20TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

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FL- Current Gaps of Treatment

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20TH ULTMANN
CHICAGO LYMPHOMA SYMPOSIUM

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Disclosures

I have received honorarium from:

Abbvie, ADC Therapeutics, BMS, Caribou Biosciences, Daiichi Sankyo, DeNovo, Genentech, Genmab, Gilead/Kite, Janssen, Interius Bio, MEI, Merck, Novartis, and Takeda

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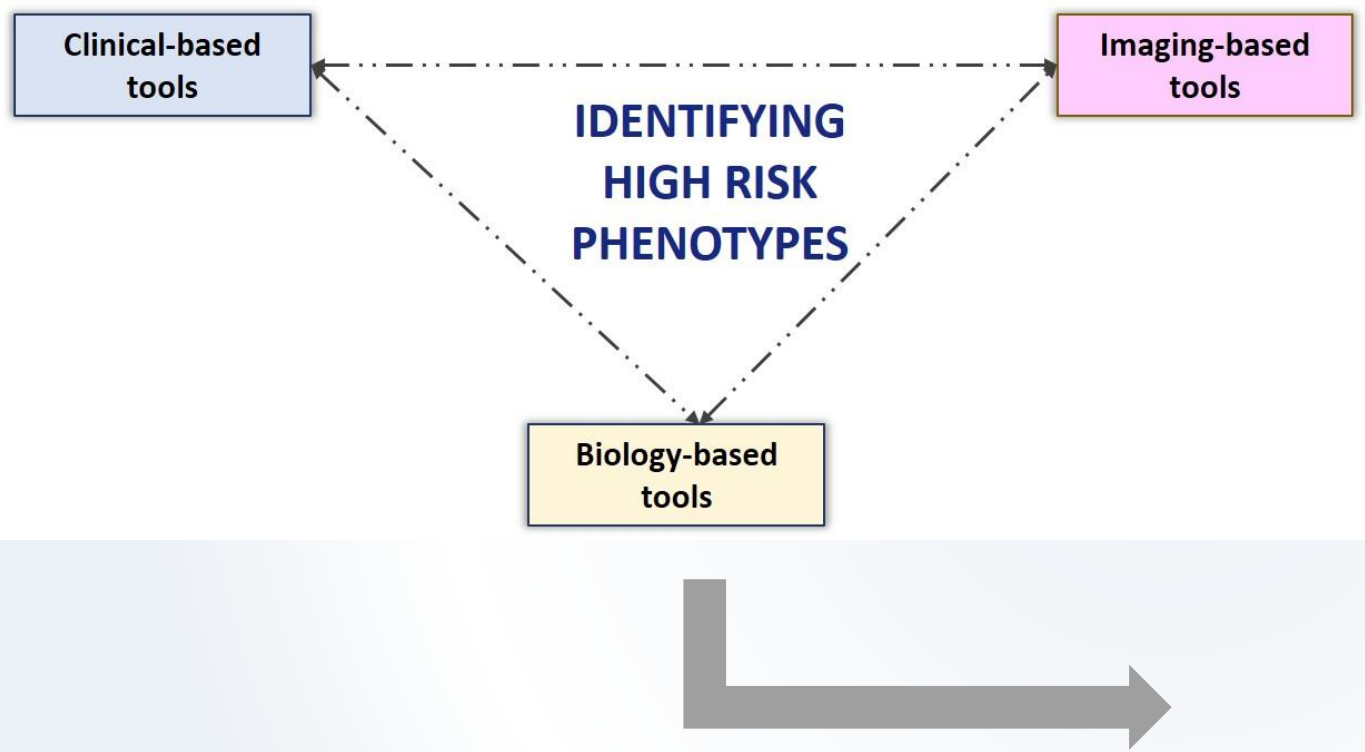
What are the Gaps in FL?

1. Can we cure FL?
2. Risk Stratification
3. Predictive biomarkers
4. Optimal Sequencing
5. Toxicity Mitigation

GAP- Risk Stratification



At Diagnosis/Pre-treatment:

- Clinical: FLIPI, FLIPI2, PRIMA-PI, FLEX
- Biology: m7-FLIPI, PRIMA 23-gene, PD-L2
- Imaging: Baseline PET metrics

At End of Induction/After therapy:

- Imaging: EOI PET
- Biology: MRD (*not standard*)
- Response-based: POD24, Transformation

At Intervals/Dynamic:

- Biology: circulating tumor DNA (*Research tools*)

Clinical Prognostic Indices: FLIPI, FLIPI-2, PRIMA-PI and FLEX

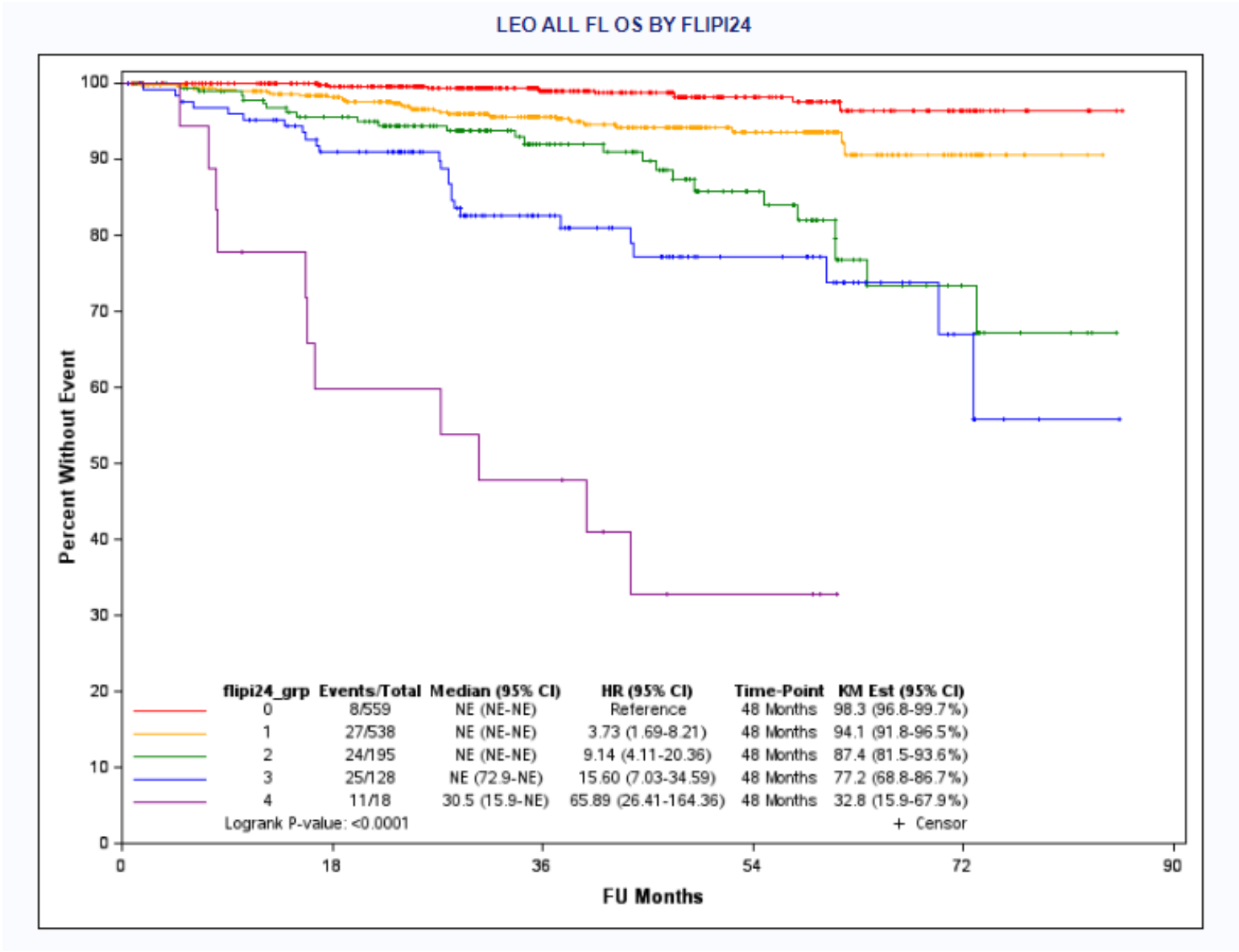
RISK FACTORS	FLIPI[1]	FLIPI-2[2]	PRIMA-PI[3]	FLEX[4]
	Age > 60 yrs	Age > 60yrs	BM involvement	Male sex
	Stage III/IV	BM involvement	β_2-M > 3mg/L	SPD in the highest quartile
	LDH > normal	β_2-M > normal		LDH > normal
	Hb <120g/L	Hb <120g/L		Hb <120g/L
	>4 nodal sites	Tumour mass > 6cm		>2 extranodal sites
				Histologic grade 3A PS > 1; NK cell count < 100/µL; β2-M > normal
	Pre-rituximab era	*R-treated*	*R-treated*	*R-treated*
	Predicts OS	Predicts PFS and OS	Predicts PFS	Predicts PFS
	Low: 5-yr OS 91% Inter: 5-yr OS 78% **High: 5-yr OS 53%**	Low: 5-yr PFS 80% Inter: 5-yr PFS 51% **High: 5-yr PFS 19%**	Low: 5-yr PFS 69% Inter: 5-yr PFS 55% **High: 5-yr PFS 37%**	Low: 3-yr PFS 86% **High: 3-yr PFS 68%**

