, TRANSFORM, ZUMA 12 trial)
  - Recent authorization in 2nd line also possible in elderly patient (Alycante, Pilot studies)
- Peri-CART → immunomodulation : LEN
- Post failure strategies
  - Checkpoint modulation : pembrolizumab at time of relapse
  - Bispecific Antibodies
  - Other?

How to predict the failure: Clinical and biological parameters

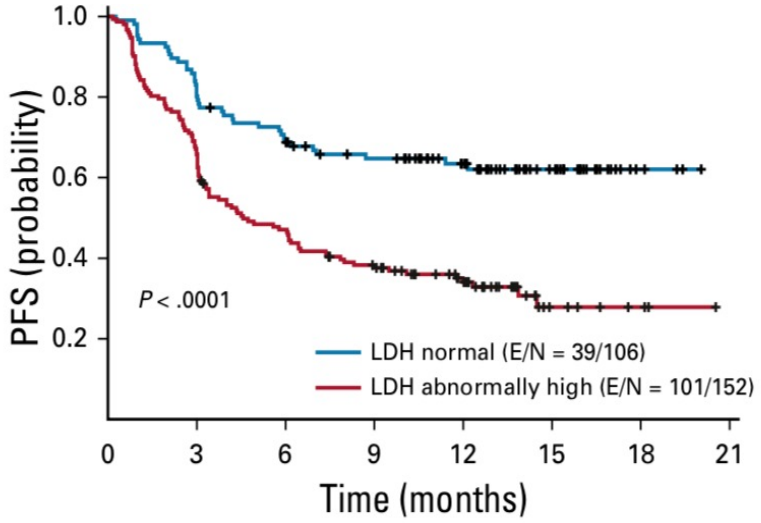
CRP[1]



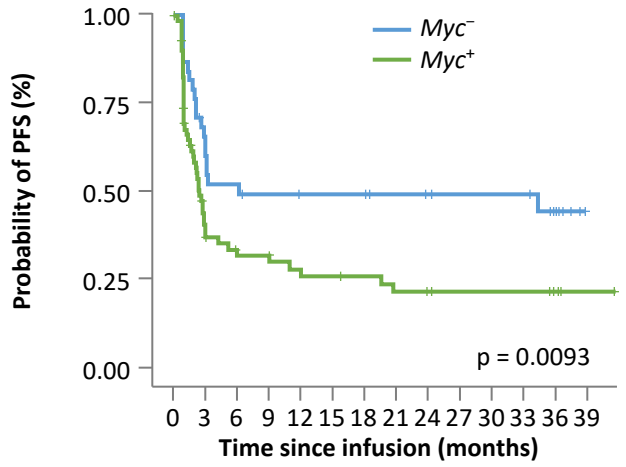
ECOG[2]



LDH[2]



Myc + LDH [3]



PFS in JULIET trial
(N = 111)

- Patients with high LDH levels had poor PFS outcomes
- Patients with *Myc*⁻ status and normal pre-infusion LDH levels (n = 16) had longer PFS

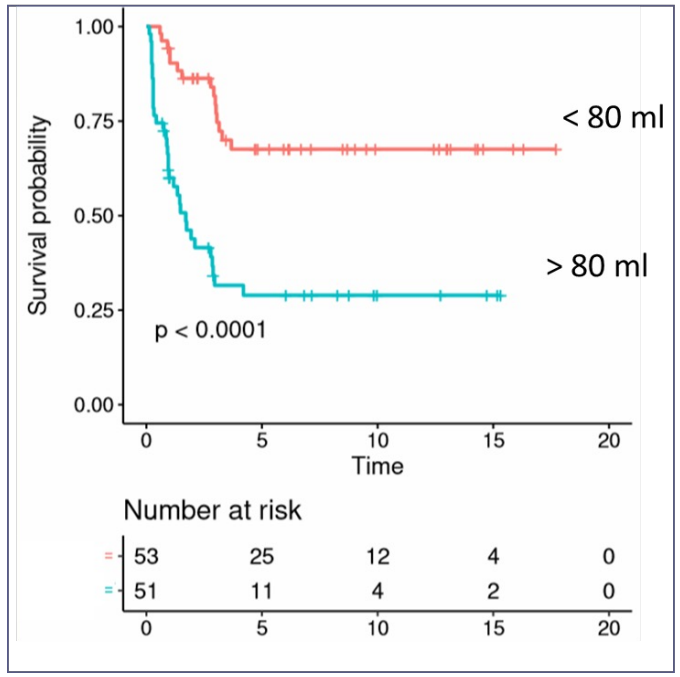
	Events, n	Median (95% CI)
Negative (n = 38)	20	6.2 (2.9–NA)
Positive (n = 73)	49	2.5 (1.7–3)

