Follicular Lymphoma: POD24 today

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THE UNIVERSITY OF TEXAS
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Disclosures

Consultant: Abbvie, Bayer, BeiGene, Celgene, Denovo Biopharma, Foresight Diagnostics, Genentech/Roche, Genmab, Gilead, Karyopharm, N-Power Medicine, Pharmacyclics/Janssen, SeaGen, Spectrum.

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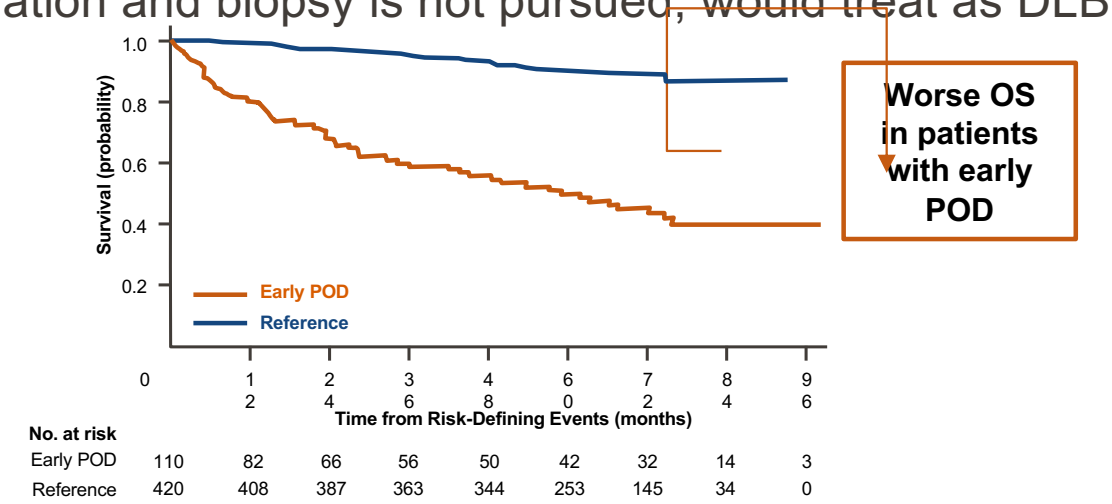
R/R FL: POD24 is associated with inferior survival

Early progression of disease (≤2 years) after frontline chemoimmunotherapy (POD24) occurs in approximately 20% of patients

- Associated with a poor prognosis[3]
- Represents a population that should be targeted for trials.

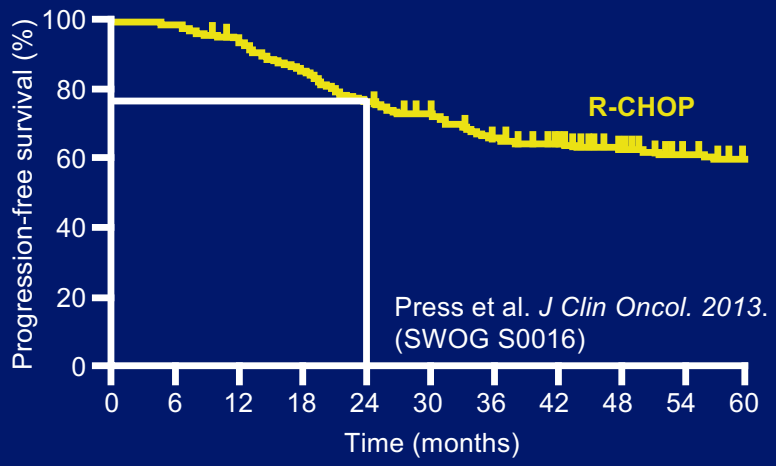
Biopsy recommended to detect histologic transformation of FL, which is reported to occur at a rate of 2% per year[1]

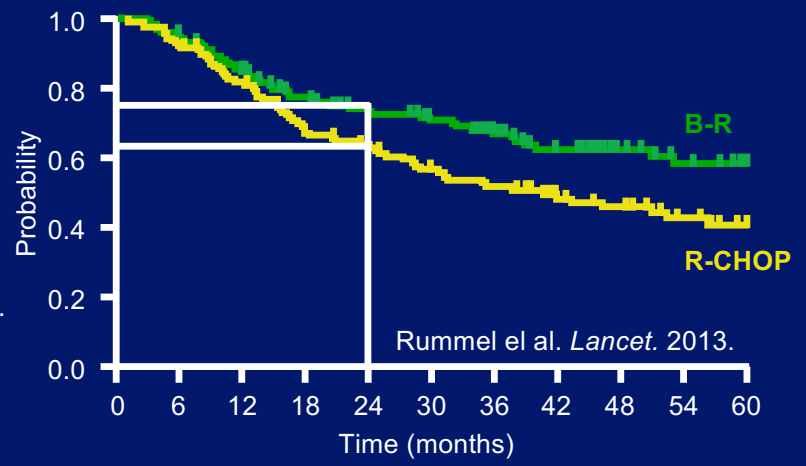
- If concerned for clinical transformation and biopsy is not pursued, would treat as DLBCL[2]



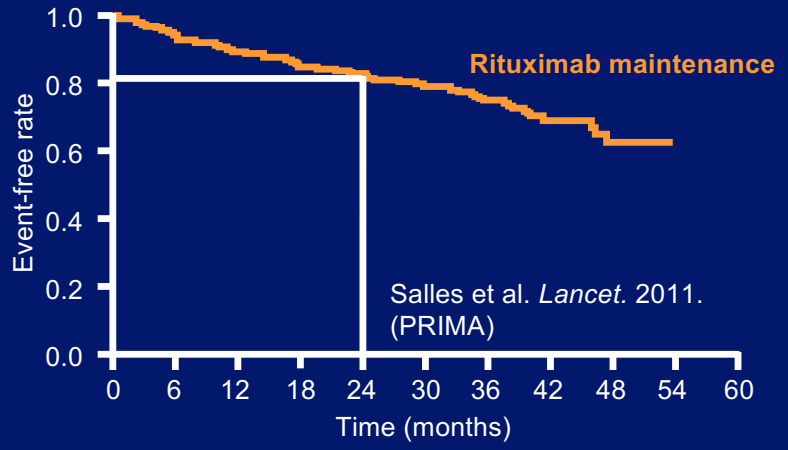
Casulo C, et al. *J Clin Oncol.* 2015;33:2516.

20% of Patients With FL Will Experience Disease Progression Within 24 Months of Treatment



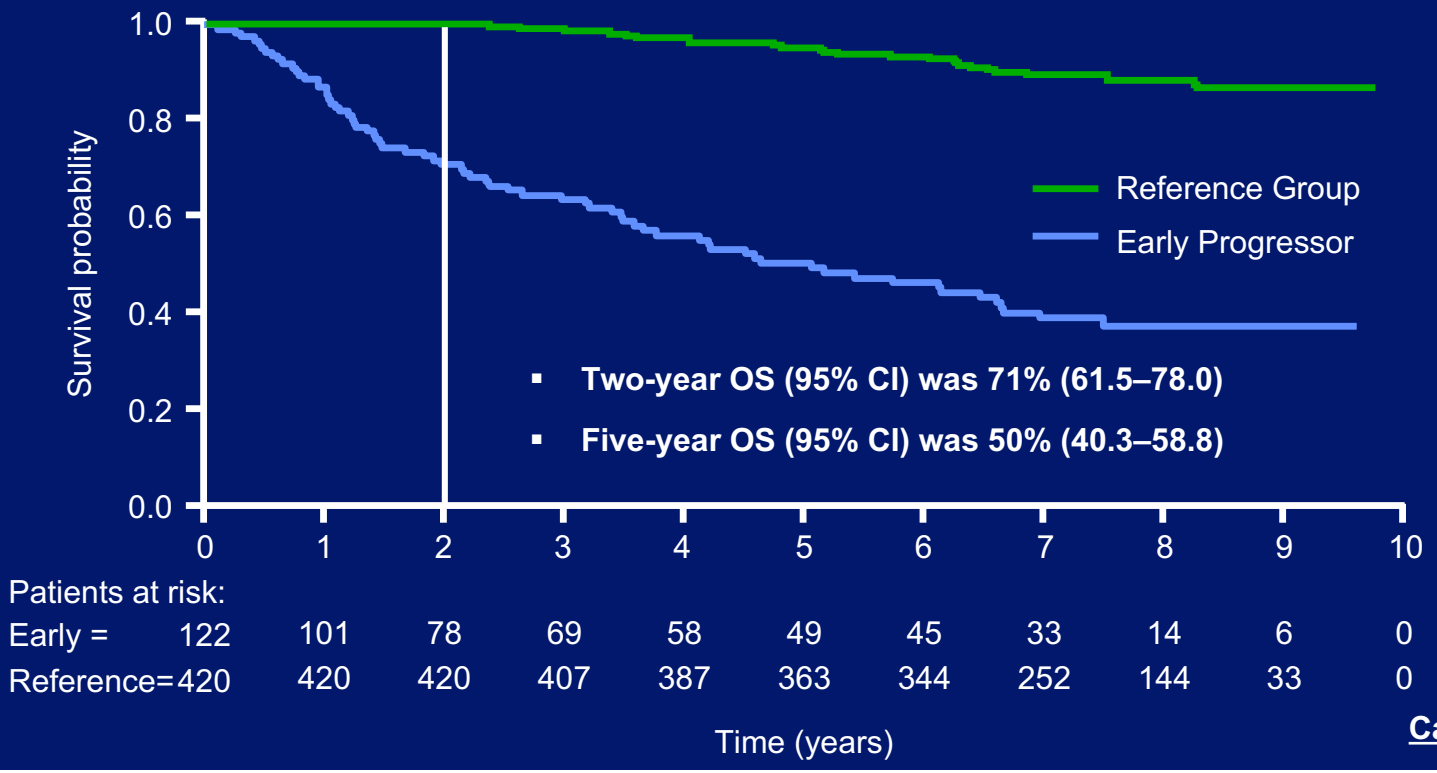


FL includes high-risk group of patients who will relapse early despite different treatment approaches; maintenance



OS of Patients With FL Who Relapsed Within 2 Years of R-CHOP ("Early POD") – National LymphoCare Study

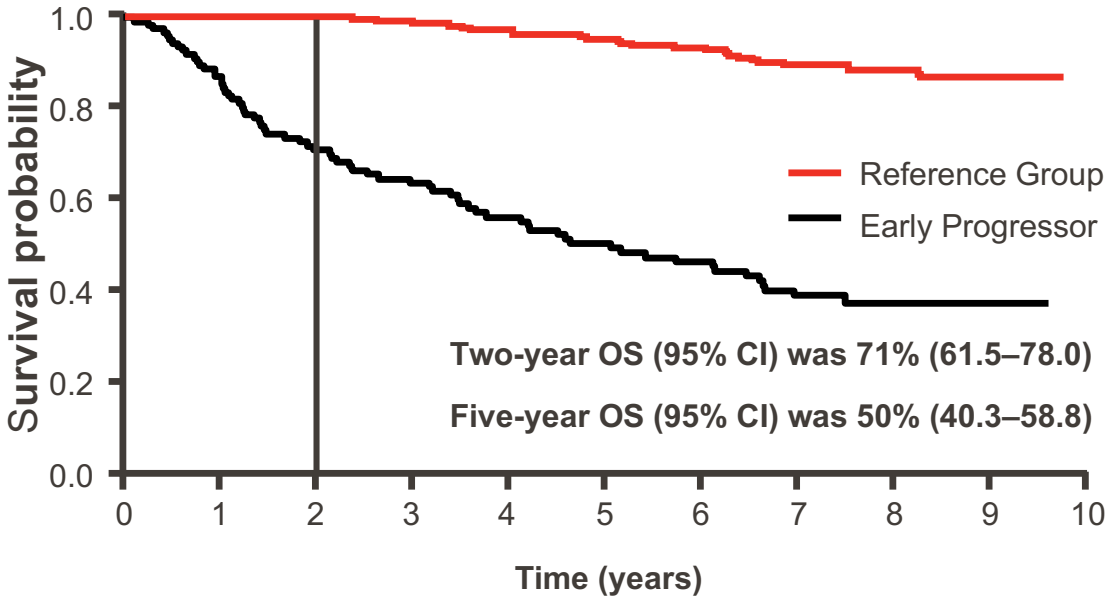
- 122 patients were classified as early progressors



