NHL Immunotherapy Update

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Disclosures

- Consulting Fees: Gilead/Kite, Incyte, Epizyme, TG Therapeutics, Atara Bio, Karyopharm

- Contracted Research: Novartis, BMS, Merck, CRISPR

- I will be discussing non-FDA approved indications during my presentation

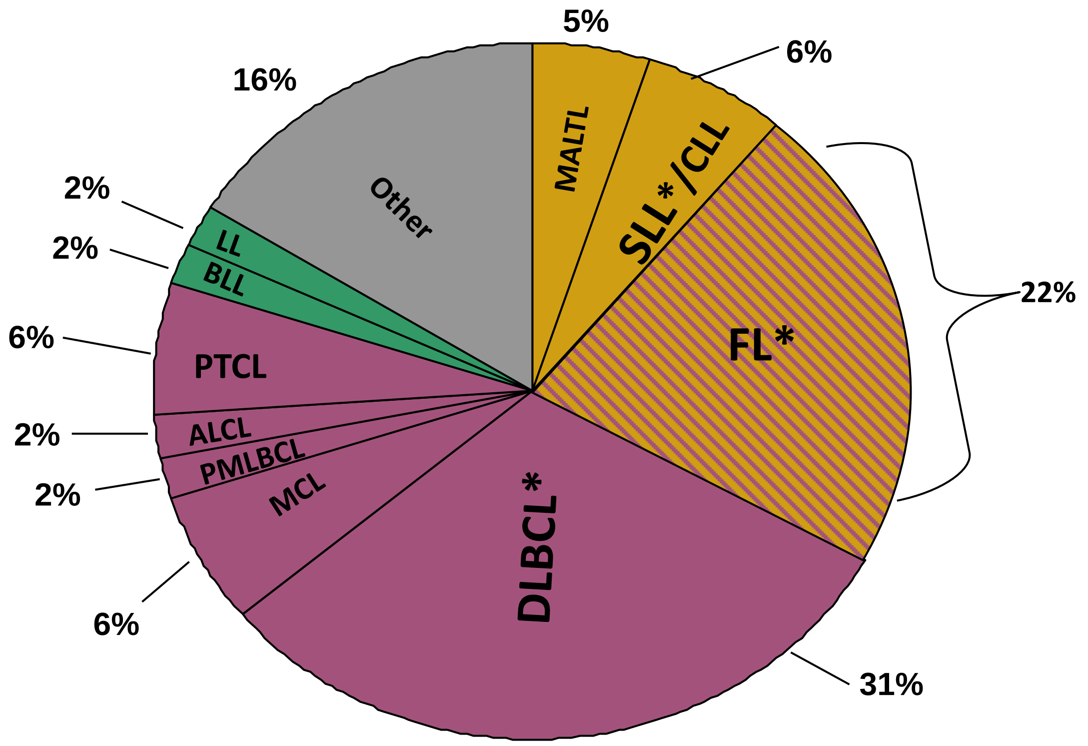
Outline

- CART19 and BiTE: Current and Evolving Management of aggressive NHL

- Immunotherapy breakthroughs in indolent NHL

- Treatment Complications in the COVID19 era

Clinical Course and WHO Classification



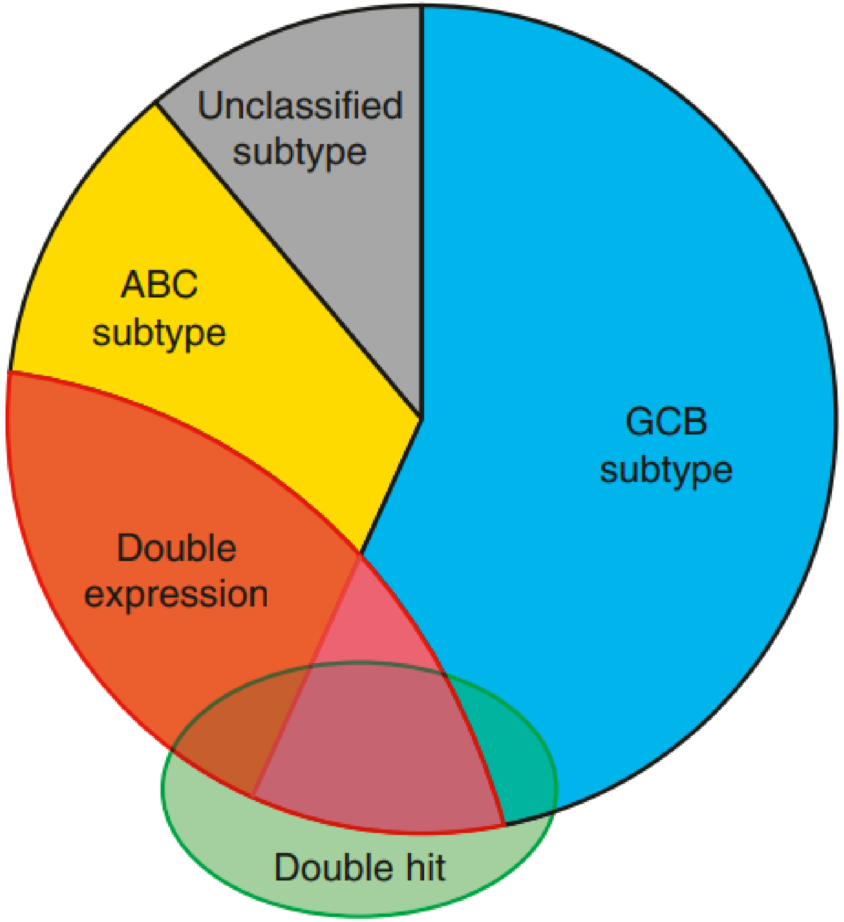
Grades I, II- **Indolent**
Grade III- **Agressive**

Indolent (low grade)	**Aggressive (intermediate grade)**	**Very aggressive (high grade)**
• Slowly progressive • 5-year OS ≤95%	• Rapid clinical course • 5-year OS ≤50%	• Grows rapidly • Survival 0.5-2 years

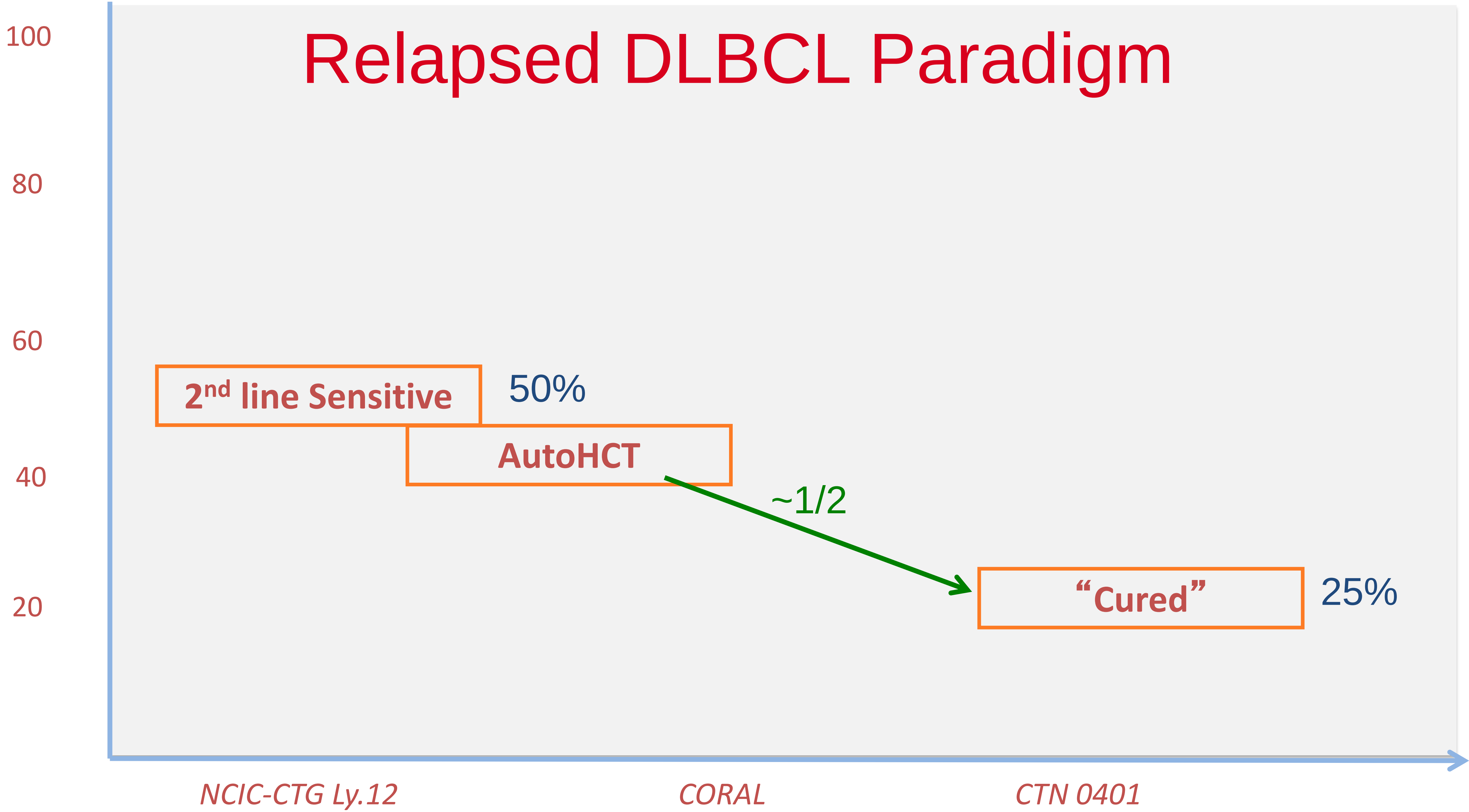
Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16:2780-2795; Harris NL et al. *Ann Oncol*. 1999;10:1419-1432; Hiddemann W et al. *Blood.* 1996;88:4085-4089; Horning SJ. *Blood.* 1994;83:881-884; Liu Q et al. *J Clin Oncol*. 2006;24:1582-1589; Fisher RI et al. *N Engl J Med*. 1993;328:1002-1006; Skarin AT, Dorfman DM. *CA Cancer J Clin*. 1997;47:351-372.

DLBCL Taxonomy

- Most common lymphoma, 5th leading cause of US cancer deaths
- Aggressive disease but potentially curable with chemotherapy in 1st line
- Auto transplant standard approach for relapsed or refractory disease
- Genetically defined subtypes are evolving and are predictive of treatment outcomes

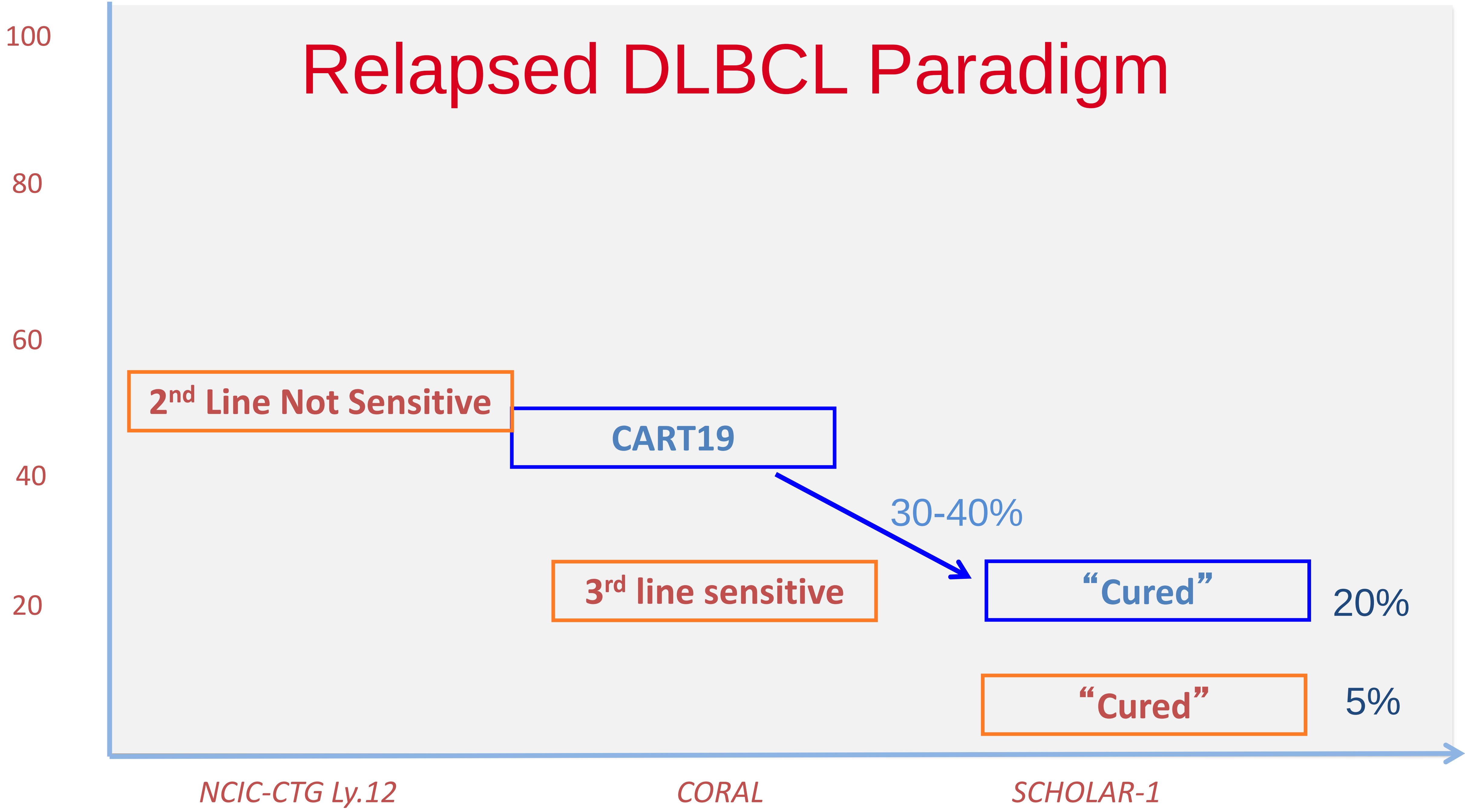


Friedberg. BLOOD, 2017



Relapsed DLBCL Paradigm
100
80
60
40
20
2nd line Sensitive
50%
AutoHCT
~1/2
"Cured"
25%
NCIC-CTG Ly.12
CORAL
CTN 0401