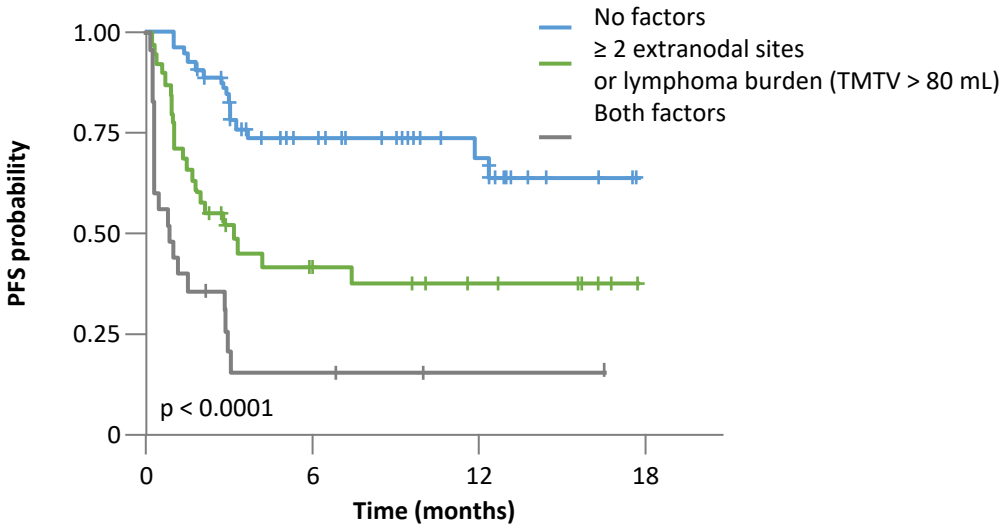
[1]Jacobson CA, et al. J Clin Oncol. 2020;38:3095-106. [2]Nastoupil LJ, et al. J Clin Oncol. 2020;38:3119-28. [3].Jaeger U, et al. Presented at ASH 2020; abstract 1194.

How to predict the failure: Extranodal sites and lymphoma burden (TMTV)

PFS in LYSA cohort[1]

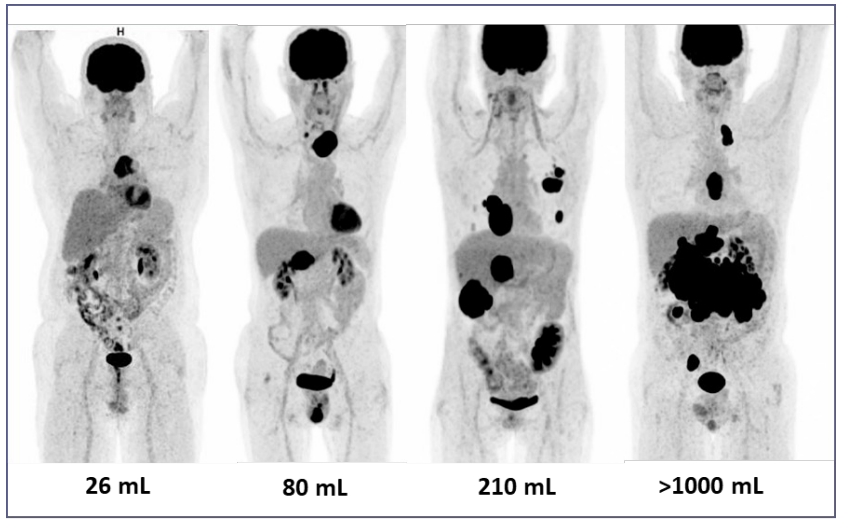
N = 116 (Axi-Cel: N = 49; Tisa-Cel: N = 67)