Each index segregates patients into 2 or 3 risk groups:

Low, ***Intermediate*** and ***High*** risk

1. Solal-Céligny P et al. *Blood.* 2004;104:1258-1265. 2. Federico M et al. *J Clin Oncol.* 2009;27:4555-4562. 3. Bachy E et al. *Blood.* 2018;132:49-58. 4. Mir et al. *Am J Hematol.* 2020;95:1503-1510.

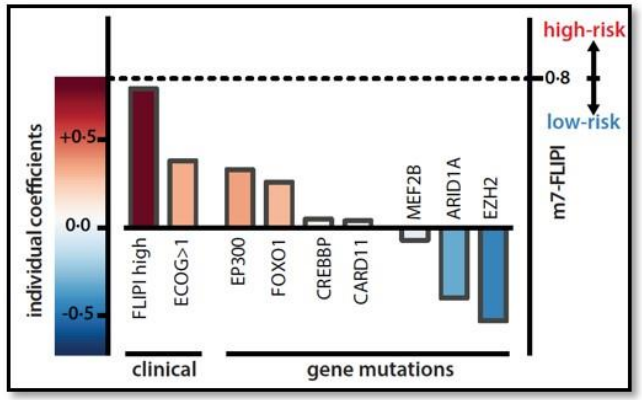
FLIPI-24, Another Prognostic Tool



Variable
Age
LDH/ULN
B2M
HGB
WBC

Biological Prognostic Tools: Incorporating Tumor Genotype and TME

m7-FLIPI

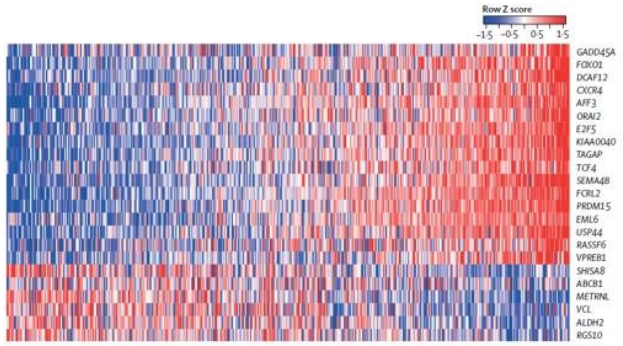


Model: **7 genes** + **PS** + **FLIPI** score

	5 yr PFS	5 yr OS
High risk m7-FLIPI	38.29%	65.25%
Low risk m7-FLIPI	77.21%	89.98%

Pastore A et al. *Lancet Oncol.* 2015;16:1111-1122.

PRIMA 23-Gene expression



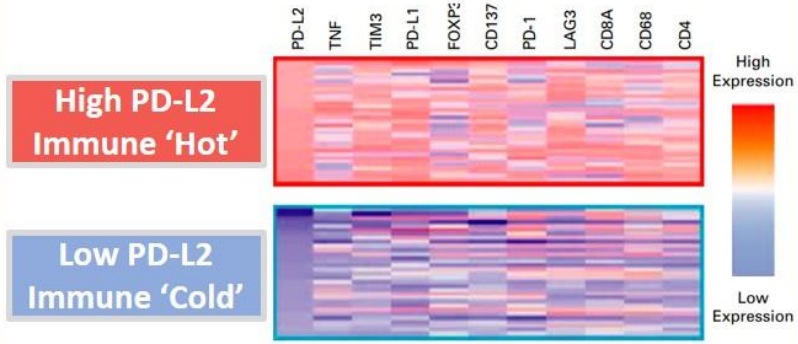
N = 134 patients (Training cohort)
Confirmed in 3 validation cohorts

	5 yr PFS
High risk	26%
Low risk	73%

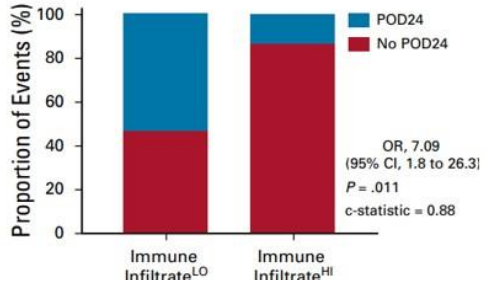
No effect on OS

Huet S et al. *Lancet Oncol.* 2018;19:549-561.

PD-L2 expression



Immune 'cold' = higher POD24



Tobin JWD et al. *J Clin Oncol.* 2019;37:3300-3309.

Can We Routinely Use These Tools to Guide Clinical Decision-Making?

- What is the prognostic ACCURACY? →

ABILITY TO IDENTIFY POD24 PATIENTS?

