Prognostication for Follicular Lymphoma in 2026

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Disclosures

- Consultancy and honoraria: AbbVie, BMS, Genentech/Roche, Genmab, Incyte
- Research funding: Genentech, Genmab, Gilead, Lymphoma Research Foundation
- Leadership: American Society of Hematology, Lymphoma Research Foundation

The Paradox of Follicular Lymphoma in 2026

- Most patients have OS comparable to age-matched population
- 15–20% experience POD24
- FLIPI high-risk ≠ POD24 (30% never progress early)
- FLIPI low-risk ≠ safe (20% experience POD24)
- Instruments designed for a disease that no longer exists at the same scale of lethality; insensitive at capturing high risk

Jóna et al. Diagnostics 2025

Three Destinies Define Follicular Lymphoma

~20%

POD24

Progression within 24 months of 1L therapy

5-yr OS: 29–54%
vs ~90% in non-POD24
Drives ~80% of lymphoma mortality

~15%

Transformation

Histologic transformation to DLBCL over lifetime

5-yr OS post-tFL: ~40%
Majority of remaining lymphoma deaths in FL

~42%

Functional Cure

OS comparable to age-matched general population after EFS24

S0016: 15-yr follow-up
No excess lymphoma mortality after landmark

Casulo et al. *Jour Clin Oncol* 2015; Casulo et al. *Blood* 2022, Wästerlid et al. *eJHaem* 2024, Trotman and Falconer, *Hematology* ASH 2024; Shadman et al. *JAMA Oncol* 2026

Old, New and Emerging Tools

- Next-generation clinical scoring: FLIPI24, FLIPI-C
- Biological / genomic prognostication: m7-FLIPI, FOXO1, gene signatures
- Liquid biopsy and MRD
- Imaging: TMTV, radiomics
- Predicting transformation risk?

Current Clinical Prognostic Calculators: low vs. high

	FLIPI[1,2]	FLIPI2[3–5]	PRIMA PI[6]	M7-FLIPI[7]
Components	Age, stage, hemoglobin, LDH, nodal sites	β2M, diameter lymph node, BMI, hemoglobin, age	β2M, BMI	FLIPI, ECOG PS, mutation status of seven genes
5 yr OS by risk group	Low: 91% High: 53%	Low: 96% High: 67%	Low: 93% High: 81%	Low: 84–90% High: 42–65%

	FLEX score[8]	POD24-PI[2]
Components	Male sex, sum of lesion dimension, Grade 3a, extranodal sites, ECOG PS, hemoglobin, β2M, NK cell count, LDH	High-risk FLIPI, mutation status of three genes
5 yr OS by risk group	Low: 97% (3-year) High: 87% (3-year)	Low: 89–91% High: 48–71%

Don't guide treatment selection!

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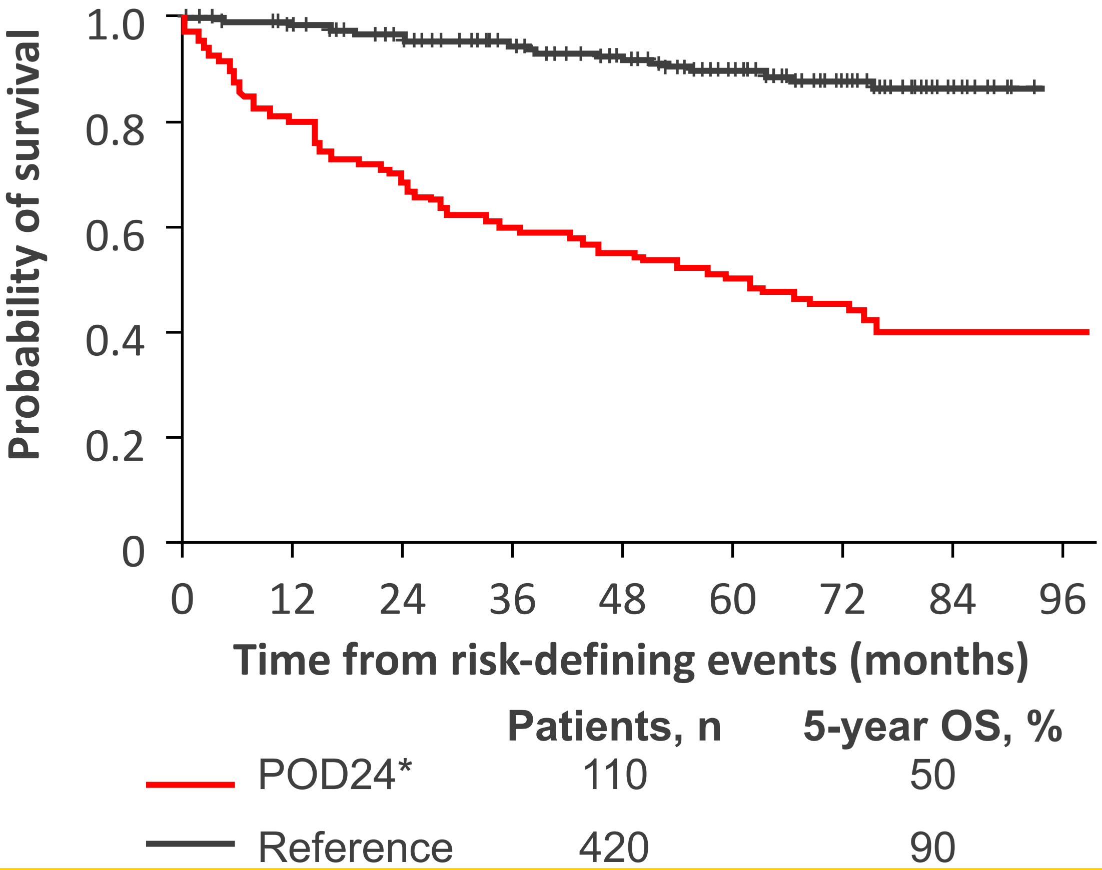
1. Solal-Céligny P, et al. Blood 2004;104:1258–65; 2. Jurinovic V, et al. Blood 2016;128:1112–20;
3. Terol MJ, et al. Blood 2010;116:3128; 4. Rodríguez-Sevilla JJ, et al. Blood Adv 2023;7:1606–14;
5. Federico M, et al. J Clin Oncol 2009;27:4555–62; 6. Bachy E, et al. Blood 2018;132:49–58;
7. Pastore A, et al. Lancet Oncol 2015;16:1111–22; 8. Mir F, et al. Am J Hematol 2020;95:1503–10;
9. Casulo C, et al. ASH 2023; Abstract (abstract #1657);

Narrowing Focus to Predict Who Will Have Early Progression Given Unmet Need

OS according to POD24* (N=588)



	Patients, n	5-year OS, %
🟥 POD24*	110	50
▬ Reference	420	90

POD24

- 15% to 20% after 1L
- High risk of transformation (30-70%)
- FL histology still does worse
- Chemorefractoriness
- Rapidly gets to 3L+ of therapy

Casulo et al. *Jour Clin Oncol* 2015

FLIPI24: Finally Asking The Right Question?

Clinical Prediction Model Built for EFS24

- Developed and internally validated to predict 24-month event rates
- Captures POD24, transformation, death in one pre-treatment metric

Validated across 10 cohorts, N = 4,485

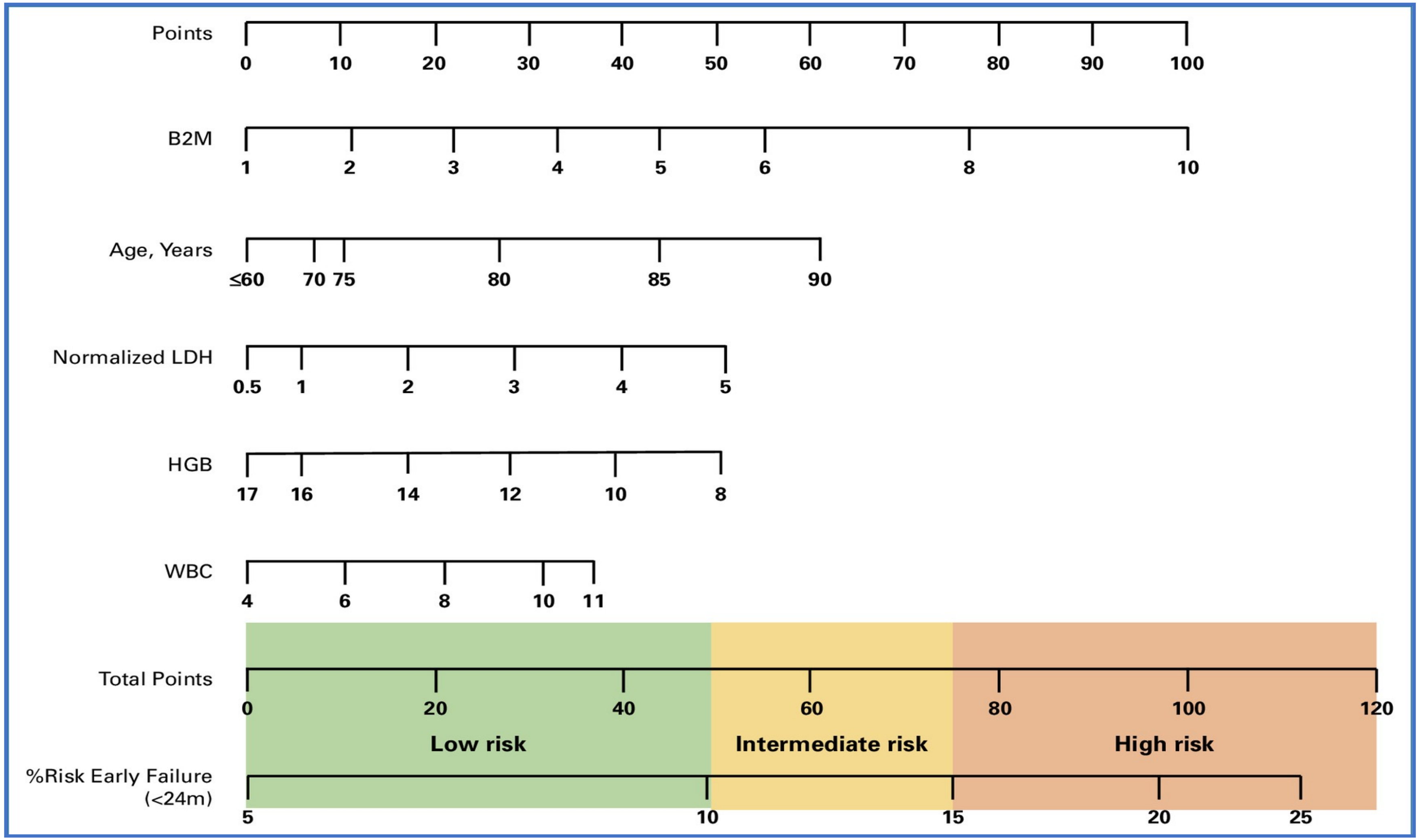
- Any 1L chemoimmunotherapy (some R maintenance)