No. at risk

Factor = 0	53	27	14	0
Factor = 1	38	11	6	0
Factor = 2	25	3	1	0



1. Vercellino L, et al. Blood Adv. 2020;4:5607–15.

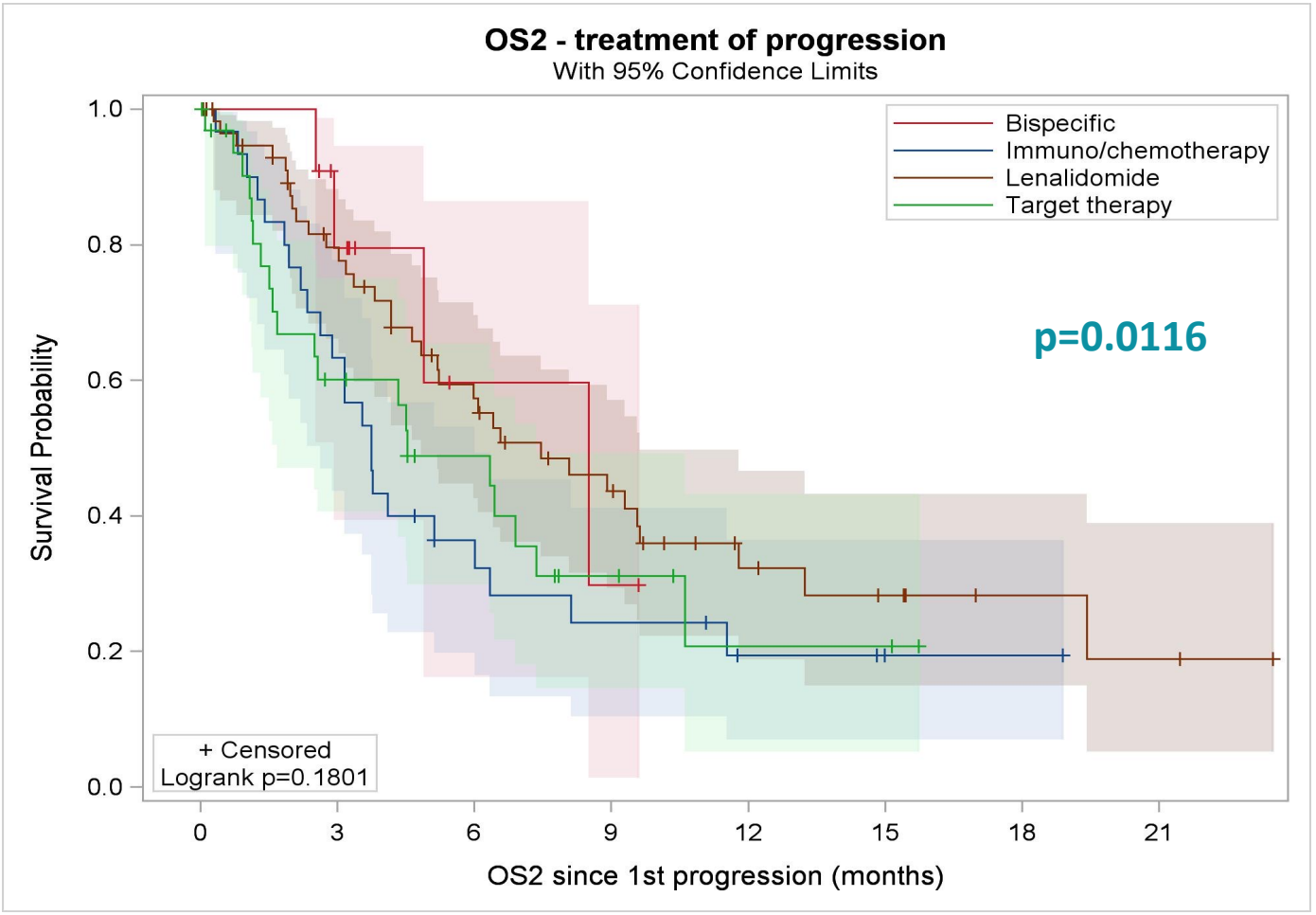
In routine practice, high-risk DLBCL patients are identified

- **Total metabolic tumor volume at diagnosis TMTV0**
- **Performance status**
- **Agressive histologies : double expressor (FISH?)**
- **Extranodal sites**

