CART Cell Therapy and Emerging Bispecifics for the Treatment of Follicular Lymphoma

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Disclosures

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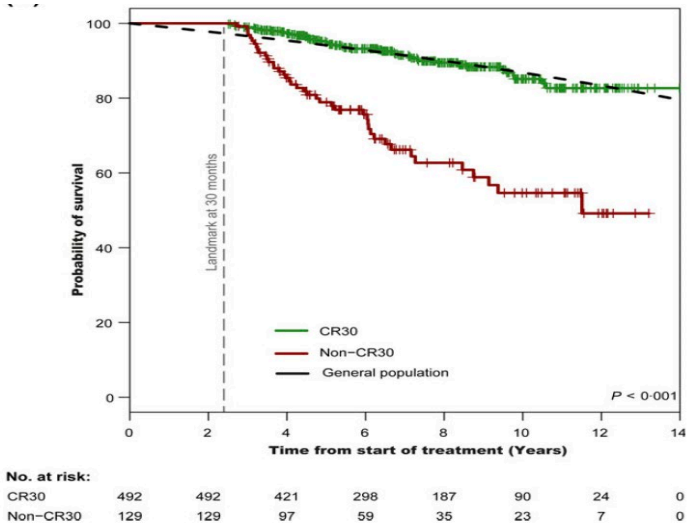
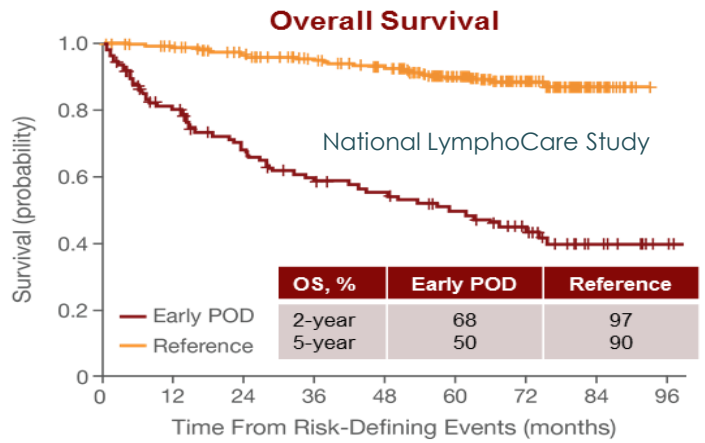
Follicular lymphoma is characterized by recurrent relapses but not all FL is the same

- Survival for patients with follicular lymphoma has improved considerably with incorporation of anti-CD20 antibodies and chemotherapy or more recently, immunomodulatory agents like lenalidomide
- These approaches yield overall response rates of more than 90%, and nearly half of patients remain alive without progression at 10 years
- Life expectancy of FL patients in CR30 is similar to general population but shorter for non-CR30
- Early relapse denotes a significantly poorer survival and defines a *High-Risk* group needing better therapies