Outperforms FLIPI, FLIPI2, PRIMA-PI

- For EFS24, OS

Maurer et al. *Jour Clin Oncol* 2026

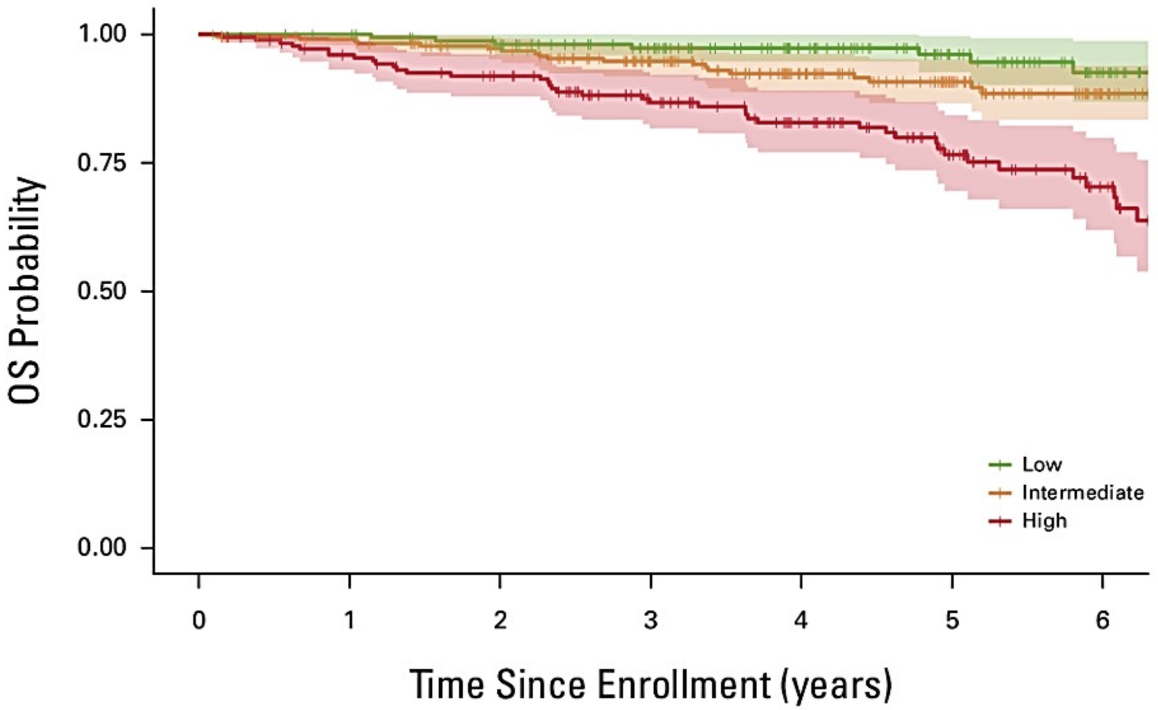
FLIPI24 Nomogram Estimates Early Event Probability



https://qxmd.com/calculate/calculator_865/flipi24?buildpack=medscape

Corresponding 5-year Survival Based on FLIPI24 Risk Score

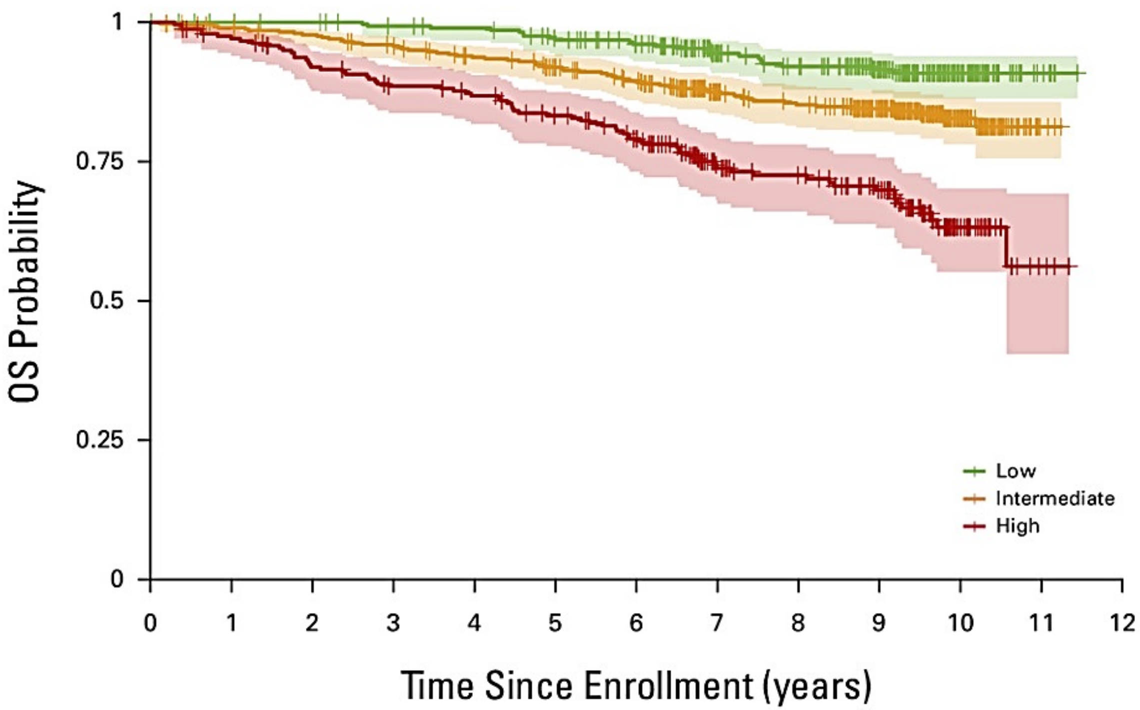
Original LEO Cohort



Number at risk (number censored)

	0	1	2	3	4	5	6
Low	160 (0)	157 (3)	149 (8)	130 (26)	98 (58)	66 (89)	36 (117)
Intermediate	226 (0)	218 (6)	200 (20)	170 (45)	129 (82)	88 (121)	45 (162)
High	179 (0)	165 (7)	152 (13)	120 (37)	96 (56)	63 (83)	37 (105)

PRIMA Validation Cohort



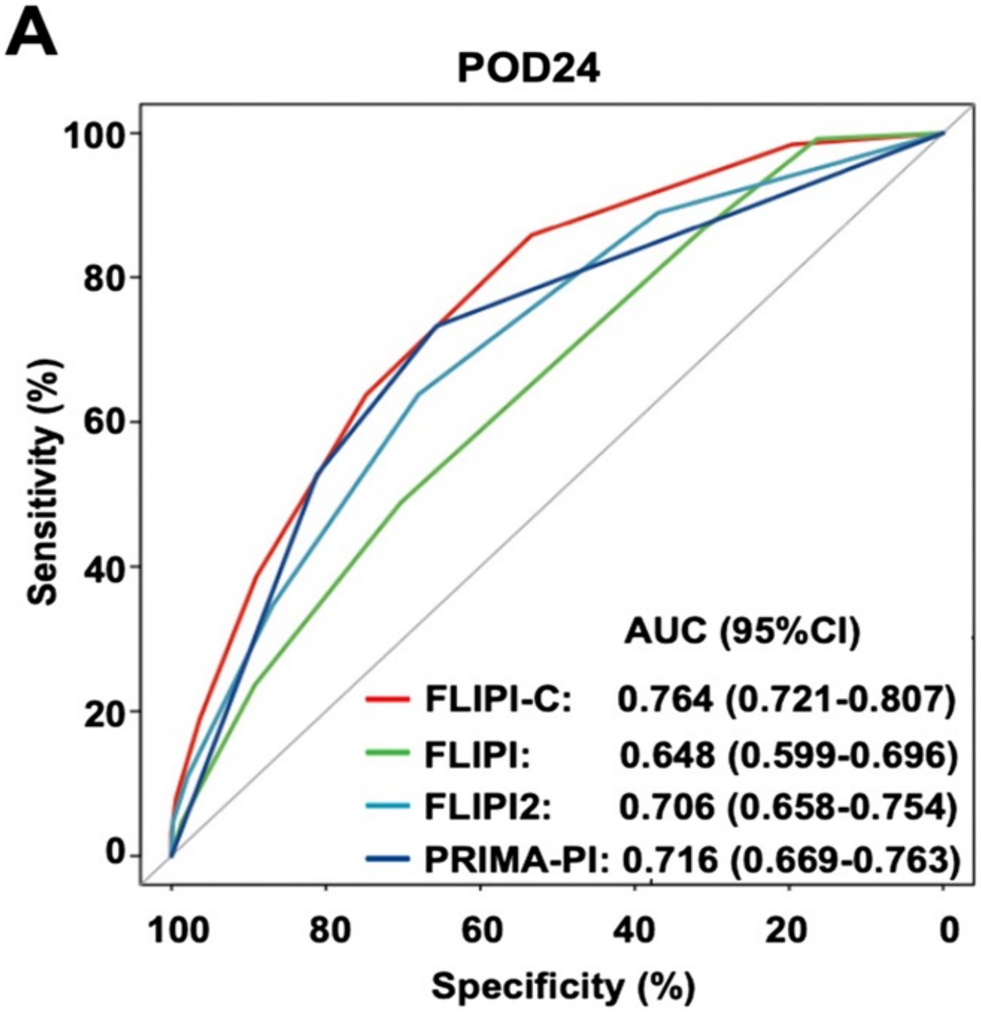
Number at risk (number censored)

	0	1	2	3	4	5	6	7	8	9	10	11	12
Low	294 (0)	290 (4)	288 (6)	282 (10)	279 (12)	268 (17)	256 (27)	210 (69)	193 (81)	156 (117)	60 (212)	7 (265)	0 (272)
Intermediate	406 (0)	397 (5)	390 (7)	379 (10)	364 (17)	349 (25)	332 (33)	272 (86)	257 (94)	219 (130)	83 (263)	3 (342)	0 (345)
High	242 (0)	231 (4)	215 (8)	204 (11)	198 (13)	185 (18)	167 (27)	124 (60)	114 (68)	96 (82)	31 (140)	3 (167)	0 (170)

🟩 Low-risk 96%-97% 🟧 Intermediate-risk 91%-92% 🟥 High-risk 77%-83%

FLIPI-C: Using AI For Prognostication

- Machine learning-based model to predict POD24 using AI algorithms
- 17 Chinese centers across 20 years, N= 1,938, external validation GALLIUM (N=1,145)
- Outperformed FLIPI, FLIPI2, PRIMA-PI, and FLEX