POD24	High-risk FLIPI	High-risk FLIPI2	PRIMA-PI	FLEX	M7-FLIPI	23-gene$^{high\ risk}$	PD-L2
Sensitivity	53-78%	53%	69%	60%	43-61%	43%	66-74%
Specificity	56-62%	59-76%	48%	68%	77-86%	79%	60-62%

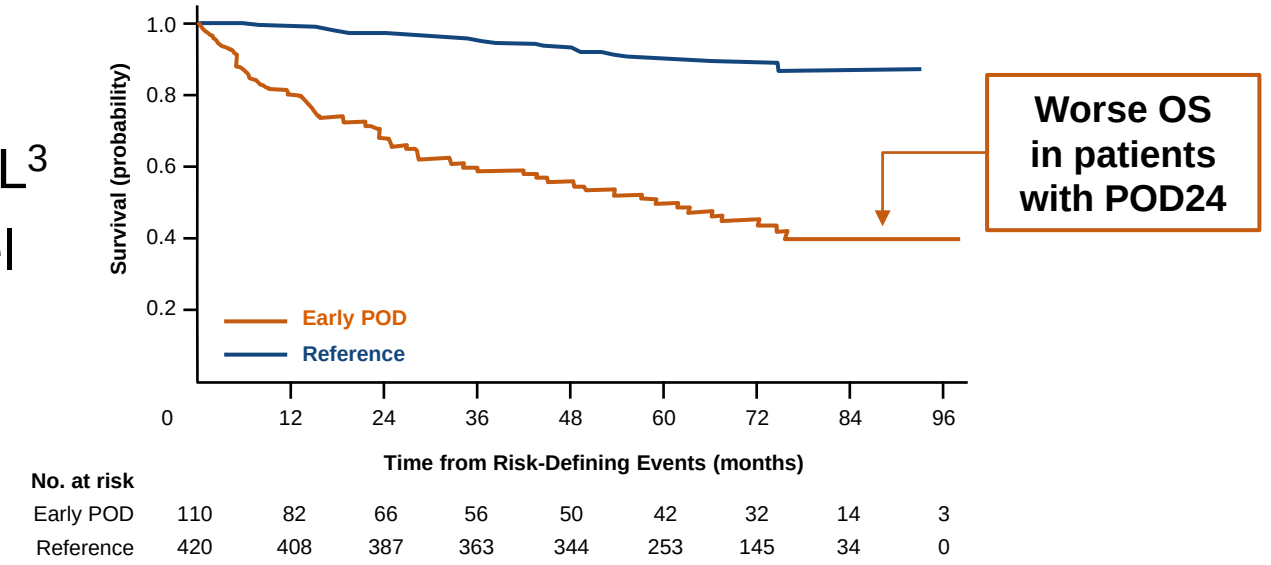
- Is it widely ACCESSIBLE/AFFORDABLE? → Clinical prognostic tools – straightforward
  Genotyping/gene expression - research tools
- Is it ACTIONABLE? Guide therapy selection? → **None guide treatment**

Casulo C. *Hematol Oncol*. 2021;39 Suppl 1:88-93; Pastore A et al. *Lancet Oncol.* 2015;16:1111-1122; Huet S et al. *Lancet Oncol.* 2018;19:549-561; Tobin JWD et al. *J Clin Oncol.* 2019;37:3300-3309.

Early Relapse (POD24)

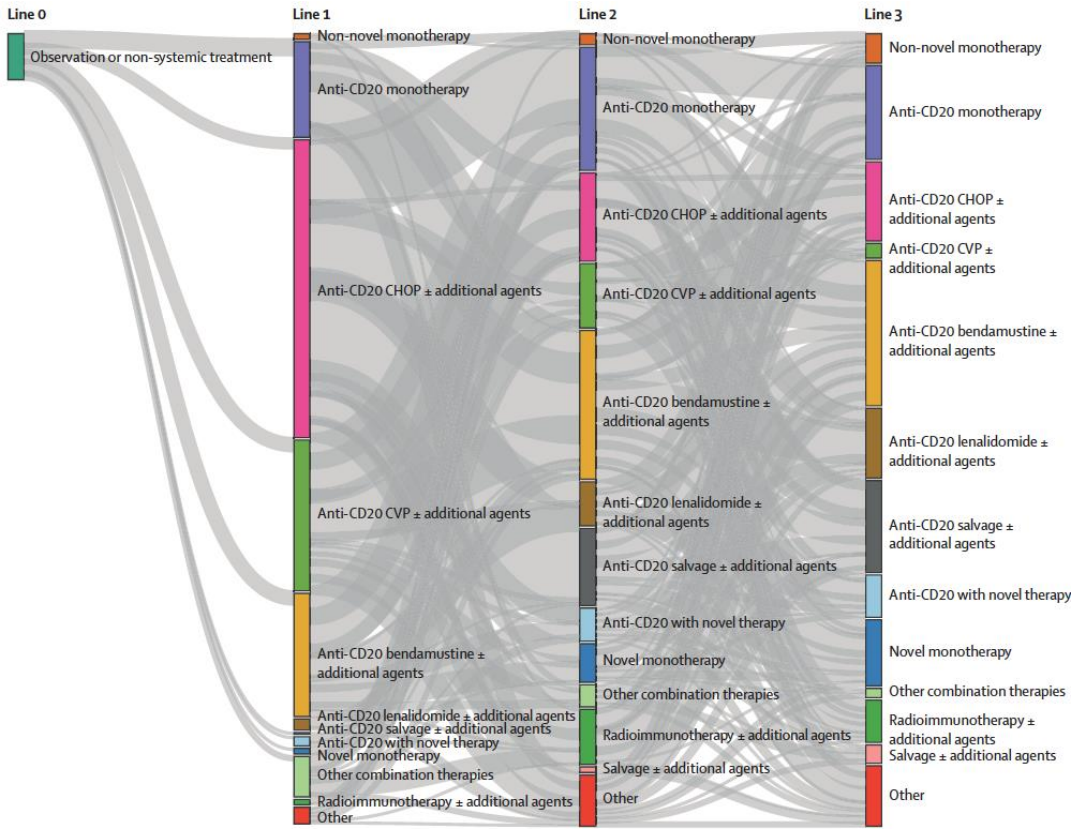
- Biopsy recommended to detect histologic transformation of FL, which is reported to occur at a rate of 2% per year[1,2]
  - Particularly for BR treated patients, transformation rates are higher