FL OS vs. General Population



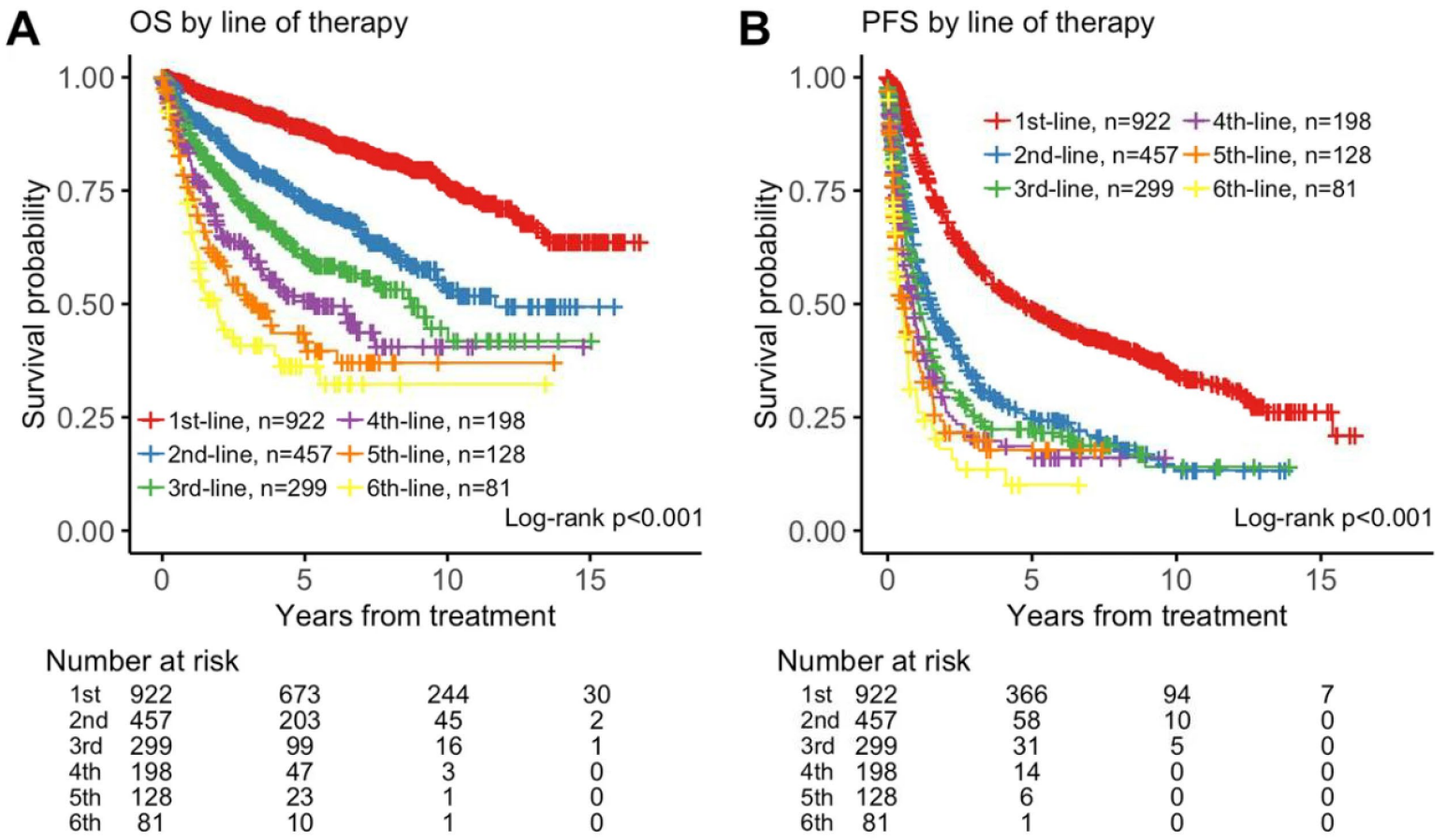


Casulo C. JCO. 2015;33:2516-22

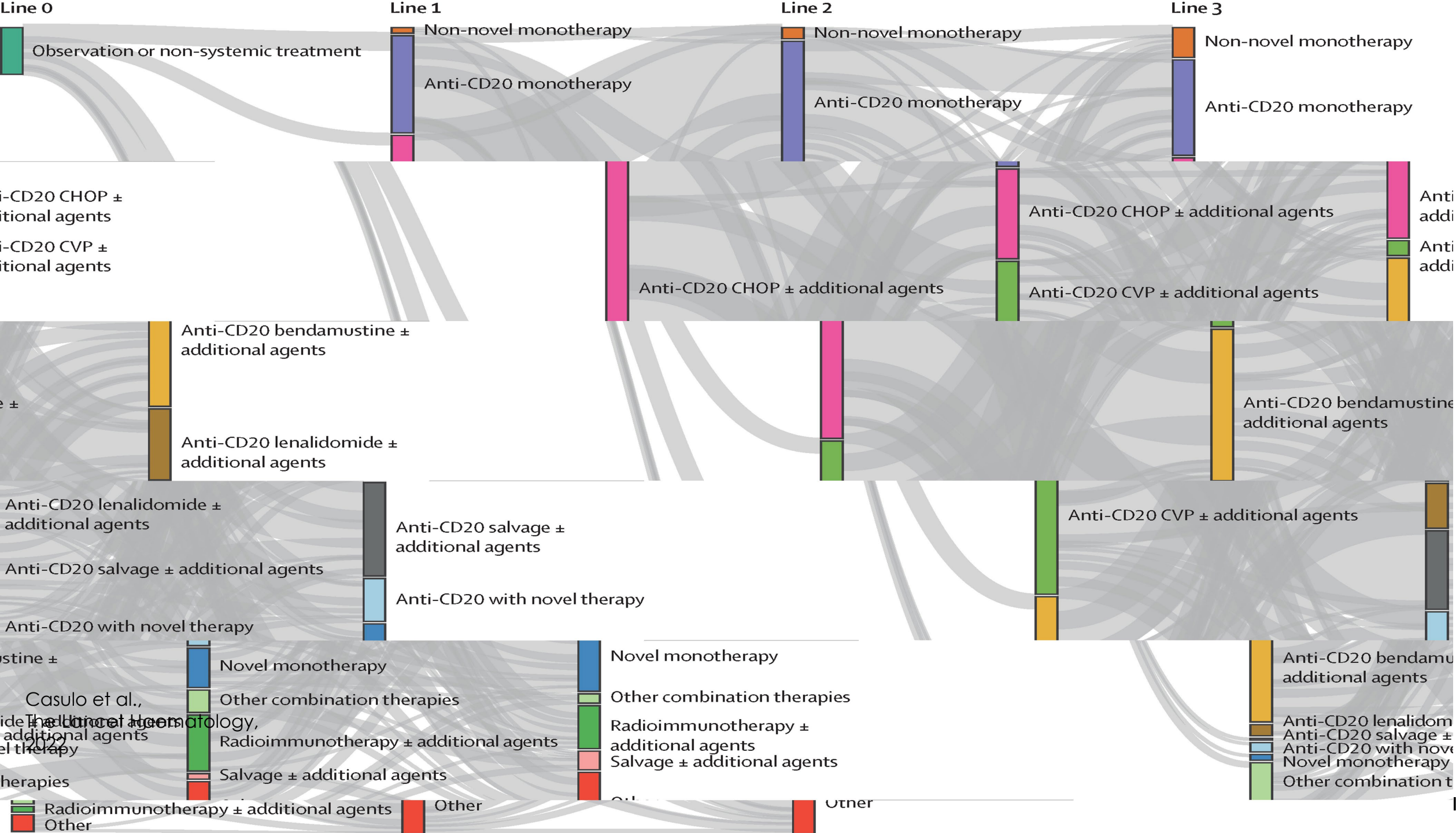
Magnano et al. *Br J Haematol* 2019

Disease Response Changes By Line of Therapy

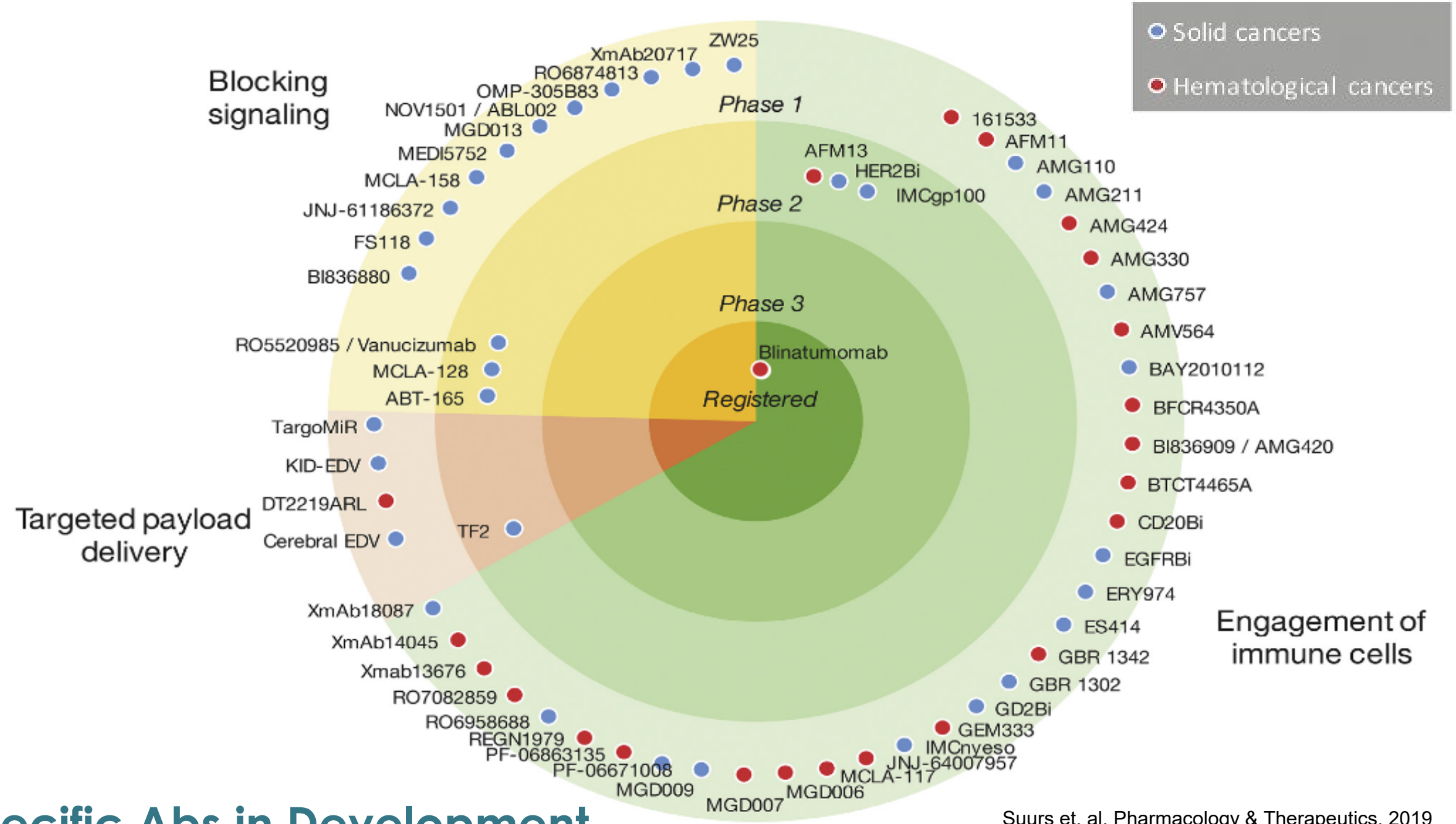
- As the disease recurs, patients are treated with multiple lines of therapies during their lifetime
- However response to therapy decreases with subsequent lines as does overall survival



Batlevi, C.L., et al. Blood Cancer J. 10, 74 (2020)