Relapsed DLBCL Paradigm

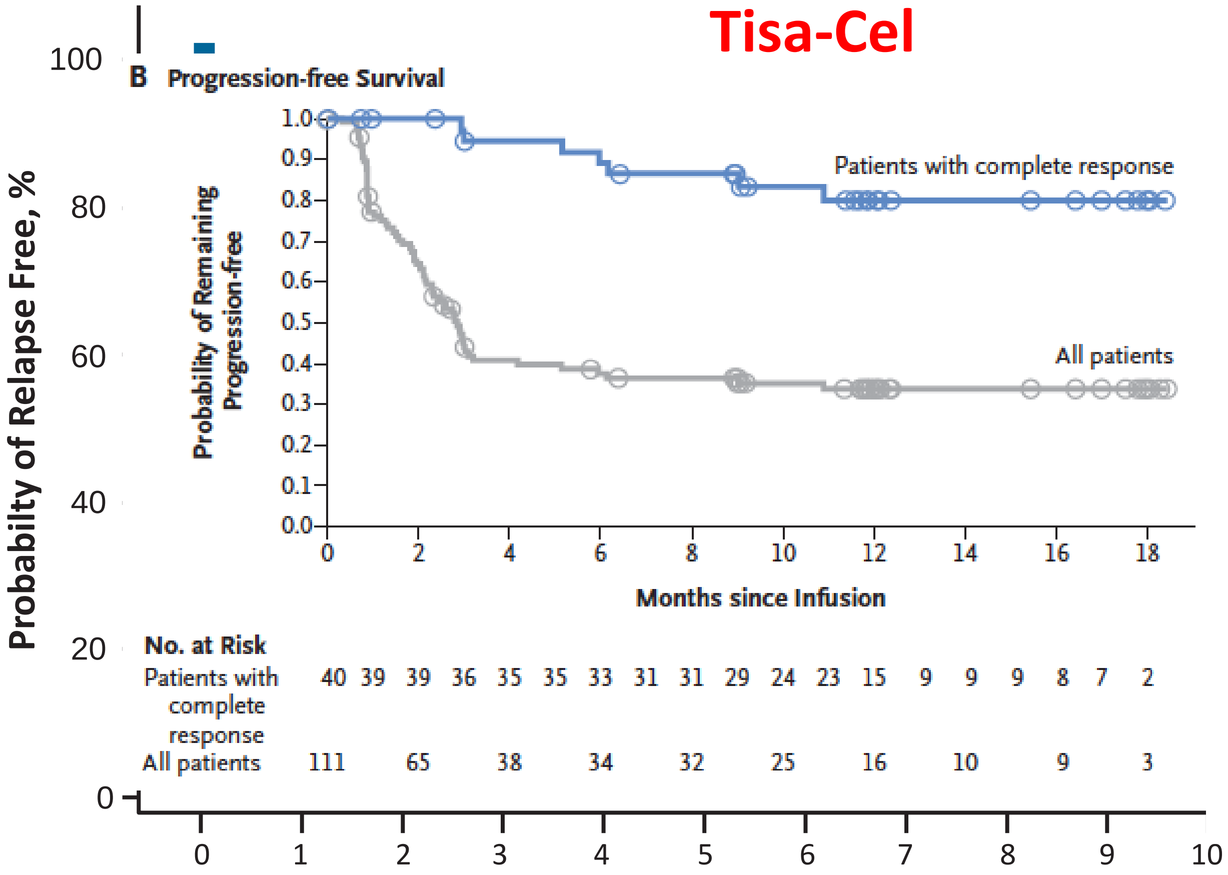


CART19s in Lymphoma Space

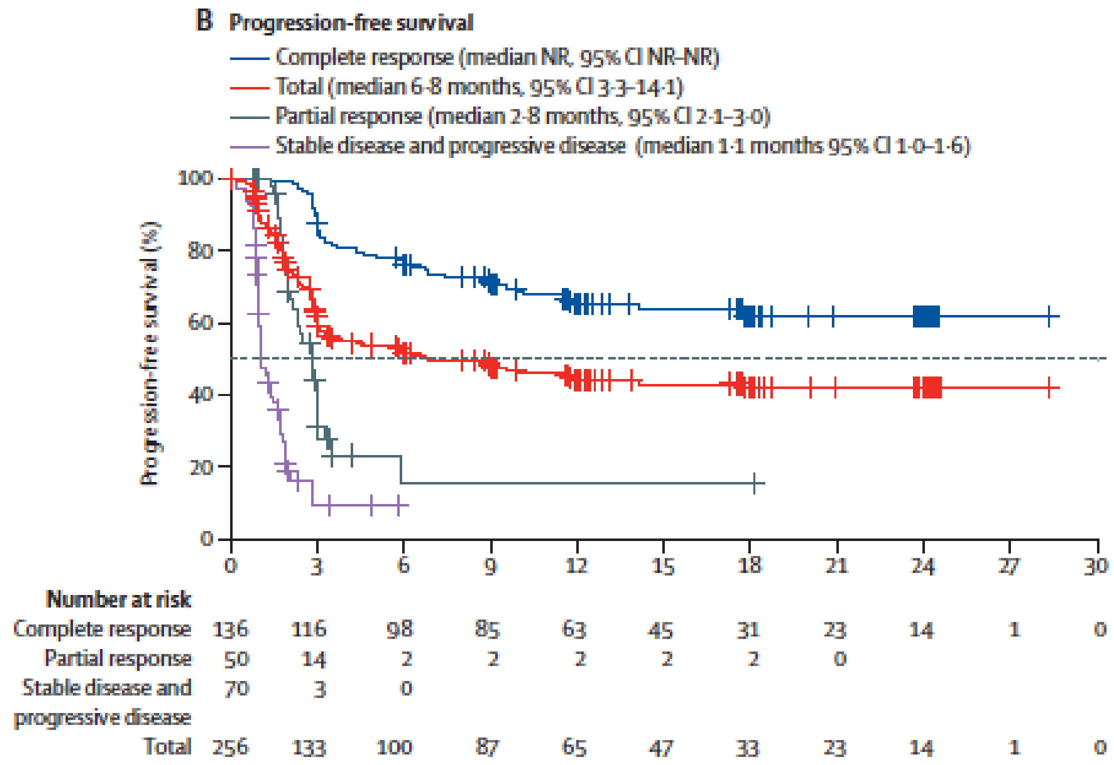
- ***Axicabtagene Ciloleucel (CD28 costim),*** *Kite/Gilead*
  - **Approved for adults in 3rd line DLBCL** (+ primary mediastinal, transformed, double hit)
  - **Approved for Mantle Cell lymphoma (Brexucabtagene Autoleucel)**
  - **Approved for follicular lymphoma**
- ***Tisagenleucleucel (41BB costim),*** *Novartis*
  - **Approved for adults in 3rd line DLBCL** (+ transformed, double hit)
  - In clinical trials for follicular, pediatric NHL
- ***Lisocabtagene Maraleucel (41BB costim, CD4:CD8),*** *Juno/Celgene/BMS*
  - **Approved for adults with 3rd line DLBCL** (+ primary mediastinal, transformed, double hit, Folicular 3b, mantle cell)
  - In clinical trials for CLL