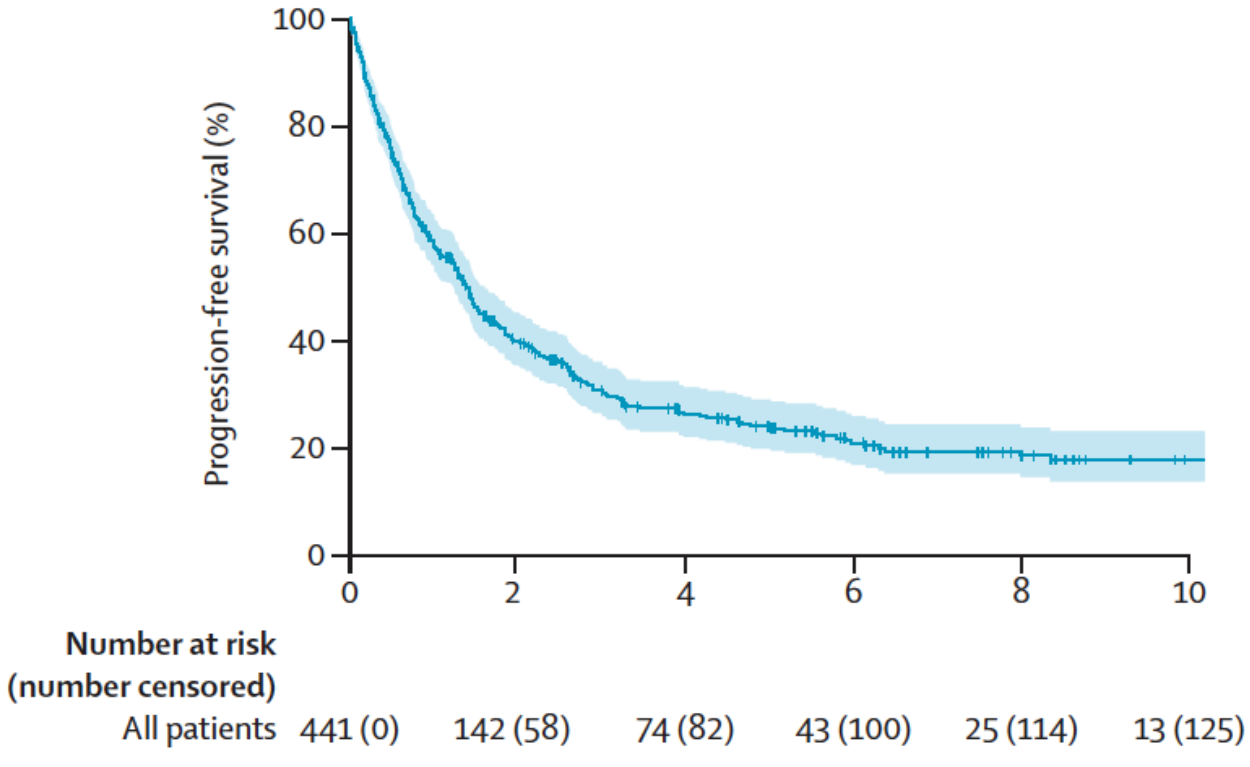
- Early progression of disease (≤2 years) after frontline chemoimmunotherapy (POD24) occurs in approximately 10-20% of patients
  - Associated with a poor prognosis and represents an unmet medical need in FL[3]
  - Represents a population requiring novel intervention with non-chemoimmuntherapeutic agents



1. Link BK, et al. *J Clin Oncol.* 2013;31:3272. 2. Casulo C, Barr PM. *Blood.* 2019;133:1540. 3. Casulo C, et al. *J Clin Oncol.* 2015;33:2516.

Outcomes in FL: Third Line and Beyond

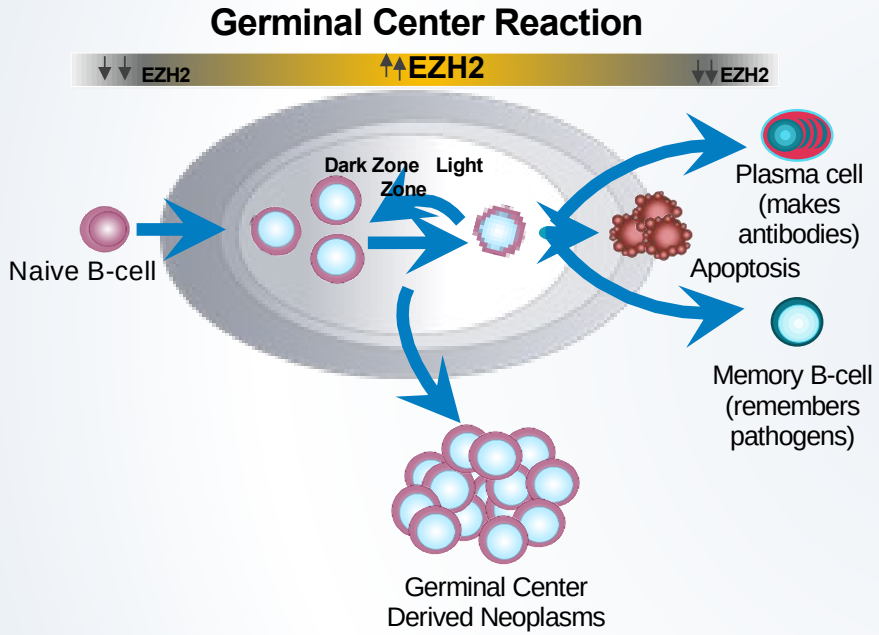


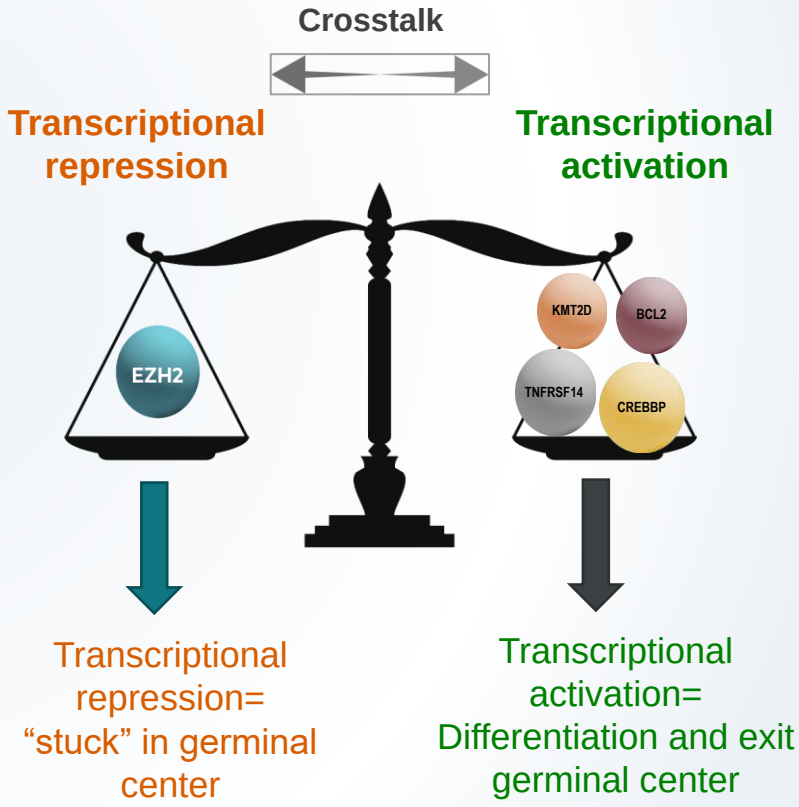


Casulo C et al. *Lancet Haematol.* 2022;9:e289-e300.