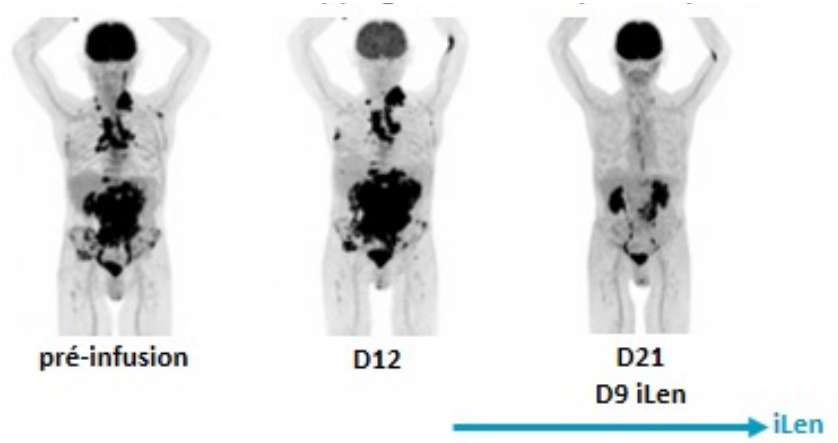
Patients annoted in the L2 program

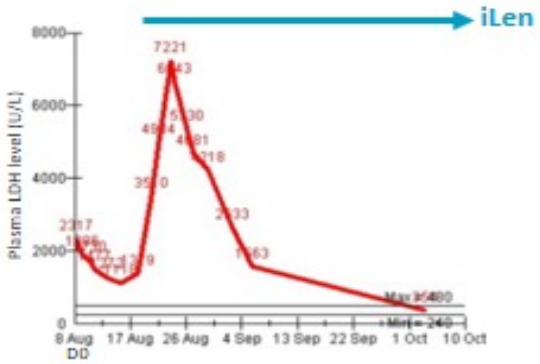
Immunomodulation by Lenalidomide, may improve prognosis

DESCAR-T



PERI CART LEN in immuno-modulation





Clinical trial in progress (LYSA)

Roberta Di Blasi, et al. Blood 2022

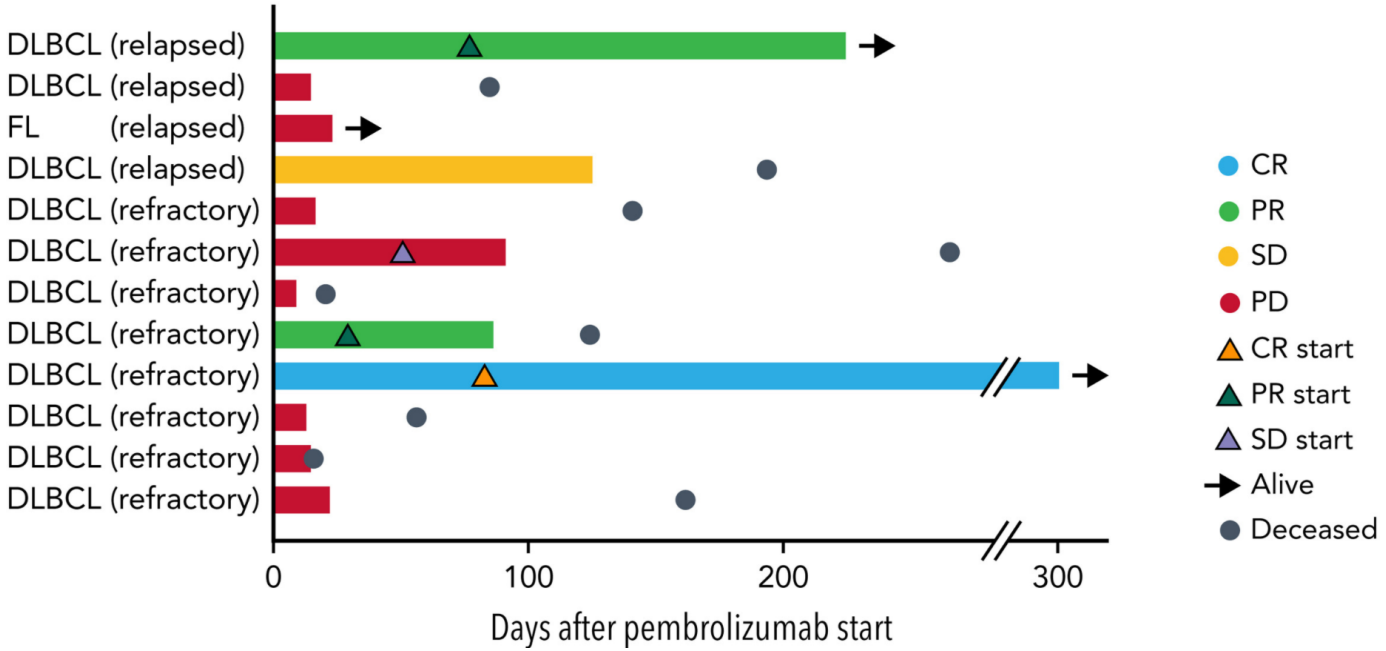
Lemoine J et al . ASH 2021

Pembrolizumab for B-cell lymphomas relapsing after or refractory to CD19-directed CAR T-cell therapy

12 pts:
pembrolizumab 200 mg IV every 3 weeks for 1 year or until progression of disease, therapy-limiting toxicity, or elective protocol discontinuation.