Casulo et al., The Lancet Haematology, 2022

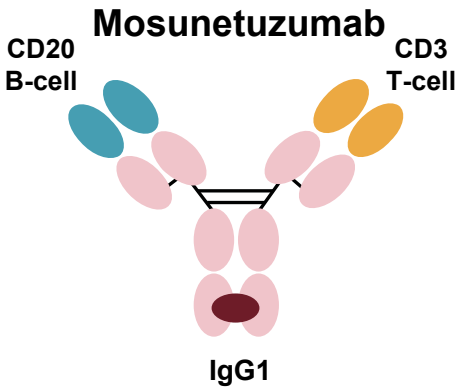


Bispecific Abs in Development

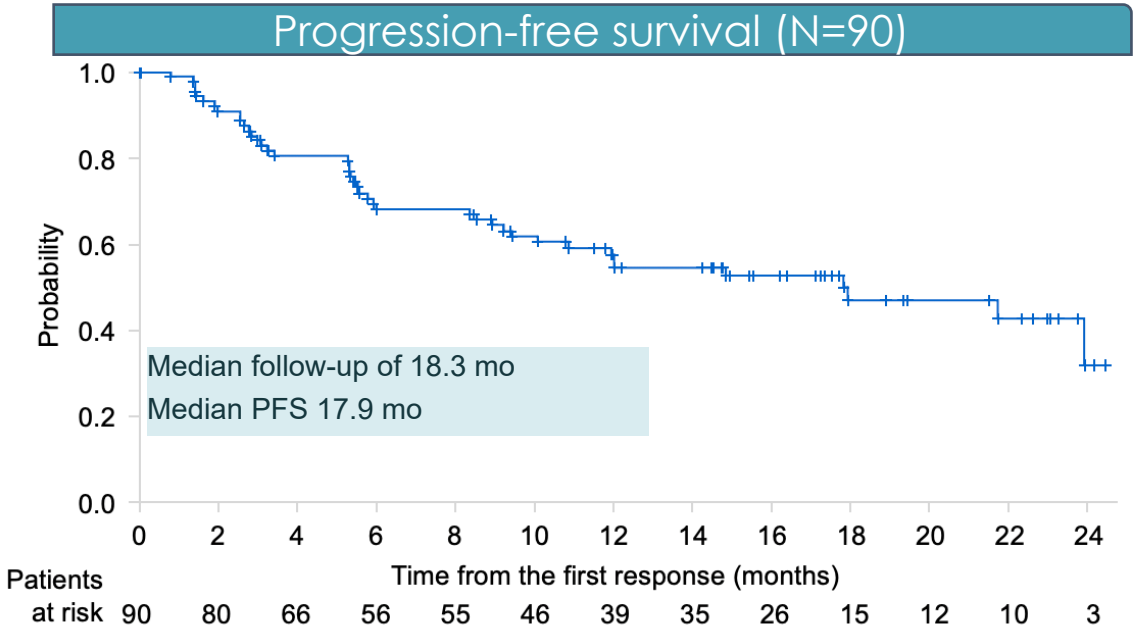
19th International Ultmann Chicago Lymphoma Symposium

Suurs et. al. Pharmacology & Therapeutics. 2019

Mosunetuzumab (IV/SQ)

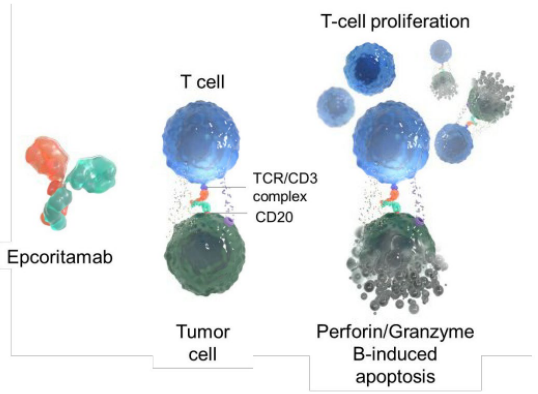


- single agent and combinations
  - Monotherapy as third-line or greater in FL: ORR 79%, CR 58%, 1-yr EFS 65%, CRS primarily grade 1-2 (Budde et al, ASH 21 #127)
  - Monotherapy as second-line or greater: with *subcutaneous step-up dosing,* low CRS rates and ORR 80% in recurrent FL (Bartlett et al, ASH 21 #3573)
  - M+Len in R/R FL as second-line of greater – ORR 92% in 13 pts evaluable for efficacy, CMR 77% (Morschhauser et al., ASH 21)



		N=90
Median # of prior lines,n (range)		3 (2–10)
Prior systemic therapy	Anti-CD20	90 (100%)
	Alkylator	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 prior aCD20 and alkylator (double refractory)		48 (53.3%)
POD24		47 (52.2%)

Epcoritamab (SQ dosing)



- Monotherapy and combinations
  - Monotherapy (NCT03625037) DLBCL = 46 FL = 12
    - In FL 80% ORR, 60% CR (dose 12-48 mg)
    - When given at a dose of 0.76 mg or higher, ORR of 90% (95% CI, 55%-100%)
    - among the 10 evaluable patients with RR FL
    - CRS 59%; 0% Grade 3+ CRS

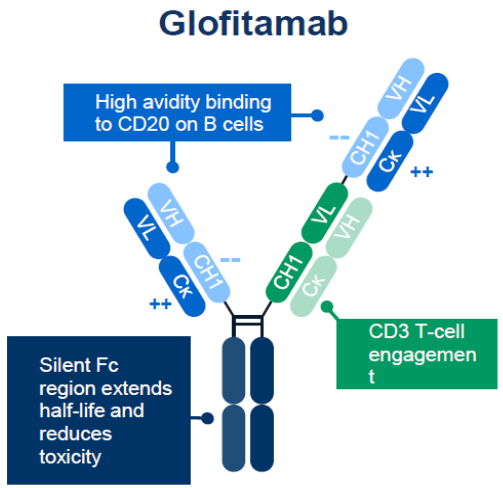
Number of lines of previous therapy	3·0 (2·0–4·0)	4·5 (2·5–8·0)	3·0 (2·0–4·5)
Previous therapies			
Anti-CD20 monoclonal antibody	46 (100%)	12 (100%)	68 (100%)
Anthracyclines	46 (100%)	9 (75%)	62 (91%)
Alkylating agents	46 (100%)	12 (100%)	67 (99%)
Autologous stem-cell transplantation	7 (15%)	1 (8%)	10 (15%)
CAR-T therapy	5 (11%)	0	6 (9%)
Treatment-refractory patients by therapy			
Last line of systemic therapy	41 (89%)	10 (83%)	58 (85%)
Alkylating agents	40 (87%)	9 (75%)	56 (82%)
Last anti-CD20 monoclonal antibody	41 (89%)	10 (83%)	59 (87%)

Trial in progress EPCORE NHL-2 phase I/II trial with epcoritamab + R^2 for R/R CD20+ FL;

All 5 response-evaluable pts achieved an objective response by week 7, with 4 achieving complete metabolic response. CRS 31% (grade 1/2; median time to onset was 15 days, median resolution 2 days (Linton et al., ASH 21 #3535)

Glofitamab (IV)

- single agent and combinations



  - ORR 81% with monotherapy (n = 53) and 100% with obinutuzumab (n = 19), CRS primarily grade 1/2 (Morschhauser et al, ASH 21 #138)
  - With obinutuzumab (n = 75 with FL): ORR 81%, 69% CR, median duration of CR not reached (Dickinson et al, ASH 21 #2478)
  - CRS rate was 78.9% in the combination cohort and CRS in the monotherapy cohorts was 66% - with almost all being grade 1-2