Zha et al. *Bioinfor Res* 2025

Old, New and Emerging Tools

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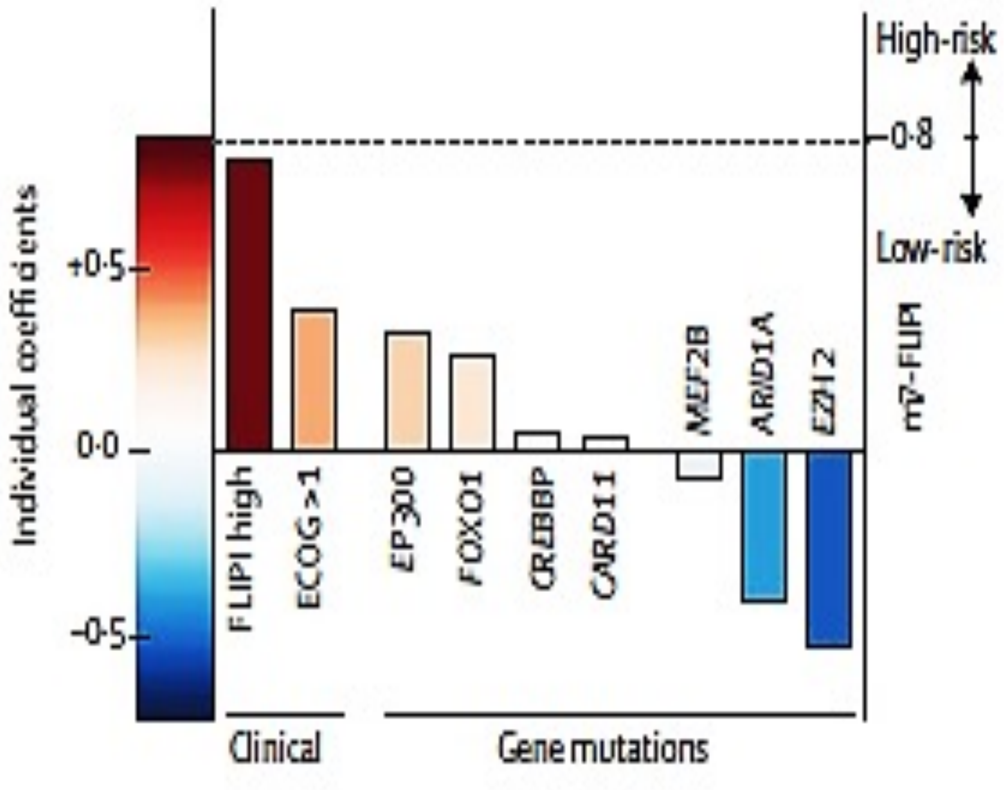
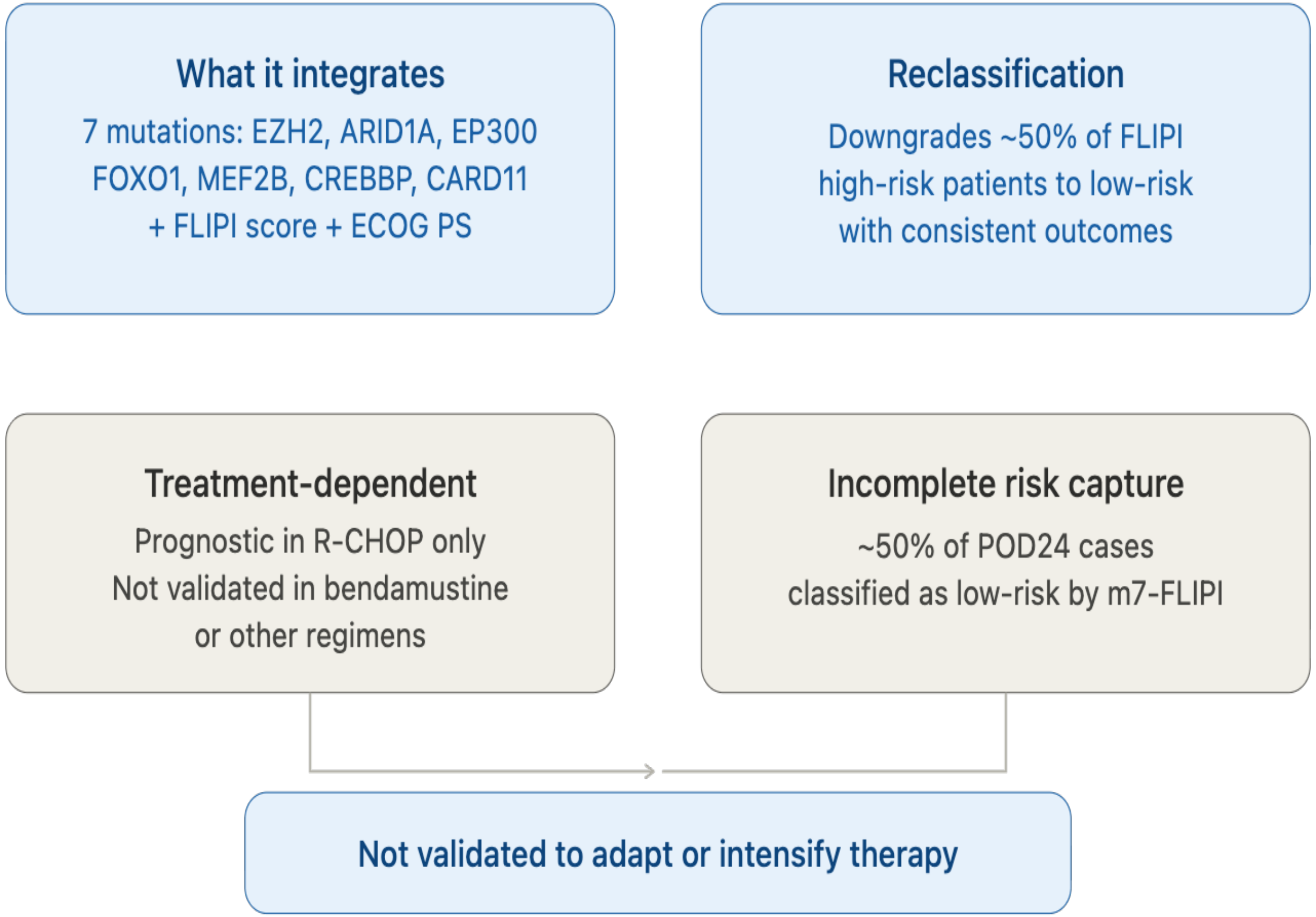
Biologic Classifiers: Promises and Limitations of m7FLIPI





What it integrates

7 mutations: EZH2, ARID1A, EP300
FOXO1, MEF2B, CREBBP, CARD11
+ FLIPI score + ECOG PS

Reclassification

Downgrades ~50% of FLIPI
high-risk patients to low-risk
with consistent outcomes

Treatment-dependent

Prognostic in R-CHOP only
Not validated in bendamustine
or other regimens

Incomplete risk capture

~50% of POD24 cases
classified as low-risk by m7-FLIPI

Not validated to adapt or intensify therapy

🟦 strengths ▨ limitations

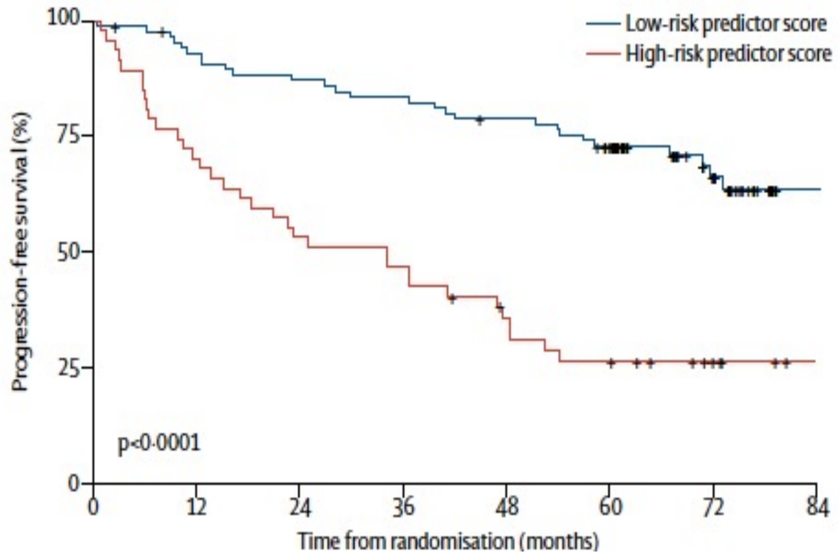
Pastore et al. *Lancet Oncol* 2015; Bantilan and Zelenetz *ASH* 2023

FOXO1 mutation independently predicts shorter PFS, OS after adjusting for FLIPI, ECOG

Gene Expression Signatures in FL Predict Outcome But Depend on Treatment

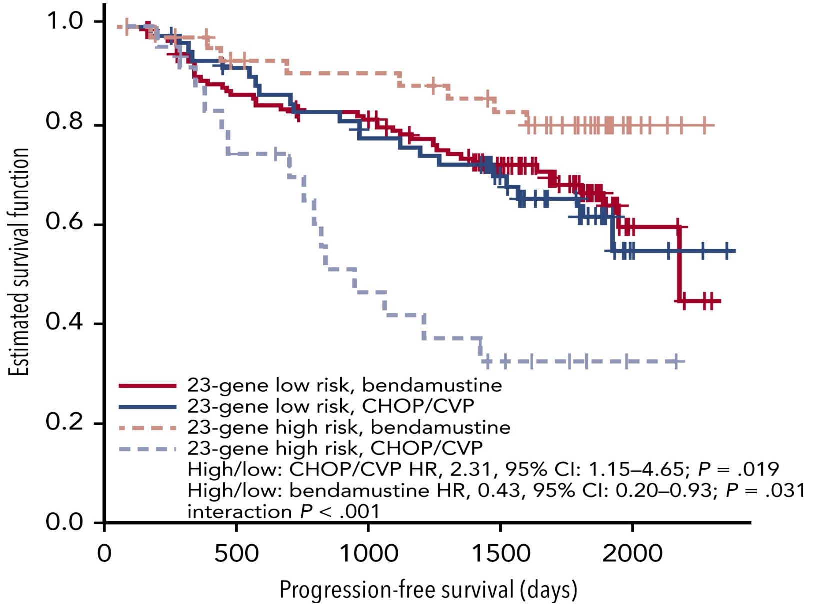
23-gene score in PRIMA trial

- Fresh-frozen tumor biopsies from 149 patients
- Independently predicts PFS
- High-risk patients 3.7× greater risk of progression vs. low-risk (HR 3.68)