GAP- Predictive Biomarkers

Tazemetostat: Follicular Lymphoma and *EZH2*

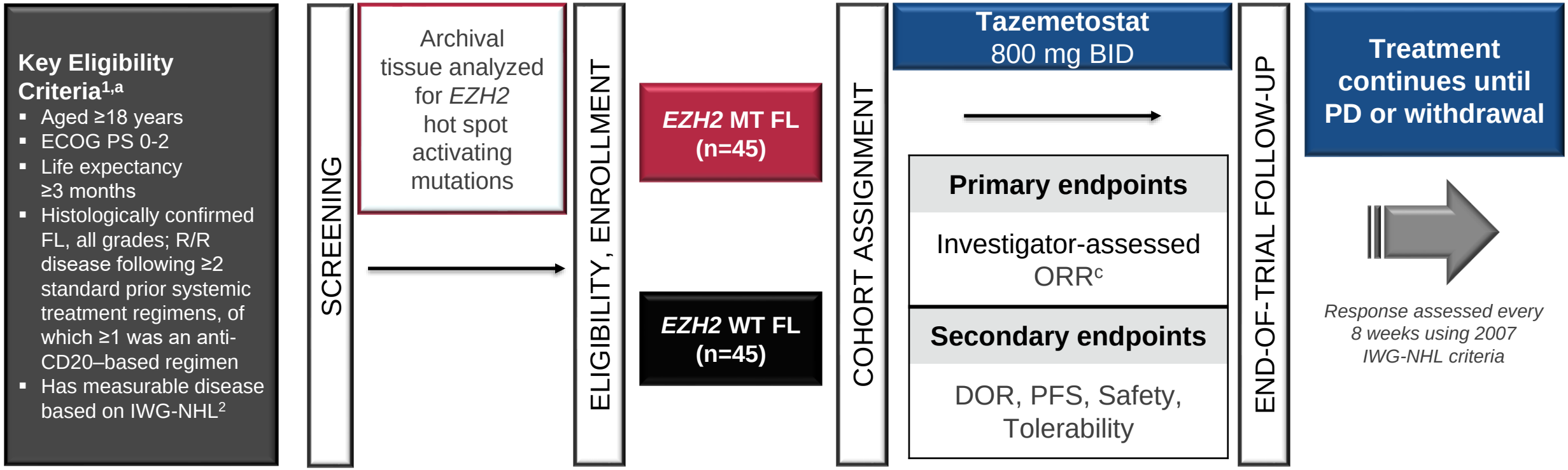




- EZH2 an epigenetic regulator of gene expression and cell fate decisions[1]
- EZH2 is required for normal B-cell biology and germinal center
  - Oncogenic mutations in EZH2 suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]
- formation[2]

1. Gan L et al. *Biomark Res*. 2018;6:10. 2. Béguelin W et al. *Cancer Cell*. 2013;23:677-692.

Tazemetostat for R/R FL
Phase 2, Open-Label, Multicenter Study



[a]For a full list of study eligibility criteria, please see Clinicaltrials.gov/ct2/show/NCT01897571. [b]Actual enrollment: n=54. cORR defined as the number of participants with a best objective response of CR or PR.

1. Morschhauser F et al. *Lancet Oncol.* 2020;21:1433-1442. 2. Cheson BD et al. *J Clin Oncol.* 2007;25:579-586.

Tazemetostat for R/R FL
Phase 2, Open-Label, Multicenter Study

Response in the MT *EZH2* Cohort

Response in MT EZH2 (n=45)	IRC	INV
ORR, n (%) [95% CI[a]]	31 (69) [53, 82]	35 (78) [63, 89]
CR, n (%)	6 (13)	4 (9)
PR, n (%)	25 (56)	31 (69)
SD, n (%)	13 (29)	10 (22)
PD, n (%)	1 (2)	0

- 44 of 45[b] (98%) patients with evidence of tumor reduction, by IRC
- mPFS, 13.8 mos (95% CI, 10.7-22.0)

Response in the WT *EZH2* Cohort

Response in WT EZH2 (n=54)	IRC	INV
ORR, n (%) [95% CI[a]]	19 (35) [23, 49]	18 (33) [21, 48]
CR, n (%)	2 (4)	3 (6)
PR, n (%)	17 (31)	15 (28)
SD, n (%)	18 (33)	16 (30)
PD, n (%)	12 (22)	16 (30)
NE/missing/unknown,[b] n (%)	5 (9)	4 (7)

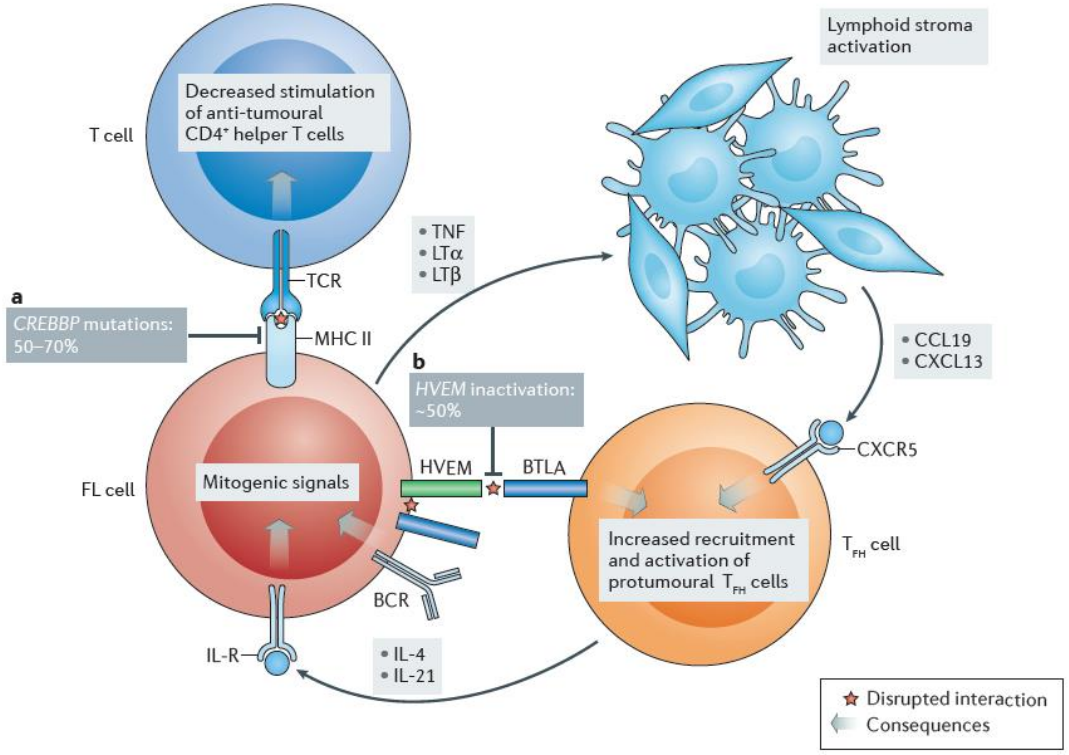
- 37 of 49[c] (69%) patients with evidence of tumor reduction, by IRC
- mPFS, 11.1 mos (95%CI, 3.7-`14.6)

[a]By Brookmeyer and Crowley method. [b]4 subjects with missing post-baseline values and 1 subject with poor image. [c]Best overall response based on Cheson (2007) criteria for lymphomas.

Morschhauser F et al. *Lancet Oncol.* 2020;21:1433-1444.