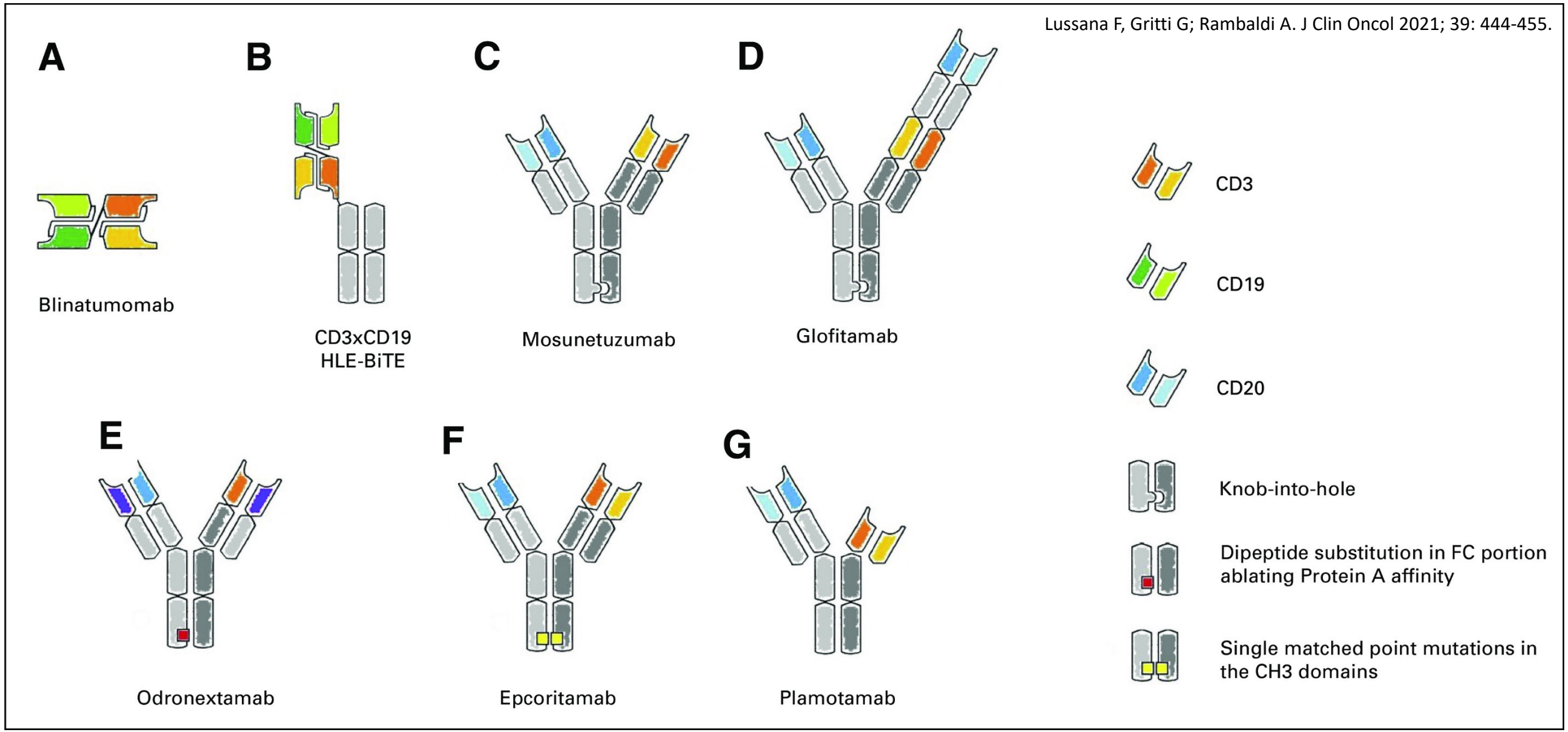
Best ORR : 25%
1 CR
2 PR

= 4 of 12 (33%) patients had clinical benefit



Elise A. Chong, et al. Blood 2022