Casulo *J Clin Oncol*. 2015

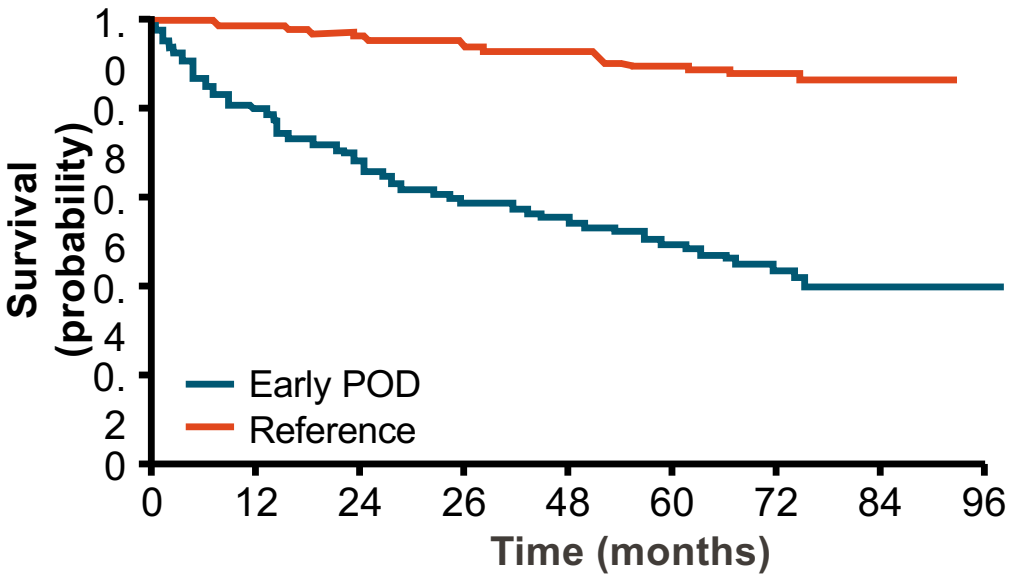
Connections Between Cohort Study and RCTs

NLCS: Survival With POD24 (n=542) (progression < 24 months after initial therapy)



Casulo. *JCO.* 2015

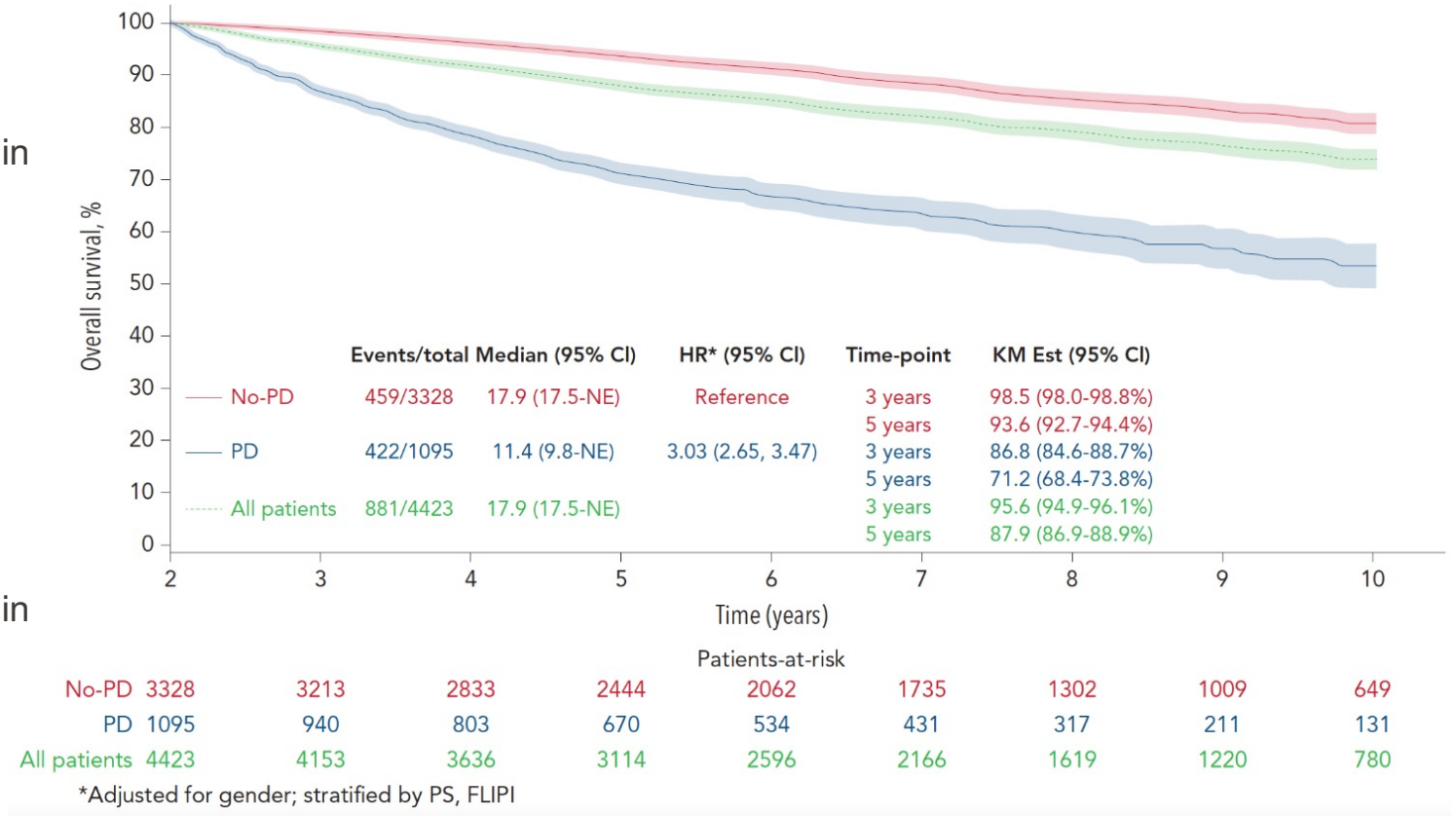
FLASH: Survival With POD24 (n=5,453) (progression < 24 months after initial therapy)



Casulo et al. *Blood*. 2022

Progression of Disease in 24 Months Predicts Poor Survival

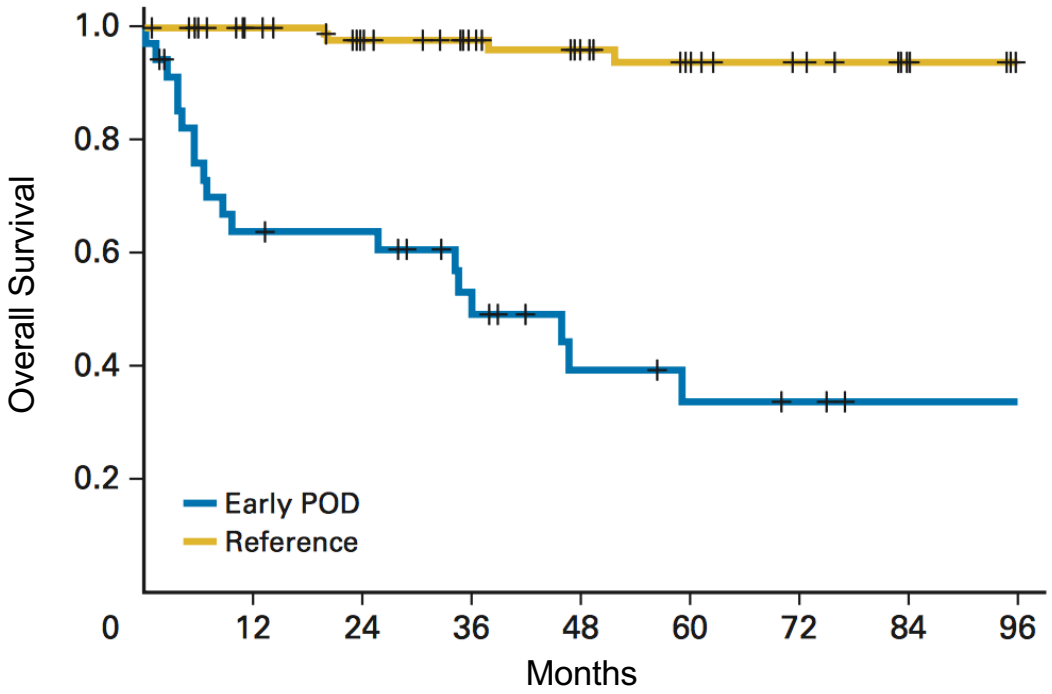
- **POD24 predicted by:**
  - Male sex
  - Poor PS
  - High-risk FLIPI
  - Elevated ß2-macroglobulin
- For patients with POD24, **death more likely in:**
  - Age >60
  - Male sex
  - PS ≥2
  - High-risk FLIPI
  - Hgb <12
  - Elevated ß2-macroglobulin