Table: CMR rates with glofitamab as monotherapy or in combination with obinutuzumab by high-risk subgroup

	CMR rate	
Patients n (%)	**Glofitamab monotherapy (n=53)**	**Glofitamab in combination with obinutuzumab (n=19)**
Double-refractory*	8/16 (50%)	3/7 (43%)
POD24	11/19 (58%)	7/10 (70%)
PI3Ki-refractory	3/7 (43%)	1/2 (50%)
SPD ≥3000mm^2	15/24 (63%)	3/7 (43%)

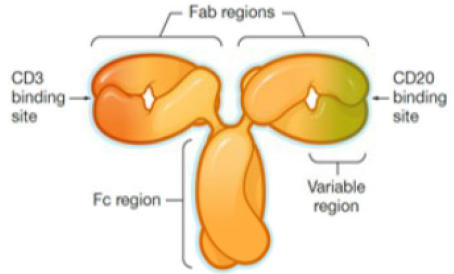
*Pts refractory to anti-CD20 antibodies and alkylating agents
CMR, complete metabolic response; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease within 24 months of frontline treatment; SPD, sum of the product of the diameters

Odronextamab (IV)

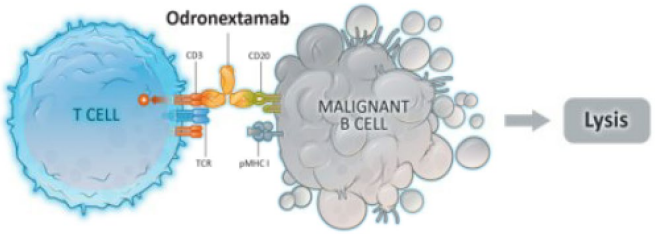
- trials in progress
  - Monotherapy trial with 25 FL pts; CRS rate was 57% (n = 7 with grade ≥ 3)
  - Grade 3 or higher neurotoxicity occurred in two patients
  - The trial was suspended temporarily due to toxicity
  - Responses were evaluated over a broad range of dosages with dosage-dependent responses seen
  - With treatment ≥ 80 mg, the FL cohort demonstrated an
  - ORR of 95.5% (CR rate = 77.3%)

  - A global phase II study is currently enrolling 5 separate disease cohorts of rel/ref NHLs, one of which is rel/ref FL

Odronextamab bispecific antibody structure



Odronextamab mechanism of action



	N=96
Disease, n	
DLBCL	53
FL Grade 1-3a	25
MCL	6
MZL	6
Other	6
Prior therapies	
Median (range)	3 (1-11)
	12 (efficacy analysis)
CAR T therapy, n	6 (safety analysis)
Status at Reporting, n	
Remain on therapy	24
Completed treatment	18
Discontinuation due to PD	54

Bannerji R, et al. *Blood.* 2019;134(Suppl_1):762.

Conclusions: Bispecific Antibodies

- CD20-CD3 bispecific monotherapy is effective off the shelf therapy for R/R FL
  - Poor-risk Indolent NHL
    - CD20- and alkylating agent-refractory disease
    - PI3K inhibitor-refractory disease
    - history of POD24 months
- CRs have been maintained after completion of therapy
- CRS may reduce with step up dosing and SC administration
- Single-agent and combination studies ongoing

CAR T-cell therapy and bispecific antibodies for R/R FL

	CAR T-Cell Therapy		Bispecifics			
	Axi-cel	**Tisa-cel**	**Glofitamab**	**Odronextamab**	**Mosunetuzumab**	**Epcoritamab**
Patient Pop.	R/R FL patients after ≥ 2 prior therapies	R/R FL patients after ≥ 2 prior therapies	R/R NHL patients after ≥ 2 prior therapies	2L+ Indolent B-cell NHL (prior CD20 treatment)	R/R aggressive NHL patients after ≥ 1 prior therapies	Aggressive NHL patients after anti-CD20 treatment and/or ASCT
Trial/Phase	NCT03105336 ZUMA-5, P2	NCT03105336 ELARA, P2	NCT02500407 GO29781, P1/1b	NCT02290951, P1	NCT03075696 NP30179, P1	NCT03625037 P1/2
Efficacy	CR: 80% ORR: 95%	CR: 65% ORR: 83% (ITT population)	CR: 50% ORR: 68%	CR: 75%[c] ORR: 93%[c]	CR: 50% ORR: 67%	CR: 60% ORR: 80% (dose ≥ 12 mg)
Safety (Severe AEs)	CRS: 84% (8% grade 3+) Neutropenia: 41% (for all patients with iNHL)	CRS: 48% Grade 3+ Neutropenia: 28% Serious Neurologic Events:10%	CRS: 23% (SAE CRS: 6%) Hypophosphatemia: 23% Neutropenia: 21%	CRS: 62.2% (7.1% grade 3+) Gr 3 neurologic AEs: 4%	CRS: 56.4% Neutropenia: 30.8%	CRS: 59% (Total population); no Grade ≥ 3 CRS events

CAR T vs. Current SOC Treatment for ≥3rd line FL

Therapy	Axi-cel	Tisa-cel	Copanlisib	Tazemetostat	Ibrutinib
Trial	ZUMA-5	ELARA	CHRONOS-1	NCT0189757	NCT01849263.
N	84	52	104	42 (*EZH2*^{mut})	110
CR rate	79%	69%	14%	12%	12.5%
PFS at 1 yr	78%	67%	~42%[a]	14%	20.4% (2 yr PFS)
Therapy duration	1 mo	1 mo	Until PD	Until PD	Until PD
Reference	Jacobson et al. Lancet Oncol 2022	Fowler et al, Nat Med 2021	Dreyling et al, JCO 2017	Morschhauser et al, Lancet Oncol 2020	Bartlett NL et al, Blood 2018

[a]Includes FL, MZL, SLL, and/or LPL

ELARA Study Design

ELARA

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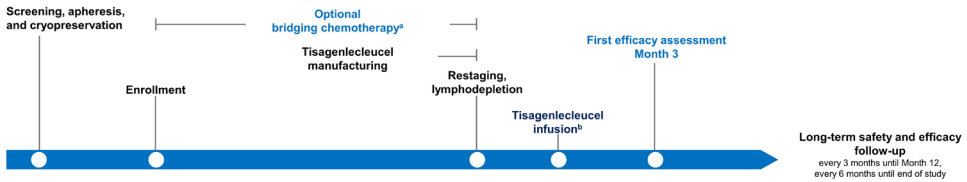
Study Design



Key eligibility criteria	Study treatment	End points

• ≥18 years of age
• FL grade 1, 2, or 3A
• Relapsed/refractory disease[c]
• No evidence of histological transformation/FL 3B
• No prior anti-CD19 therapy or allogeneic HSCT
	• Lymphodepleting chemotherapy options were
	  • Fludarabine (25 mg/m^2 IV daily for 3 days) + cyclophosphamide (250 mg/m^2 IV daily for 3 days)
	  • Bendamustine 90 mg/m^2 IV daily for 2 days
	• Tisagenlecleucel dose range (single IV infusion) was: 0.6-6×10^8 CAR-positive viable T cells
		Primary: CRR by IRC (Lugano classification 2014)
		