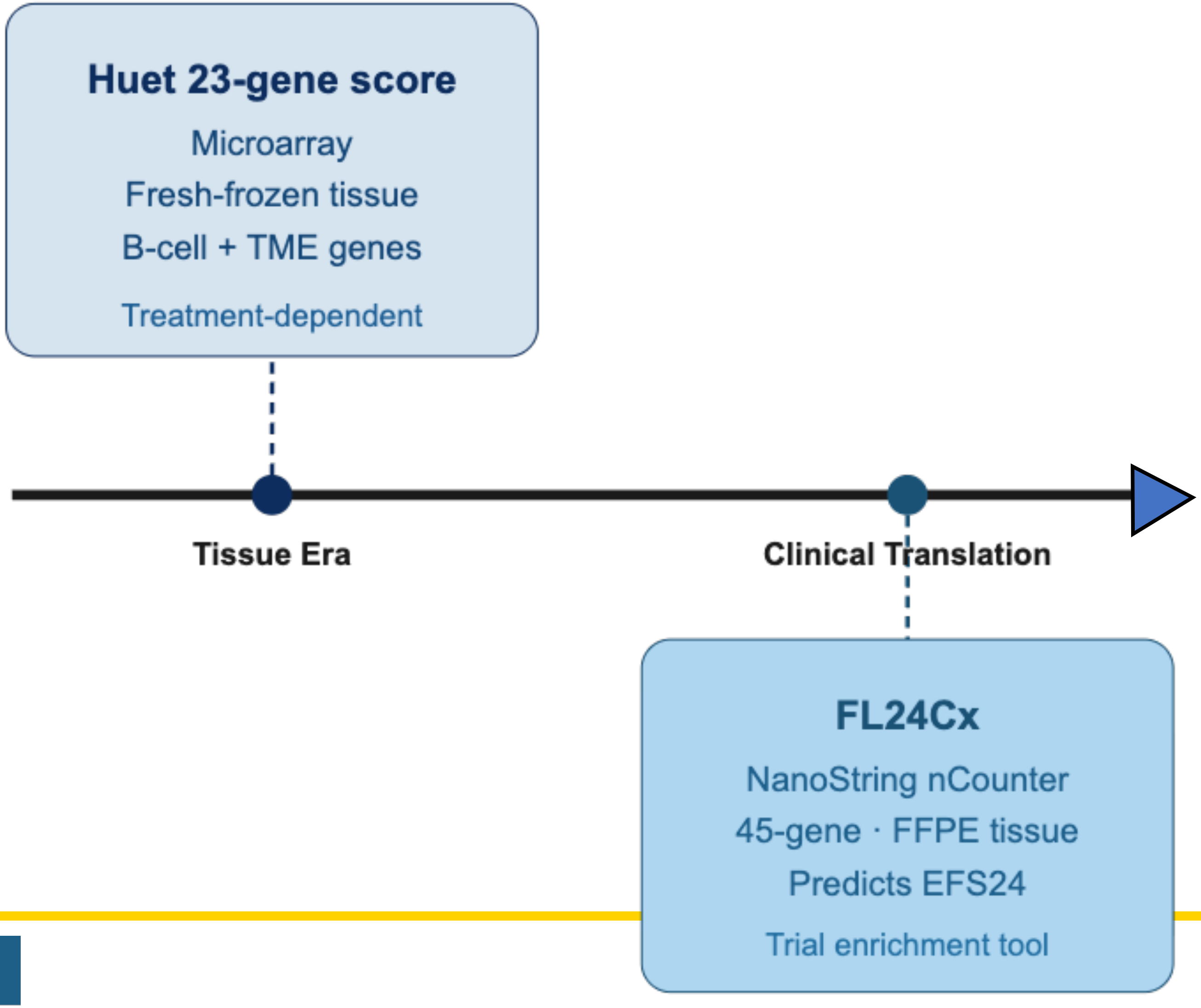
23-gene score in GALLIUM trial

- Performance validated in 274 patients
- Does not hold with Bendamustine treatment
- ~50% of gene interactions treatment-dependent



Huet et al. *Lancet Oncol* 2018 Bolen et al. *Blood* 2021

Moving From Fresh Tissue to FFPE For Clinical Use



Huet 23-gene score

Microarray

Fresh-frozen tissue

B-cell + TME genes

Treatment-dependent

Tissue Era

Clinical Translation

FL24Cx

NanoString nCounter

45-gene · FFPE tissue

Predicts EFS24

Trial enrichment tool

Gene Expression Signature To Identify POD24

FL24Cx

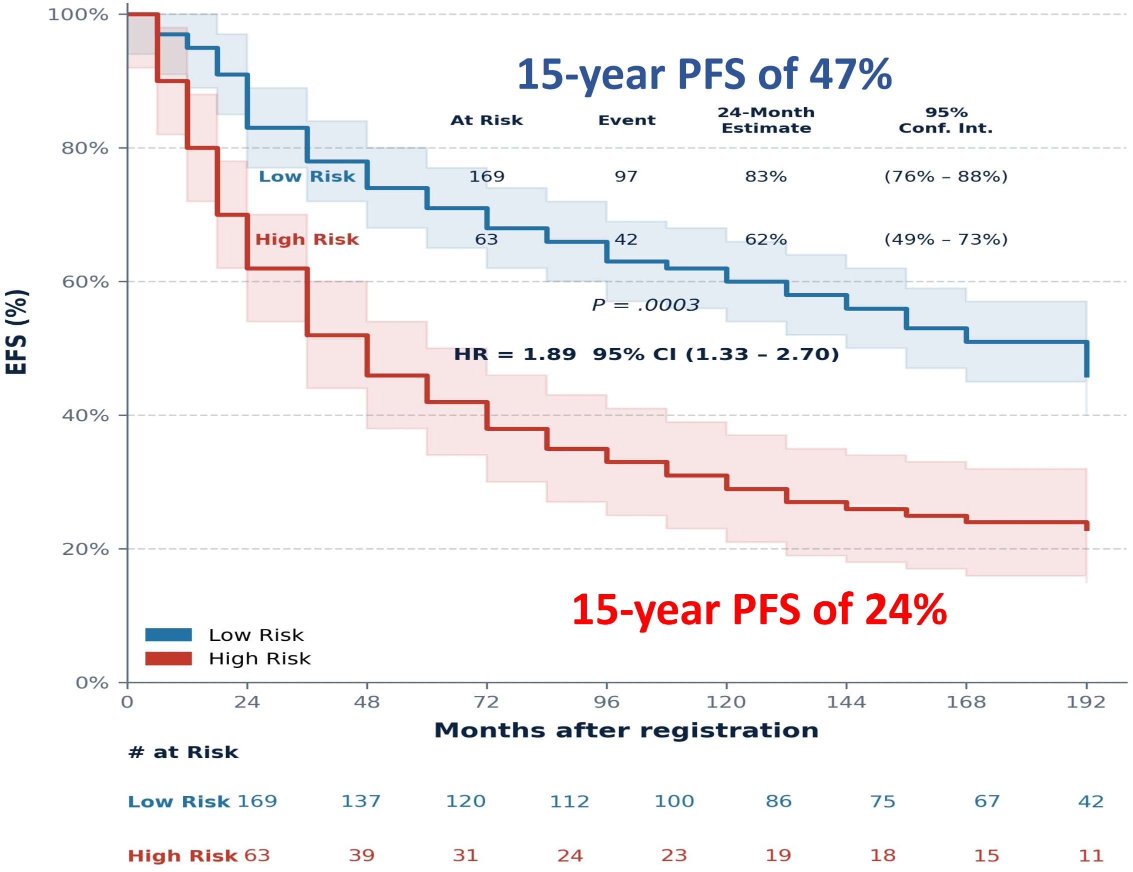
- 45-gene expression assay using FFPE
- NanoString platform
- Patients from PRIMA, multiple registries
- Logistic regression model predicting EFS24

Built on Prior Signatures

- Incorporated IR1+ IR2 immune response gene sets[1]
- Extended and refined the 23-gene framework
- Validated in SWOG S0016 (n=232)
- R-CHOP, chemoimmunotherapy treatment

Outcomes

- High and low risk of POD24 gene signature
- Risk of POD24 twice as high in high-risk group
- Not validated to guide therapy adaptation



15-year PFS of 47%

	At Risk	Event	24-Month Estimate	95% Conf. Int.
Low Risk	169	97	83%	(76% – 88%)
High Risk	63	42	62%	(49% – 73%)

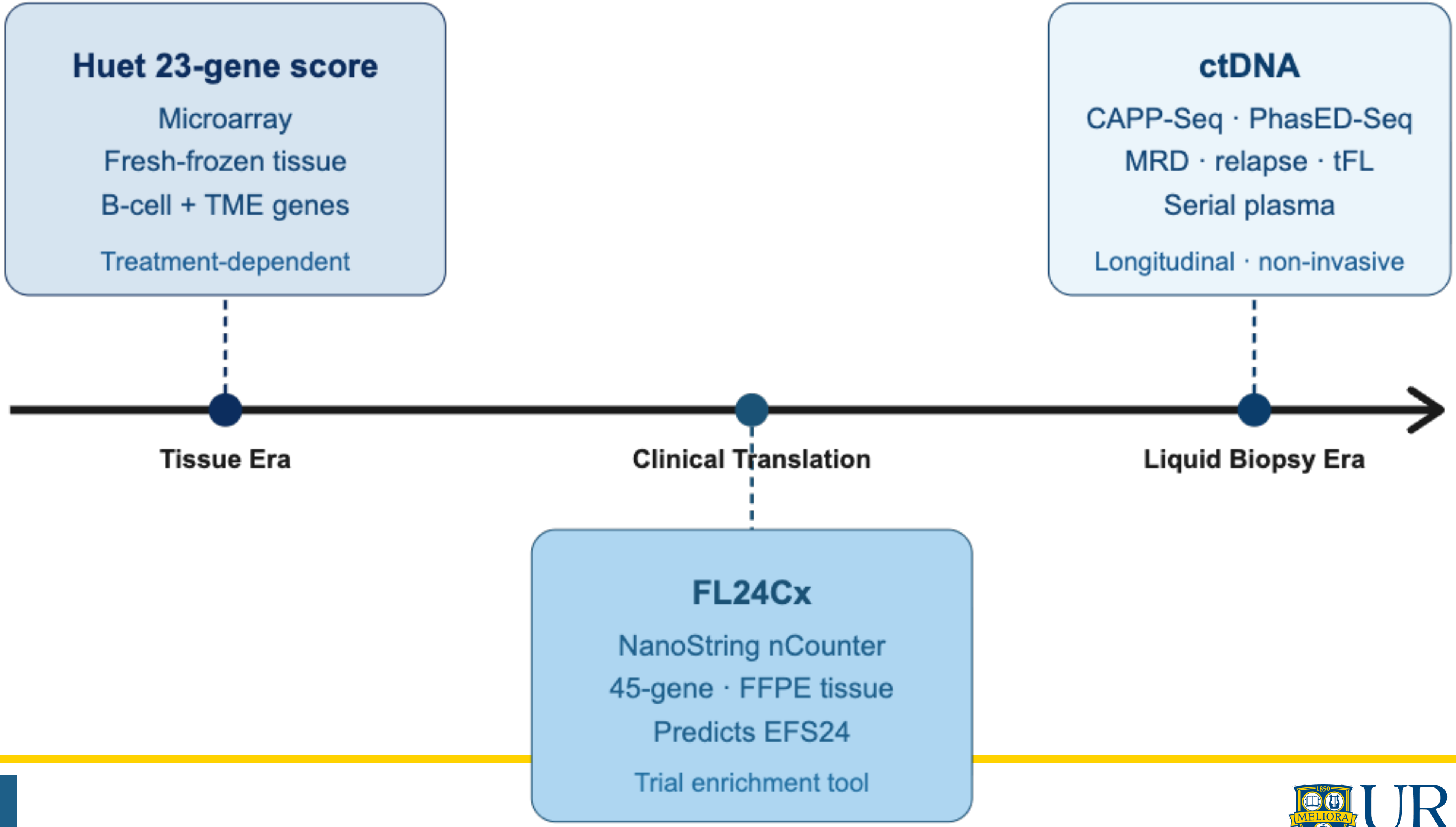
15-year PFS of 24%

 # at Risk

	0	24	48	72	96	120	144	168	192
Low Risk	169	137	120	112	100	86	75	67	42
High Risk	63	39	31	24	23	19	18	15	11

Ramsower et al. *Blood Adv* 2025
Dave et al. *NEJM* 2004

Moving From Fresh Tissue to Blood Based Markers



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Predicts EFS24

Trial enrichment tool

Liquid Biopsy Era

ctDNA

CAPP-Seq · PhasED-Seq

MRD · relapse · tFL

Serial plasma

Longitudinal · non-invasive

MRD Assessment: A Powerful Prognostic Signal in FL

- Longitudinal, non-invasive
- Baseline prognostication, early treatment resistance, disease kinetics, monitor disease burden and clonal evolution

PCR and Flow Cytometry Assays

- PCR primers for *IGH:BCL2*
- Cannot be identified in up to 50% of FL

Cell free DNA (cfDNA)