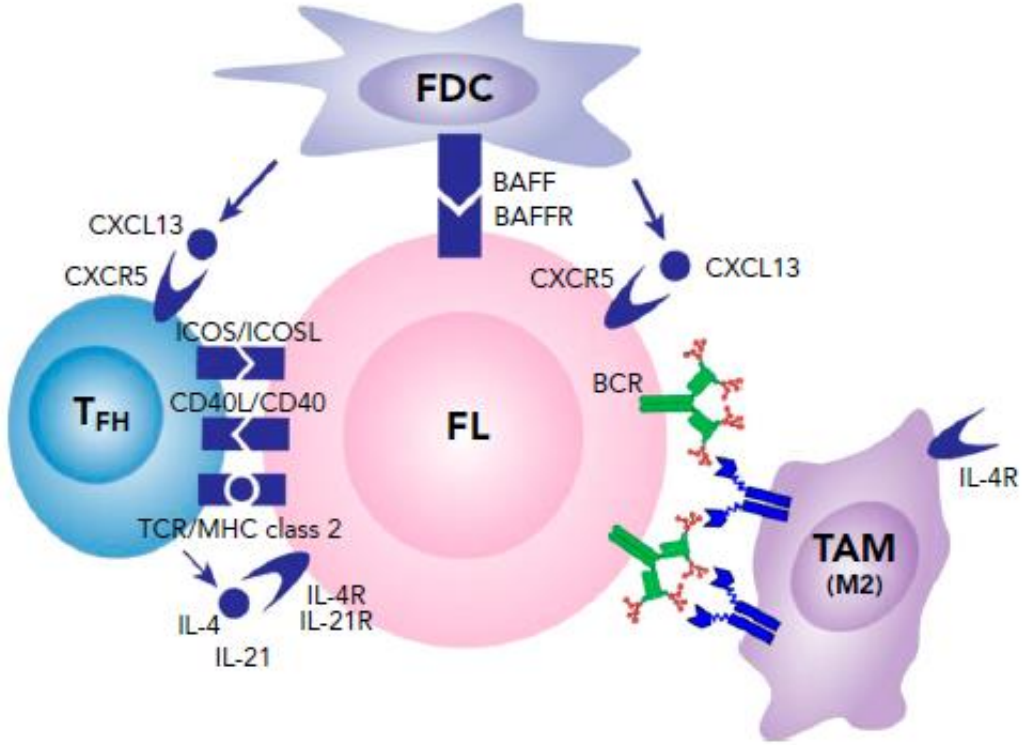
Influences of the Microenvironment on FL cells

Recurrent genetic alterations allow immune escape, shifting immune and stromal cells towards a supportive phenotype.



Huet. *Nature*. April 2018

Interactive loop between FL cells and macrophages in FL tissue provides a persistent low-level signal essential for survival.

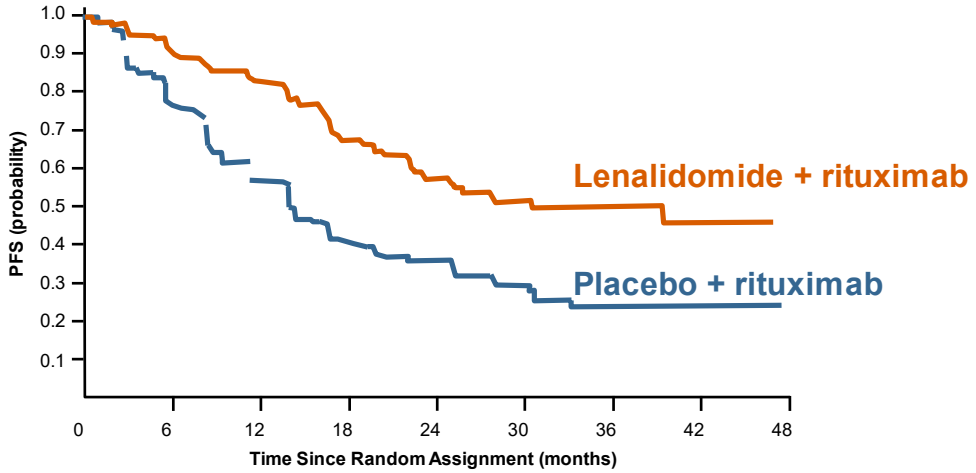


Kuppers & Stevenson. *Blood*. May 2018

R^2 vs R in R/R FL and MZL Phase III AUGMENT Study: PFS, OS

Progression-free Survival

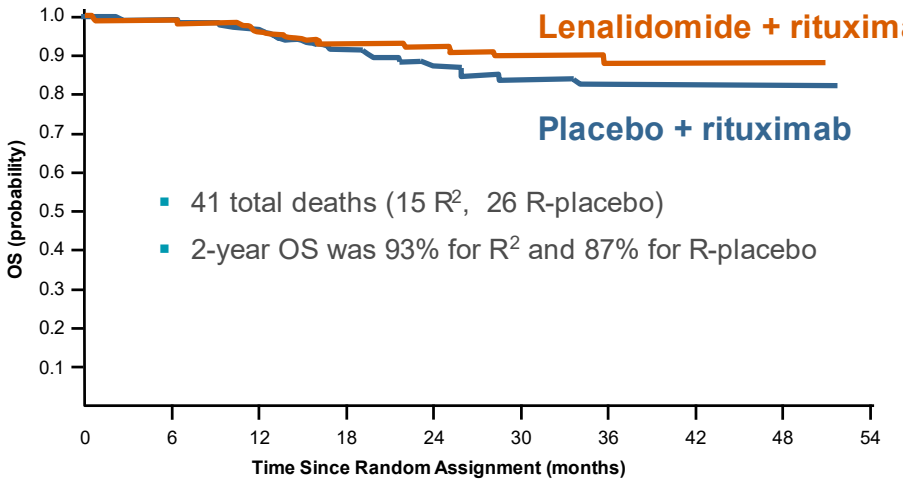
HR, 0.46 (95% CI, 0.34 to 0.62)
P < 0.0001



No. at risk									
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

Overall Survival

HR, 0.61 (95% CI, 0.33 to 1.13)



No. at risk										
Lenalidomide + rituximab	178	167	155	143	122	80	44	15	1	0
Placebo + rituximab	180	176	167	145	116	79	40	14	3	0

Median PFS	R^2 (n=178)	R-Placebo (n=180)	HR	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	<0.0001
By INV, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	<0.0001

Median follow-up: 28.3 months

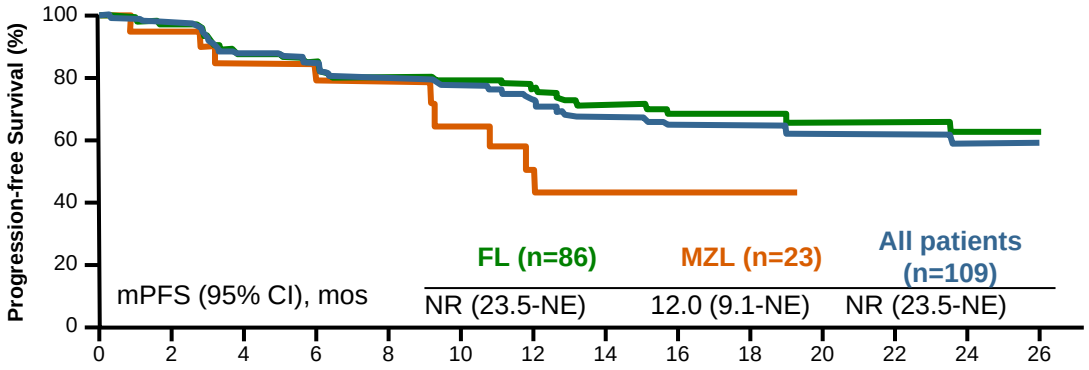
Leonard J et al. *J Clin Oncol*. 2019;37:1188-1199.