CART19 in Aggressive NHL

Tisa-Cel



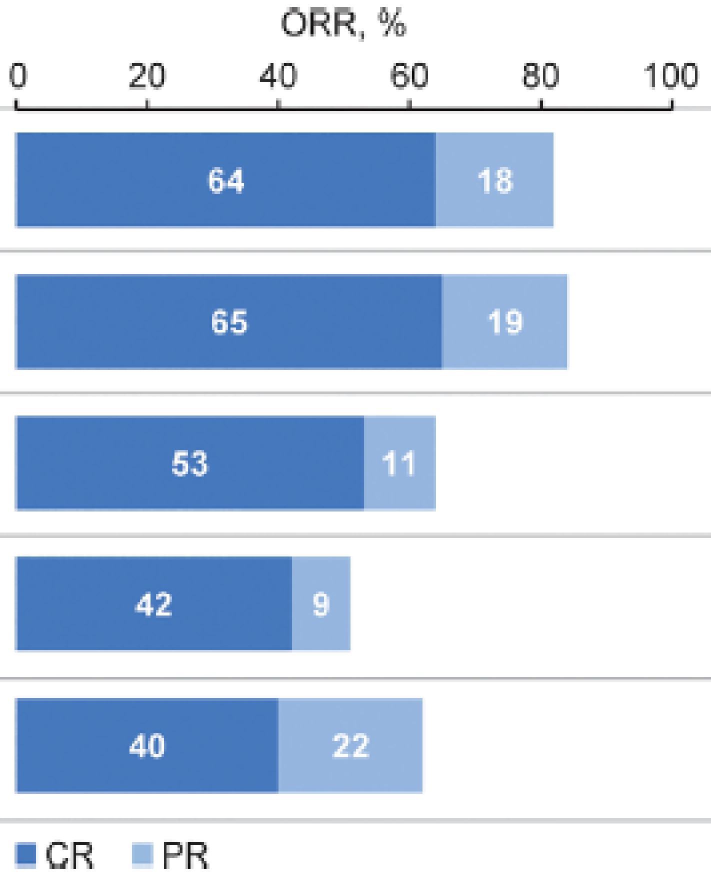
Liso-Cel



Schuster et al, NEJM 2019

Abramson et al, Lancet Oncology 2020

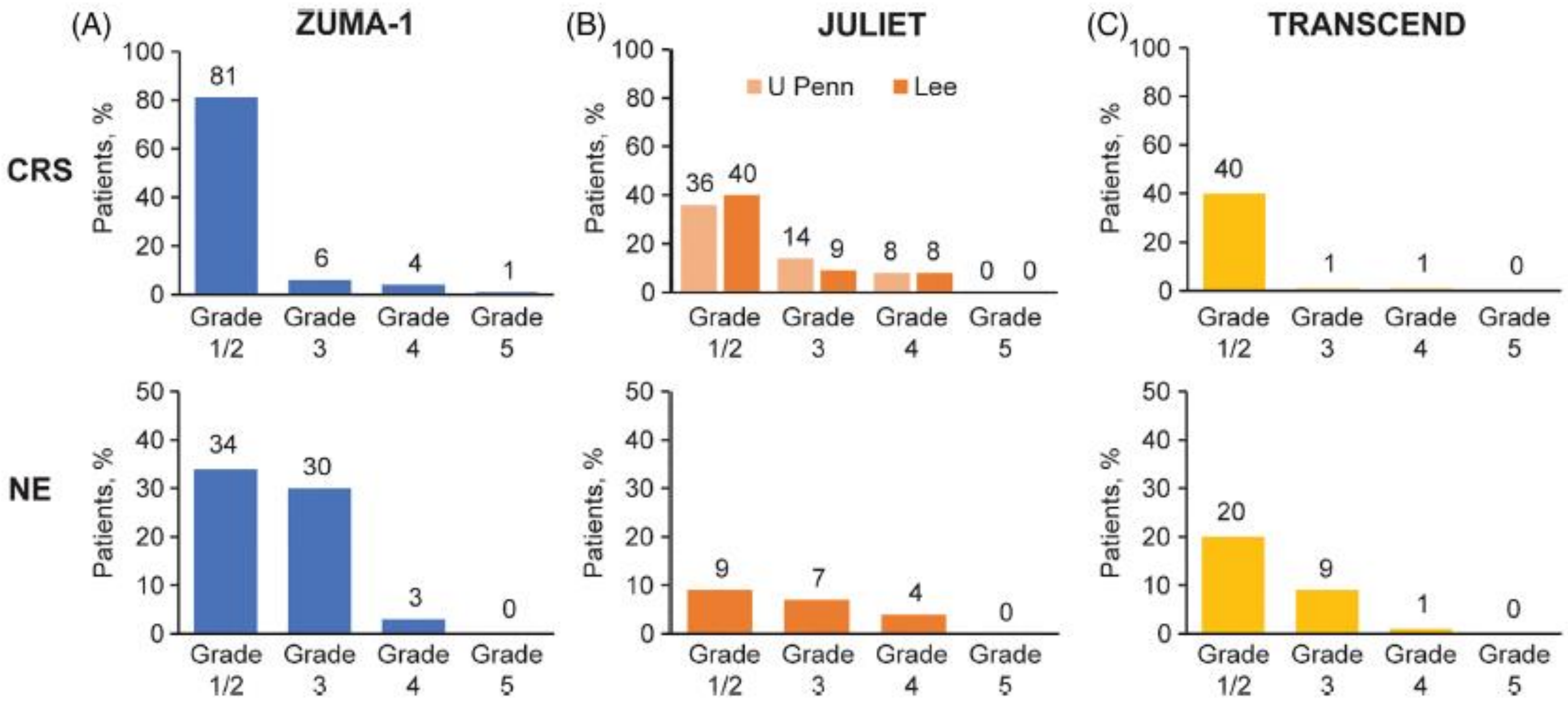
CART19 Real-World Comparison



	ORR	Endpoint	Median follow-up, mo
Nastoupil et al (N = 275) Axi-cel	82	Best ORR of patients with ≥90 days follow-up	12.9
Pasquini et al (N = 326) Axi-cel	84	Best ORR of patients with ≥6 months follow-up	6+
Riedell et al (N = 158) Axi-cel	64	ORR at Day 90	7.6
Riedell et al (N = 86) Tisa-cel	51	ORR at Day 90	6.2
Pasquini et al (N = 152) Tisa-cel	62	BOR	11.9

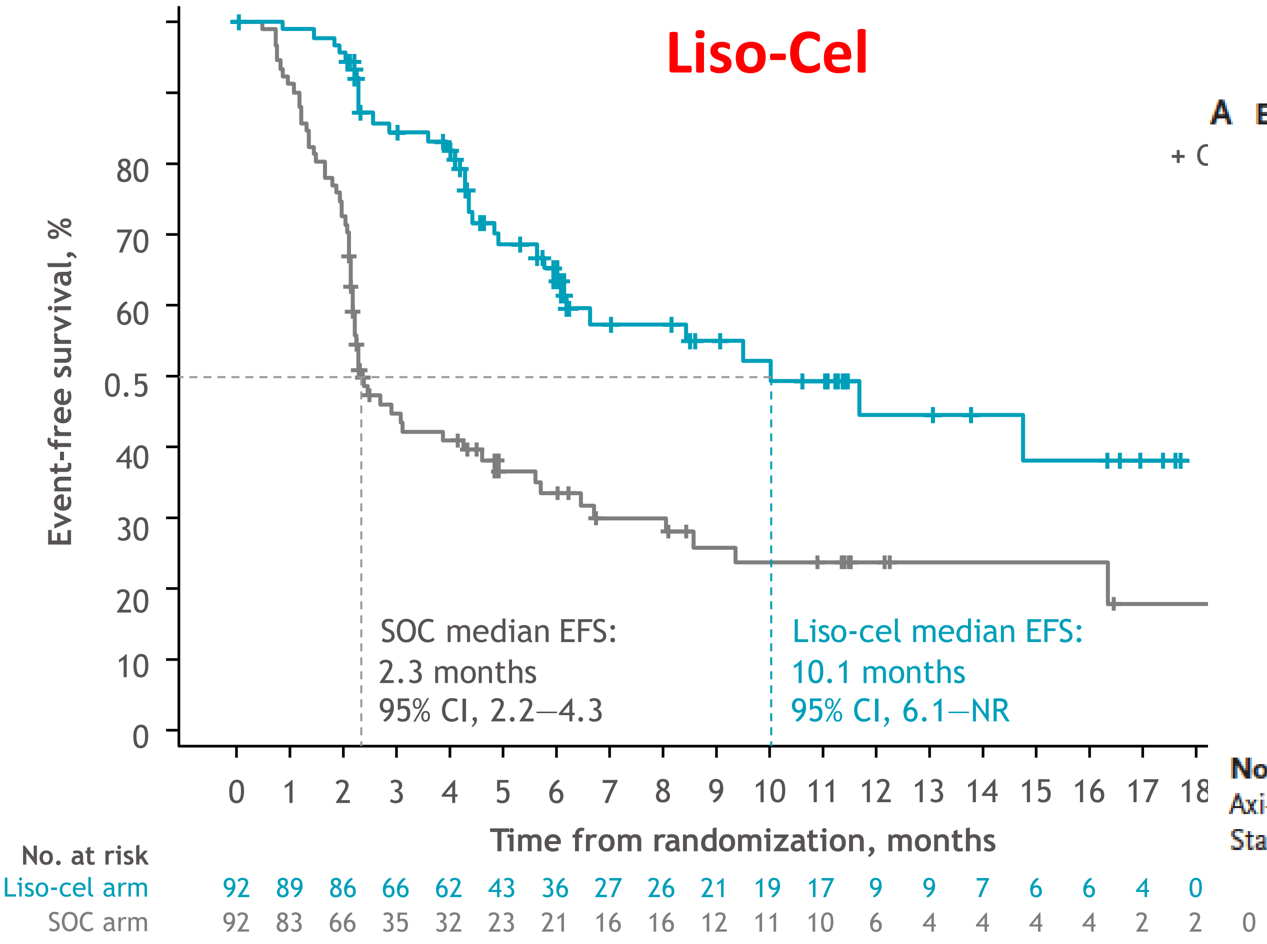
Andreadis Am J Hematol. 2021;96(10):1295-1312

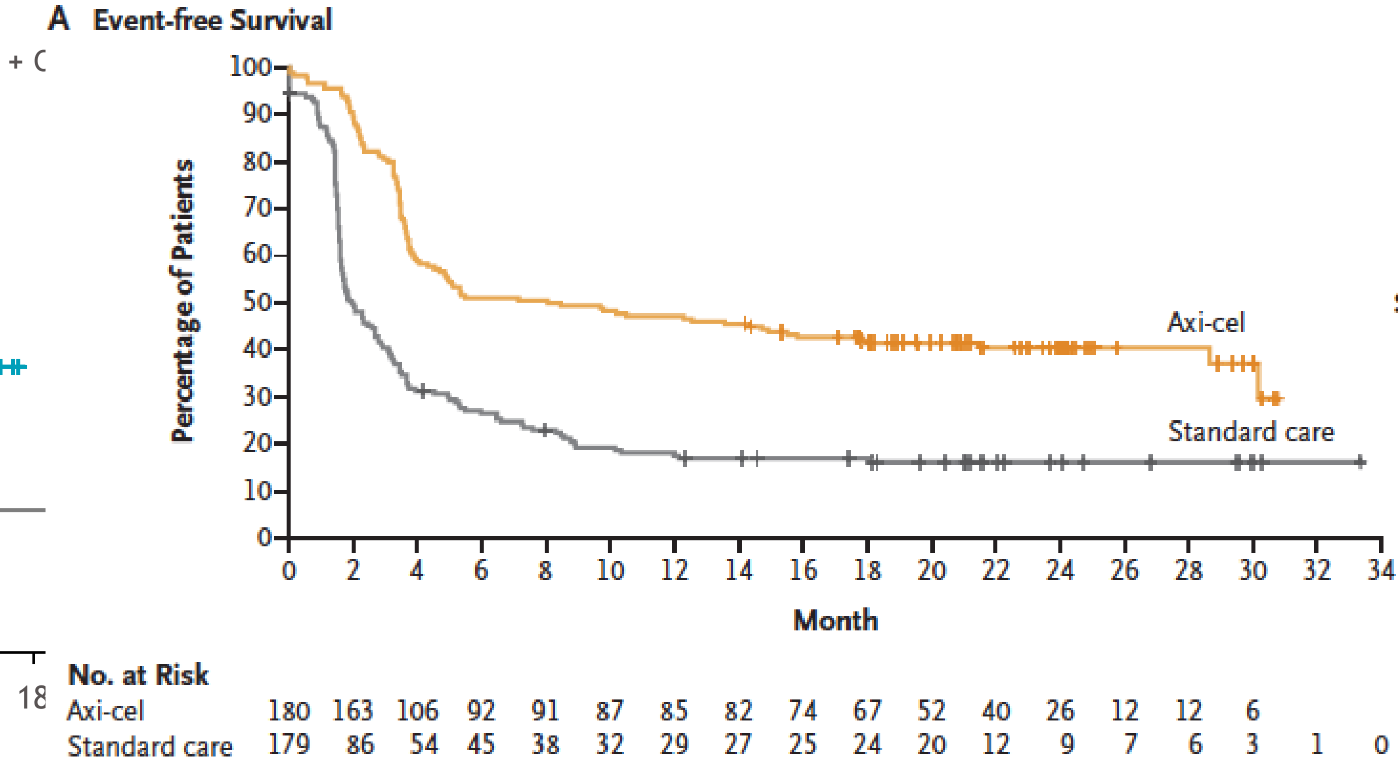
CART19 Toxicity



Andreadis Am J Hematol. 2021;96(10):1295-1312

Moving CART19 to 2nd line?





Reasons for CAR-T Cell Failure

Tumor Bulk/Progression

CD19 Antigen Loss

T cell exhaustion phenotypes

Lymphoma Tumor Biology

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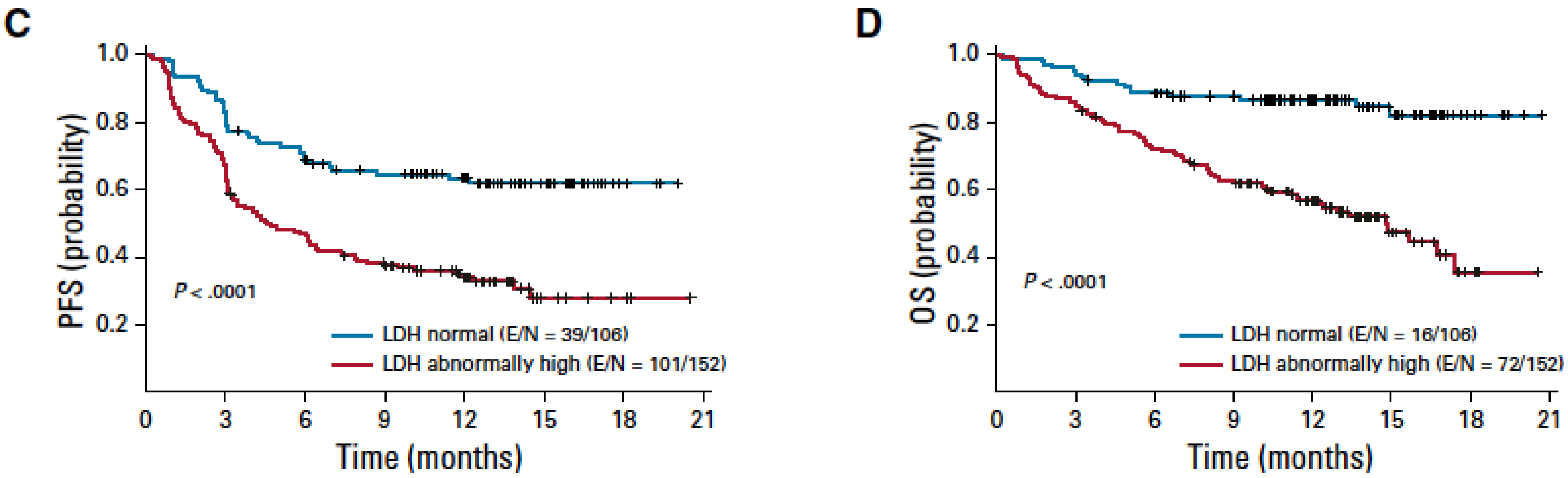
CART Consortium
LDH Level Predicts Survival



No. at risk:

LDH normal	106	85	72	62	48	24	4	0
LDH abnormally high	152	100	70	53	32	7	3	0

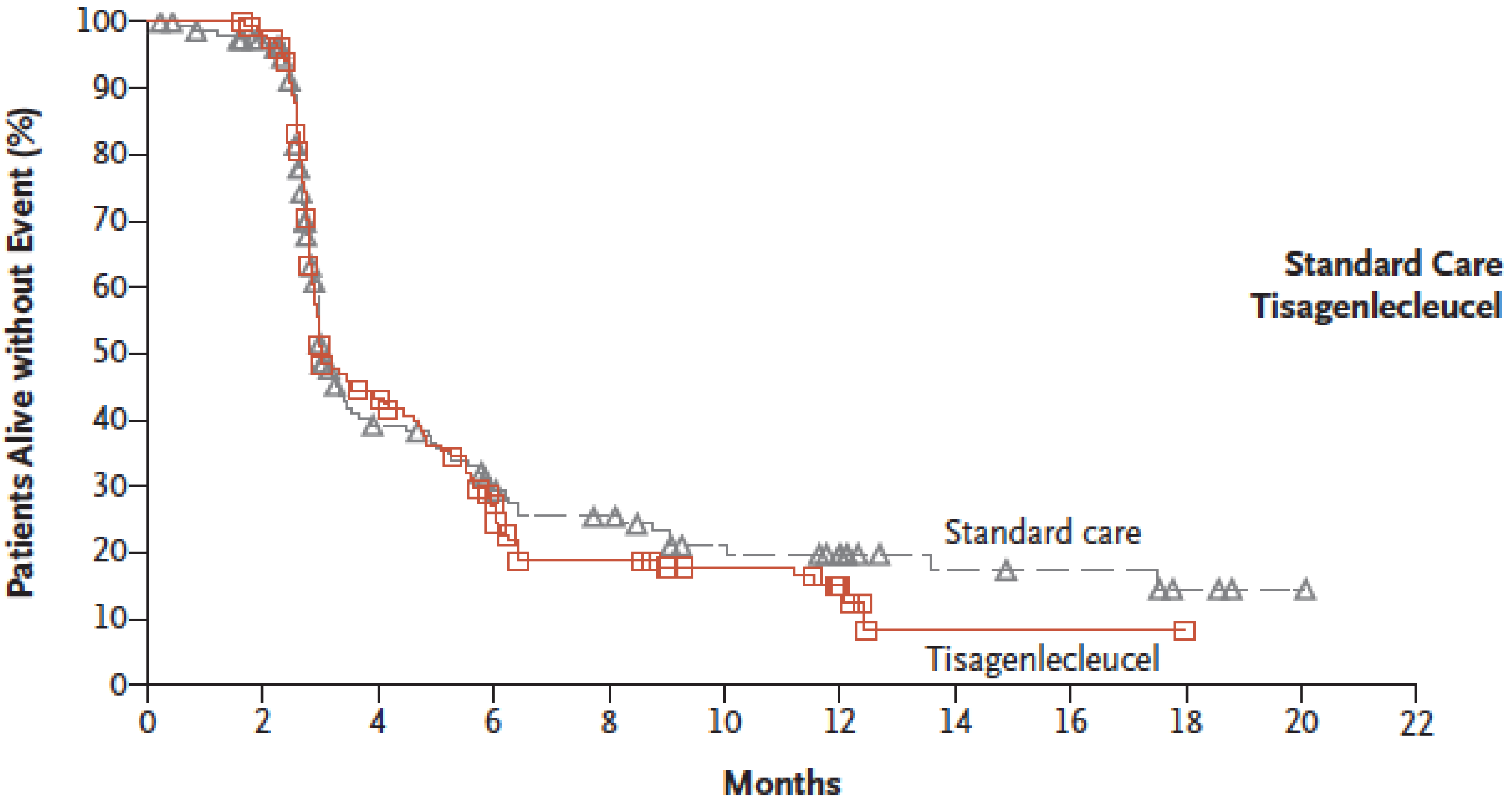
No. at risk:

LDH normal	106	101	93	84	61	32	8	0
LDH abnormally high	152	129	107	88	57	19	4	0

Nastoupil et al, JCO 2020

Tumor Bulk an issue in 2nd line?

Tisa-Cel

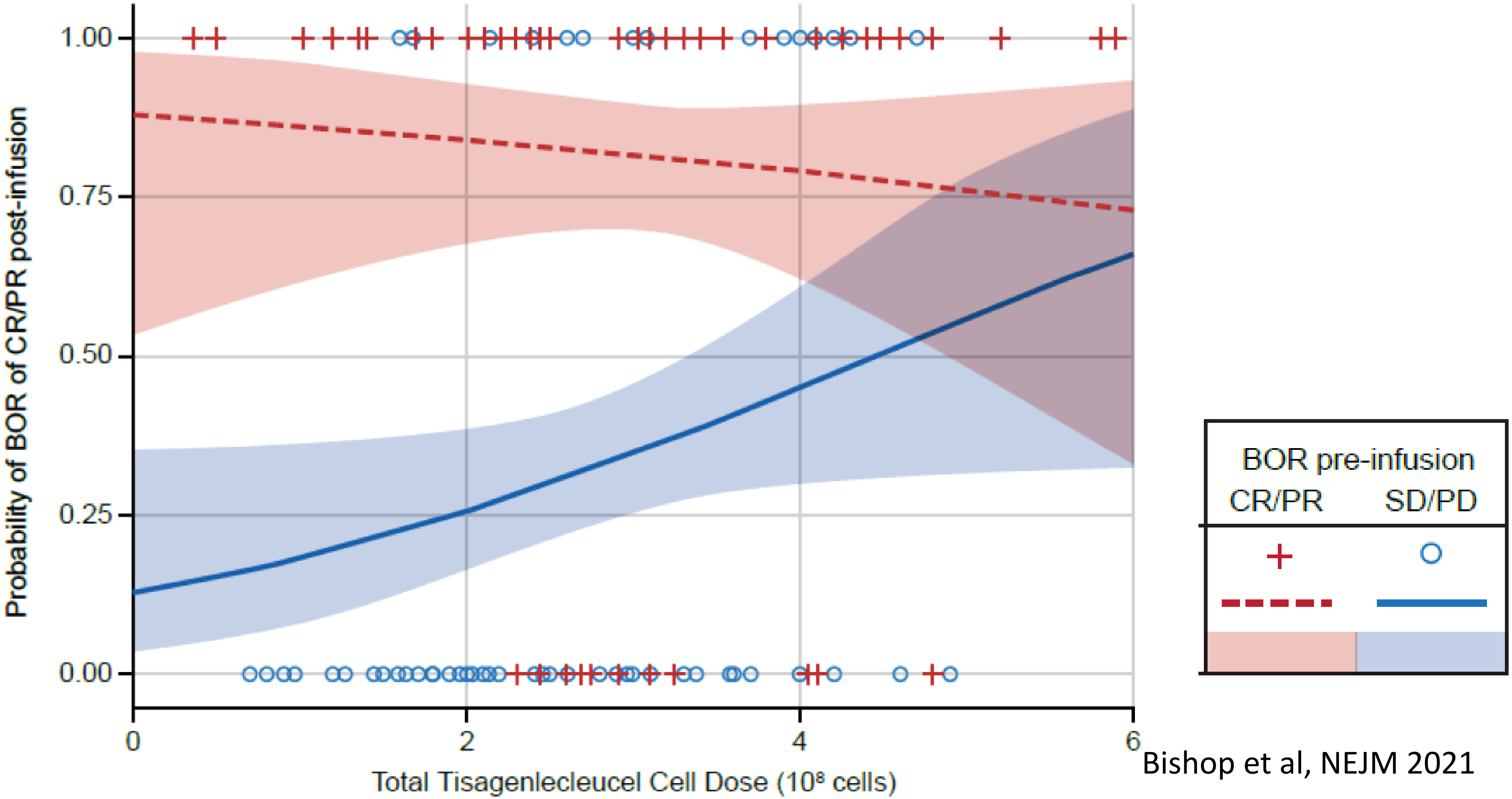


No. at Risk

Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

Bishop et al, NEJM 2021

Tumor Burden vs. CART19 Balance



Bishop et al, NEJM 2021

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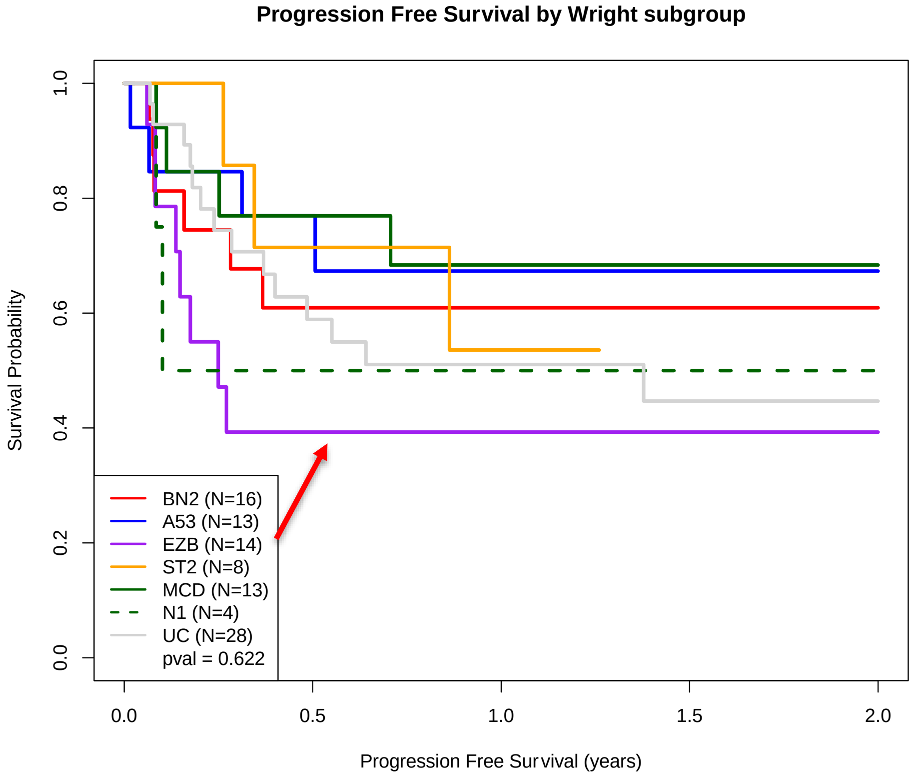
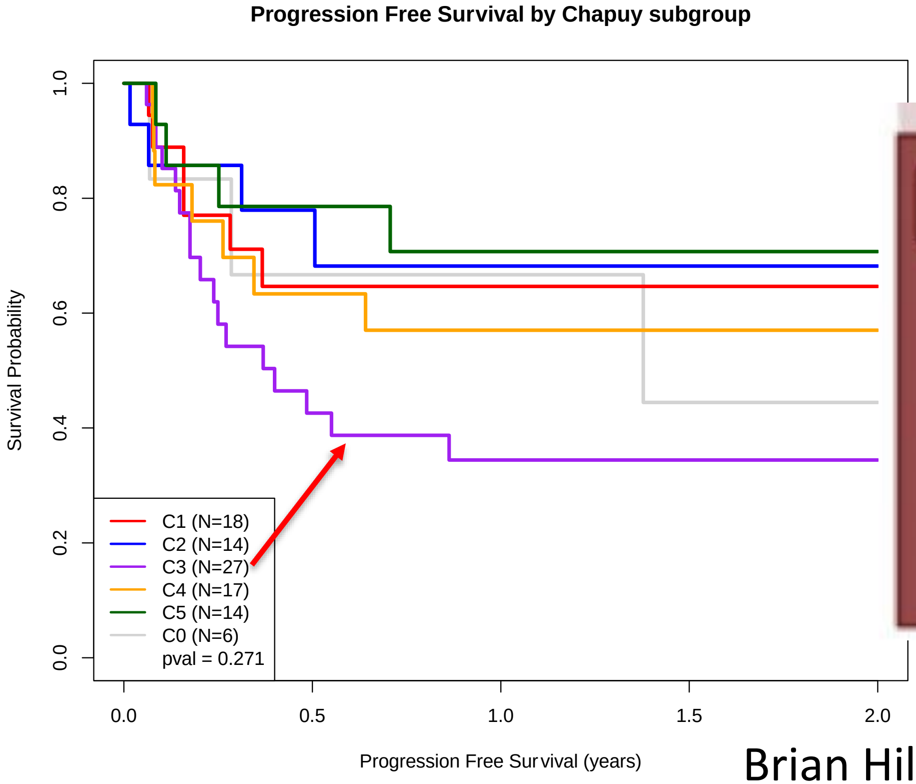
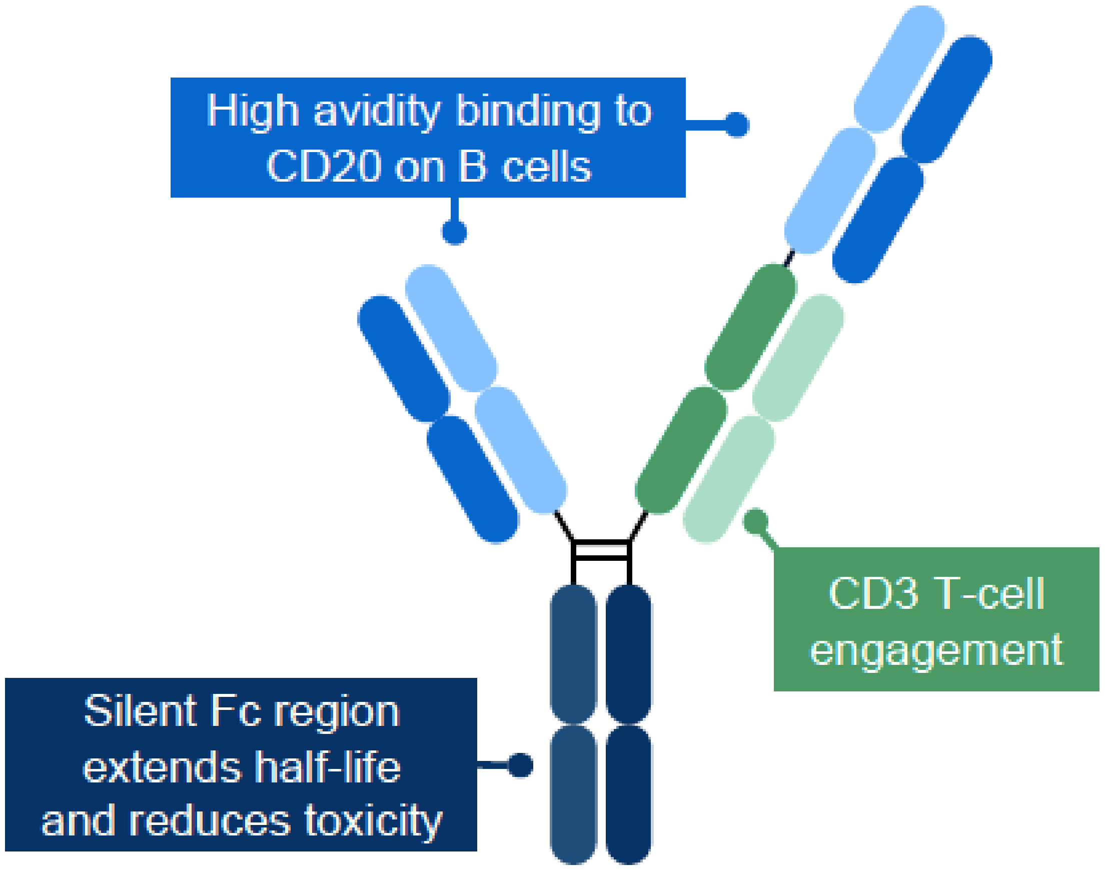
Molecular Subtype Predicts Outcome- Gene Consortium