- DNA released during apoptosis
- Lymphoma derived: ctDNA
- Low in FL

NGS Based

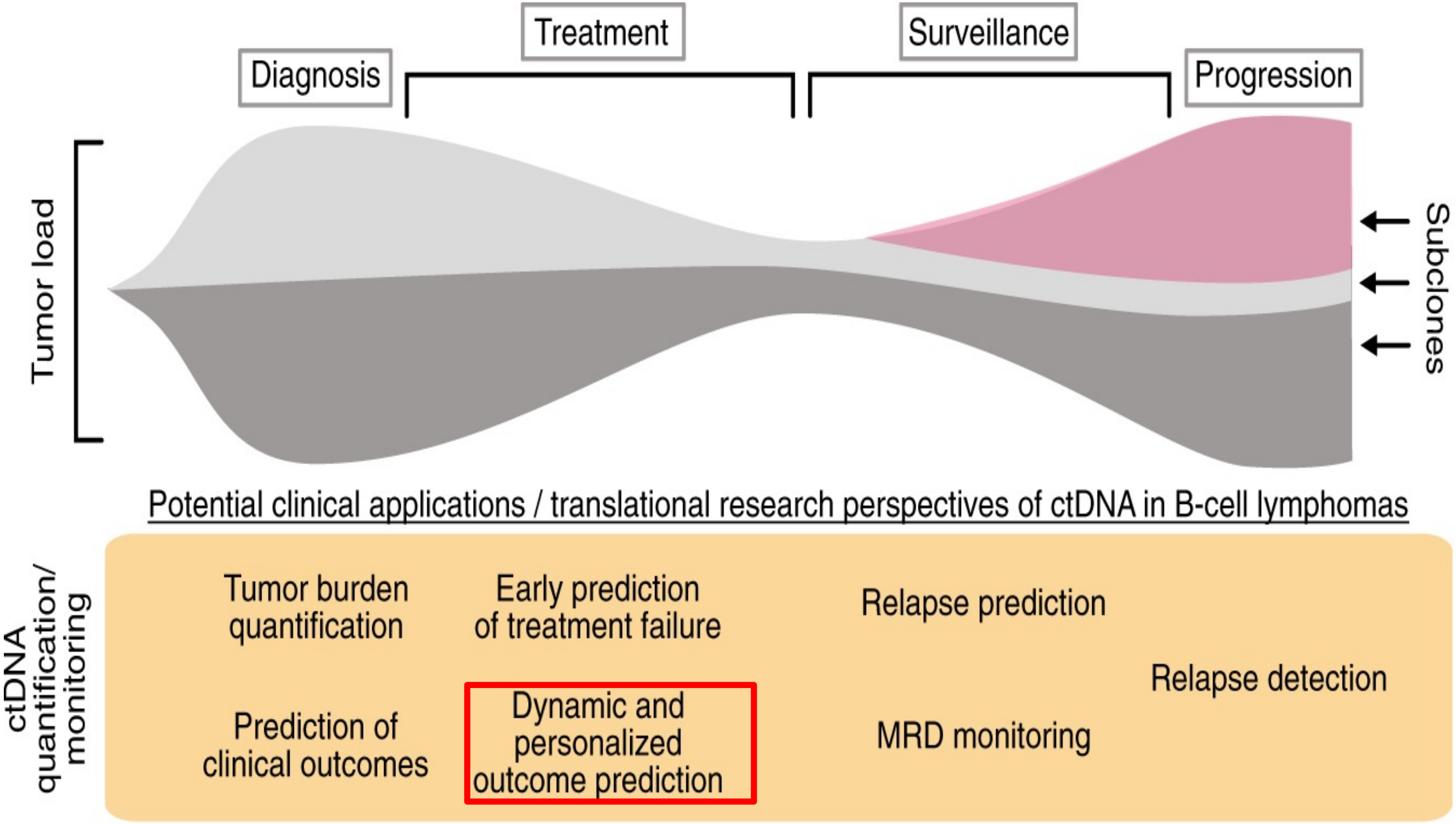
CAPP Seq

- Tracks individual single nucleotide variants (SNVs)
- Background error rate 10^{-4}

PhasED Seq

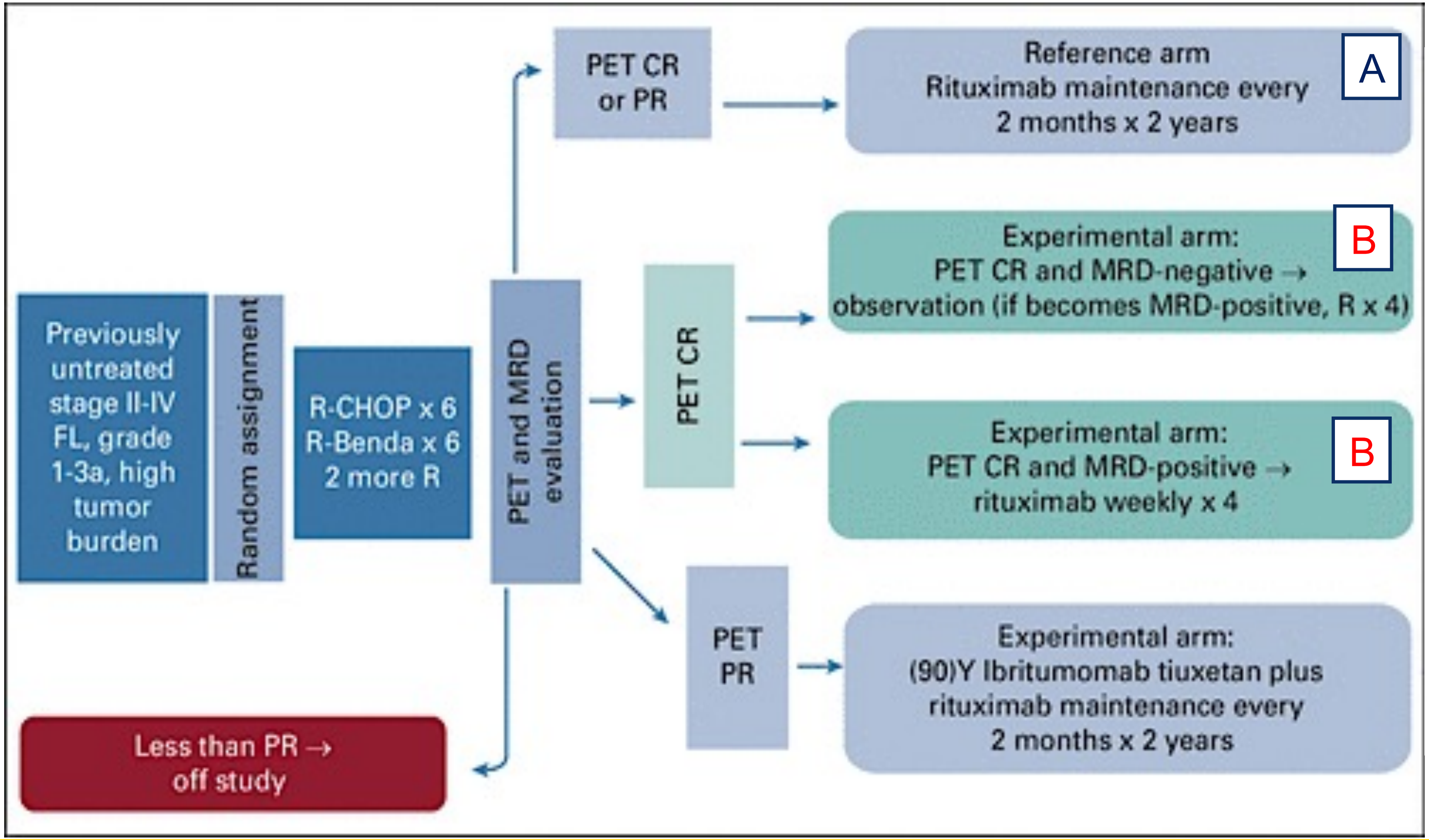
- Tracks multiple somatic mutations on same DNA
- Background error rate 10^{-7}

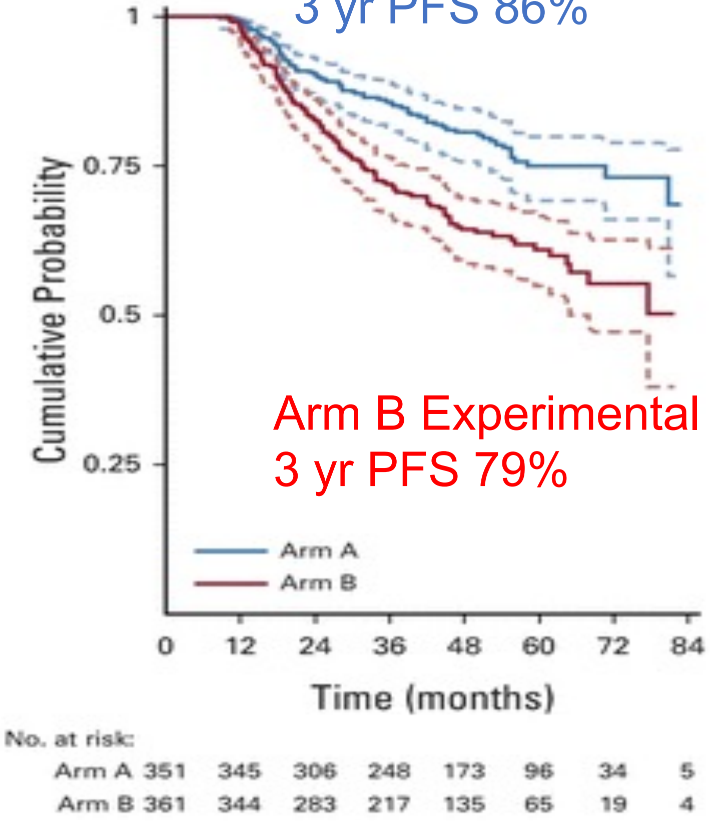
Potential Applications of MRD/ctDNA in FL



Lauer et al.
Leukemia 2022

Can you Response-Adapt Treatment Based on MRD at End of Therapy? FOLL 12 Study





Arm A Maintenance
3 yr PFS 86%

Arm B Experimental
3 yr PFS 79%

Luminari et al. *Jour Clin Oncol* 2022
Casulo *Jour Clin Oncol* 2022

Old, New and Emerging Tools

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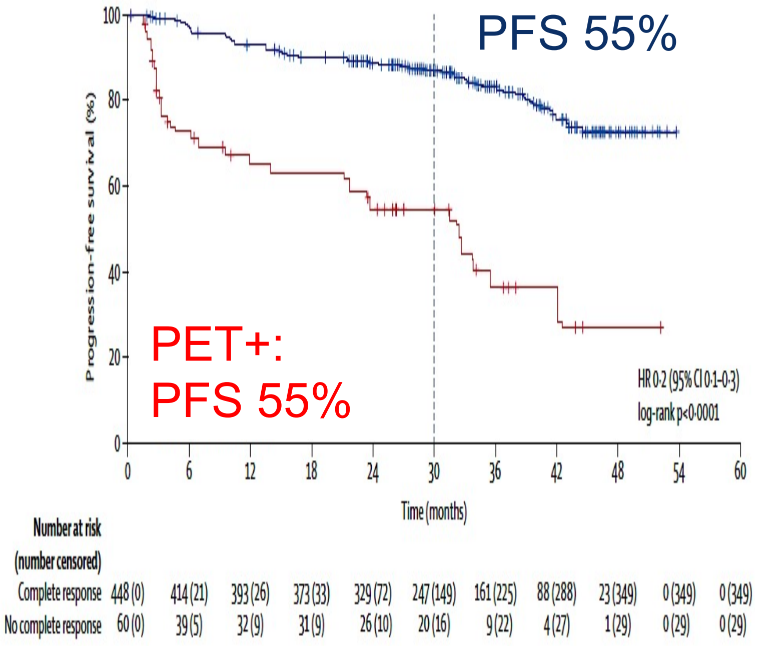
Using PET as Platform to Identify High Risk Groups