		Secondary: ORR, DOR, PFS, OS, safety, cellular kinetics

[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Refractory to ≥ 2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥ 2nd line of therapy or after an autologous HSCT.
CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response rate; DOR, duration of response; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; IRC, Independent Review Committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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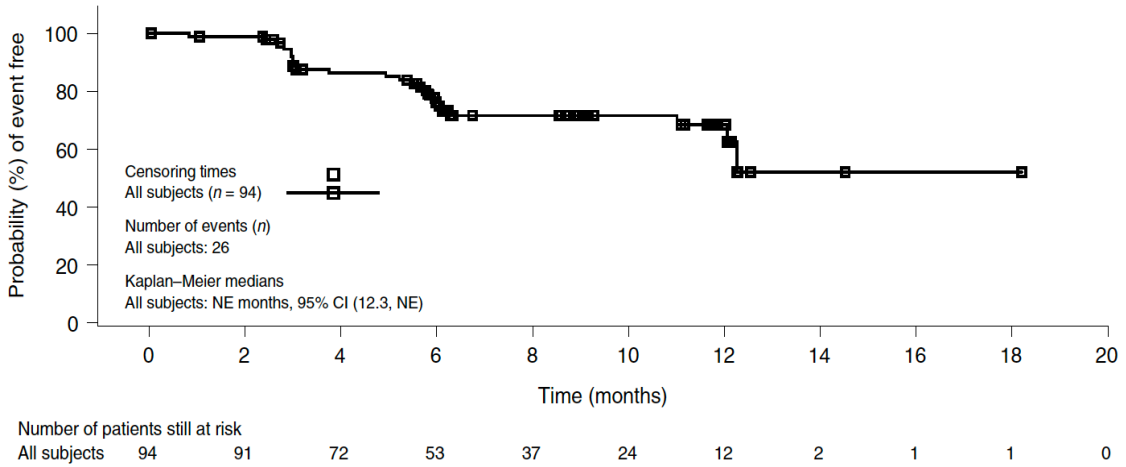
2021 ASCO ANNUAL MEETING

ELARA PFS



Median follow-up of 16.6 months

12-month PFS rate for FL was 67%

Fowler et al, *Nat Med*, 2021

CRR Was Consistent Across Subgroups

		CRR n/N (%)	[95% CI]
All patients	**N=94**	62/94 (66.0)	[55.5-75.4]
Age	<65 y (n=70)	46/70 (65.7)	[53.4-76.7]
	≥65 y (n=24)	16/24 (66.7)	[44.7-84.4]
Sex	Female (n=30)	21/30 (70.0)	[50.6-85.3]
	Male (n=64)	41/64 (64.1)	[51.1-75.7]
Number of prior lines of antineoplastic therapy	≤2 lines (n=24)	12/24 (50.0)	[29.1-70.9]
	3-4 lines (n=43)	34/43 (79.1)	[64.0-90.0]
	>4 lines (n=27)	16/27 (59.3)	[38.8-77.6]
PI3K inhibitor use	Pretreated (n=19)	15/19 (78.9)	[54.4-93.9]
	Naïve (n=75)	47/75 (62.7)	[50.7-73.6]
Prior HSCT therapy	Yes (n=35)	22/35 (62.9)	[44.9-78.5]
	No (n=59)	40/59 (67.8)	[54.4-79.4]
Disease status to last line of prior antineoplastic therapy	Refractory (n=74)	48/74 (64.9)	[52.9-75.6]
	Relapsed (n=17)	12/17 (70.6)	[44.0-89.7]
POD24 from first-line anti-CD20 mAb containing therapy	Yes (n=58)	32/58 (55.2)	[41.5-68.3]
	No (n=34)	29/34 (85.3)	[68.9-95.0]

CI, confidence interval; CRR, complete response rate; HSCT, hematopoietic stem cell transplant; ORR, overall response rate; PI3K, phosphatidylinositol 3-kinase; POD24, progression of disease within 24 months.

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ZUMA-5 Study Design

ZUMA-5 Study Design

R/R iNHL (N=157) → Leukapheresis → **Conditioning Chemotherapy** Fludarabine 30 mg/m² IV and cyclophosphamide 500 mg/m² IV on Days –5, –4, –3 → **Axi-Cel Infusion** 2×10^6 CAR+ cells/kg on Day 0 → Post-treatment assessment and long-term follow-up periods

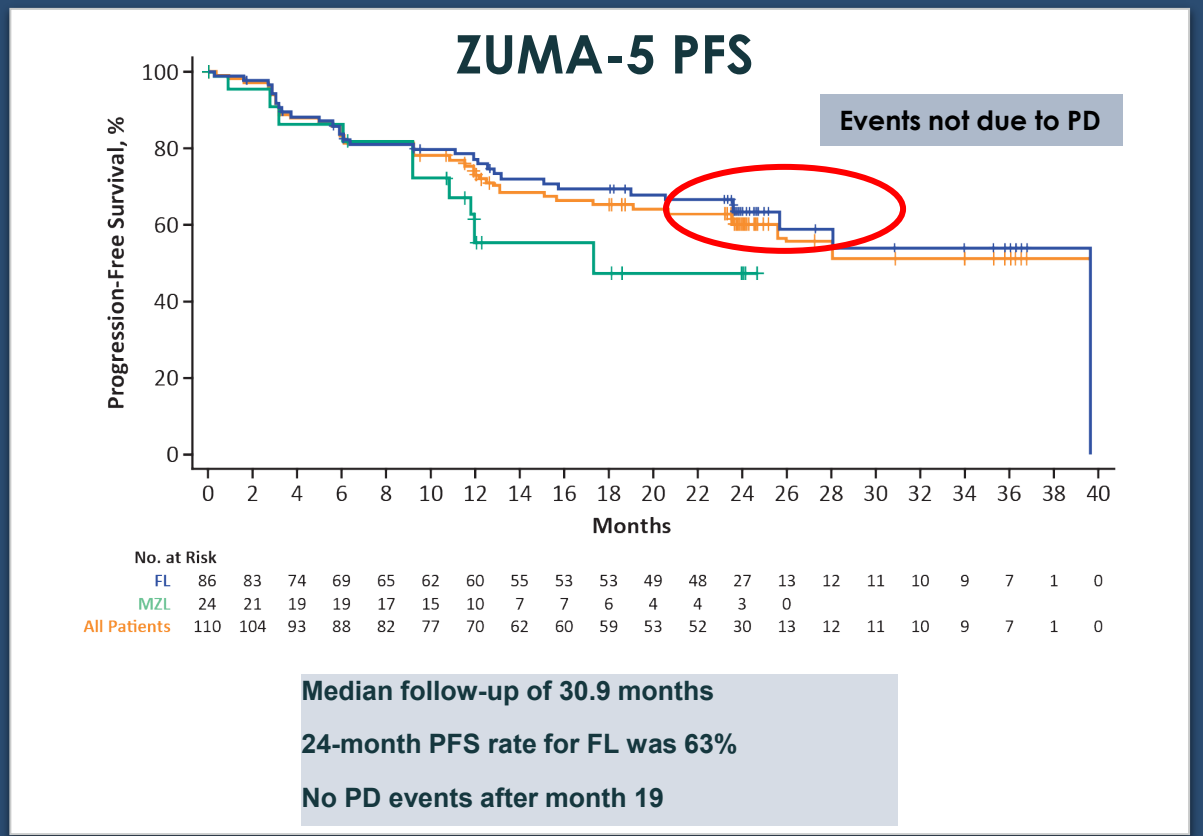
Key ZUMA-5 Eligibility Criteria
- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)*
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint
- ORR (IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints
- CR rate (IRRC assessed)
- Investigator-assessed ORR*
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

* Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible. [b]Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.
1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

