4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, March 26-27, 2026
Starhotels Majestic

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Biology of High-Risk Indolent Lymphoma: Focus on FL

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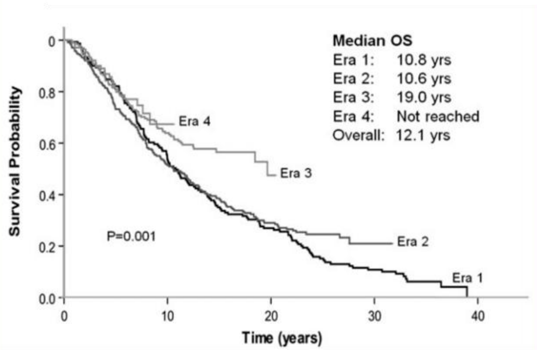
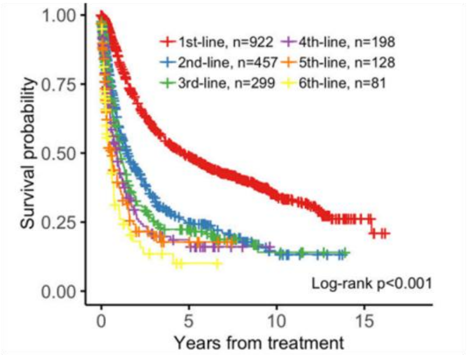
Disclosures of Jessica Okosun

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						X	
Astra Zeneca	X					X	
BeOne	X					X	
Genmab	X					X	
Gilead	X						
Incyte			X			X	
Roche							X

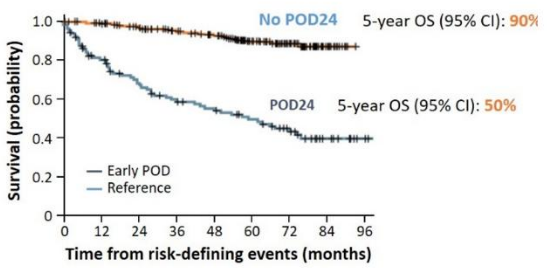
Natural history of Indolent B-cell Lymphomas: Focus on FL





Early Progression (POD24)

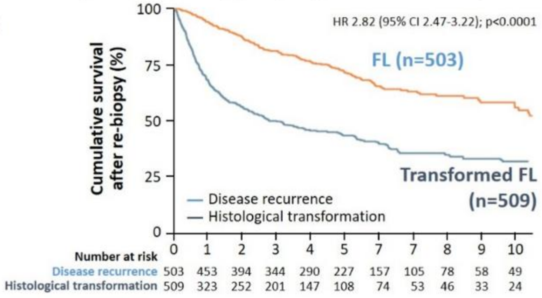
LymphoCare: 530 R-CHOP-treated patients



~15% of FL patients

Transformation (tFL)

5-year OS post-transformed FL: **43%**
(**34%** with early [≤1 year] transformation)



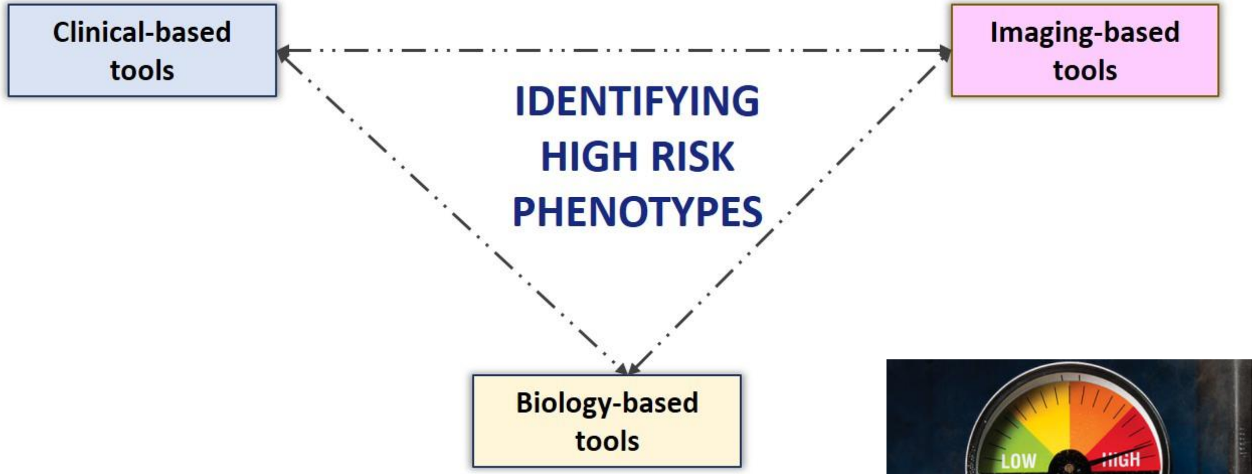
Long OS, Treatable[1]