Casulo et al. *Blood*. 2022

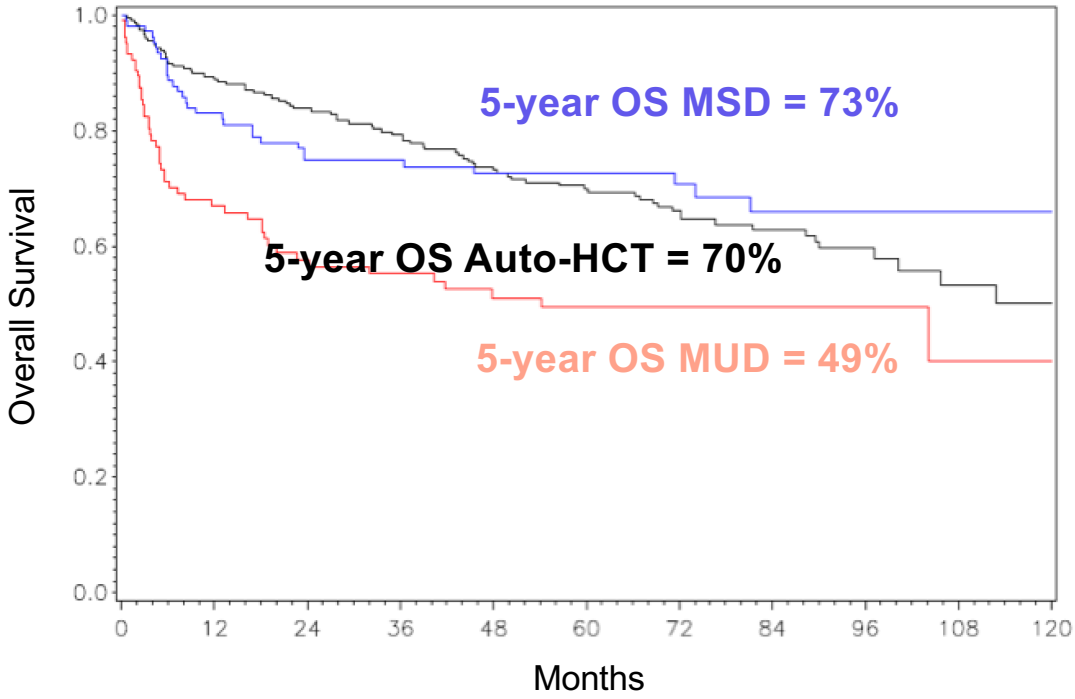
Placing SCT in Context

National LymphoCare Study



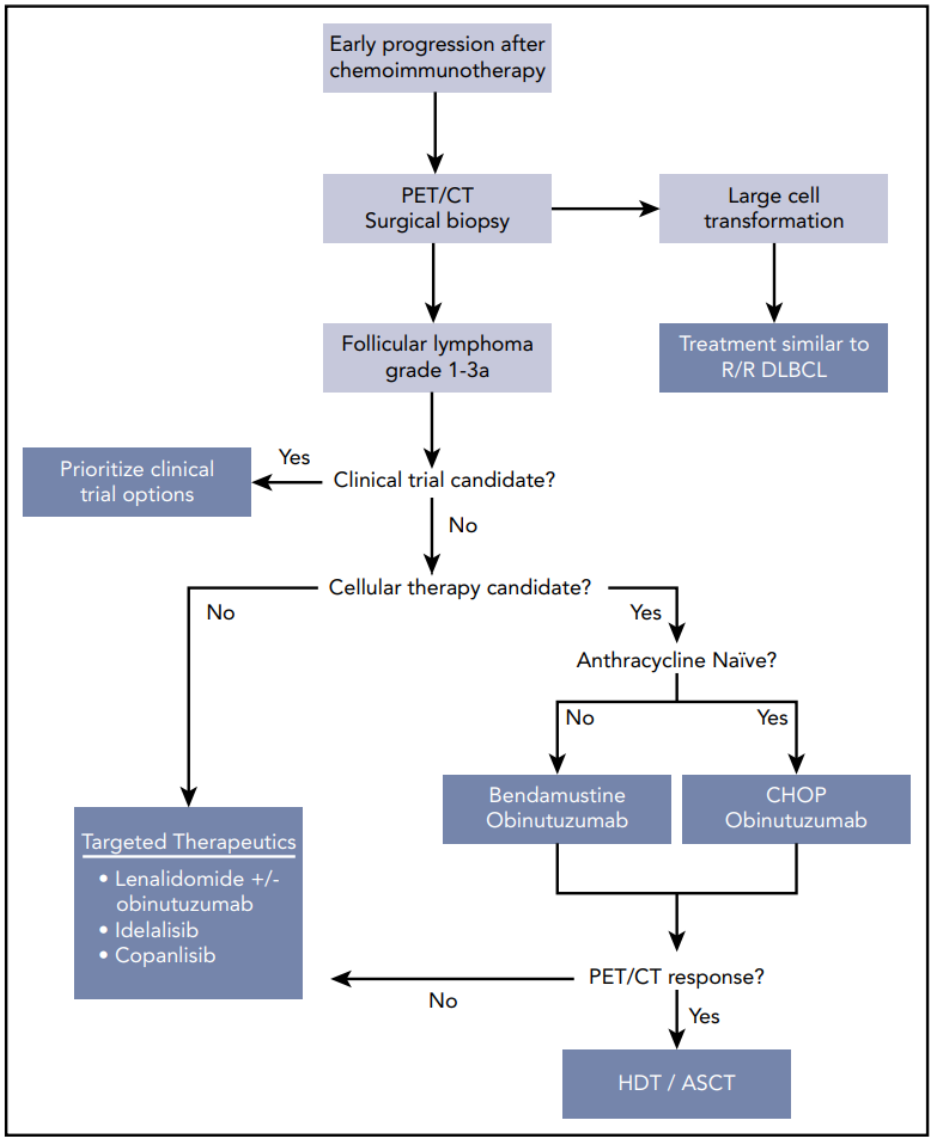
Casulo. *JCO.* 2015

CIBMTR Study



Casulo, et al. Biol Blood Marrow Transplant. 2017

Management of Early Relapsed FL (<24 mos.)



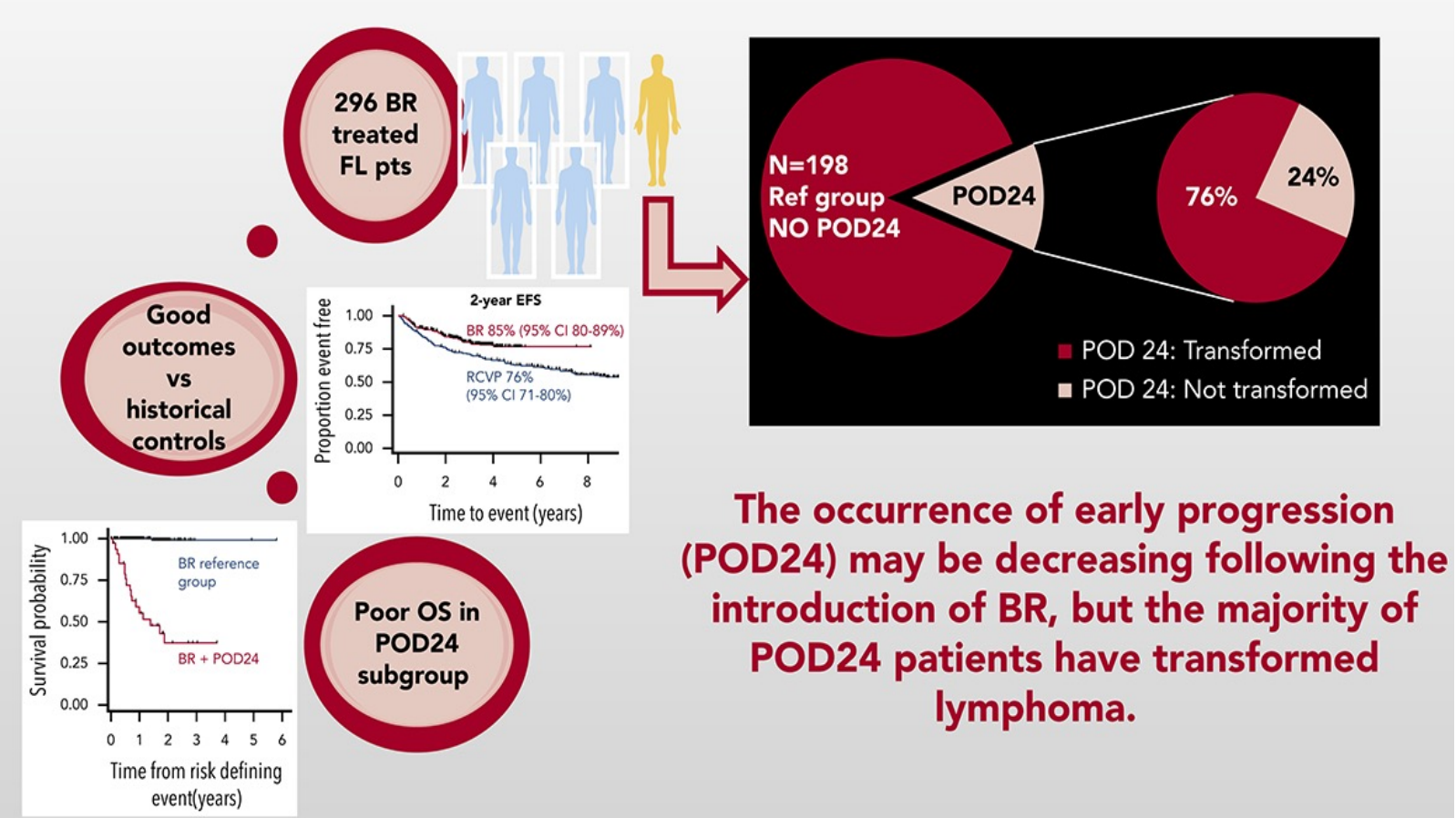
Casulo et al. *Blood*. 2019

Early Progression after BR Associated with Transformation

Study Overview

- Retrospective study of a population-based cohort of n=296 patients with advanced stage FL grades 1-3A
- Treated with frontline BR and maintenance rituximab

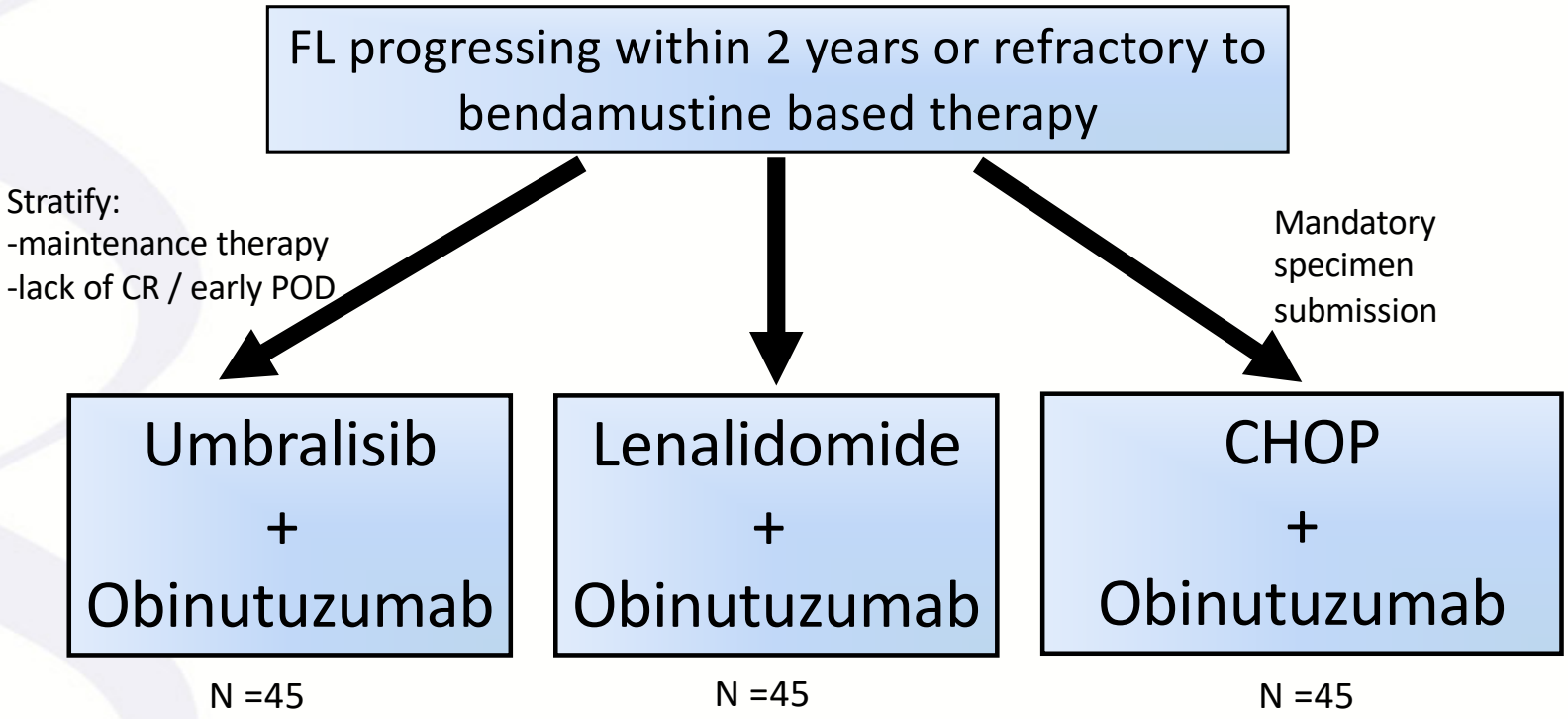
- POD24 was defined as progression or relapse, death from lymphoma, or treatment toxicity within 24 months of initiation of systemic therapy



Freeman CL, et al. *Blood*. 2019;134(9):761-764.

S1608: Randomized phase II trial in early progressing or refractory FL

Paul Barr (SWOG), Brian Link (Alliance), Chris Flowers (ECOG)



Primary clinical objective: CR by PET/CT

Primary translational objective: Validation of m7-FLIPI in this high-risk population

Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study

Carla Casulo, Melissa C Larson, Julianne J Lunde, Thomas M Habermann, Izidore S Lossos, Yucai Wang, Loretta J Nastoupil, Christopher Strouse, Dai Chihara, Peter Martin, Jonathon B Cohen, Brad S Kahl, W Richard Burack, Jean L Koff, Yong Mun, Anthony Masaquel, Mei Wu, Michael C Wei, Ashwini Shewade, Jia Li, James Cerhan, Christopher R Flowers, Brian K Link, Matthew J Maurer

Summary

Background Novel therapies for relapsed or refractory follicular lymphoma are commonly evaluated in single-arm studies without formal comparison with other treatments or historical controls. Consequently, rigorously defined treatment outcomes informing expectations for novel therapeutic strategies in this population are sparse. To inform outcome expectations, we aimed to describe treatment patterns, survival outcomes, and duration of response in patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy.