Positive End Treatment PET

Inferior PFS, OS, in GALLIUM



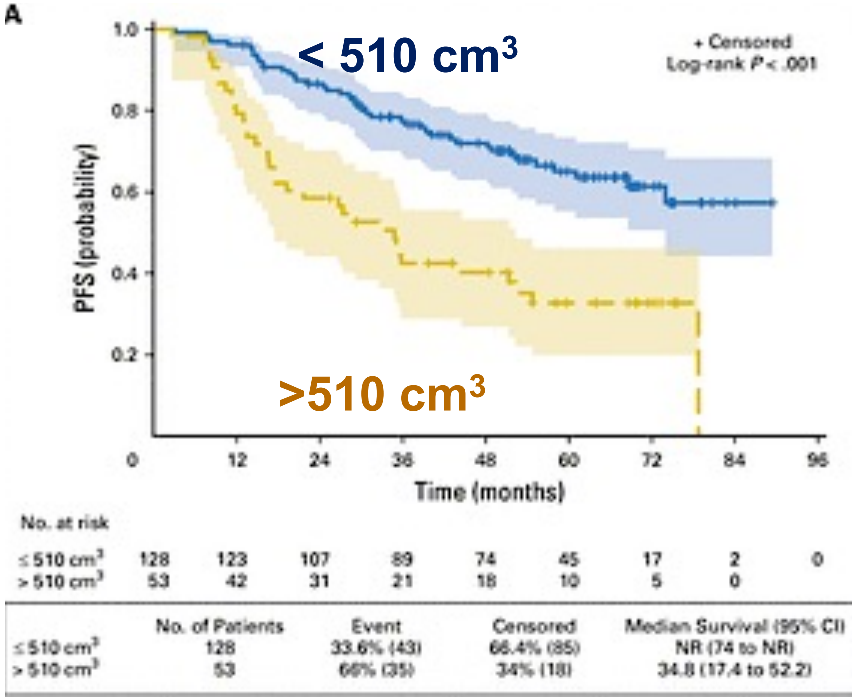
PET-
PFS 55%

PET+:
PFS 55%

Number at risk (number censored)	0	6	12	18	24	30	36	42	48	54	60
Complete response	448 (0)	414 (21)	393 (26)	373 (33)	329 (72)	247 (149)	161 (225)	88 (288)	23 (349)	0 (349)	0 (349)
No complete response	60 (0)	39 (5)	32 (9)	31 (9)	26 (10)	20 (16)	9 (22)	4 (27)	1 (29)	0 (29)	0 (29)

Total Metabolic Tumor Vol. (TMTV)

Identifies patients at risk for POD24, worse PFS



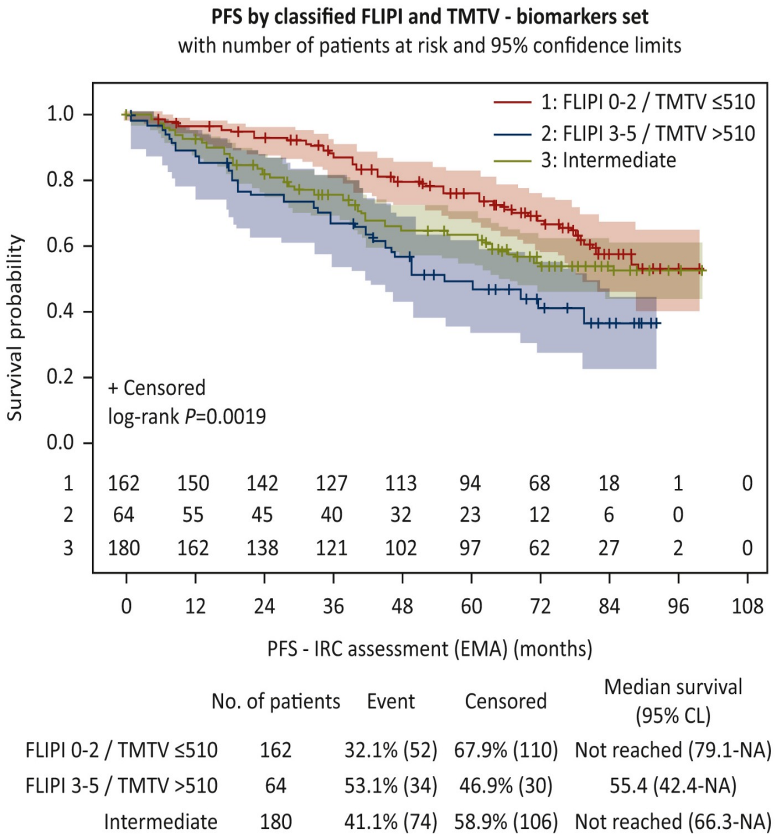
< 510 cm³

>510 cm³

No. at risk	0	12	24	36	48	60	72	84	96
≤ 510 cm³	128	123	107	89	74	45	17	2	0
> 510 cm³	53	42	31	21	18	10	5	0	

	No. of Patients	Event	Censored	Median Survival (95% CI)
≤ 510 cm³	128	33.6% (43)	66.4% (85)	NR (74 to NR)
> 510 cm³	53	66% (35)	34% (18)	34.8 (17.4 to 52.2)

TMTV + FLIPI


PFS by classified FLIPI and TMTV - biomarkers set
with number of patients at risk and 95% confidence limits

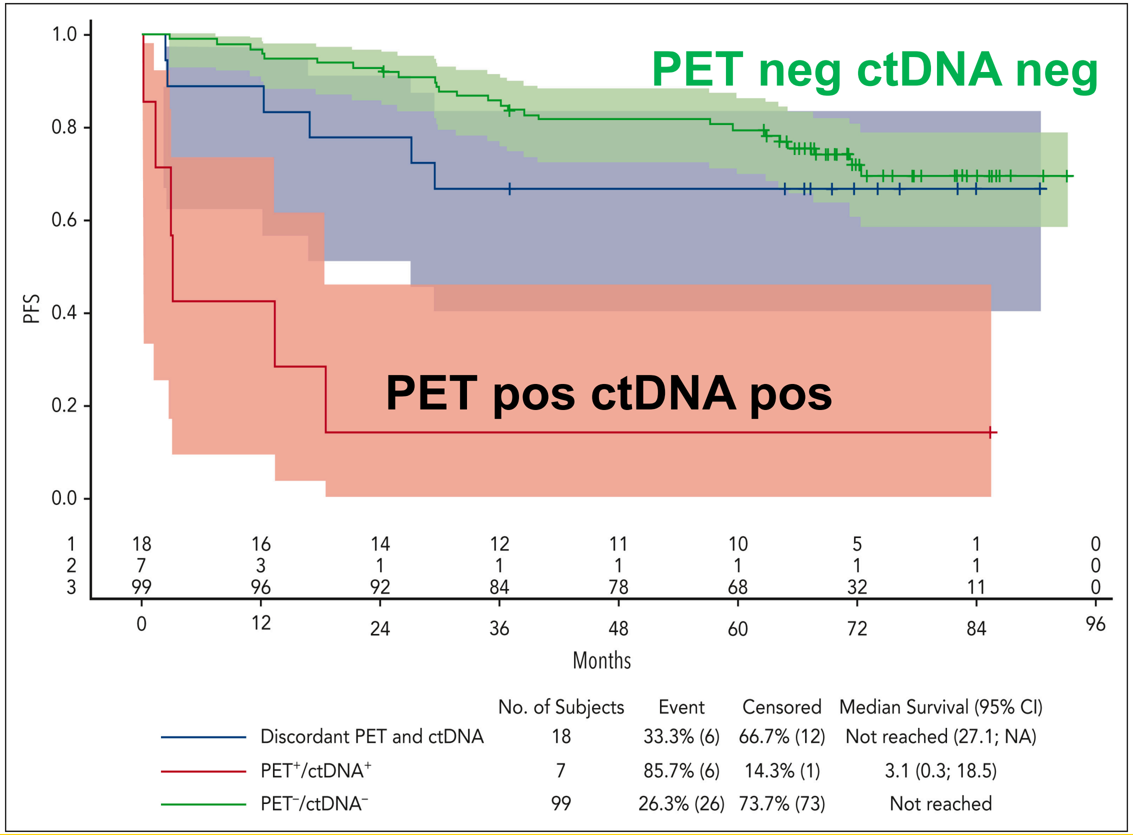
	0	12	24	36	48	60	72	84	96	108
1	162	150	142	127	113	94	68	18	1	0
2	64	55	45	40	32	23	12	6	0	0
3	180	162	138	121	102	97	62	27	2	0

	No. of patients	Event	Censored	Median survival (95% CL)
FLIPI 0-2 / TMTV ≤510	162	32.1% (52)	67.9% (110)	Not reached (79.1-NA)
FLIPI 3-5 / TMTV >510	64	53.1% (34)	46.9% (30)	55.4 (42.4-NA)
Intermediate	180	41.1% (74)	58.9% (106)	Not reached (66.3-NA)

Trotman et al. *Lancet Oncol 2018,* Claudel et al. *Blood* 2025

Can We Identify POD24 Patients Before Progression Using Combination of PET and ctDNA?