Multiple Relapses[2]

High Risk groups[3,4]

1. Tan D, et al. *Blood*. 2013; 122(6):981-7; 2. Batlevi C, et al. Blood Cancer J. 2020; 10(7):74;
3. Casulo C, et al. *J Clin Oncol.* 2015;33:2516-22; 4. Federico M, et al. Lancet Haematol. 2018;5:e359-67;

Recognising High risk FL: When and How can we risk stratify?



Clinical-based tools

Imaging-based tools

IDENTIFYING HIGH RISK PHENOTYPES

Biology-based tools

At Diagnosis/Pre-treatment:

- Clinical: ***FLIPI, FLIPI2***, PRIMA-PI, FLEX, FLIPI24
- Biology: m7-FLIPI, PRIMA 23-gene, BioFLIPI
- Imaging: ***Baseline PET SUVmax***/TMTV (?)

At End of Induction/After therapy:

- Imaging: ***EOI PET***
- Biology: MRD by t(14;18), ctDNA +/-
- Clinical: POD24, Transformation

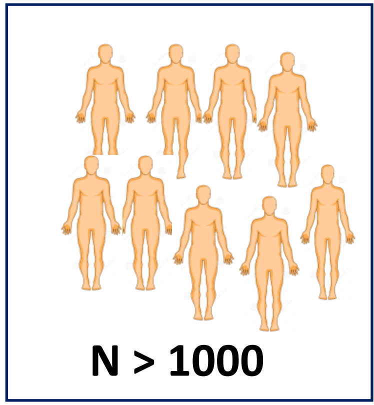
At Intervals/Dynamic:

- Biology: MRD, ctDNA (?)

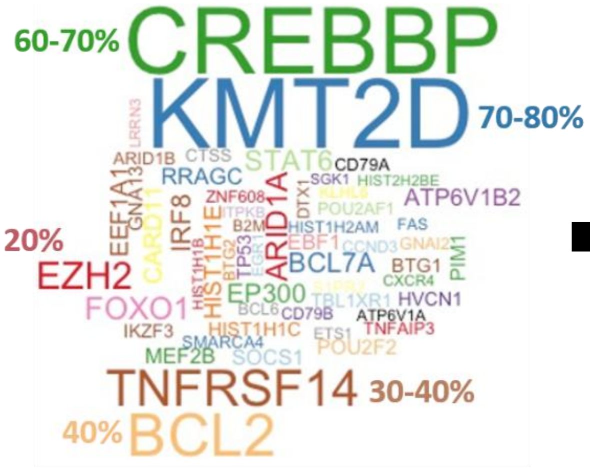
Genetic landscape in FL: Well established