3 Neelapu et al ASH 2021 Abstract 93



Median follow-up of 30.9 months

24-month PFS rate for FL was 63%

No PD events after month 19

Neelapu et al. ASH 2021; Abstract 93 Jacobson et al, *Lancet Oncol*, 2022

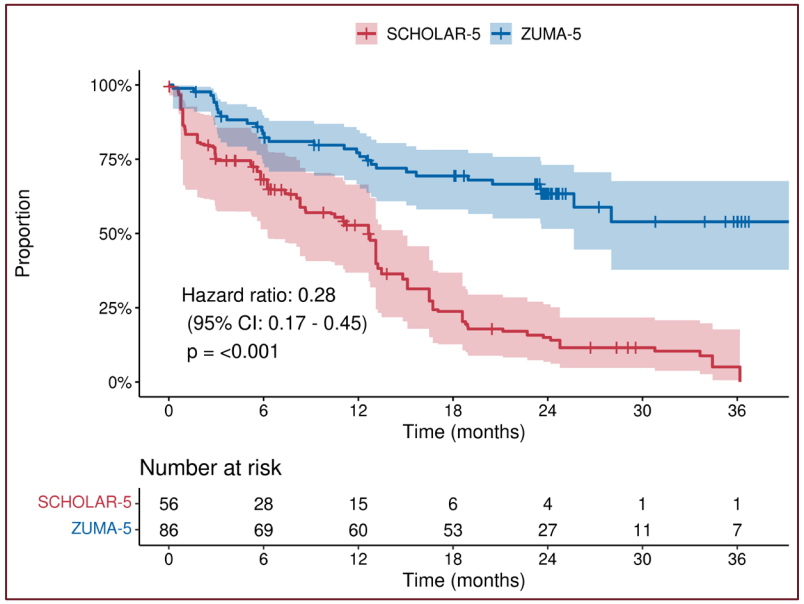
ZUMA-5: PFS rates at 24 mo were consistent in key subgroups

	Follicular Lymphoma (n=78)[a]	
Parameter (95% CI)	With POD24 (n=49)	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)

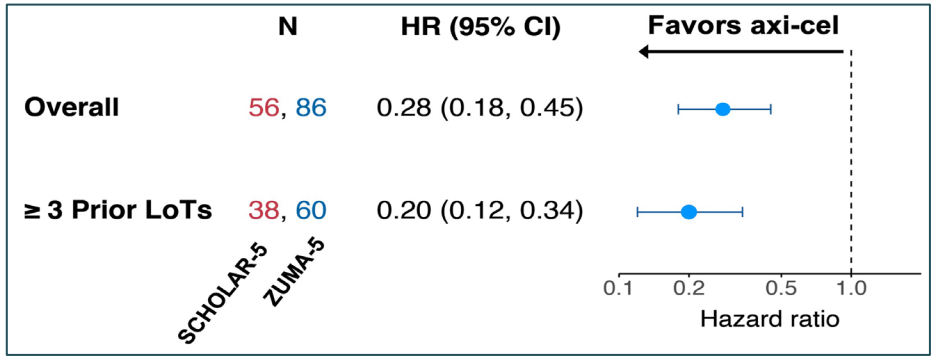
Neelapu et al. ASH 2021; Abstract 93
Jacobson et al, *Lancet Oncol*, 2022

PFS and OS was significantly higher in ZUMA-5 compared to SCHOLAR-5

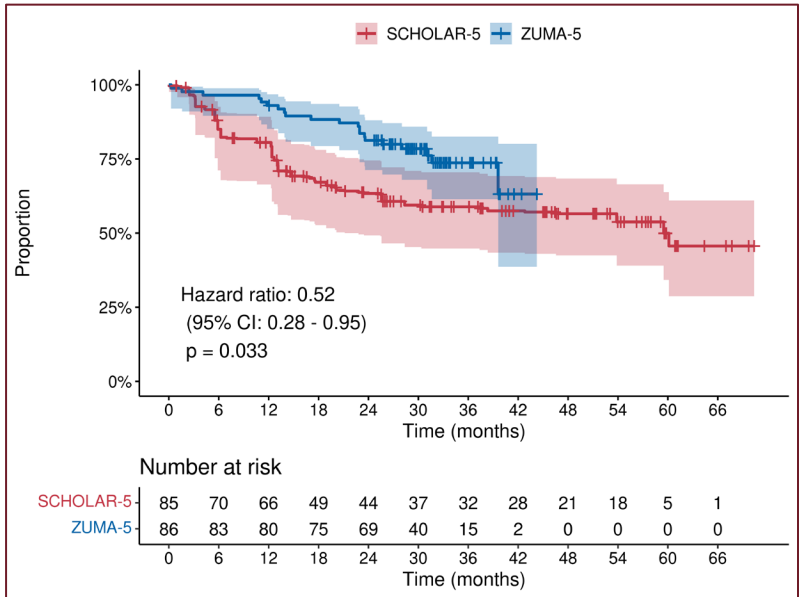
PFS

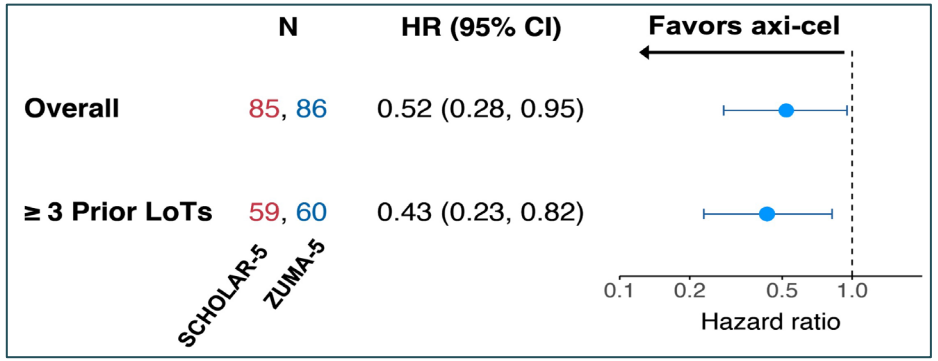


- Findings were consistent in sub-groups including patients with disease failing ≥ 3 prior LoT



OS





SCHOLAR-5 is an international, multicenter external control cohort, generated to provide comparative evidence in r/r FL patients meeting ZUMA-5 eligibility criteria with at least 24 months follow up

Patel et al JSMO 2022

Median follow-up time for ZUMA-5 was 23.3 months and for SCHOLAR-5 was 26.2 months

We Don't Talk About Cure

- Lifetime costs for treated FL pts in US is ~$560k in 2021 – how will that change in the future… *(Eichten et al, Pharmacoeconomics, 2021)*
- New therapies increase the cost of care
- However, addition of rituximab to chemotherapy or R maintenance improved clinical outcomes in a cost-effective manner *(Monga et al, Pharmacoeconomics, 2020)*
- Can we define "cure" for FL or Should "functional cure" be the goal
- Considerations for time toxicity with "on treatment" and "treatment-free" periods in FL; how to sequence novel therapies;