ZUMA-5 Study of Axi-cel in Relapsed/Refractory FL and MZL

Characteristic	FL n=124	MZL N=24	All Patients N=148
Median age (range)	60 (53-67)	65 (61-72)	61 (53-68)
FLIPI 3-5	54 (44%)	N/A	N/A
High tumor burden (GELF)	64 (52%)	10 (42%)	74 (50%)
Median prior tx (IQR)	3 (2-4)	3 (2-5)	3 (2-5)
Refractory to last tx	84 (68%)	18 (75%)	102 (69%)
POD24	68 (55%)	13 (57%)	81 (55%)

	All patients (n=109)	FL (n=86)	MZL (n=23)
ORR	92%	94%	83%
CRR	76%	79%	65%

Progression-free survival



AEs of Special Interest (n=148)	
Cytokine Release Syndrome	
Any grade	82%
Grade ≥ 3	7%
Neurologic Events	
Any grade	59%
Grade ≥ 3	19%

Jacobson, et al. *Lancet Oncol.* 2022;23(1):91-103.

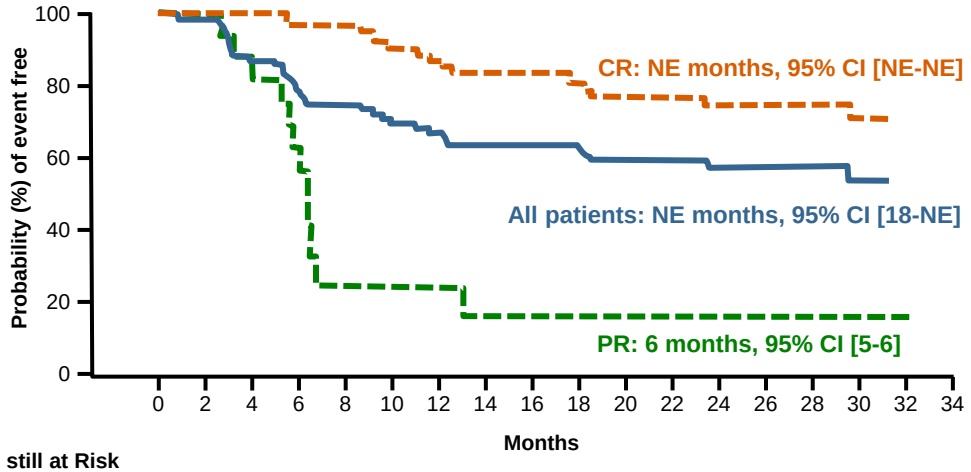
ELARA Study of Tisa-cel in Relapsed/Refractory FL

Characteristic	n=97
Median age (range)	57 (49-64)
Median prior tx (range)	4 (2-13)
Refractory	78%
POD24	63%

	All patients n=94
ORR	**86%**
CRR	**69%**

AEs of Special Interest (n=97)	
Cytokine Release Syndrome	
Any grade	49%
Grade ≥ 3	0%
ICANS	
Any grade	4%
Grade ≥ 3	1%

Progression-free Survival



No. of patients still at Risk																	
All patients (N=94)	94	91	78	67	63	59	57	54	54	49	47	47	32	19	19	6	0	0
CR (N=64)	64	64	64	61	60	56	54	52	52	47	45	45	31	18	18	5	0	0
PR (N=17)	17	16	13	5	3	3	3	2	2	2	2	2	1	1	1	1	0	0

Median PFS not reached

Event-free Probability	% (95% CI)
24-month PFS, all patients	57 (46-67)
24-month PFS, patients in CR	75 (62-84)

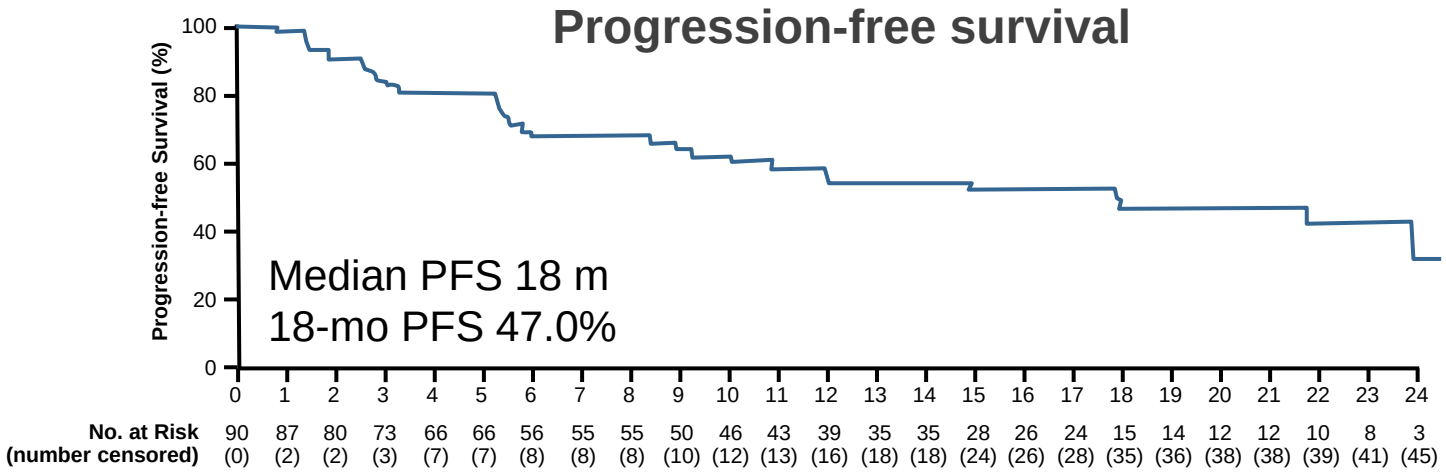
Dreyling, at al. Proc ASH 2022. Fowler, et al. Nat Med. 2022;28:325–332.