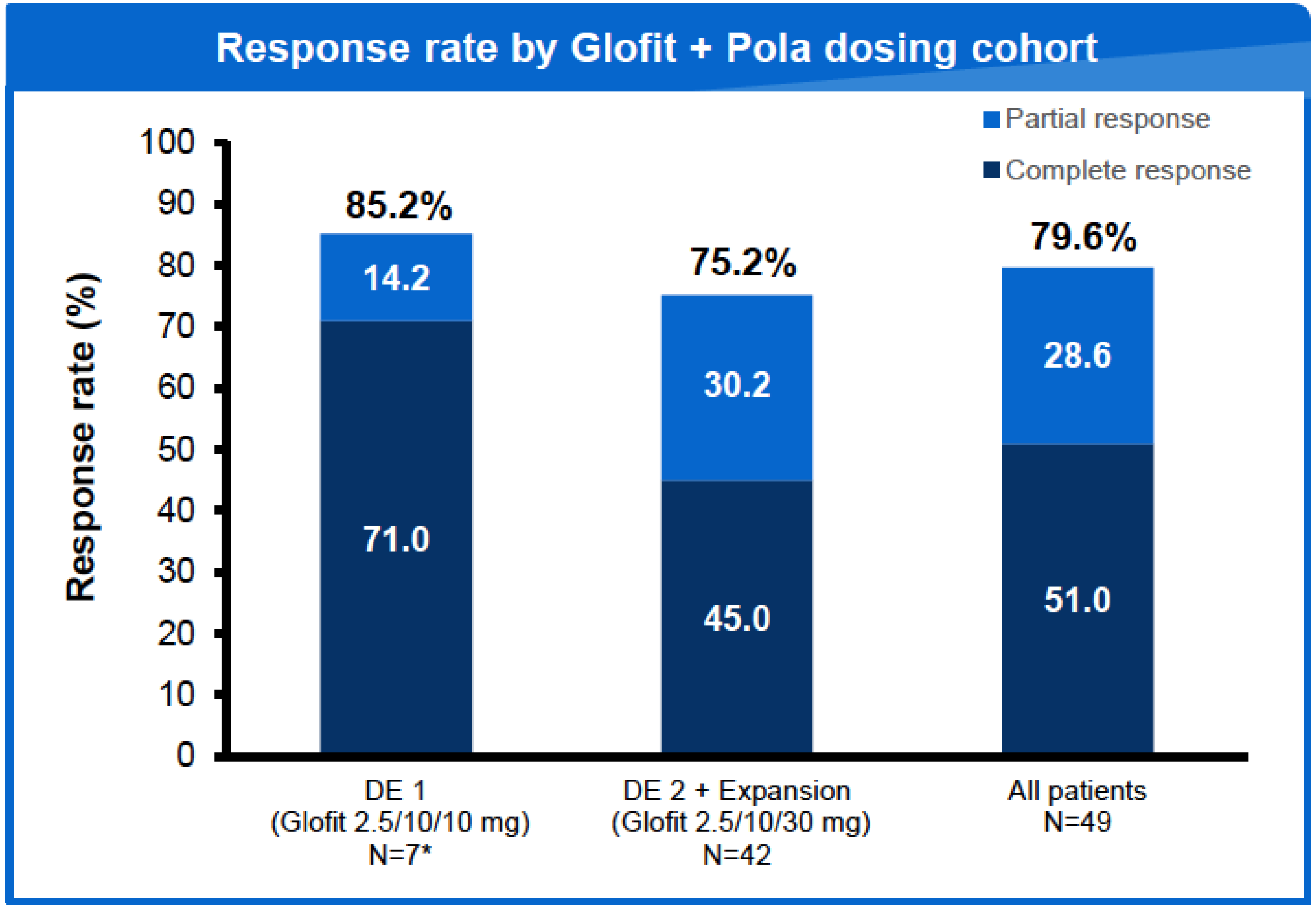




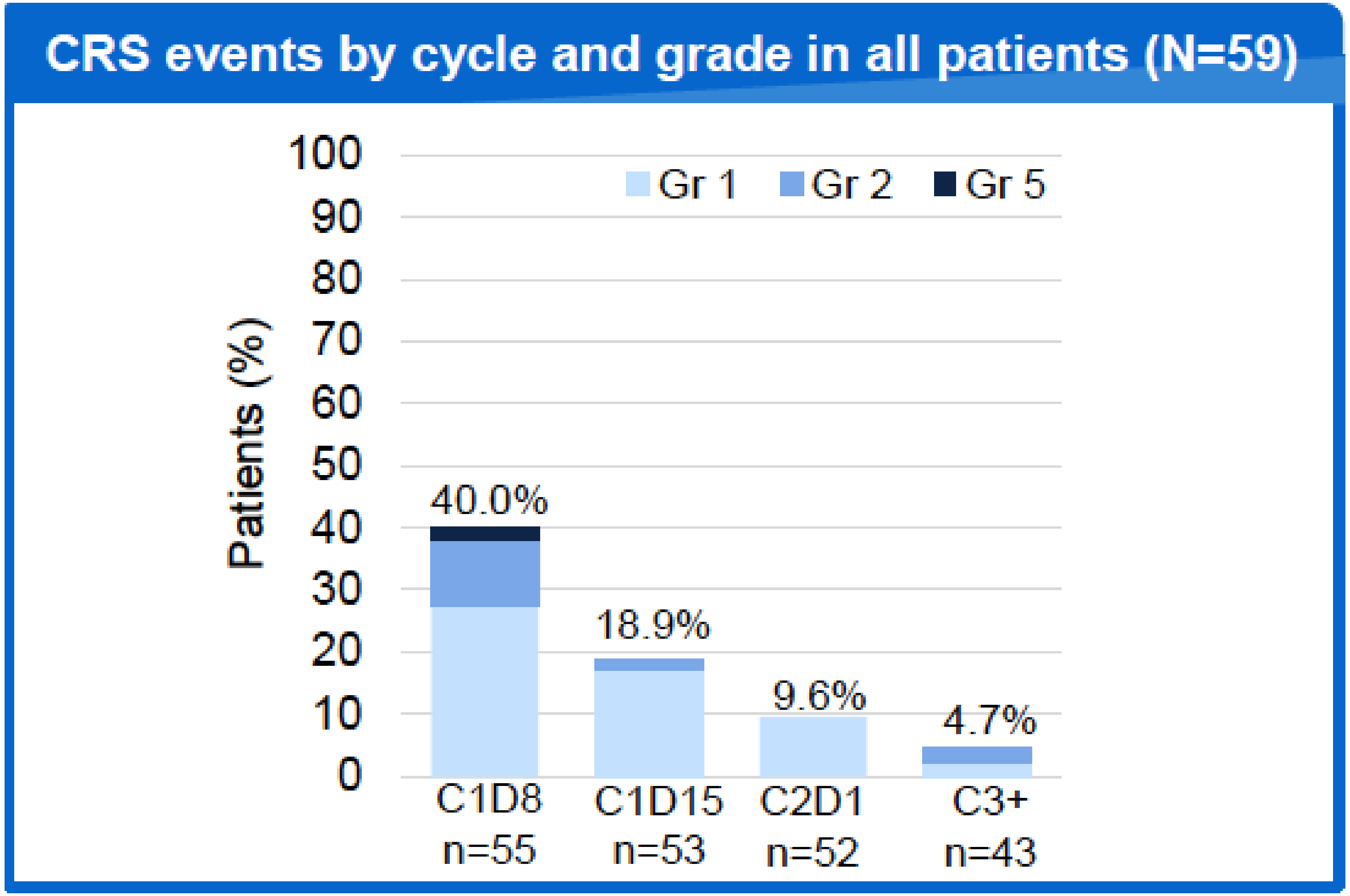
Brian Hill et al, ASH 2021

BITEs Coming Soon in DLBCL



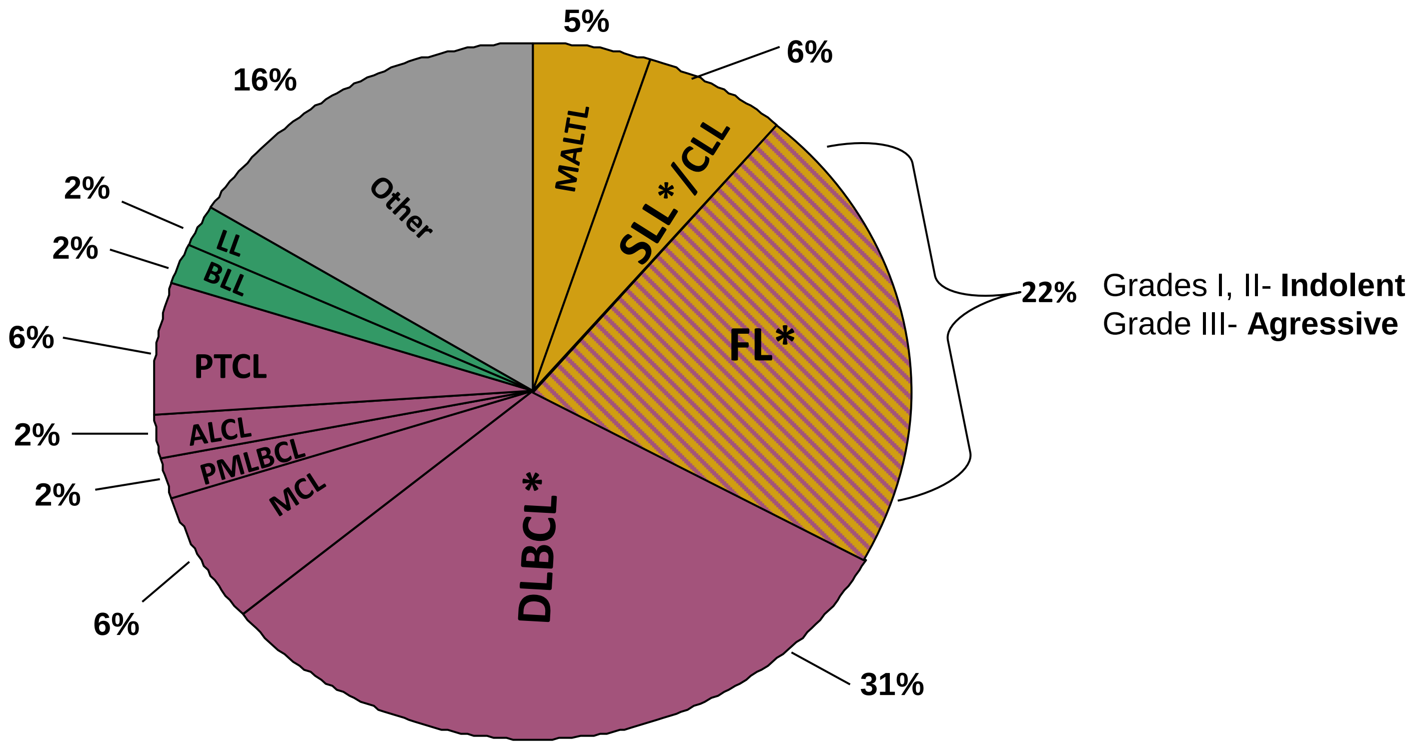


Glofit/Pola Toxicity



Hutchings et al, ASH 2021

Clinical Course and WHO Classification



Indolent (low grade)	→	**Aggressive (intermediate grade)**	→	**Very aggressive (high grade)**
• Slowly progressive • 5-year OS ≤95%		• Rapid clinical course • 5-year OS ≤50%		• Grows rapidly • Survival 0.5-2 years