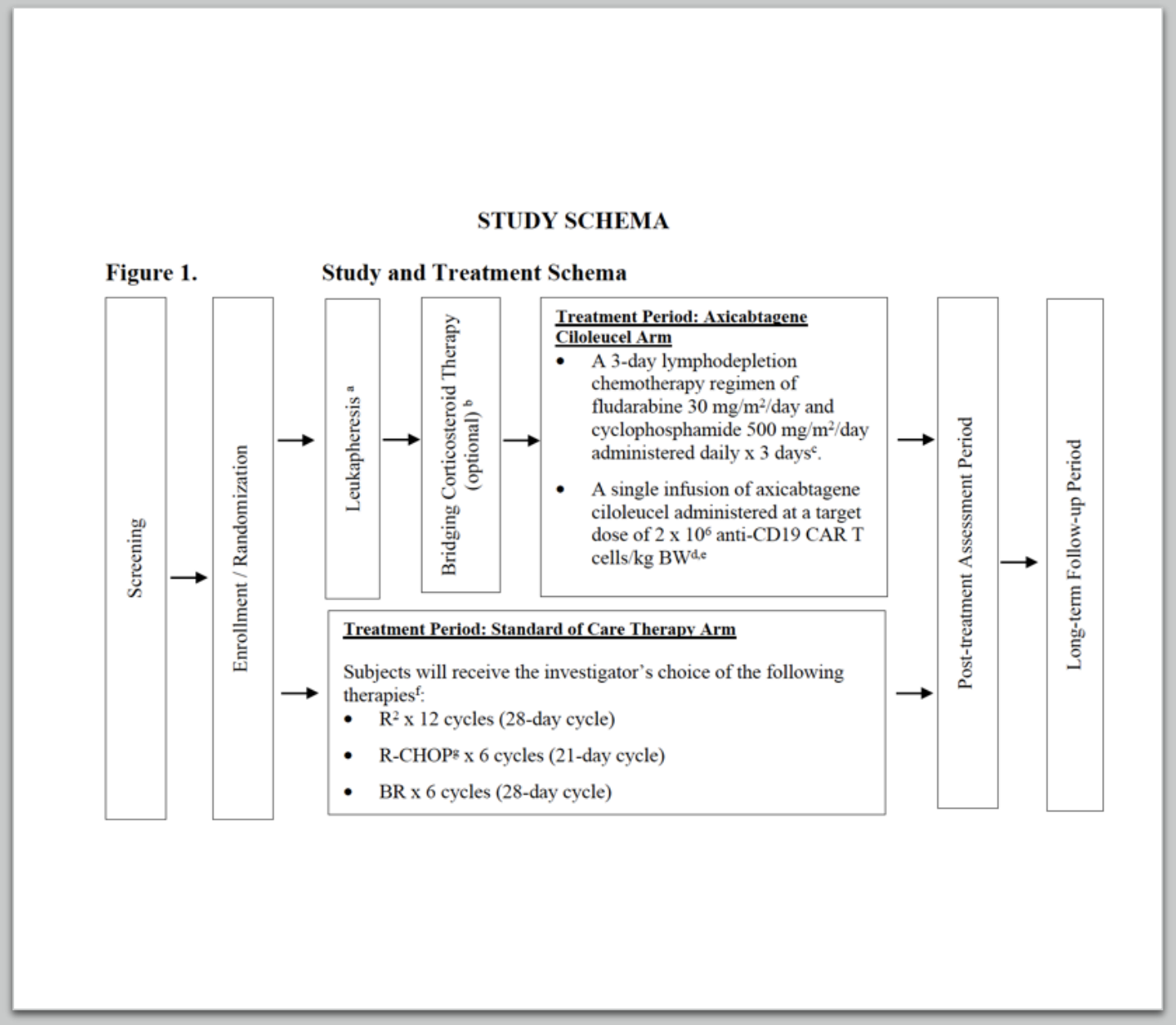
ZUMA-22 - Phase 3 study for R/R FL comparing axi-cel to SOC

Designed to determine if axi-cel is superior to SOC as measured by PFS

- Will include FL, grade 1-3a R/R after at least 1 prior line and
  - high-risk disease (POD24)

  OR
  - ≥ 2 prior lines

- EXCLUDES Prior CD19 targeted therapy



Parting Thoughts…

- How can we better choose individualized “QoL-targeted” treatment? (fixed duration vs ongoing treatment)

- For regimens with similar OS, consider value of PFS benefit vs QoL
  - Is there a benefit for fixed time immunosuppression vs prolonged immunosuppression?

- It is possible that developing “curative” therapies may both improve overall survival for FL but also be cost-effective in the long run and improve QoL

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- Chitra Hosing
- EJ Shpall

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Sherry Adkins - CART APP lead

Nicole Johnson – CART data lead

Thank you! Questions?

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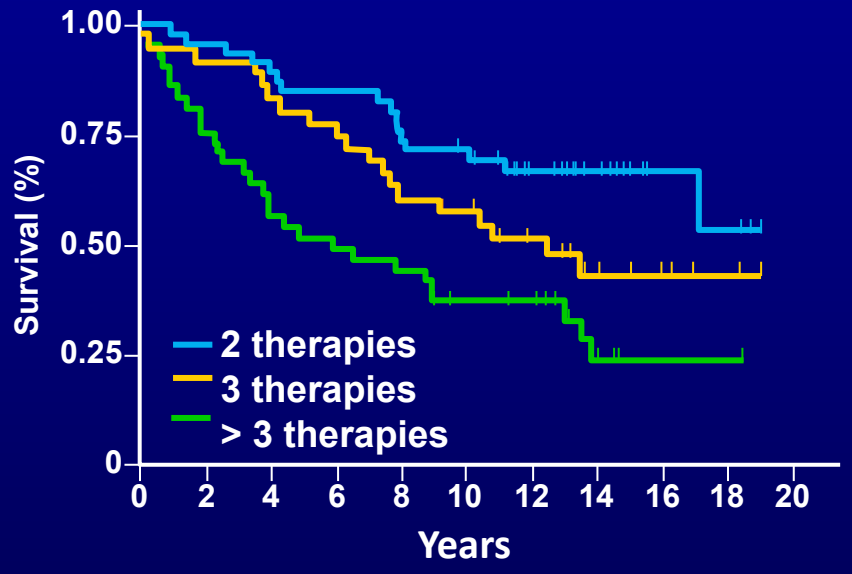
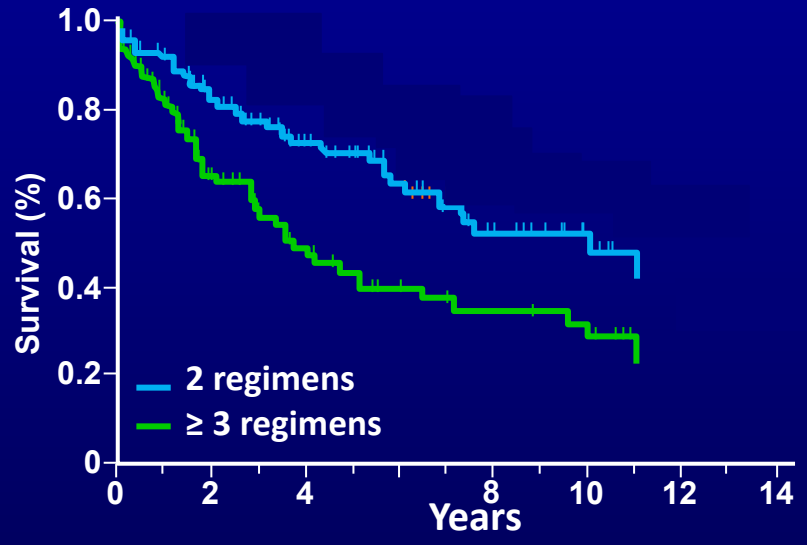
@sairah_ahmed

Number of Prior Regimens often used to judge suitability for AutoHCT in FL



N = 121; Median F/U = 13yrs

Rohatiner et al, JCO 2007;25:2554.