Bispecific CD3/CD20 antibodies in B-NHL

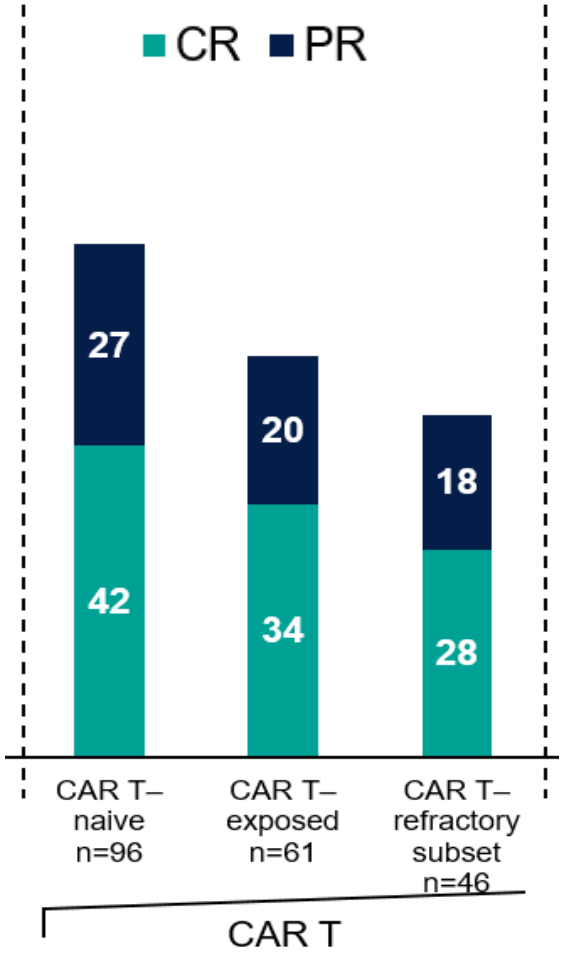


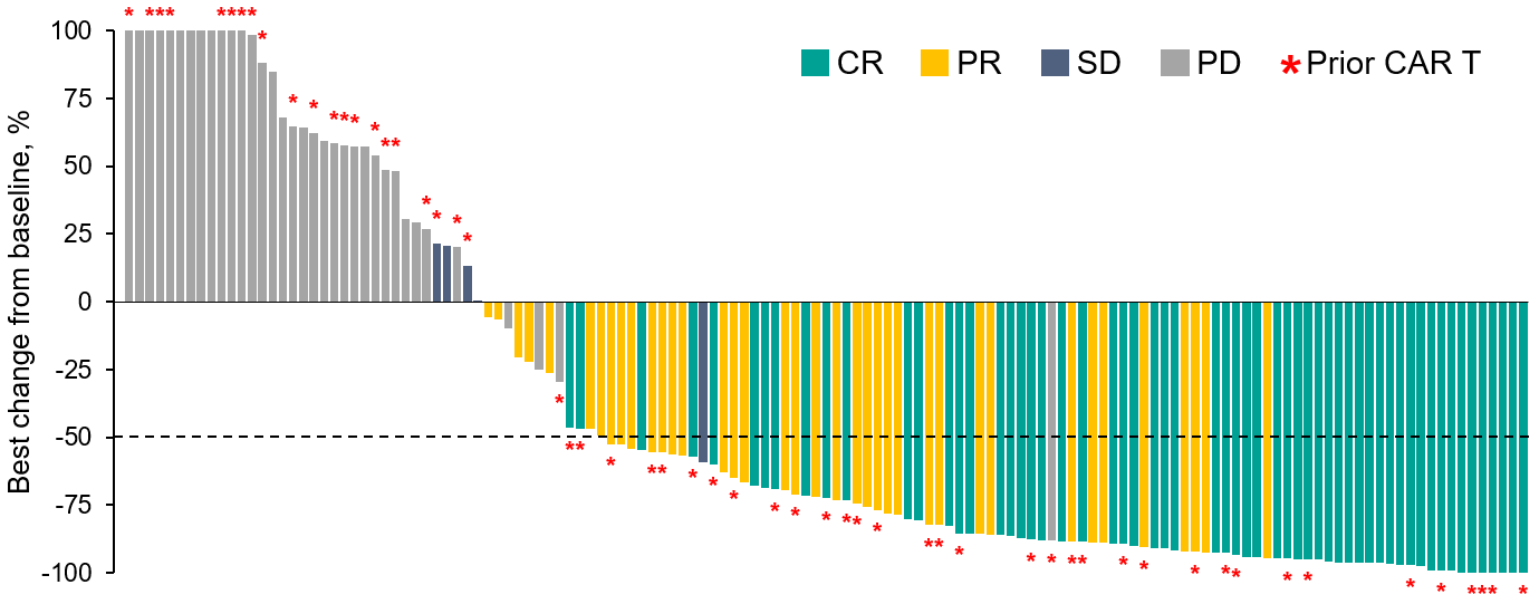
Lussana F, Gritti G; Rambaldi A. J Clin Oncol 2021; 39: 444-455.