Lancet Haematol 2022; 9: e289–300

See Comment page e241

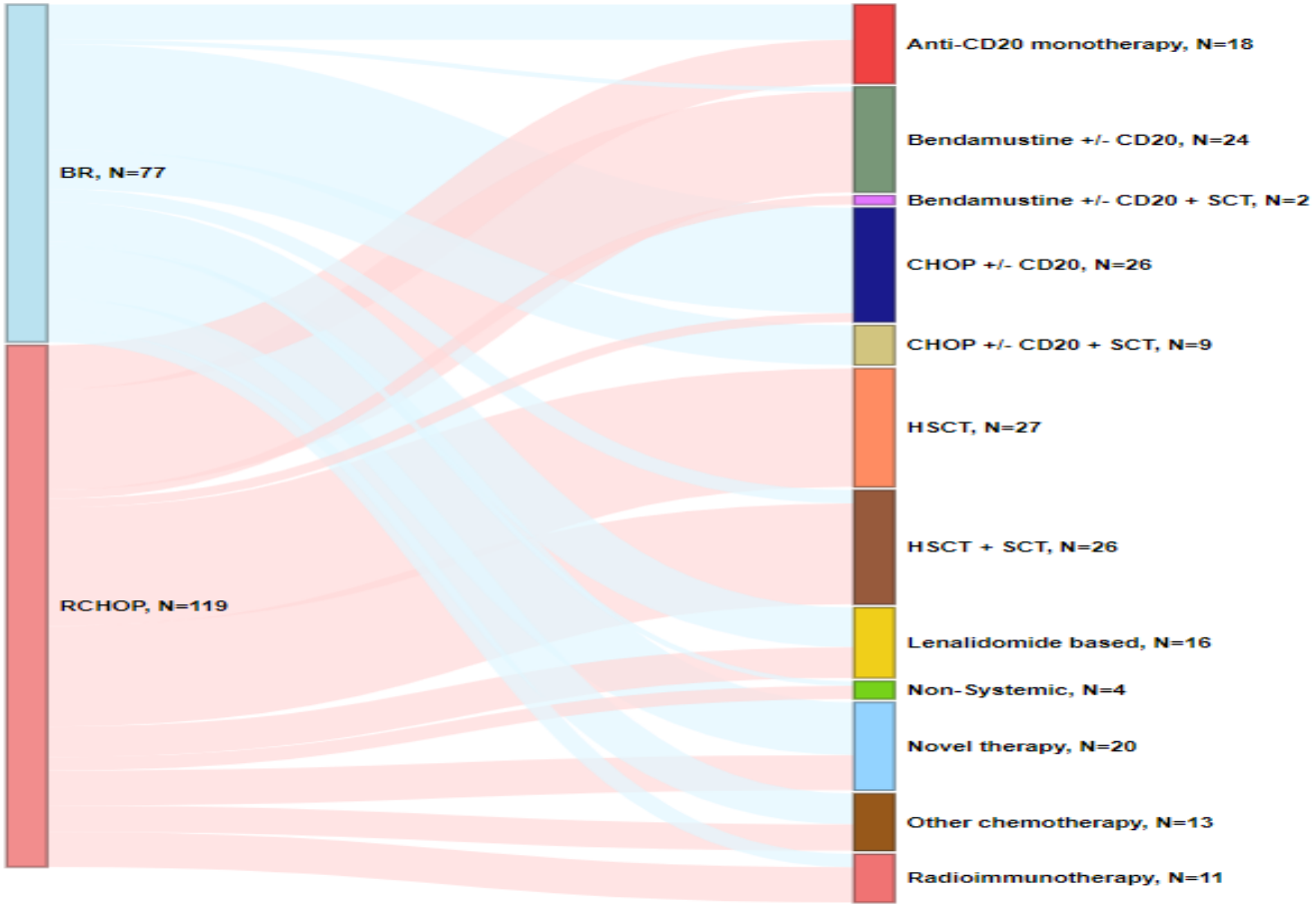
Department of Medicine, Wilmot Cancer Institute (C Casulo MD) and Department

Third and Later Lines of Therapy for FL (LEO CReWE)

Therapy	N	Overall response rate	Progression-free survival		Overall survival	
			2-year	HR	5-year	HR
Immunochemotherapy	133	84%	43%	1 (ref)	74%	1 (ref)
Anti-CD20 monotherapy	53	66%	47%	1.26	78%	0.88
PI3K ± anti-CD20	25	38%	25%	1.94	71%	1.38
Lenalidomide ± anti-CD20	37	55%	27%	1.72	58%	2.29
Novel therapy ± anti-CD20	39	49%	31%	1.59	72%	1.18
Salvage therapy, cellular therapy, or both	94	76%	48%	.79	75%	1.15
Other	60	67%	33%	1.43	81%	.99
Treatment on trial						
No	323	72%	40%	1 (ref)	72%	1 (ref)
Yes	98	65%	40%	1.04	83%	0.65

Casulo et al. *Lancet Haem*, 2022

FL (LEO CReWE) POD24 (n=196)



Lymphoma Epidemiology of Outcomes

Casulo et al. *ASH* 2023

FL (LEO CReWE) POD24 (n=196)

Outcomes by Treatment Group (%)	CR % (95% CI)	5 yr OS % (95% CI)
HSCT (27)	40 (27-54)	67 (56-81)
CHOP +/- CD20 (18)	29 (15-48)	66 (51-86)
Bendamustine +/- CD20 (13)	55 (32-76)	83 (71-100)
Novel therapy (10)	17 (4,42)	84 (65-100)
Anti-CD20 Monotherapy (9)	35 (15-61)	73 (53-100)
Lenalidomide based (8)	53 (27-78)	75 (53-100)
Other Chemotherapy (7)	23 (6-54)	76 (55-81)
Radioimmunotherapy (6)	30 (8-65)	46 (22-93)
Non-systemic (2)	100 (6-100)	100 (100-100)

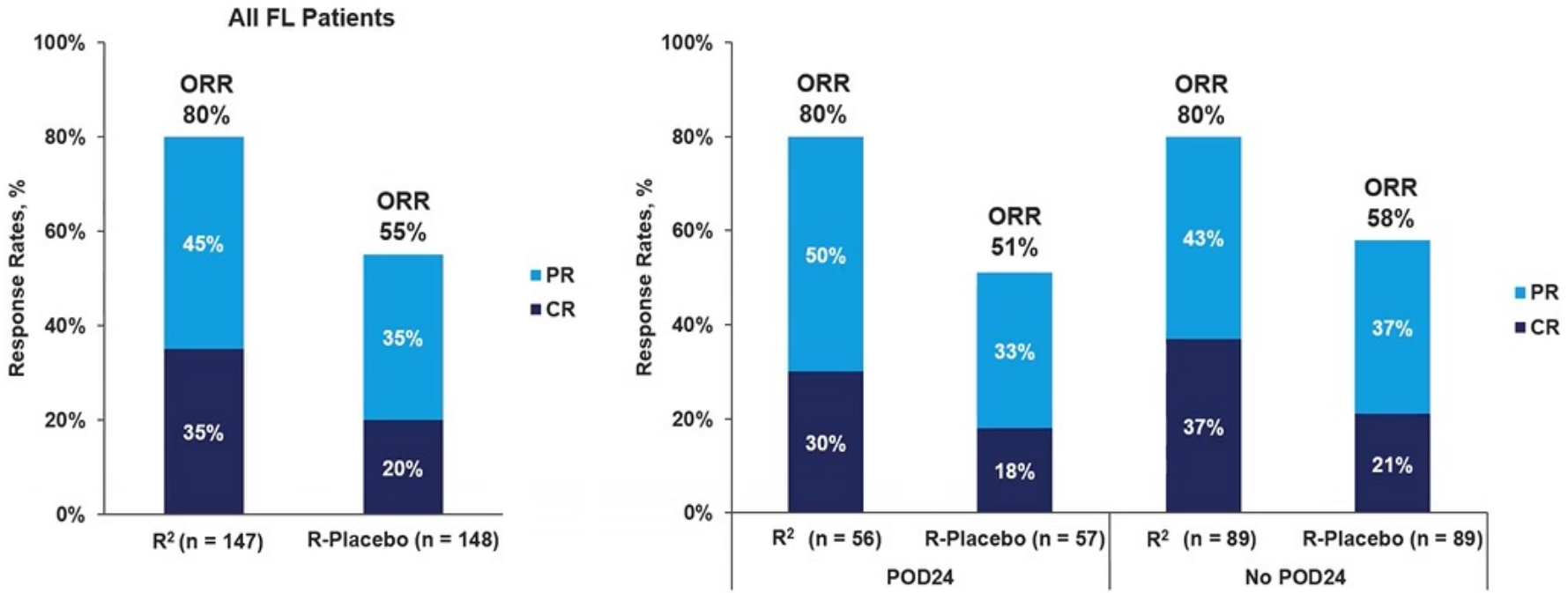
Casulo et al. *ASH* 2023

Options for Rel/Ref Follicular Lymphoma

- Bendamustine + Obinutuzumab
- Tazemetostat
- Lenalidomide + Rituximab
- Zanubrutinib + Obinutuzumab
- CAR T cells
- Bispecific antibodies

AUGMENT: POD24 for Rel/Ref FL receiving R2 vs R-Placebo

BEST RESPONSE IN ALL FL PATIENTS AND BY POD24 STATUS (ITT)

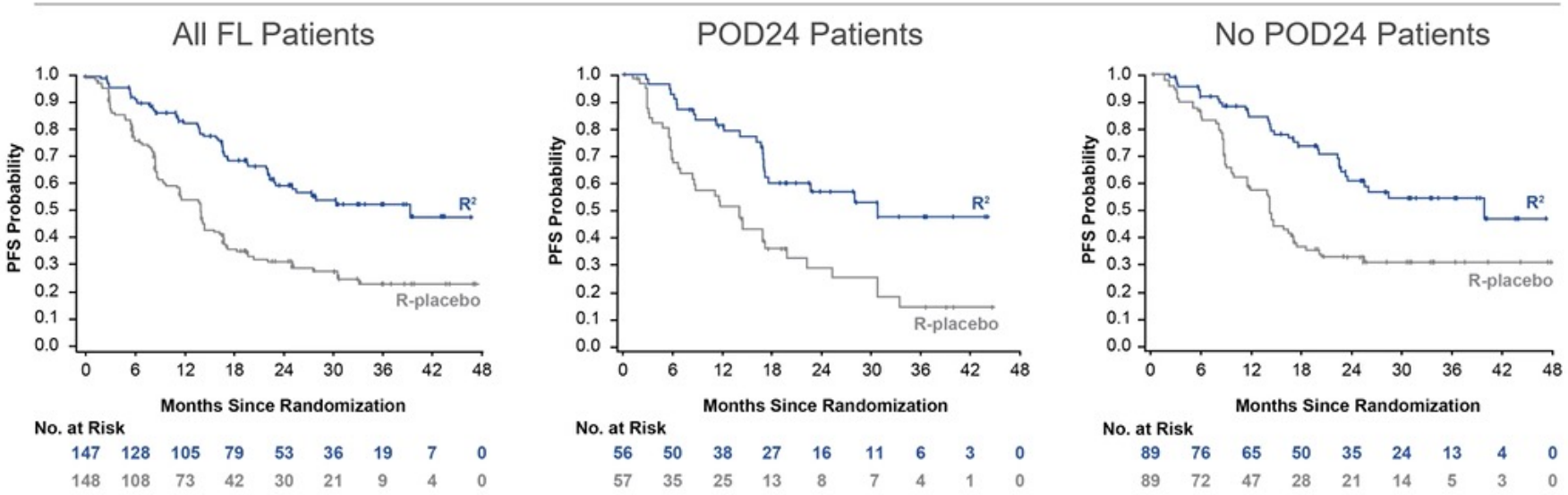


- Best responses were similar within each arm (R^2 or R-placebo) for all patients and those with or without POD24

Leonard et al. ICML 15, 2019, Abst 069.