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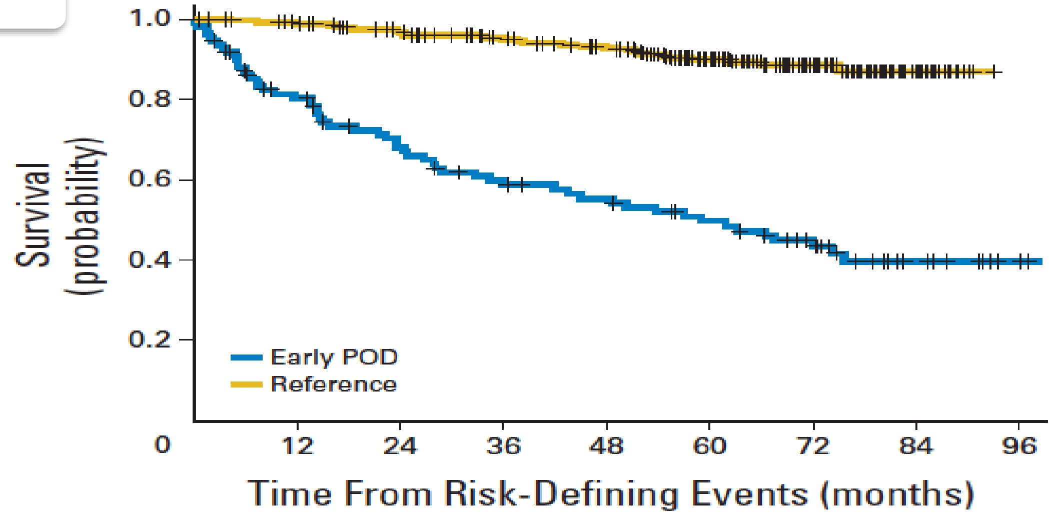
Follicular Lymphoma

- 2nd most common NHL (22%)
- Noncurable with conv. therapy
- Median survival of >10 years
- Poster child for immunotherapy
  - – **Rituximab, 1998** (first indication)
  - – αIg Vaccine: BioVax, 2009
  - – **IMIDs: Lenalidomide 2019**

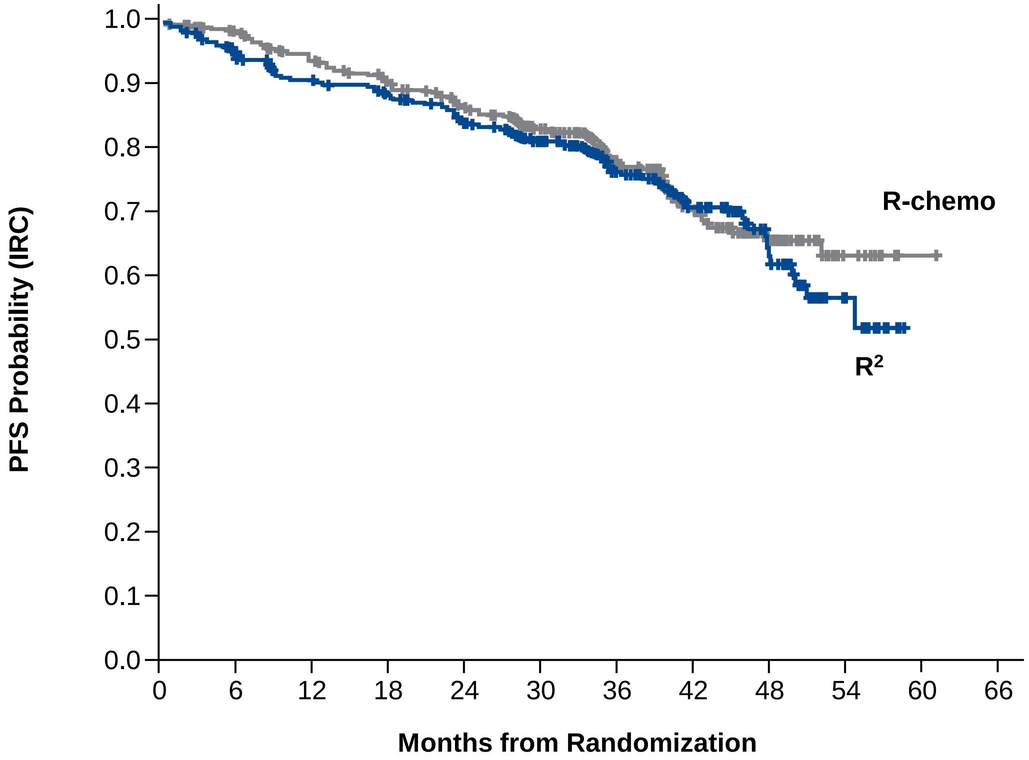


POD 24

Casullo et al, JCO 2015; 33:2516

Relevance: R-Lenalidomide vs. R-Chemo

Co-Primary Endpoint: Interim PFS (~50% events)



Number of Patients at Risk

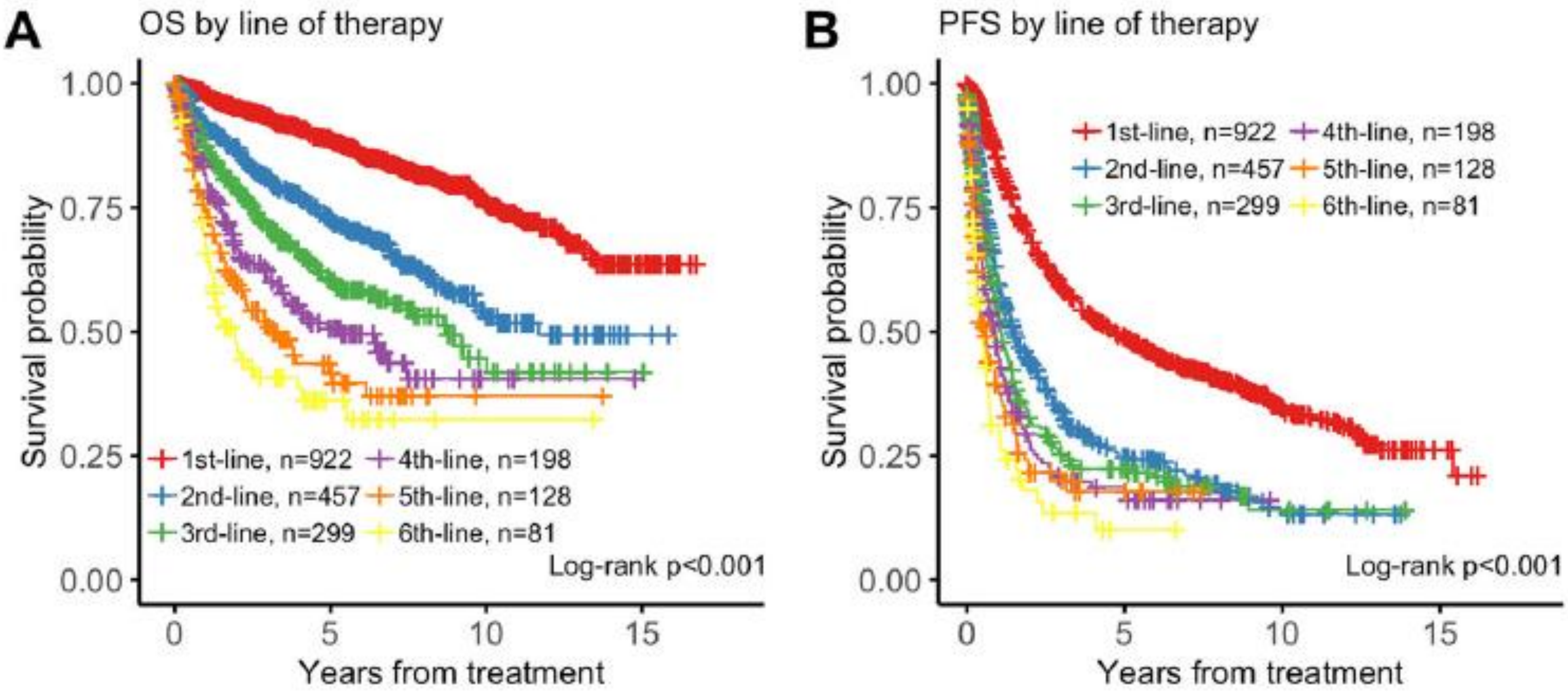
R^2	513	435	409	393	364	282	174	107	49	13	0	
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

	R^2 (n = 513)	R-chemo (n = 517)
Events, n (%)	119 (23)	111 (21)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-82%)
HR (95% CI)	1.10 (0.85-1.43)	
P value	0.48	

OS: 94% both arms

Data cut-off 31May2017.

Current Snapshot of Natural History



Batlevi et al, Blood Cancer Journal 2020

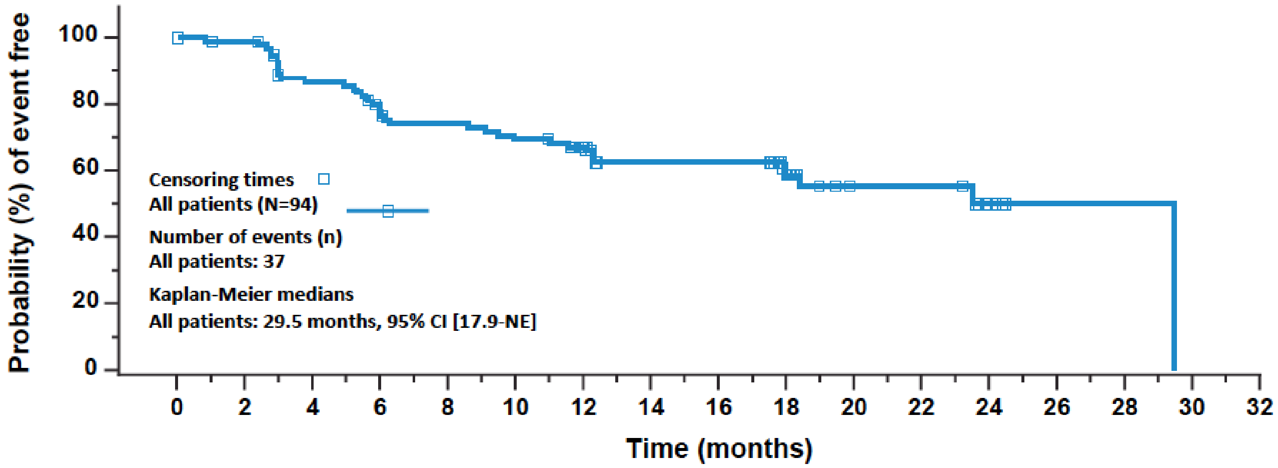
CART19 Promising in 3rd line- Tisa-Cel

Efficacy Results of Extended Follow-up Analysis

Endpoint	% (95% CI)
ORR[a]	**86.2** (77.5-92.4)
CRR[a]	**69.1** (58.8-78.3)
12-mo PFS	**67.0** (56.0-75.8)
9-mo DOR	**76.0** (64.6-84.2)

[a]ORR and CRR were comparable with the primary efficacy analysis (ORR 86.2% and CRR 66.0%).