Bispecific antibodies: first results

	Glofitamab n=154	Epcoritamab n=157
Histology	DLBCL ≥2 lines	DLBCL ≥2 lines
PS	0-1	0-2 (n=5 PS2)
Age	66.0 (21–90)	64 (20–83)
Median prior lines of therapy (range)	3 (2–11)	3 (2–7)
Prior CAR T therapy, n (%) Refractory/progressed within 6mo	**51 (33.1)** 132 (85.7)	**61 (39)** 46/61 (75)
Median Follow-up (months)	12.6 (0–22)	10.7 (0.3–17.9)
ORR CR	**80 (51.6%) ORR** **61 (39.4%) CR**	**99 (63%) ORR** **61 (39%) CR**
Median OS	**NR**	**11.5 (7.9, 15.7)**
Median PFS	**4.4 (3.0–7.9)** **NR for pts in CR**	**4.9 (3.4, 8.1)**
Gr ≥ 3 CRS / ICANS	2,5%/0,6%	3,9% /2,6%

Epcoritamab CD20xCD3 bispecific antibody





p=ns

Promising results in the BiCAR Therapy study with Glofitamab….

Thieblemont et al .EHA 2022

Other options in L2+

Regimen	n	ORR	CR	
POLA-BR	40	45%	40%	Sehn L. J Clin Oncol
SELINEXOR	175	28%	17%	Kalakonda N Lancet oncol 2020
TAFA-LEN	156	43%	18%	Salles G et al. Lancet Oncol 2020
LONCASTUXIMAB TESIRINE	145	48%	24%	Caimi PF et al Lancet Oncol 2021

Failure after CAR T-cells: Italian experience

51 pts , failure after CAR T-cell treatment

-refractory (61%)
-transient responders (39%)

- CD19 /CD20 loss = 12 (41%) /8 (28%)

- Further treatment: 76% pts

22 (43%) → clinical trial

n=18, glofitamab;
n=4, loncastuximab-tesirine +Ibrutinib

29 (57%) standard therapies (n=17, 33%)
/supportive care only (n=12, 24%).

Salvage	N°	CR	PR	SD/PD	CR rate
Glofitamab	18	6	5	7	6/18 **(33%)**
Loncastuximab+I	4	1	1	2	1/4 **(25%)**
Checkpoint Inh	4	3	0	1	3 /4 **(75%)**
Lenalidomide	4	2	0	2	2/4 **(50%)**
Ibrutinib	2	0	1	1	0/2 **(0%)**
Chemotherapy	6	1	2	3	1/6 **(16%)**
Radiotherapy	1	0	1	0	0/1 **(0%)**

Dodero A et al, BJHem . 2023

Italian experience: responses of patients in clinical trials

GLOFITAMAB = 18

ORR 61% (n=11) **CR** 33% (n=6)

Better response in patients who experienced a transient response to CAR T-cells

1-year OS = 47% (95% CI: +21%–24%)
=57% (95% CI: +21%–29%)
for pts receiving full target dose

LONCA+ IBRU = 4

2 pts responded : CR (n=1) or PR (n=1).

ORR in pts receiving T-cell-activating treatment = 42%
(glofitamab, CPI or LEN)