AUGMENT: POD24 for Rel/Ref FL receiving R2 vs R-Placebo

PFS FOR ALL FL PATIENTS AND BY POD24 STATUS



Median PFS, mo (95% CI) *(n R²/n R-placebo)*	All FL Patients *(n = 147/148)*	POD24 *(n = 56/57)*	No POD24 *(n = 89/89)*
R²	39.4 (23.1-NR)	30.4 (16.8-NR)	39.4 (22.9-NR)
R-placebo	13.9 (11.2-16.0)	13.8 (6.7-16.9)	13.9 (11.2-16.6)
HR (95% CI)	0.40 (0.29-0.56)	0.41 (0.24-0.68)	0.43 (0.28-0.65)
P value	< 0.0001	0.0004	< 0.0001

Leonard et al. ICML 15, 2019, Abst 069.

Study Design

Key Eligibility Criteria

- Adults with grade 1-3a FL
- R/R disease, previously treated with ≥2 systemic treatments including an anti-CD20 antibody and an appropriate alkylator-based combination therapy
- Measurable disease
- ECOG PS 0-2
- Adequate organ functions
- No prior BTK inhibitor

ClinicalTrials.gov: NCT03332017

Arm A
Zanubrutinib[a] plus obinutuzumab[b]
N=145
Until PD/unacceptable toxicity

Randomization 2:1
Stratification factors
- Number of prior lines
- Rituximab refractory status
- Geographic region

Arm B
Obinutuzumab[b]
N=72
Option to crossover to combination if PD centrally confirmed or no response at 12 months

Primary Endpoint
- ORR assessed by ICR according to Lugano classification[1]

Select Secondary Endpoints
- ORR assessed by investigator
- DOR and PFS determined by ICR and investigator assessment
- Overall survival

- Patients were randomized between November 2017 and June 2021
- Median study follow-up: 12.5 months

Zinzani et al. *J Clin Oncol.* 2024

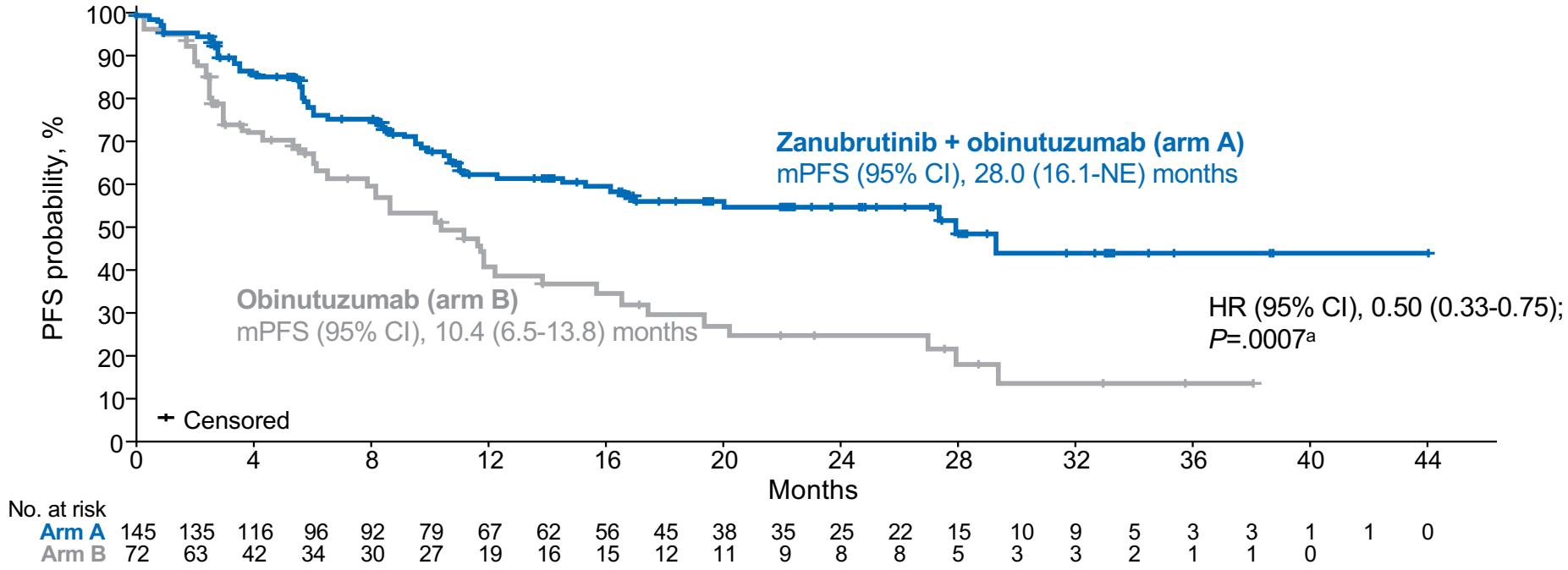
Baseline Patient Characteristics

Characteristic	Zanubrutinib plus obinutuzumab N=145	Obinutuzumab N=72
Male sex, %	51.7	45.8
Median age, years (min, max)	63.0 (31, 84)	65.5 (32, 88)
FLIPI, %		
Low (0-1)	19.3	12.5
Intermediate (2)	24.8	33.3
High (≥3)	53.1	51.4
Missing	2.8	2.8
ECOG performance status ≥1, %	40.7	56.9
Bulky disease (≥5 cm), %	39.3	43.1
Elevated LDH, %	34.5	40.3
Elevated beta-2 microglobulin, %	44.8	51.4
Median prior lines of therapy, n (min, max)	3 (2, 11)	3 (2, 9)
Patients with >3 lines of therapy, %	28.3	25.0
Patients refractory to rituximab, %	53.8	50.0
Patients refractory to the most recent line of therapy, %	32.4	40.3
Patients with PD within 24 months of starting the first line of therapy, %	34.5	41.7

Zinzani et al. *J Clin Oncol.* 2024

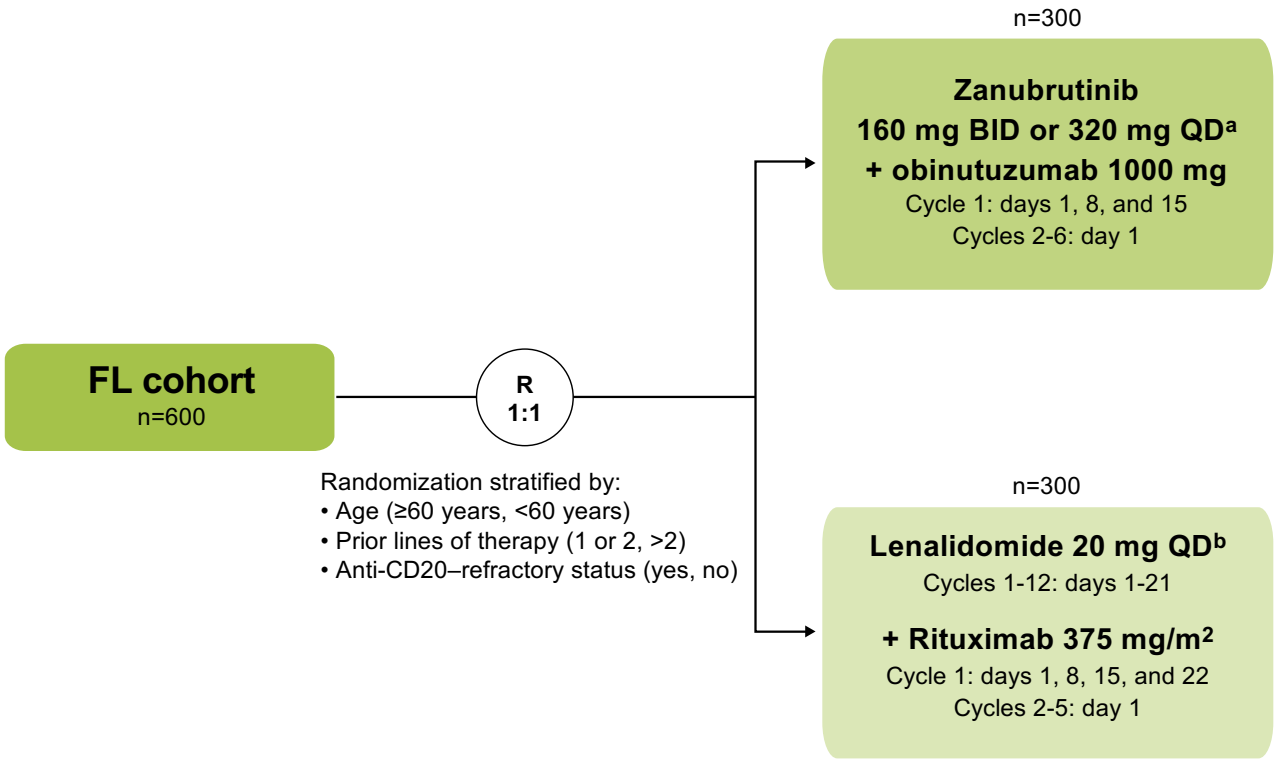
PFS by IRC in the Phase 2 ROSEWOOD R/R FL Trial

In the randomized phase 2 ROSEWOOD study in R/R FL (NCT03332017), zanubrutinib + obinutuzumab led to an IRC-assessed ORR of 69.0% (CR rate, 39.3%); mPFS at 24 months of 28 months



Zinzani et al. *J Clin Oncol.* 2024

MAHOGANY: Phase 3 Study Design: FL Cohort



Primary endpoint

- PFS per IRC using PET/CT-based Lugano 2014 criteria[1]

Key secondary endpoints

- ORR per IRC using PET/CT-based Lugano 2014 criteria[1]
- OS

Secondary endpoints

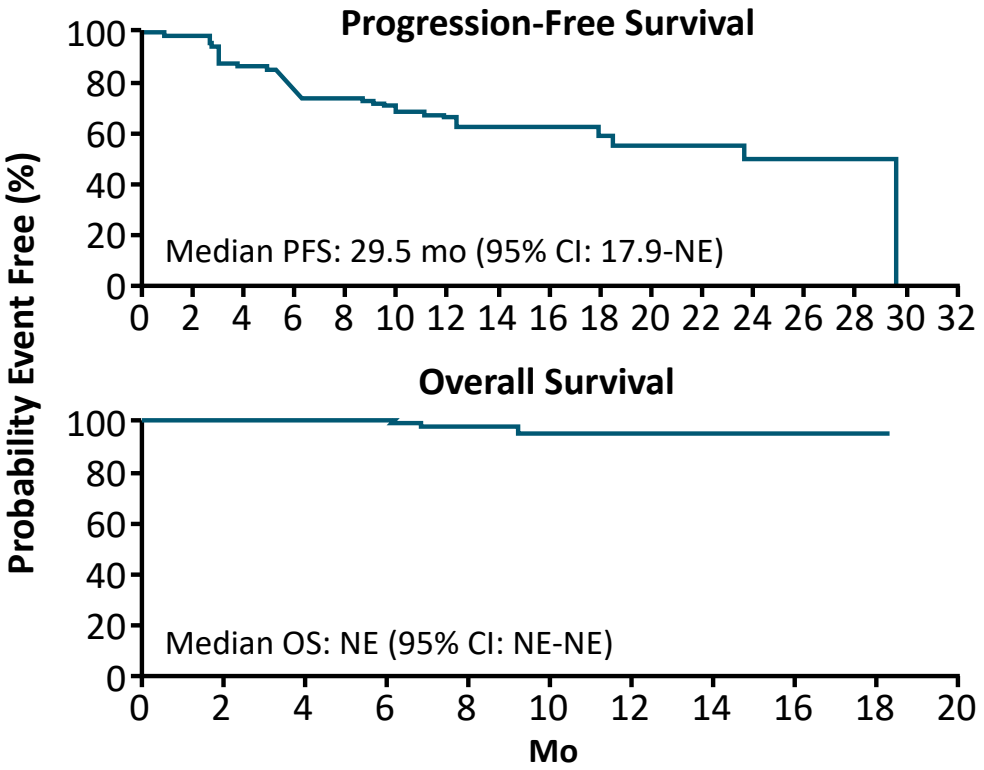
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using PET/CT-based Lugano 2014 criteria[1])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