Kaplan-Meier Curve of PFS per IRC Assessment



Number of subjects still at risk

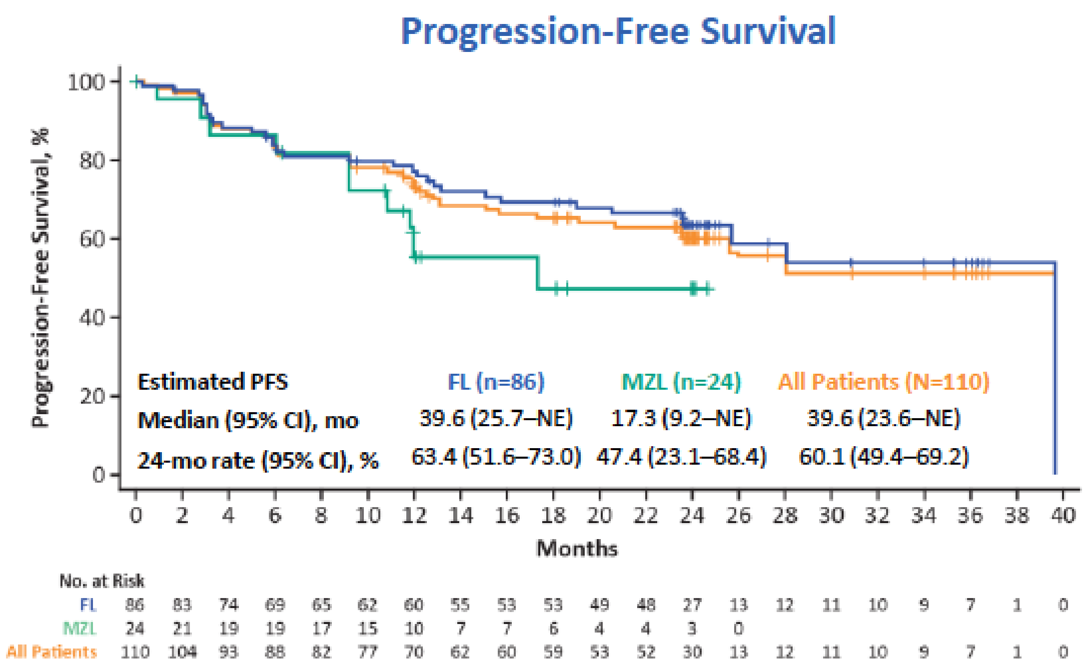
All subjects	94	91	77	67	63	59	52	41	41	28	13	13	5	1	1	0	0

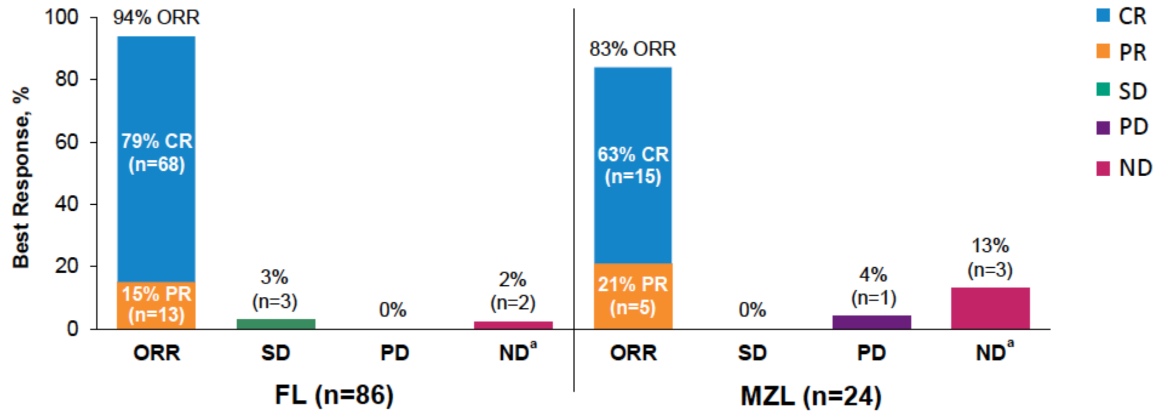
CRS[b,c]	47 (48.5)	0
All nervous system disorders[d]	36 (37.1)	3 (3.1)
ICANS	4 (4.1)	1 (1.0)
Infections	18 (18.6)	5 (5.2)

Disease Characteristic	Descriptive Analysis: High-Risk 12-Month PFS (%)	Descriptive Analysis: Low-Risk 12-Month PFS (%)	Multivariate Analysis: Hazard Ratio (95% CI)
POD24	60.8	77.9	2.3 (1.0-5.3)
TMTV[a]	54.5	68.5	2.5 (1.3-5.6)

ELARA: Thieblemont et al, ASH 2021

CART19 Longer Term Data- Axi-Cel



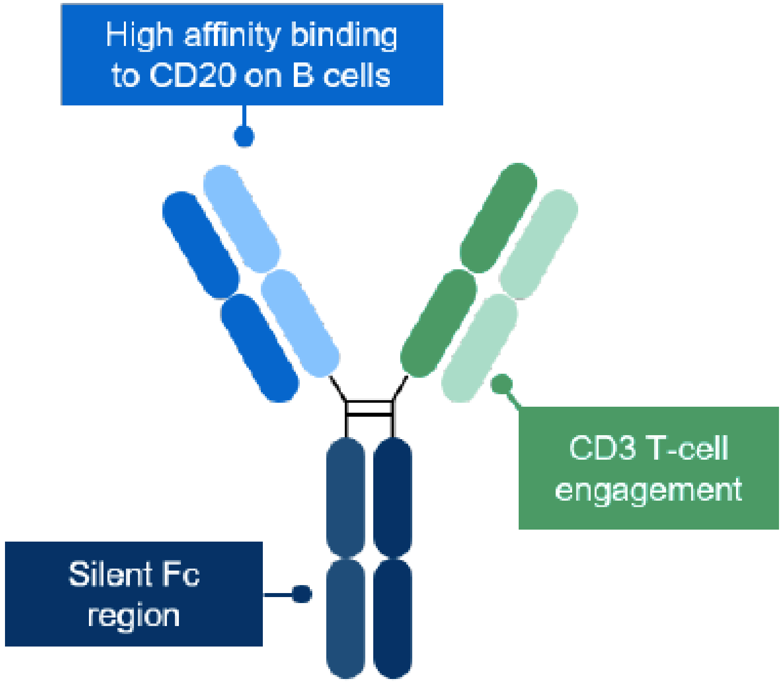


Parameter (95% CI)	Follicular Lymphoma (n=78)[a] With POD24 (n=49)	Follicular Lymphoma (n=78)[a] Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

ZUMA-5: Neelapu et al, ASH 2021

BiTEs Moving in FL 3rd Line

Mosunetuzumab:
CD20xCD3 bispecific antibody[4]

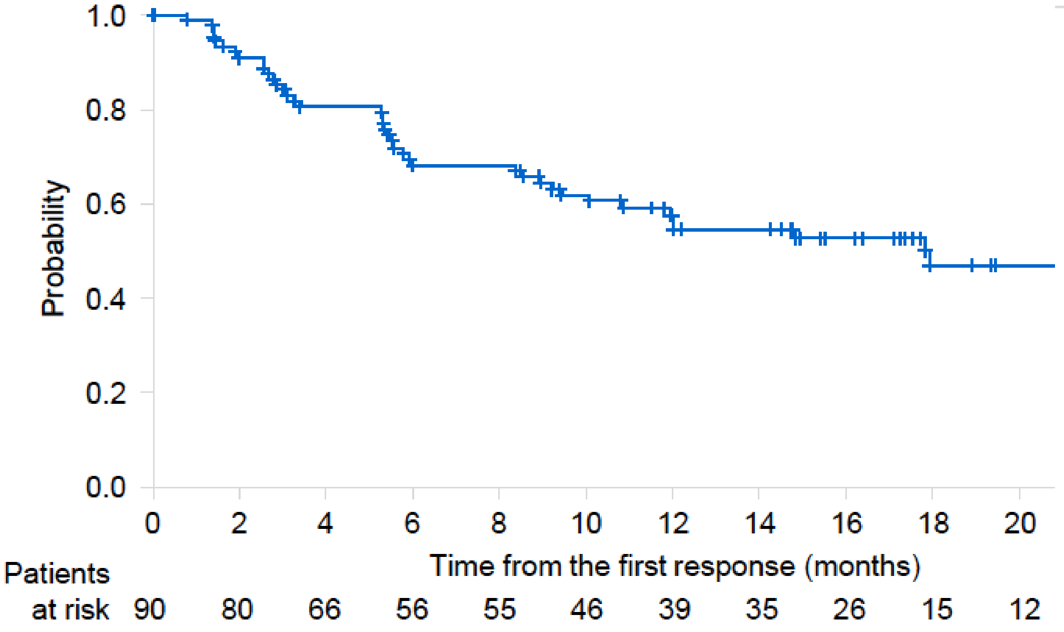


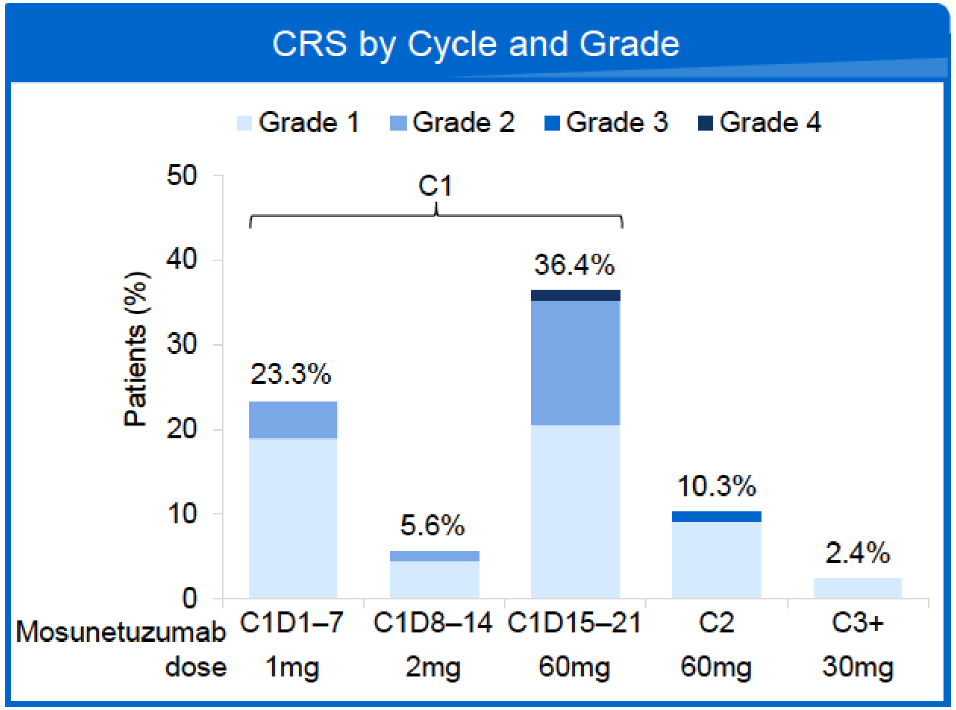
		N=90
Median number of prior lines, n (range)		3 (2–10)
Prior systemic therapy	Anti-CD20 therapy	90 (100%)
	Alkylator therapy	90 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	13 (14.4%)
	CAR-T	3 (3.3%)
Prior ASCT		19 (21.1%)
Refractory to last prior therapy		62 (68.9%)
Refractory to any prior aCD20 therapy		71 (78.9%)
Refractory to any prior aCD20 therapy and alkylator therapy (double refractory)		48 (53.3%)
POD24		47 (52.2%)

Butte et al, ASH 2021

Mosun in Follicular 3rd Line

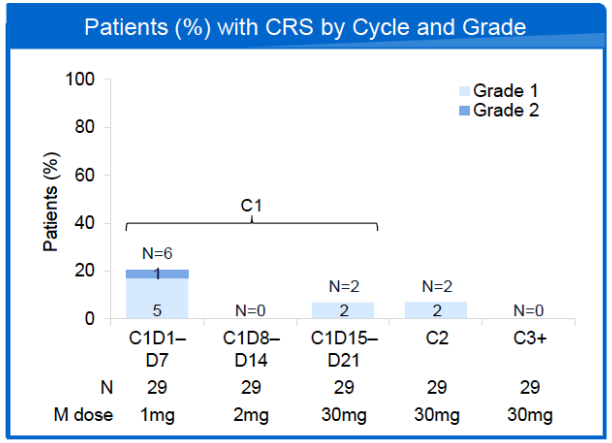
Efficacy endpoint[1]	IRF N (%) [95% CI]
CR	**54 (60%)** [49%, 70%]
ORR	**72 (80%)** [70%, 88%]