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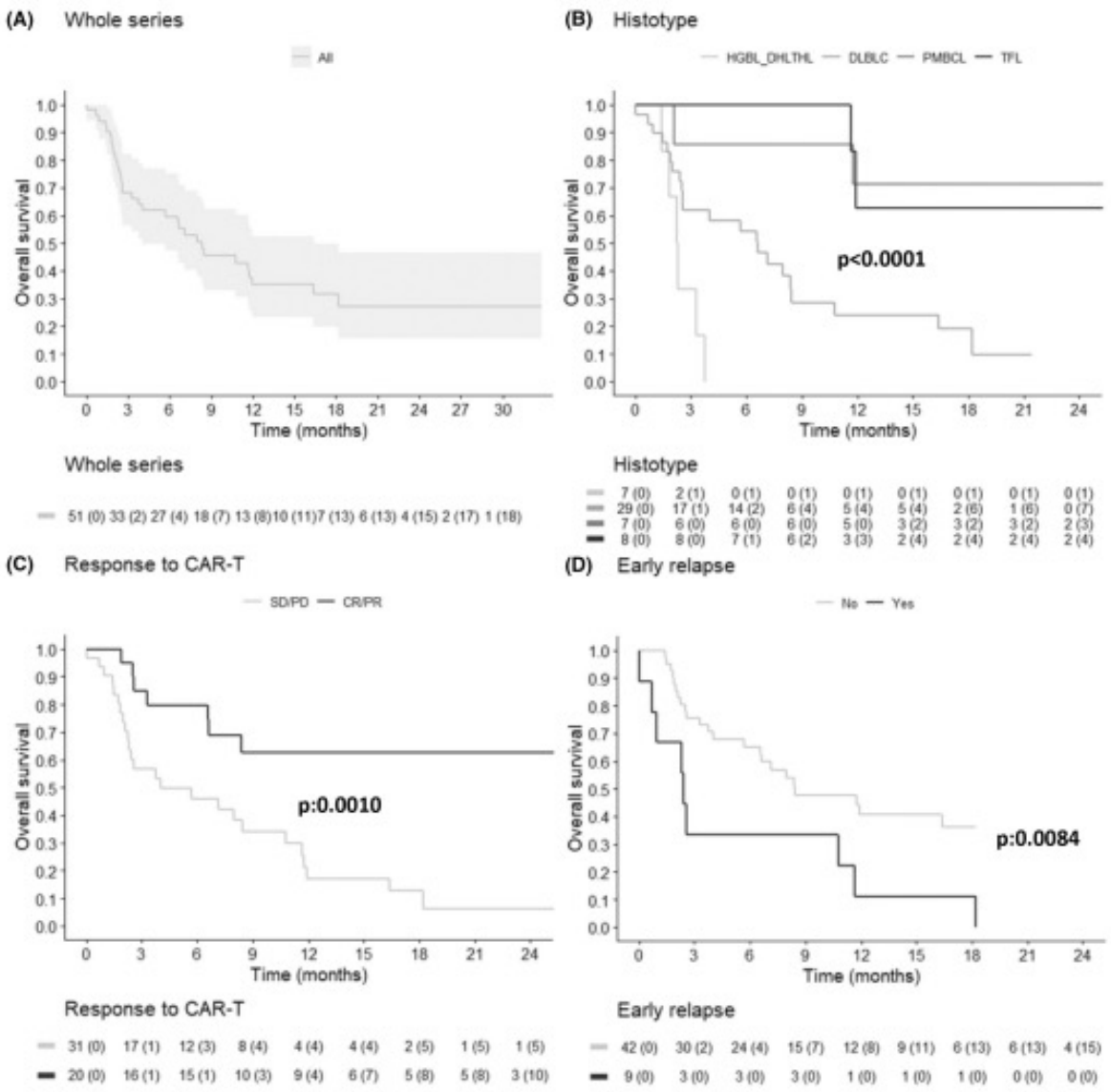
Italian experience: outcomes



12-mo OS 35% (95% CI: 23%–53%)
24-mo OS 27% (95% CI: 16%–47%)

Median OS overall 8.36months (IQR: 2.43-NA)

Median OS treated 45% (95% CI: 31%– 66%)

Median OS untreated =0%

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Italian experience: multivariable analysis

	OS				PFS			
Variable	HR	Lower 0.95	Upper 0.95	*p*-value	HR	Lower 0.95	Upper 0.95	*p*-value
Response to CAR-T—SD/PD versus CR/PR	3.64	1.30	10.20	0.0140	3.54	1.43	8.80	0.0064
Early relapse—yes versus no	2.33	0.76	7.08	0.1376	1.63	0.55	4.81	0.3740
IPI (at salvage)—≥2 versus 0–1	20.66	2.66	160.32	0.0038	11.89	2.59	54.51	0.0014
Histotype—others versus PMBCL/tFCL	5.28	1.52	18.34	0.0088	3.65	1.35	9.87	0.0106
Immunotherapy—no versus yes	2.12	0.82	5.5	0.1217	1.79	0.75	4.26	0.1878
Time to salvage—2.6 versus 1.63 months	0.88	0.61	1.27	0.4949	1	0.75	1.34	0.9987
Age – ≥60 versus <60 years	2.36	0.93	6.00	0.0723	2.73	1.17	6.37	0.0206

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CR/PR, complete remission and partial remission; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphomas; SD/PD, stable disease and progressive disease; t-FCL, transformed follicular lymphomas.

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Conclusions

- The outcome of patients at failure after CAR T-cells treatment remains poor despite innovative strategies as far as we know (ongoing studies)
- Dismal outcome of patients relapsing within the first month/not responding at all to CAR T/aggressive histoype/high tumor burden
- Some therapeutic strategies (immunotherapy by BiTE, Lenalidomide, anti CD19/ibrutinib) may improve progression free survival and overall survival
- PD-1 inhibitor therapy can be considered to attempt to stimulate the residual T cells but results are not conclusive
- Standard chemotherapy is not useful
- Further strategies in treatment pathway (i.e. timing and accouting of risk factors) are needed to improve the outcome of high risk patients

Grazie!

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