ELARA: Tisagenlecleucel for Patients With Relapsed/Refractory FL

- Single-arm phase II study of tisagenlecleucel for patients with R/R FL (N = 97)

Outcome	Evaluable Patients (n = 94)
ORR (IRC), n (%)	81 (86.2)
▪ CR	65 (69.1)
▪ PR	16 (17.0)
▪ SD	3 (3.2)
▪ PD	9 (9.6)
▪ ND	1 (1.1)
Median DoR, mo (95% CI)	NE (15.6-NE)
9-mo DoR, % (95% CI)	76.0 (64.6-84.2)

- CRS, 49% (grade ≥3, 0%); neurotoxicity, 10% (grade ≥3, 1%)



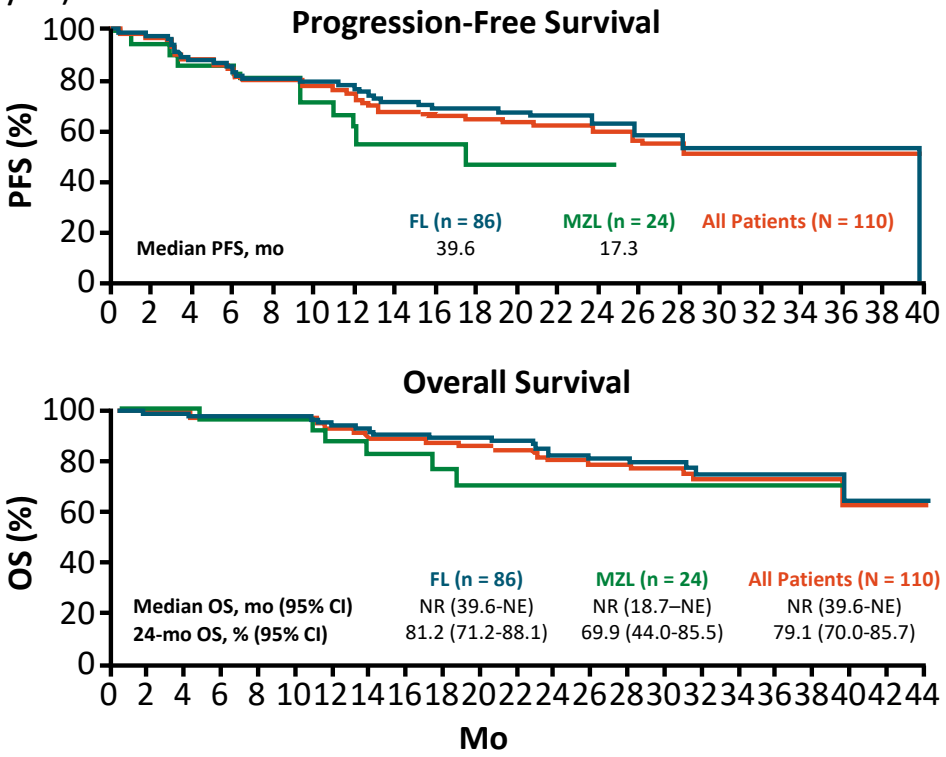
Fowler NH et al. *Nat Med*. 2022;28(2):325-332.

ZUMA-5: Axicabtagene Ciloleucel for Relapsed/Refractory Indolent NHL (FL or MZL)

- Single-arm phase II study of axicabtagene ciloleucel for patients with R/R indolent B-cell NHL (FL or MZL) **with ≥2 prior therapies** (N = 110 eligible for efficacy analysis)

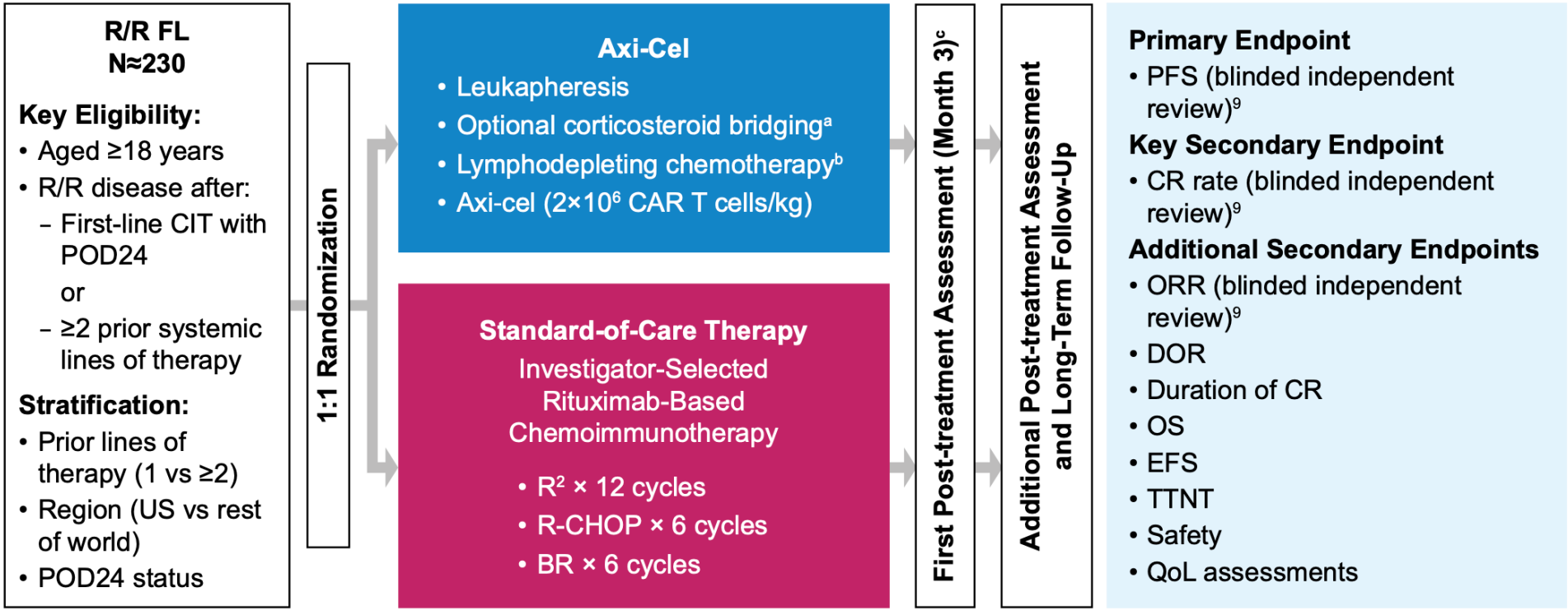
Outcome	FL (n = 86)	MZL (n = 24)	All (N = 110)
ORR, n (%)	81 (94)	20 (83)	--
▪ CR	68 (79)	15 (63)	--
▪ PR	13 (15)	5 (21)	--
▪ SD	3 (3)	0	--
▪ PD	0	1 (4)	--
▪ ND	2 (2)	3 (13)	
Median DoR, mo (95% CI)	38.6 (24.7-NE)	NR (8.2-NE)	38.6 (24.7-NE)
24-mo DoR, % (95% CI)	66.1 (53.9-75.8)	NR (NE-NE)	63.5 (52.4-72.7)

- CRS grade ≥3, 7% (6% FL); neurotoxicity grade ≥3, 19% (15% FL); tocilizumab, 49%; corticosteroids, 36%



Neelapu SS et al. Lancet Onc 2022

ZUMA-22: Axi-cel vs. SOC in POD24/3rd line FL



[a] Bridging corticosteroid therapy will be administered at the discretion of the investigator. [b] Lymphodepleting chemotherapy will consist of cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day), received days –5 to –3 before receiving axi-cel. [c] End of Month 3 after randomization.
Axi-cel, axicabtagene ciloleucel; BR, rituximab + bendamustine; CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; CR, complete response; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression within 24 months from initiating first-line chemoimmunotherapy; R², rituximab + lenalidomide; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; QoL, quality of life; R/R, relapsed/refractory; TTNT, time to next treatment; US, United States.

Flinn et al. ASCO 2023 abstract TPS7579

Bispecific Ab Mosunetuzumab in R/R FL

Phase 2 Pivotal Study

N=90

- Patients aged ≥18 yr with R/R FL grades 1-3a
- CD20+
- ECOG PS ≤1
- ≥2 prior systemic therapies including ≥1 anti-CD20 antibody and ≥1 alkylating agent

Cycle 1 (21-Day Cycles)* | **Cycle 2** | **Cycles 3-8**

Mosunetuzumab D1: 1 mg; D8: 2 mg; D15: 60 mg → **Mosunetuzumab** D1: 60 mg → **Mosunetuzumab** D1: 30 mg

*Cycle 1 step-up dosing for CRS mitigation.

Discontinue if CR by cycle 8; if PR or SD, continue treatment for 17 cycles, unless PD or unacceptable toxicity occurs

Primary endpoints

CR (best response) rate by IRF, assessed vs 14% historical control CR rate

Secondary endpoints

ORR, DoR, PFS, safety and tolerability

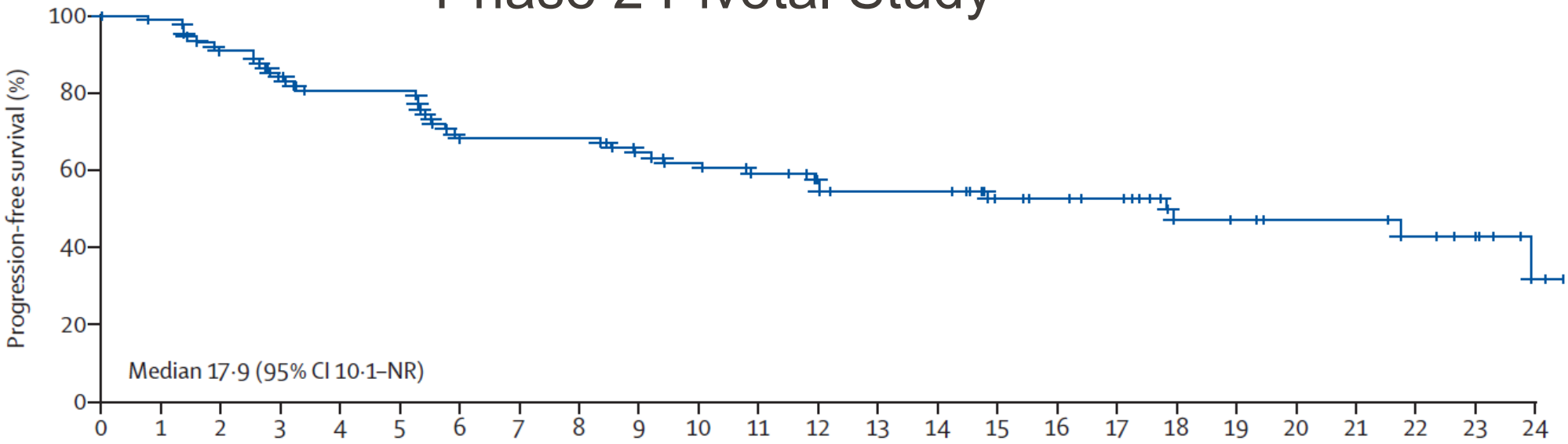
Outcome, % (95% CI)	By IRF (N = 90)	By INV (N = 90)
ORR	80 (70-88)	78 (68-86)
▪ CR	60 (49-70)	60 (49-70)

Response by Double Refractory Disease Status, % (95% CI)[1]	Yes (n = 48)	No (n = 42)
ORR	71 (56-83)	90 (77-97)
▪ CR	50 (35-65)	71 (55-84)
Response by POD ≥24 Mo of Initial Tx, % (95% CI)[1]	Yes (n = 47)	No (n = 43)
ORR	85 (72-94)	74 (59-86)
▪ CR	57 (42-72)	63 (47-77)

Budde LE et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Bispecific Ab Mosunetuzumab in R/R FL

Phase 2 Pivotal Study



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Number at risk	90	87	80	73	66	66	56	55	55	50	46	43	39	35	35	28	26	24	15	14	12	12	10	8	3
(number censored)	(0)	(2)	(2)	(3)	(7)	(7)	(8)	(8)	(8)	(10)	(12)	(13)	(16)	(18)	(18)	(24)	(26)	(28)	(35)	(36)	(38)	(38)	(39)	(41)	(45)

CRS was the most common AE (40 [44%] of 90 patients) and was predominantly grade 1 (23 [26%] of 90) and grade 2 (15 [17%]), and primarily confined to cycle 1

The most common grade 3-4 AEs were neutropenia or neutrophil count decreased (24 [27%] of 90 patients), hypophosphataemia (15 [17%]), hyperglycaemia (seven [8%]), and anaemia (seven [8%]); Serious adverse events occurred in 42 (47%) of 90 patients.