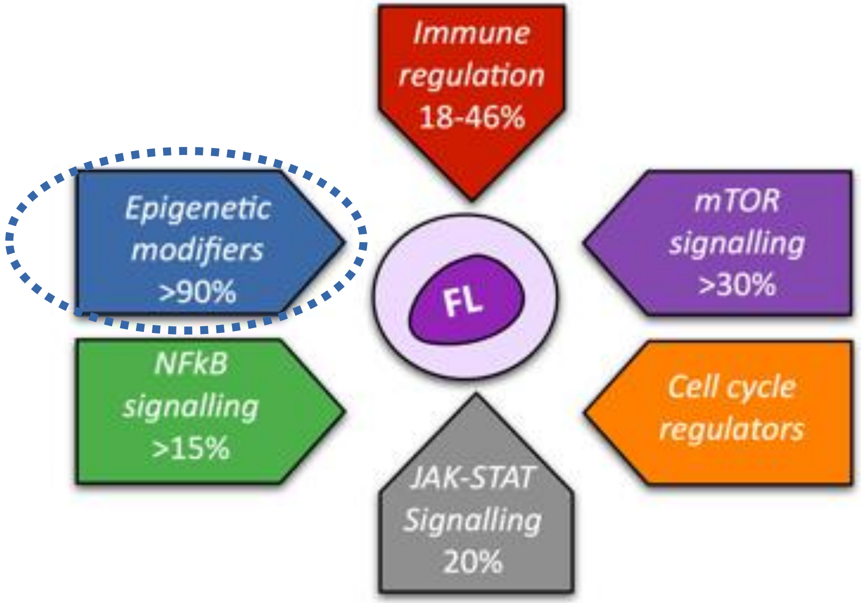
GENES FREQUENTLY MUTATED

BIOLOGICAL PATHWAYS



Sequencing
tumour DNA





Epigenetic deregulation appears fundamental

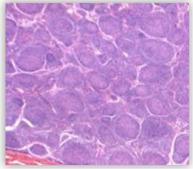
(**90% of FL cases have mutations**)

Green et al, 2013, 2015; Kridel et al, 2016; Krysiak et al, 2017; Morin et al, 2010, 2011; Okosun et al, 2014, 2016; Oricchio et al, 2017; Pasqualucci et al, 2011, 2014

Transformation occurs divergent evolution from a reservoir population

Comparing genetic profiles in sequential lymphomas

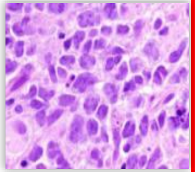
FL



Indolent lymphoma

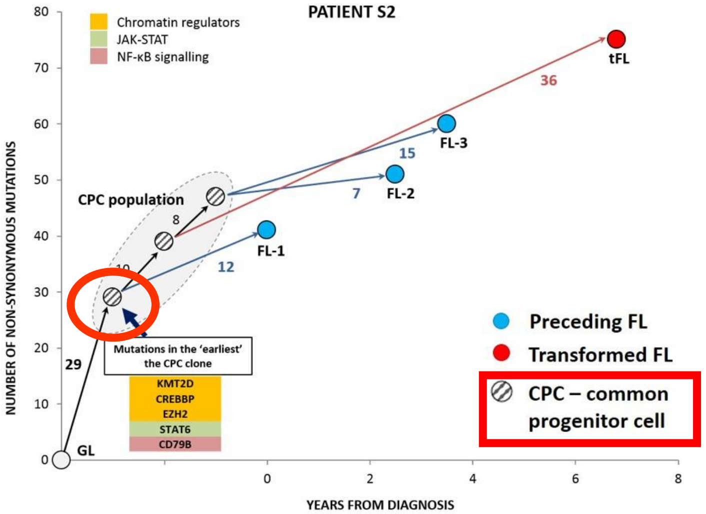
→

tFL (DLBCL)