- RELEVANCE Trial R-chemo vs. R^2, 124 patients with PET/ctDNA images and paired serum



12% of patients had POD24

Marker	PPV POD24	NPV POD24	Median PFS neg vs pos
ctDNA alone	58%	>90%	NR vs. 17.7 mos (p=0.0038)
PET alone	45%	>90%	NR vs. 28.3 mos (p=0.002)
Combined (+)	86%	>90%	

Claudel et al. *Blood* 2025

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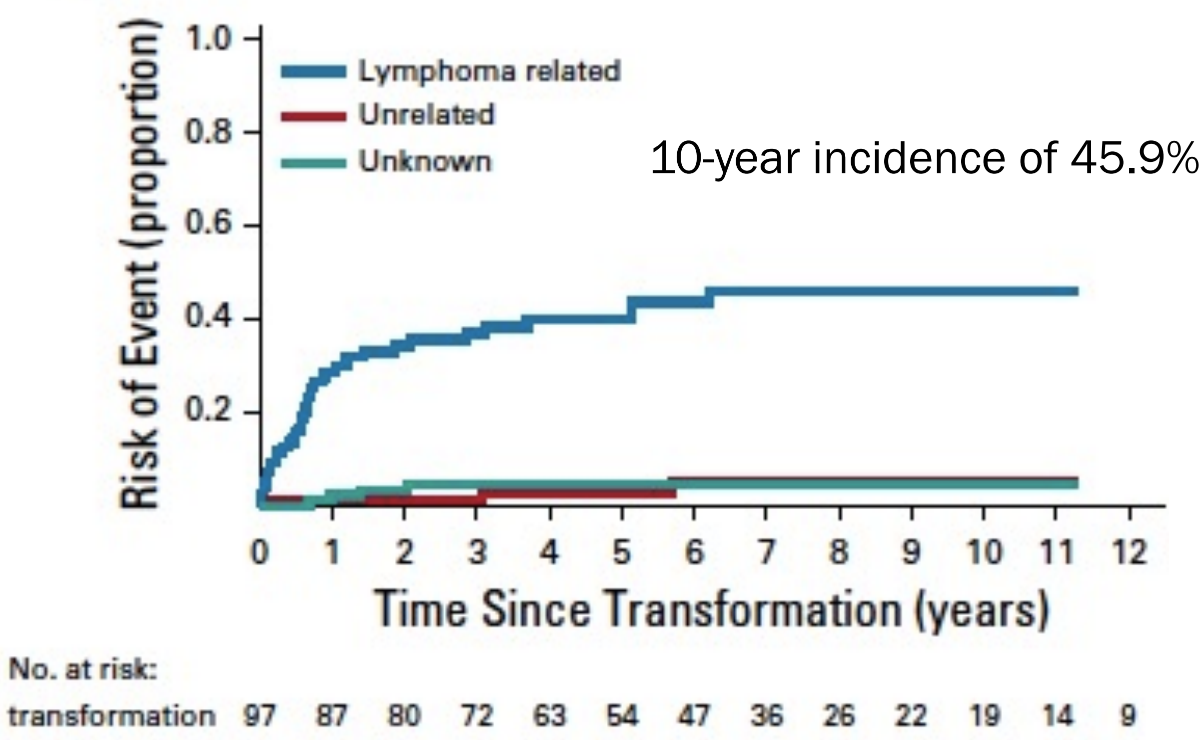
Predicting Histologic Transformation

Factors
High risk FLIPI
Elevated LDH
Grade 3a histology
Poor PS
B symptoms
Use of rituximab?
Prior therapy?
Time from diagnosis

Mortality Following Transformation

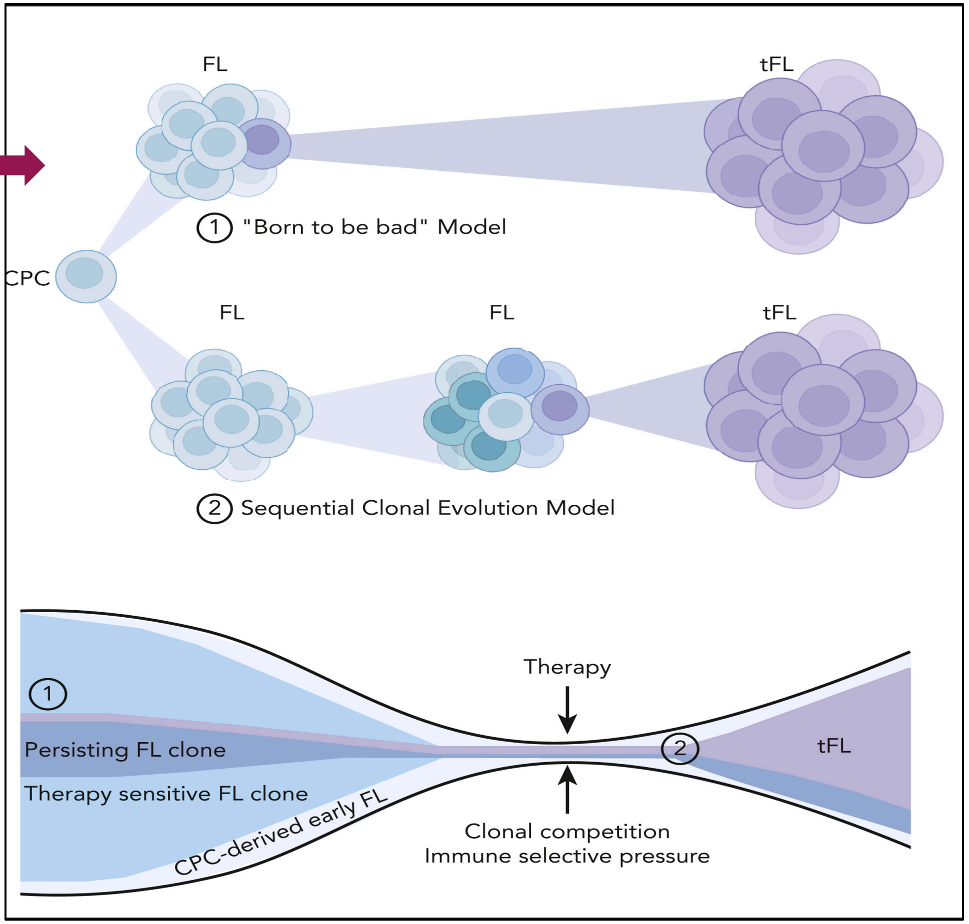


10-year incidence of 45.9%

Sarkozy et al, *Jour Clin Oncol*, 2019

Biologic Origins of Transformation

Category	Lower Transformation Risk	Higher Transformation Risk
Clonal origin	**Early CPC divergence** • Short branch from common precursor • Fewer private DLBCL mutations • May present as composite lymphoma	**Sequential clonal evolution** • Late divergence from common precursor • Shaped by therapy and immune pressure
Genetic subtype	**“Constrained FL”** • Lower mutational burden • CREBBP KAT missense mutations • mTORC1 pathway mutations • Less aberrant somatic hypermutation	**“DLBCL-like FL”** • Higher mutational burden • CREBBP nonsense mutations • Elevated aberrant somatic hypermutation
Phenotypic B-cell state	**GC-like FL** • Germinal center B-cell state • Lower intratumoral diversity • Lower transformation risk	**MEM-like FL** • Memory B-cell differentiation state • Higher intratumoral diversity
Tumor Micro-environment	**Intact immune support** • T follicular helper cells preserved • Follicular dendritic cell meshworks intact • Low $CD8^{+}LAG3^{+}$ exhausted T cells	**Immune exhaustion** • Loss of Tfh cells and FDC meshworks • $CD8^{+}LAG3^{+}PD1^{+}$ T cell expansion near tumor • Correlates with time to transformation

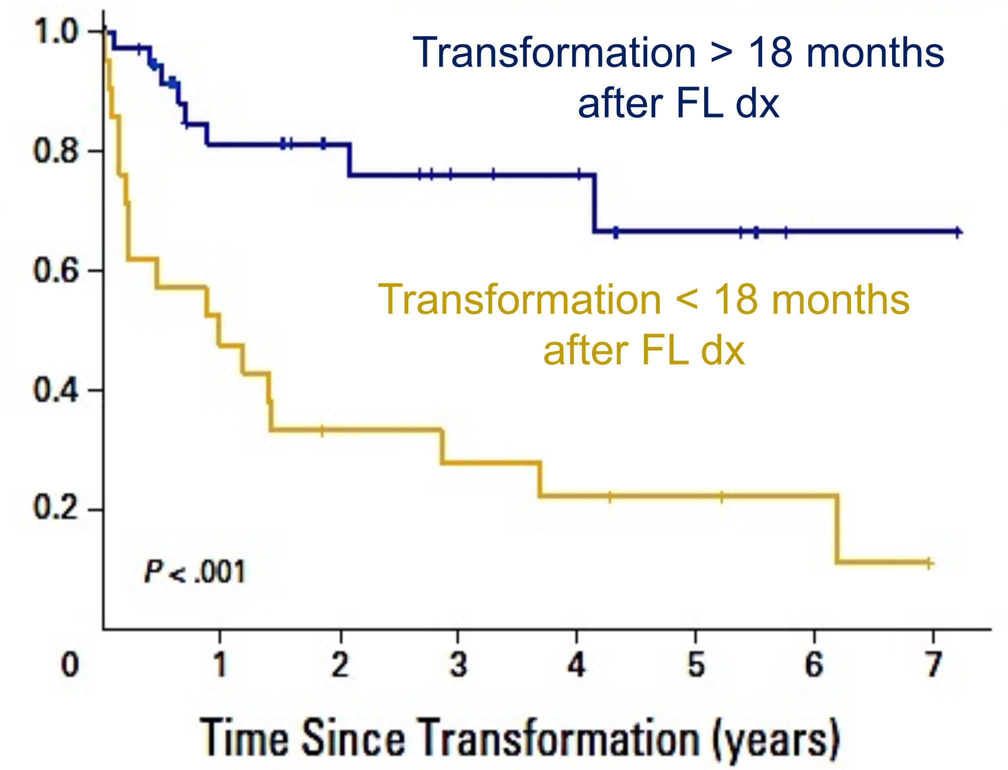


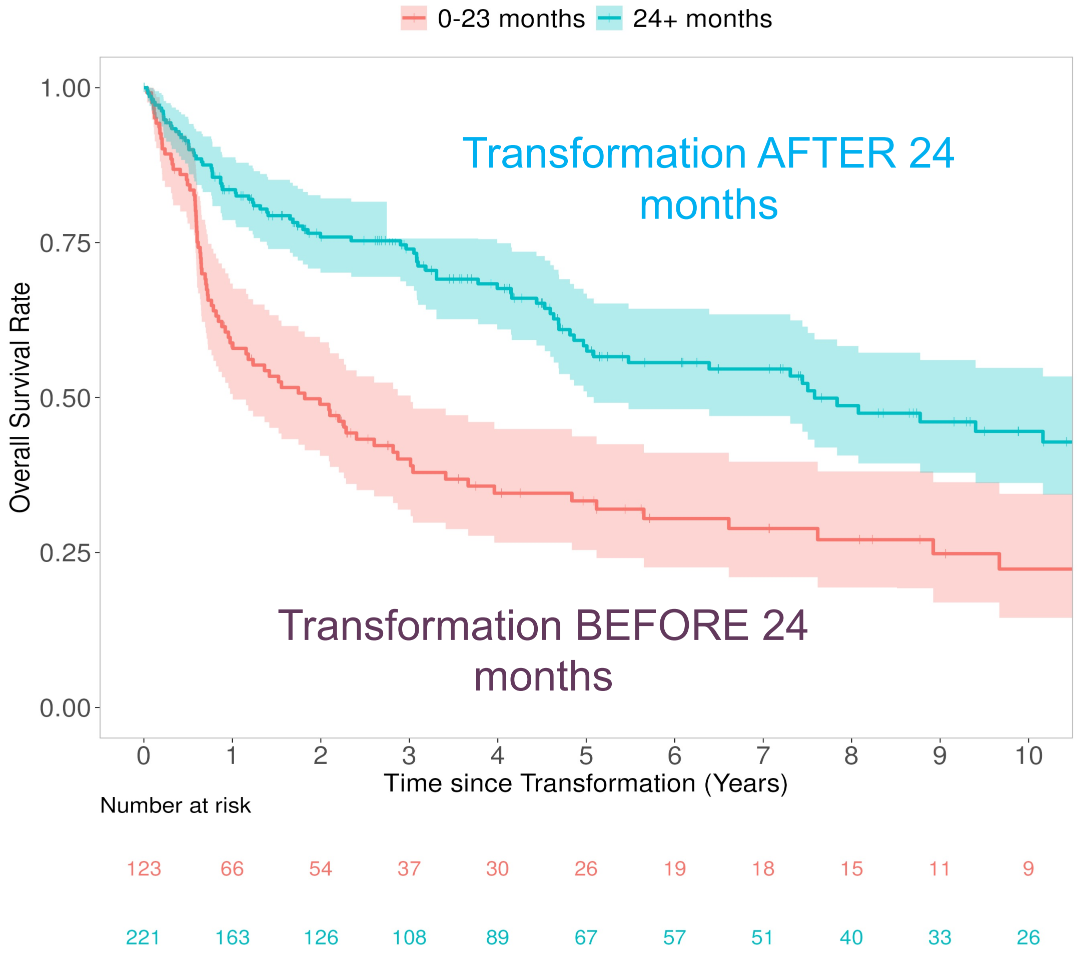
Chemotherapy backbones may select for transformation-prone clones