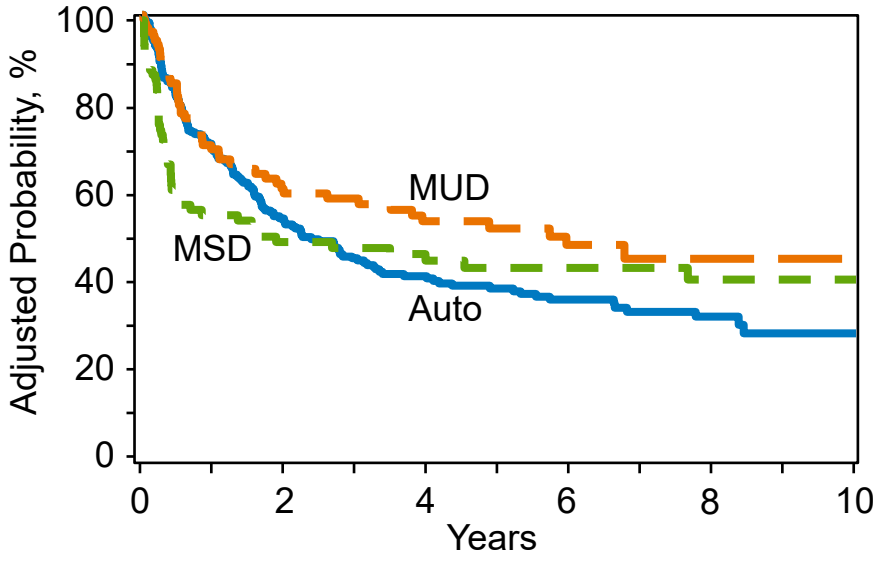


N = 248; Median F/U = 6yrs

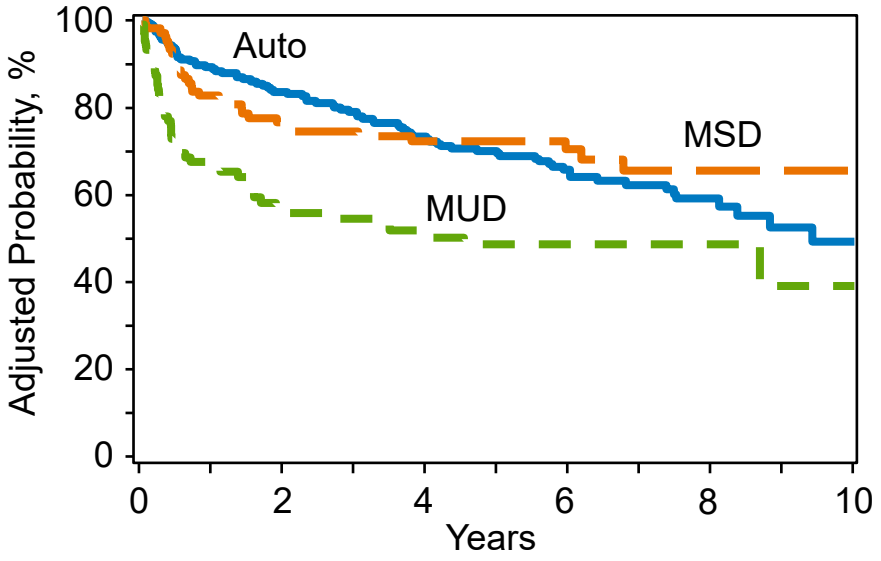
Vose et al, BBMT 2008;14:36.

Autologous vs. Allogeneic HCT for ETF Follicular Lymphoma?

Progression-free Survival



Overall Survival



	AutoHCT	MSD	MUD	Auto vs MSD	Auto vs MUD	MSD vs MUD
5-yr PFS	38 (32-45)%	52 (41-62)%	43 (32-54)%	**p=0.03**	p=0.47	p=0.24
5-yr OS	70 (64-76%)	73 (64-81)%	49 (39-60)%	p=0.60	**p<0.0007**	**p<0.0005**

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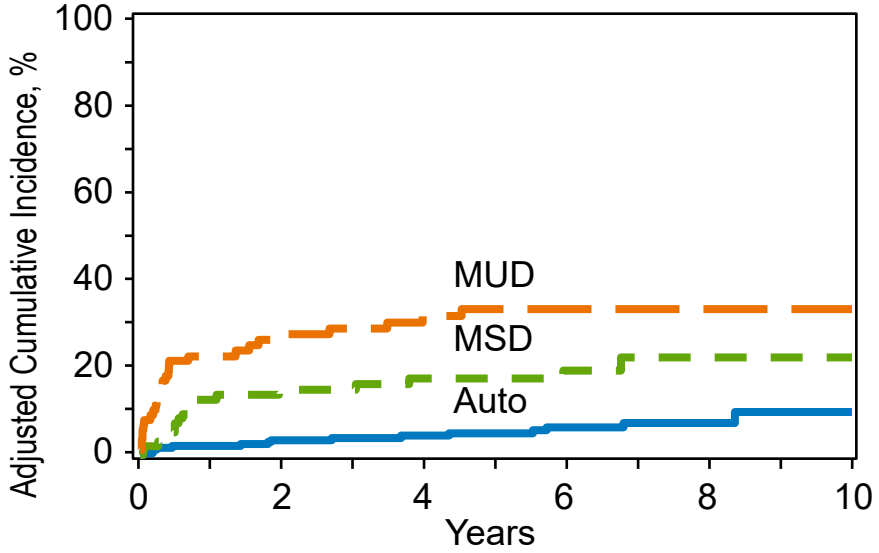
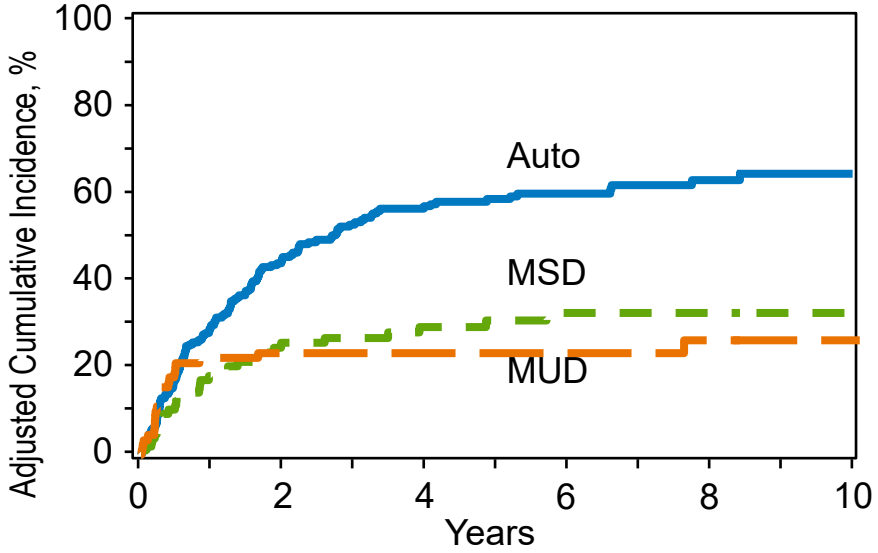
Autologous vs. Allogeneic HCT for ETF Follicular Lymphoma?

Non-relapse Mortality



Relapse / Progression



	AutoHCT	MSD	MUD	Auto vs MSD	Auto vs MUD	MSD vs MUD
5-yr NRM	5 (2-8)%	17 (10-25)%	33 (23-43%)	p=0.003	p<0.0001	p=0.01
5-yr Relapse	58 (52-65)%	31 (21-40)%	23 (14-32)%	p<0.0001	p< 0.001	p=0.25

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