Budde LE et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Comparison of Key Patient Characteristics in GO29781 vs LEO CReWE Cohort (Unweighted and MAIC Weighted)

Variable	GO29781 N=90	LEO CReWE (unweighted) N=202	Delta	Delta P-value	LEO CReWE (MAIC weighted) Weighted N=167 ESS=127	Delta	Delta P-value
Used in MAIC Matching							
Age (mean, SD)	60.0 (12.0)	60.2 (10.8)	0.2	0.85	60.3 (10.5)	0.3	0.69
Elevated LDH (%)	39%	29%	-10%	0.13	39%	0%	1.00
POD24 to 1L IC (%)	42%	43%	1%	1.00	42%	0%	1.00
Prior LOT (mean, SD)	3.3 (1.7)	2.7 (1.1)	-0.57	<0.001	3.3 (1.8)	-0.03	0.83
Double Refractory	53%	36%	-17%	0.009	53%	0%	1.00
Not used in MAIC Matching							
Male (%)	61%	58%	-3%	0.76	58%	-3%	0.68
Bulky disease (%)	18%	16%	-2%	0.73	12%	-6%	0.32
Stage III/IV (%)	77%	84%	7%	0.96	80%	4%	0.62
Prior SCT (%)	21%	13%	-8%	0.10	15%	-6%	0.32
Months since prior therapy (mean, SD)	14.2 (16.9)	18.6 (21.1)	4.4	0.004	14.8 (19.2)	0.6	0.68

MAIC=matching-adjusted indirect comparison; ESS=Effective sample size; LDH=lactate dehydrogenase; POD24=progression of disease in 24 months; 1L=first-line; IC=immunochemotherapy; LOT=line of therapy; SCT=stem cell transplant

Maurer et al. *Haematologica*, 2023

Primary results: Comparison of GO29781 to LEO CReWE Cohort

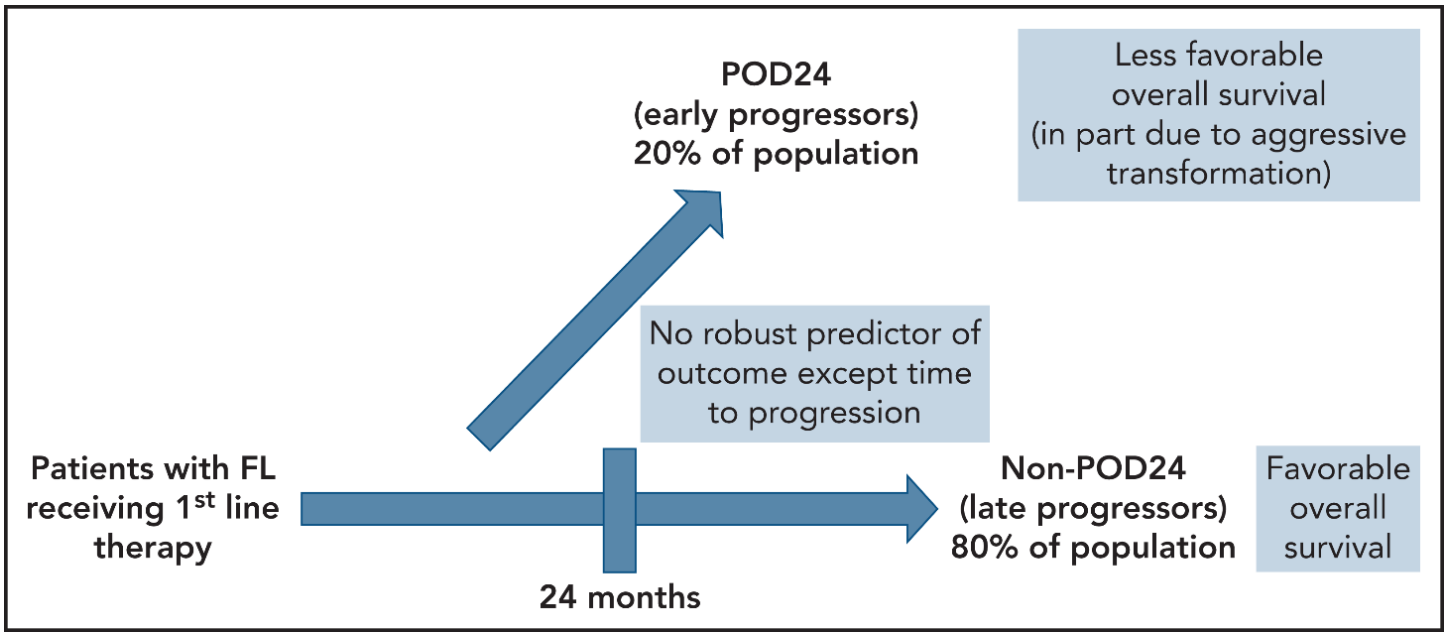
Group	N (Evaluable for Response)	ORR (95% CI)	CR Rate (95% CI)	PFS12 (95% CI)
LEO CReWE (unweighted)	202 (192)	77.6 (70.9-83.2)	57.8 (50.5-64.8)	65.0 (58.6-72.2)
LEO CReWE (MAIC Weighted)	167 (160)	73.0 (65.3-79.5)	52.9 (44.8-60.7)	59.5 (51.0-69.3)
GO29781 (trial results)	90 (90)	80.0 (70.3-87.7)	60.0 (49.1-70.2)	57.7 (46.9-68.4)
ORR=overall response rate; CR=complete response; PFS12=progression free survival at 12 months				

Maurer et al. *Haematologica*, 2023

POD24 in follicular lymphoma: time to be “wise”

John P. Leonard

“A clever person solves a problem. A wise person avoids it.”
—ATTRIBUTED TO ALBERT EINSTEIN



Leonard. *Blood* 2022

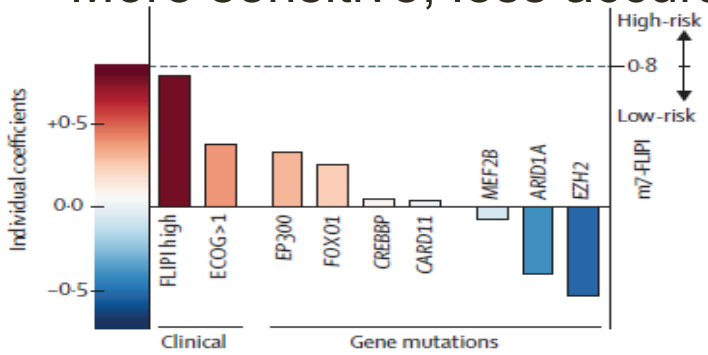
Clinicopathologic Models Identify Some Early Progressors

High risk m7-FLIPI

- 61% POD24
- 20% of patients **without** POD24 assigned high risk

POD24-PI

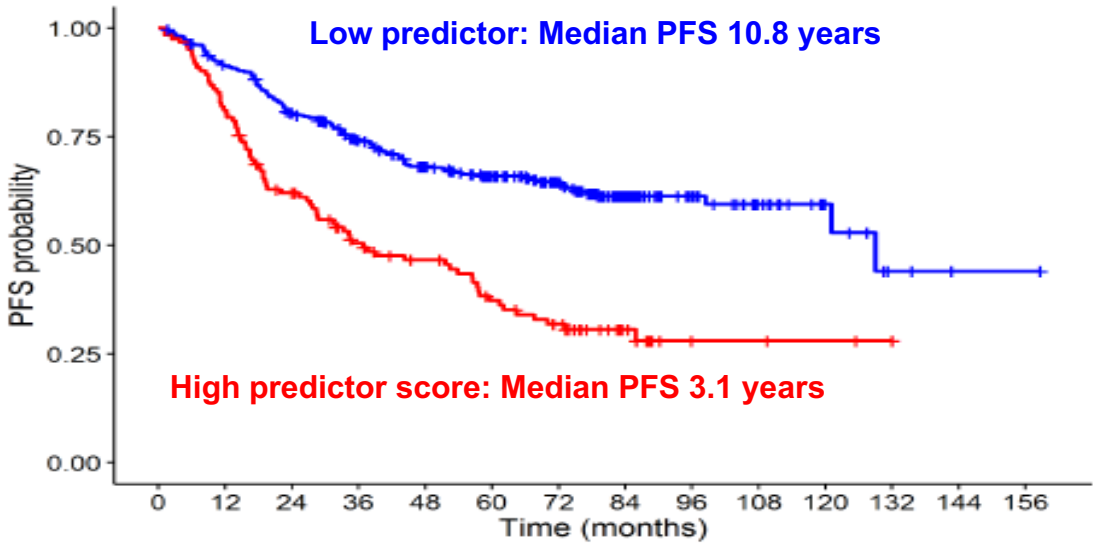
- Three m7FLIPI genes + clinical factors
- More sensitive, less accurate



Jurinovic et al. *Blood 2016*

Gene Expression Profiling

- PRIMA/Mayo/UI/Barcelona
- 23 gene signature predicts progression
- High predictor score, centroblast signature worse, enriched POD24



Huet et al, Lancet Oncology 2018

1L FL What's next? – FLIPI24

Aim: Develop a FL clinical prognostic index using early events as the primary endpoint

Harmonized individual pt data from >9,000 pts with FL from 11 international registries

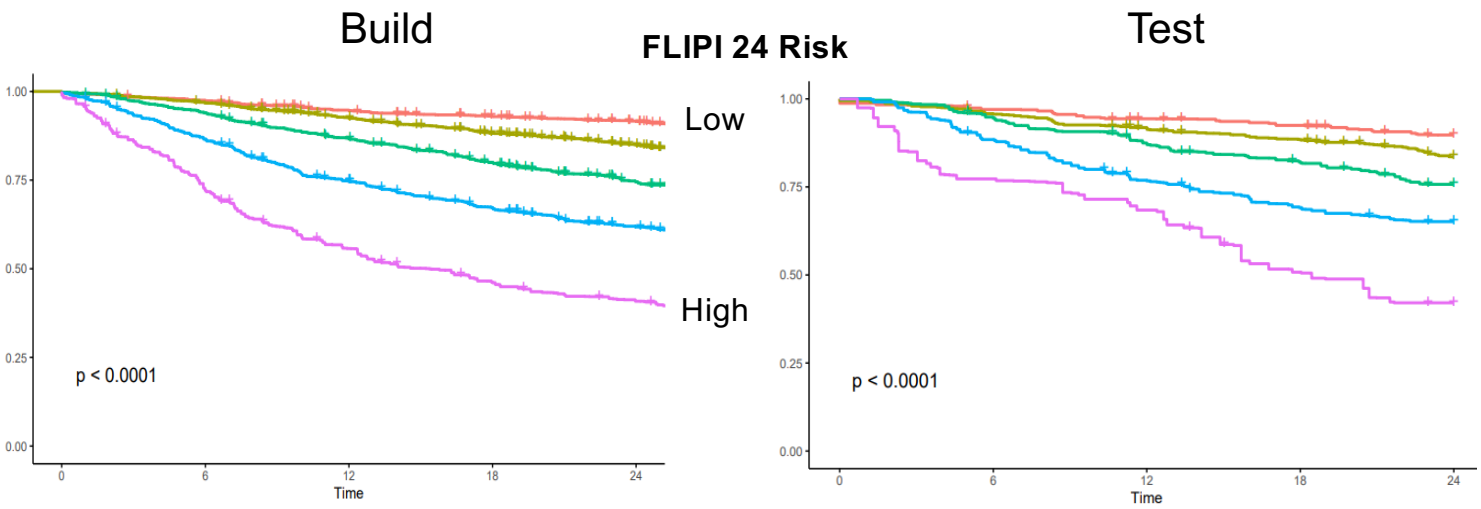
4743 1L FL pts Dx 2002-2018;vtreated with R-CHOP, B-R, R-CVP