Parry et al. *Blood* 2025

Histologic Transformation: MER/LEO Real-World

- Early vs late HT worse outcomes

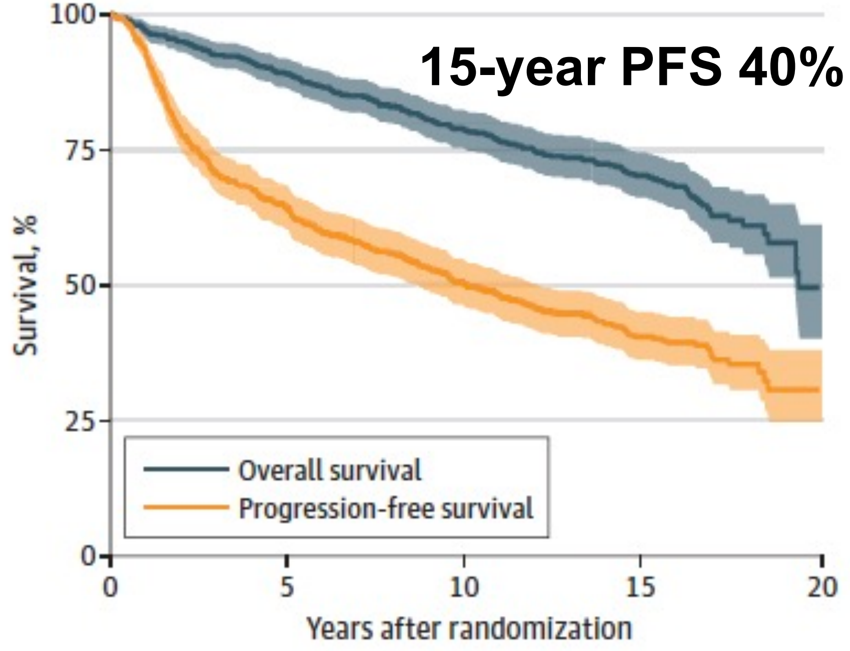




Parry et al. *Blood* 2025; Sarkozy et al. *Jour Clin Oncol* 2016; Link et al. *Jour Clin Oncol,* 2013, Day et al. *Blood* (2022) 140 (Supplement 1): 6642–664400

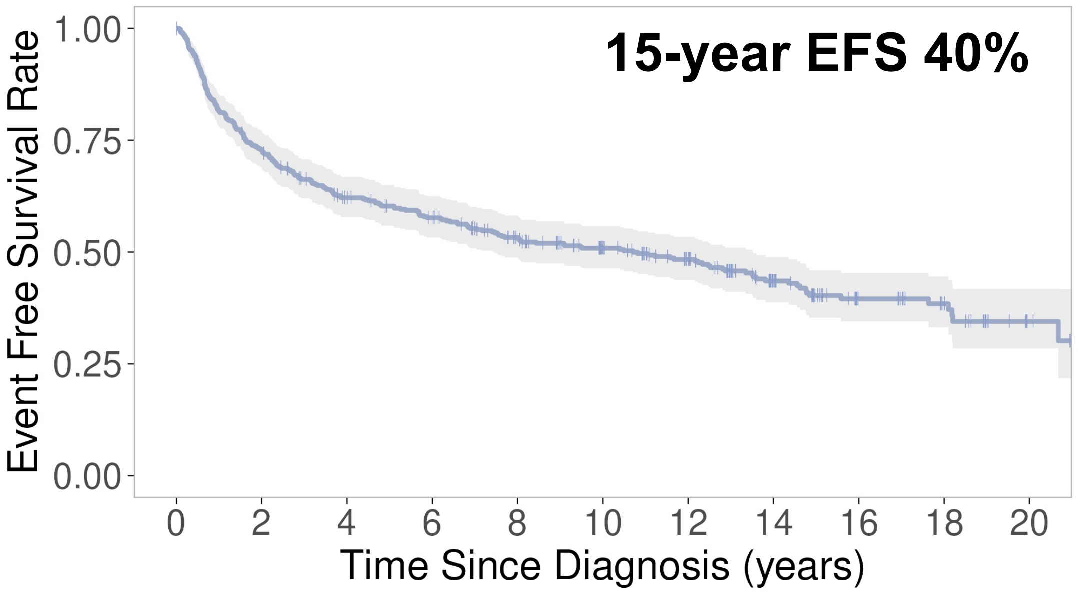
Predicting Who is Cured: Long term follow up SWOG0016 and Mayo/Iowa MER

Cure rates highest with low risk FLIPI and low $\beta 2$ microglobilin



15-year PFS 40%

No. at risk					
Overall survival	531	459	382	239	9
Progression-free survival	531	333	243	139	4



15-year EFS 40%

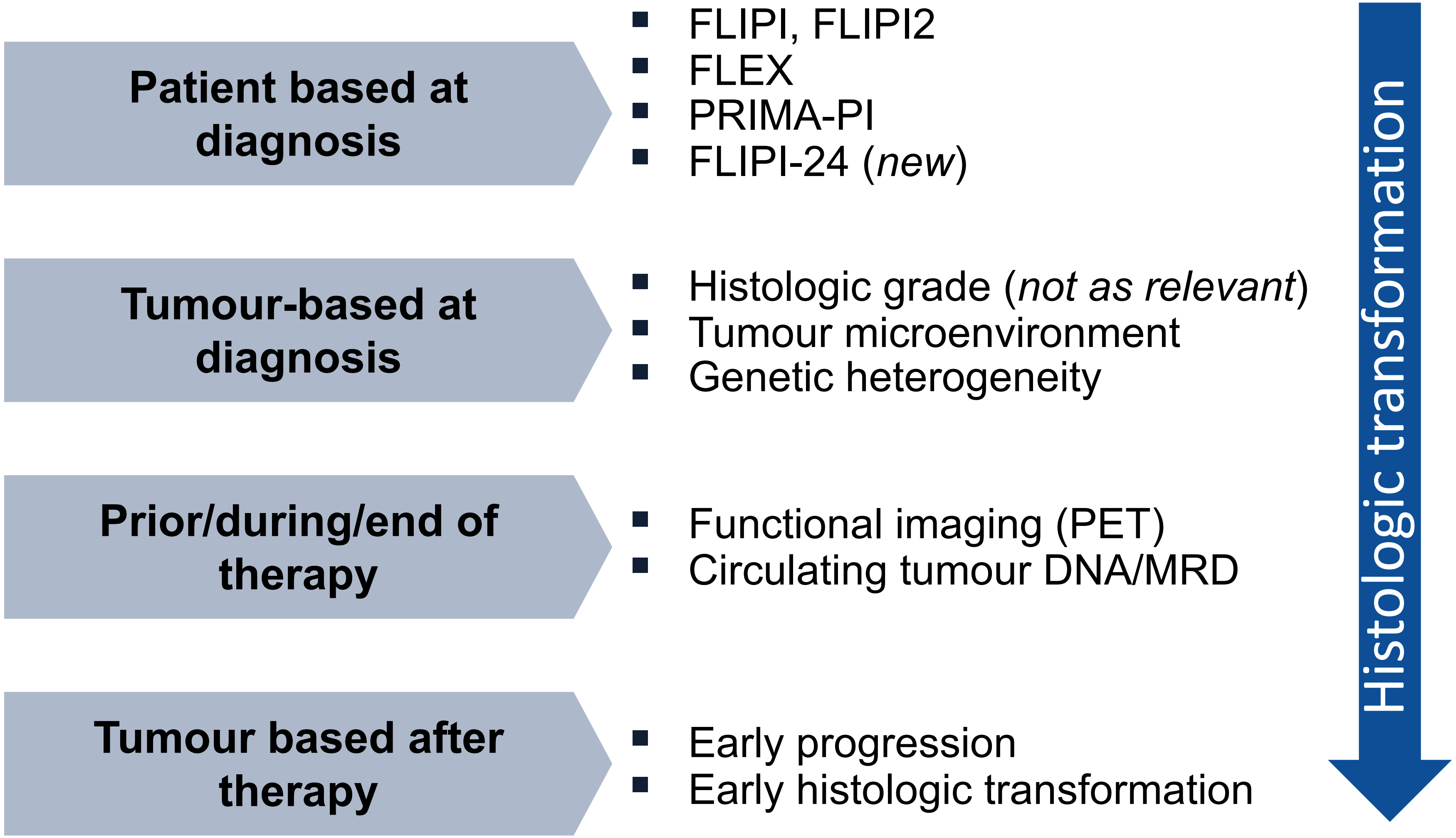
Number at risk

IC	453	327	269	243	207	171	139	87	45	31	9

Relapse rates decrease over time, 7% 1st 5 years→ >1% between years 15-20

Shadman et al. *JAMA Onc* 2026; Day et al. *ASH annual meeting* 2025

Summary of Prognostic Marker Continuum



Patient based at diagnosis

- FLIPI, FLIPI2
- FLEX
- PRIMA-PI
- FLIPI-24 (*new*)

Tumour-based at diagnosis

- Histologic grade (*not as relevant*)
- Tumour microenvironment
- Genetic heterogeneity

Prior/during/end of therapy

- Functional imaging (PET)
- Circulating tumour DNA/MRD

Tumour based after therapy

- Early progression
- Early histologic transformation

Histologic transformation

What Can Change Clinical Practice Tomorrow?

FLIPI24 and MRD-directed Treatment Decisions at Diagnosis

- High risk FLIPI24 and TMTV at diagnosis→ clinical trial?
- Multi-modal score + TME to predict histologic transformation and cure?

De-escalate

Intensify

End of Treatment and Surveillance

- In MRD-negative low-risk FL, blood-based surveillance replacing imaging?
- ctDNA+ end of treatment→ maintenance vs. novel agent?
- Retreatment vs. observation with MRD recurrence?

Thank you!


Jonathan
Friedberg

UR MEDICINE | WILMOT CANCER INSTITUTE

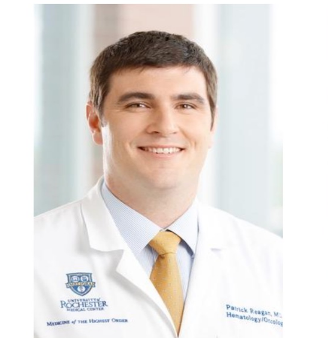

Paul Barr

NCI Cancer Center

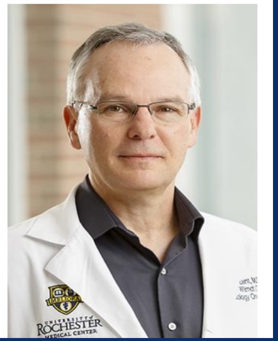
A Cancer Center Designated by the
National Cancer Institute


Jaime Flerlage


Sandy Constine


Pat Reagan


Danielle Wallace


Clive Zent