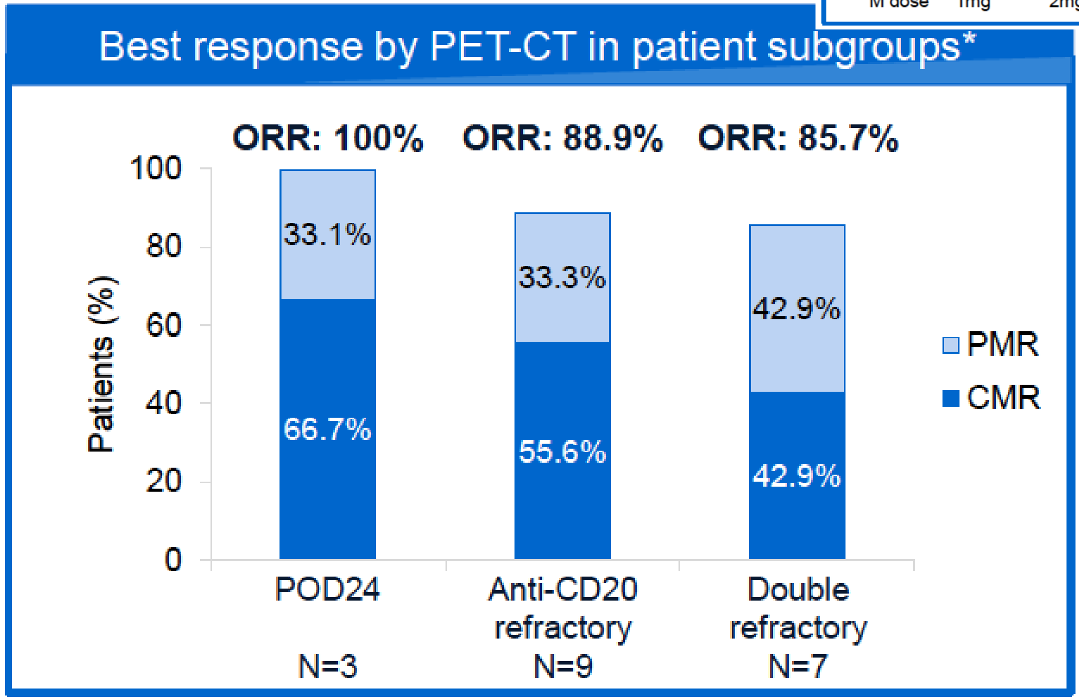




Mosun/Lenalidomide in 2nd line

	N=29
Age in years, median (range)	59 (30–79)
Male	13 (44.8%)
Ann Arbor stage at study entry	
I–II	2 (6.8%)
III–IV	27 (93.1%)
FLIPI risk factors at study entry	
0–1	7 (24.1%)
2	8 (27.6%)
3–5	14 (48.3%)
Number of prior lines of therapy, median (range)	1 (1–6)
1 prior line	16 (55.2%)
≥2 prior lines	13 (44.8%)
Refractory to any prior aCD20 therapy	9 (31.0%)
Refractory to any prior aCD20 therapy AND an alkylating agent (double refractory)	7 (24.1%)
POD24	3 (10.3%)

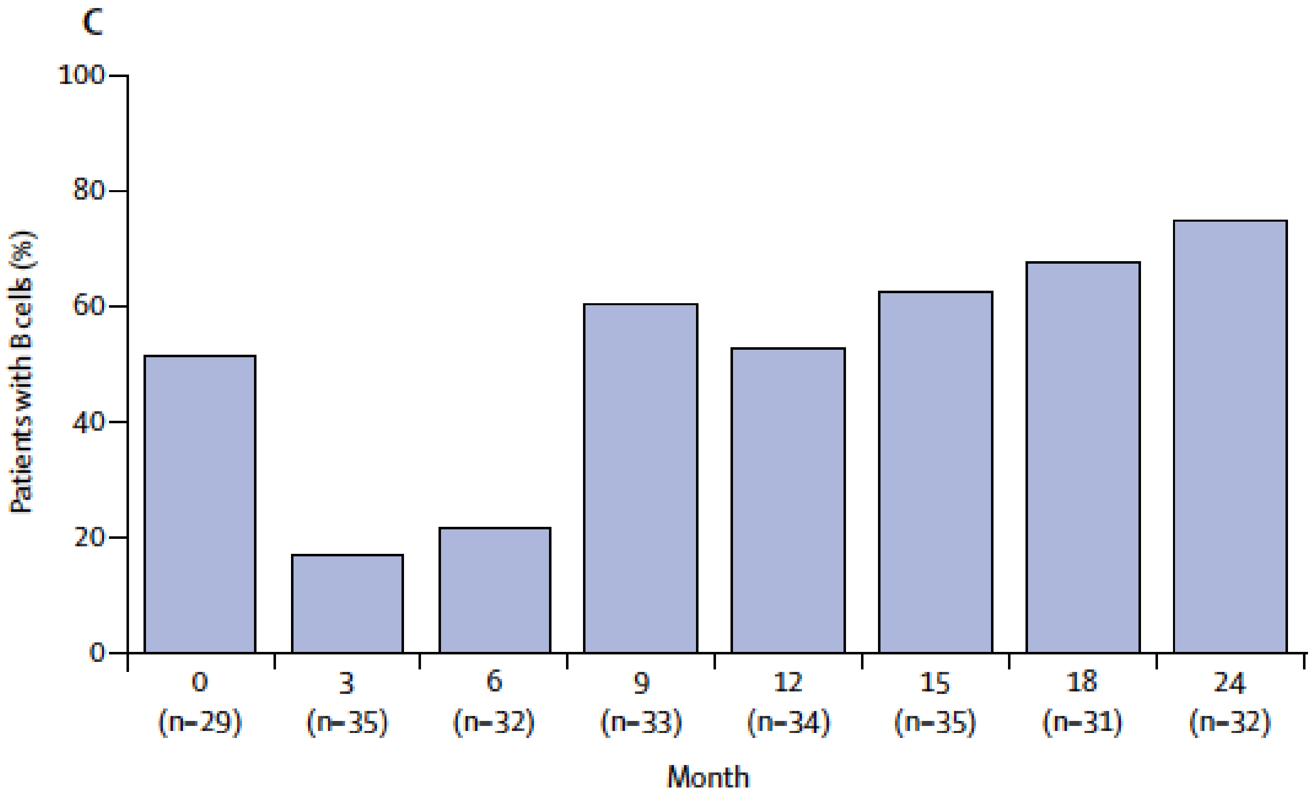




Morsschauser et al, ASH 2021

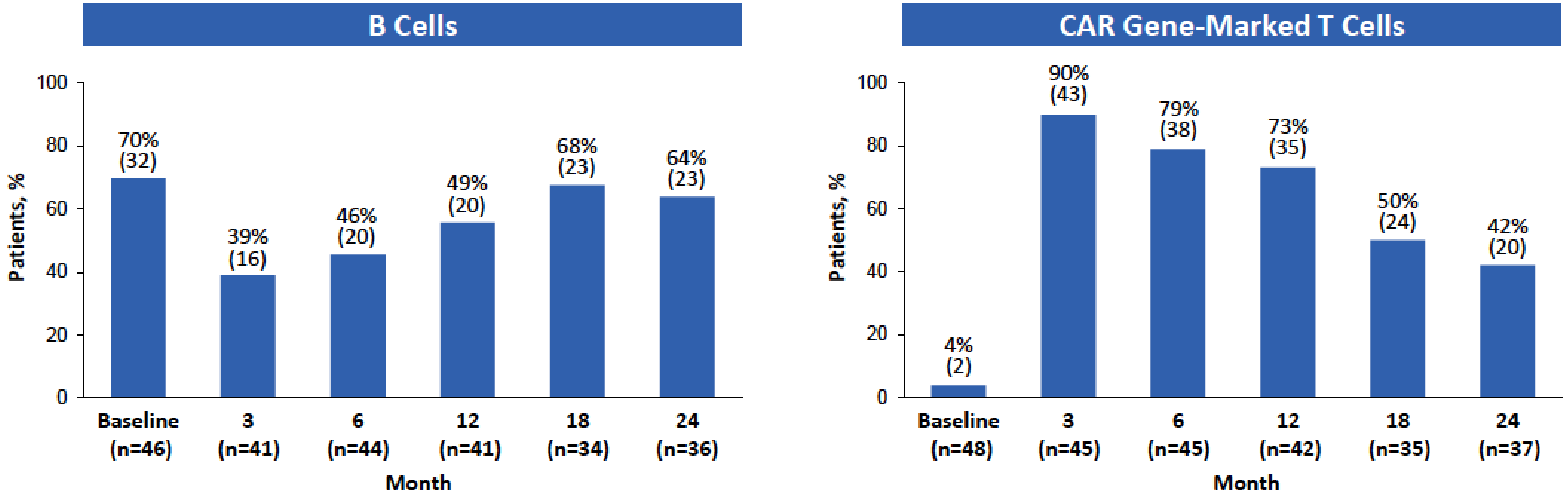
B- Cell Aplasia

- **Immunosuppression**
  - Long-term B cell aplasia
  - Support with IVIG in ~33%
  - Practice highly variable across studies and institutions



Lancet Oncol 2019; 20: 31–42

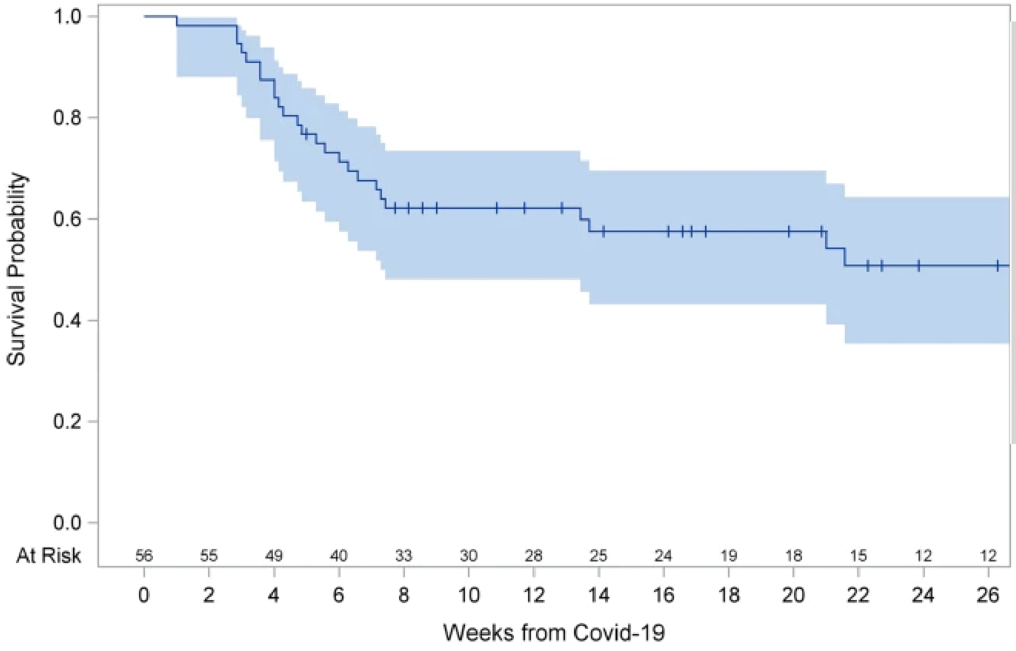
B-cell Recovery After Axi-cel



ZUMA-5: Neelapu et al, ASH 2021

COVID19 vs. CART19

Fig. 1: Overall survival of patients after COVID-19 diagnosis.



CAR T-cell therapy indication	
B-cell acute lymphoblastic leukemia	7 (12.5)
B-cell non-Hodgkin lymphoma	46 (82.1)
Multiple myeloma	3 (5.4)
Disease status at time of COVID-19 diagnosis	
Relapse/progression	14 (15)
Partial response	7 (12.5)
Complete remission	35 (62.5)

Factors associated with mortality (HR, 95% CI, *P* value)	
Age at time of COVID-19	1.39 (1.05–1.86), *p* = 0.02
Performance status at time of COVID-19	0.71 (0.56–0.89), *p* = 0.003
Metabolic comorbidity	2.75 (1.19–6.35), *p* = 0.02
Tumor not in complete remission at time of COVID-19	2.40 (1.04–5.55), *p* = 0.04

EBMT/EHA Report. Spanjaart et al, Leukemia 2021

Conclusions

- CART19 fulfills promise in relapsed or refractory aggressive NHL with activity comparable to that of 3rd line and beyond
- BiTEs form new backbone in post-CART landscape
- Is indolent NHL becoming truly chemo-free?
- Immunotherapy has unique toxicities in COVID19 era