- Model build on 80% (N=3793)
- Testing on 20% (N=950)

Final Model

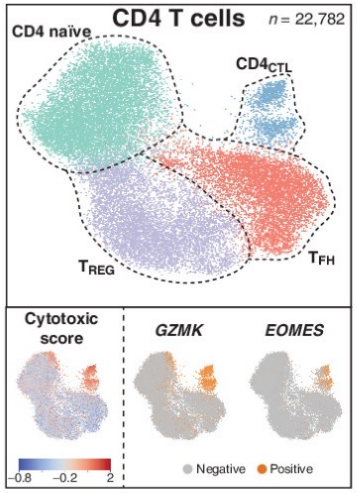
Variable	Input Range	Effect
Age	18-90	Linear 60-90 Inflection at age 75
LDH/ULN	0.5-5	Linear
B2M	1-10	Linear
HGB	8-17	Linear
WBC	4-11	Linear

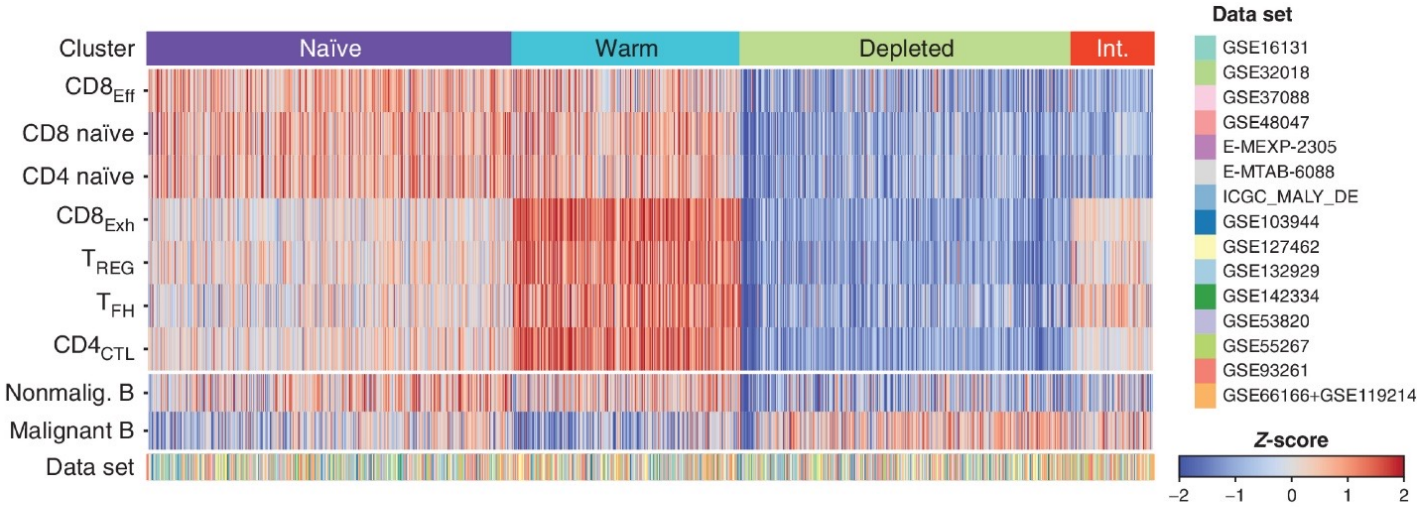
EFS Across Models

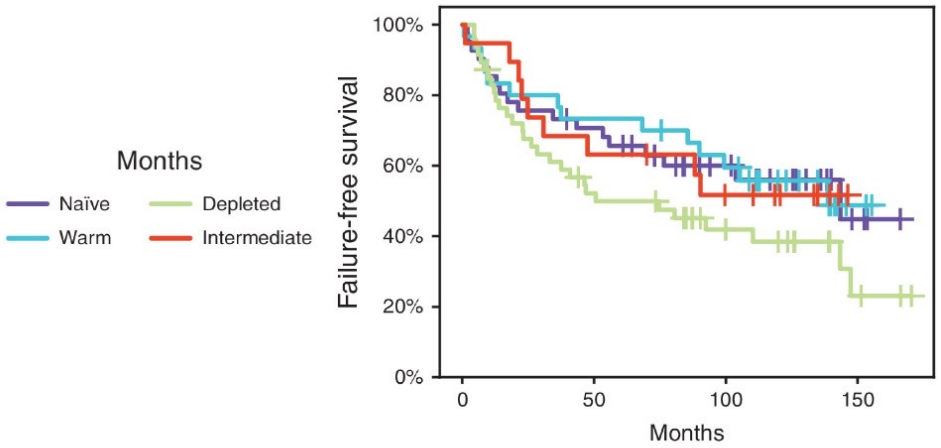


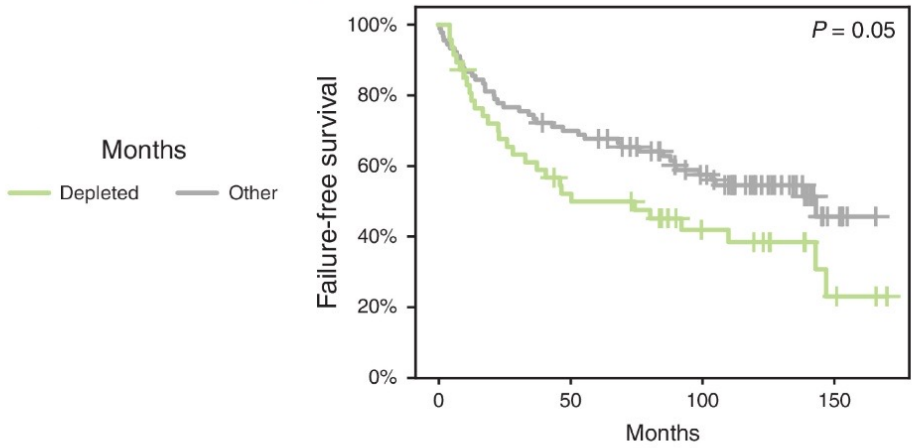
Maurer M, et al. *ASH Ann Meeting.* 2023

scRNASeq defines micrmoenvironment signature with distinct outcomes







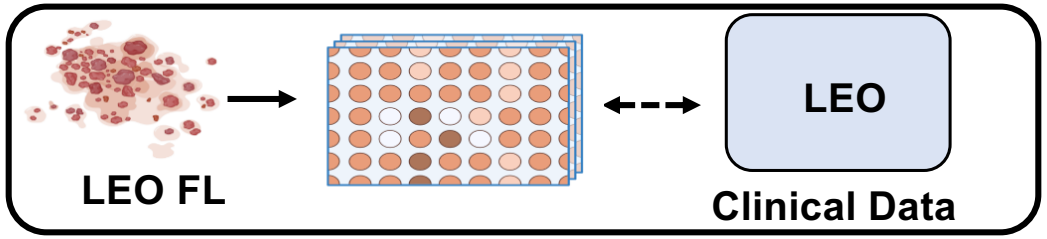


Han et al. *Blood Cancer Discov.* 2022

LEO Data/Tissue Repository Workflow

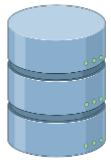
IRB Protocol: Clinical and Epidemiological Studies of Lymphoma

Matched normal +

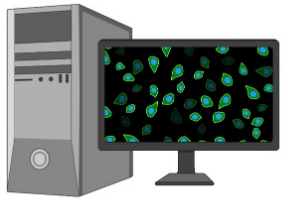


Clinical Case slides

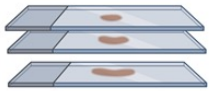
Integrated multiplex assay
- WES
- RNASeq



Data storage



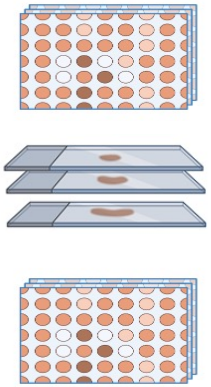
Imaging Informatics

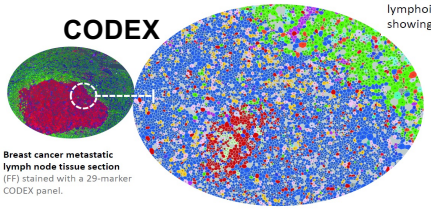


TMAs

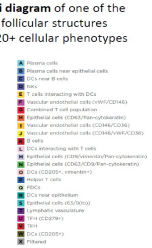
H&E IHC

Slide scanning



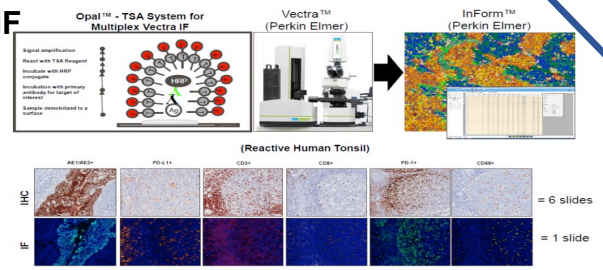


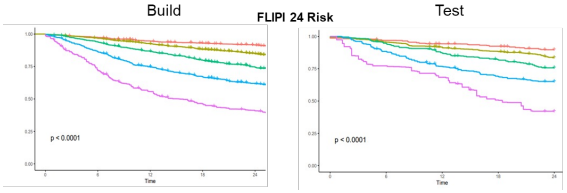
A Voronoi diagram of one of the lymphoid follicular structures showing 20+ cellular phenotypes



Special TMA & Special cuts

mIF





Conclusions

Many options for Early POD

Is there a role for BTK inhibitors?

- Would not use ibrutinib in R/R FL
- Zanubrutinib + Obinutuzumab recent FDA approval; awaiting MAHOGANY

Understanding patterns of failure

- When will we have a new frontline approach?
  - Risk stratified therapy
  - Randomized Trials
  - Biomarker directed therapy

Thank you!

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Nair
Neelapu
Al Zaki

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Chihara
Flowers
Nze
Strati
Rodriguez

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Green Lab: Yang; Li; Yu Liu
Wang Lab: Jiang; Yao; Nie; Heng-Huan Lee; Ying-Nai Wang; Yang Liu; Wei Wang
Flowers Lab: Balakrishnan; Davis; Hildebrandt

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Christopher Flowers, MD, MS, FASCO

Division Head
Chair, Professor

Division of Cancer Medicine
Department of Lymphoma/Myeloma

Contact: crflowers@mdanderson.org

Question 1

62 year old man with FL initially treated R-CHOP (at age 60) then experienced progression in 1.5 years and he is now experiencing persistent fevers and pain at the site of an enlarged left neck LN 4.5 cm and abdominal discomfort.

- Noted to have multiple enlarged LN with the largest being a 5.7 x 6.9 cm conglomerate mesenteric mass.
- PET/CT showed SUV_{max} 7.
- LDH normal. Hgb 9.6 Plts Normal
- Biopsy shows FL

What management strategy would you consider next?

A. Rituximab
B. Ibrutinib
C. R-dose adjusted EPOCH
D. R-GemOx followed by Autologous transplantation

Question 2

Which of the following is a clinical trial focused on patients with FL with POD24?

A. ROSEWOOD
B. MAHOGANY
C. ZUMA-5
D. ZUMA-22
E. SWOG S0016