The New Kid on the Block: Mosunetuzumab, an Anti-CD20/CD3 Bispecific Antibody, in Relapsed/Refractory FL

- Mosunetuzumab IV 1 mg on cycle 1 day 1, 2 mg on day 8, 60 mg on day 15 and cycle 2 day 1, and 30 mg on day 1 of cycle 3 onwards
- Total of 8 cycles for patients in CR, 17cycles for patients in PR

Characteristic	n=90
Median age (range)	60 (53-67)
FLIPI 3-5	46%
Median prior tx (IQR)	3 (2-4)
Refractory to last tx	69%
POD24	52%

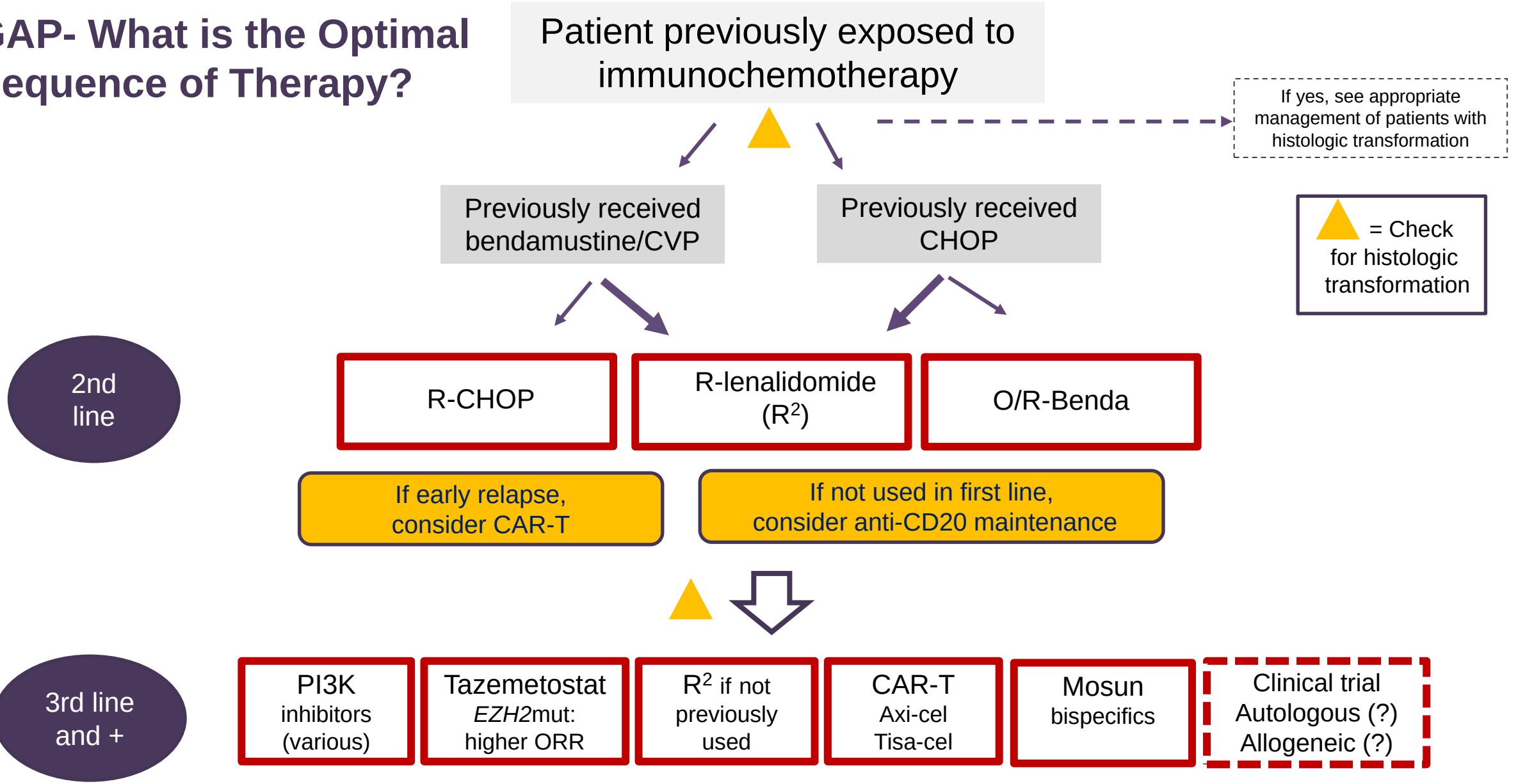
Response	n=90
ORR	80%
CRR	60%
Median DOR	23 m
18-mo DOR	57%



AEs of Special Interest (n=90)	
Cytokine Release Syndrome	
Any grade	44%
Grade ≧ 3	2%
Neurologic Events	
Any grade	5%
Grade ≧ 3	0%

Budde, at al. *Lancet Oncol.* 2022:23:1055-1065.

GAP- What is the Optimal Sequence of Therapy?



Adapted from: Salles G. How do I sequence therapy for follicular lymphoma? *Am Soc Hematol Educ Program*. 2020 Dec 4;2020(1):287-294.

ZUMA-5 CRS and Neurologic Events

Parameter	CRS[a] FL (n=124)	CRS[a] MZL (n=22)	CRS[a] All Patients (N=146)	Neurologic Events[a] FL (n=124)	Neurologic Events[a] MZL (n=22)	Neurologic Events[a] All Patients (N=146)
Any grade	97 (78)	22 (100)	119 (82)	70 (56)	17 (77)	87 (60)
Grade ≥3	8 (6)	2 (9)	10 (7)	19 (15)	9 (41)	28 (19)
Most common CRS symptoms of any grade, n/n (%)						
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)	–	–	–
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)	–	–	–
Most common neurologic events of any grade, n/n (%)						
Tremor	–	–	–	36/70 (51)	9/17 (53)	45/87 (52)
Confusional state	–	–	–	28/70 (40)	7/17 (41)	35/87 (40)
Tocilizumab use, n (%)	56 (45)	15 (68)	71 (49)	7 (6)	2 (9)	9 (6)
Corticosteroid use, n (%)	19 (15)	6 (27)	25 (17)	38 (31)	14 (64)	52 (36)
Median time to onset (range), days	4 (1–15)	4 (1–9)	4 (1–15)	7 (1–177)	7 (3–19)	7 (1–177)
Median duration of events (range), days	6 (1–27)	6 (2–14)	6 (1–27)	14 (1–452)	10 (2–81)	14 (1–452)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]	67/70 (96)	14/17 (82)	81/87 (93)

Jacobson CA et al. ASH 2020. Abstract 700.

Predictors of Response and Toxicity with CD19 Auto CARs

Improved Response

PATIENT

- Low tumor burden, low lactate dehydrogenase
- Low pretreatment inflammatory markers
- Absence of medical comorbidities
- Lack of need for bridging therapy

T CELLS

- Proportion of CCR7+ and other early memory T cells in the CAR product
- Faster doubling time in vitro
- Higher CAR T-cell peak to tumor burden ratio

TUMOR

- Low tumor myeloid-derived suppressor cells
- High tumor-infiltrating lymphocytes
- Absence of *MYC* overexpression
- Absence of *CD58* mutations

Increased Toxicity

PRE-TREATMENT

- High tumor burden, elevated pretreatment lactate dehydrogenase
- High pretreatment inflammatory markers
- ? High pretreatment monocyte levels

POST-TREATMENT

- High peak CAR T-cell levels
- High peak cytokine levels
- Markers of disseminated intravascular coagulation (including fibrinogen levels)
- Early cytokine release syndrome

What do we know about response/risk of toxicity with bispecifics?

Conclusions

- Outcomes for the majority of patients with FL are favorable.
  - Can we do a better job with risk stratification?
- Balancing the goals of therapy with patient specific characteristics generally informs treatment selection,
  - Can we be more scientific about this?
- An unmet need is identifying optimal sequencing of therapy.
  - We need more randomized trials and biomarker exploration.
- The goal of treatment is to achieve a normal life expectancy without negatively impacting quality of life.
  - Is functional cure as important as curative intent with a given line of therapy?

Acknowledgements

Patients and their loved ones

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Nathan Fowler, Sattva Neelapu, Michael Green, Paolo Strati, Dai Chihara

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