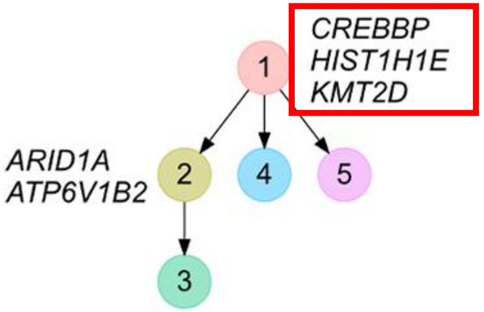


Aggressive lymphoma

Temporal heterogeneity



Okosun et al, *Nature Genetics* 2014



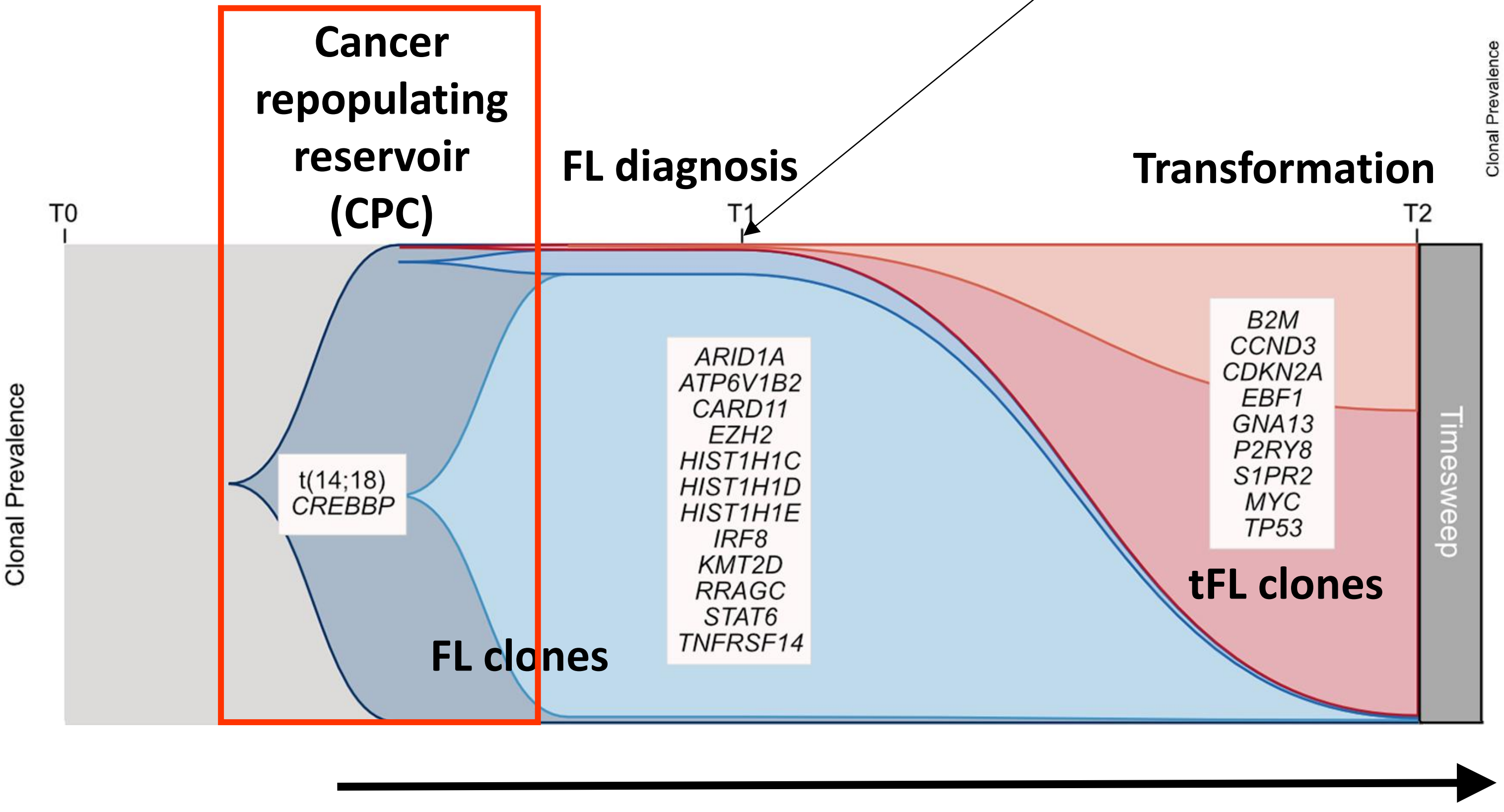
Kridel et al, *Plos Medicine* 2016

Also: Pasqualucci et al, *Cell Reports* 2014 and Green et al, *PNAS* 2015

Reservoir population 'CPC'
Genetic evolution with time

No simple genetic determinant for progression and transformation

Transformation clone undetectable at diagnoses



Cancer repopulating reservoir (CPC)

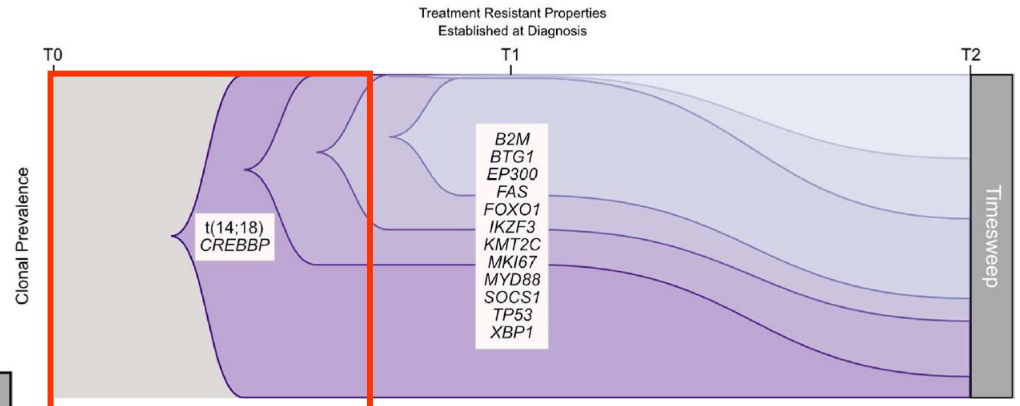
FL diagnosis

Transformation

FL clones

tFL clones

Time

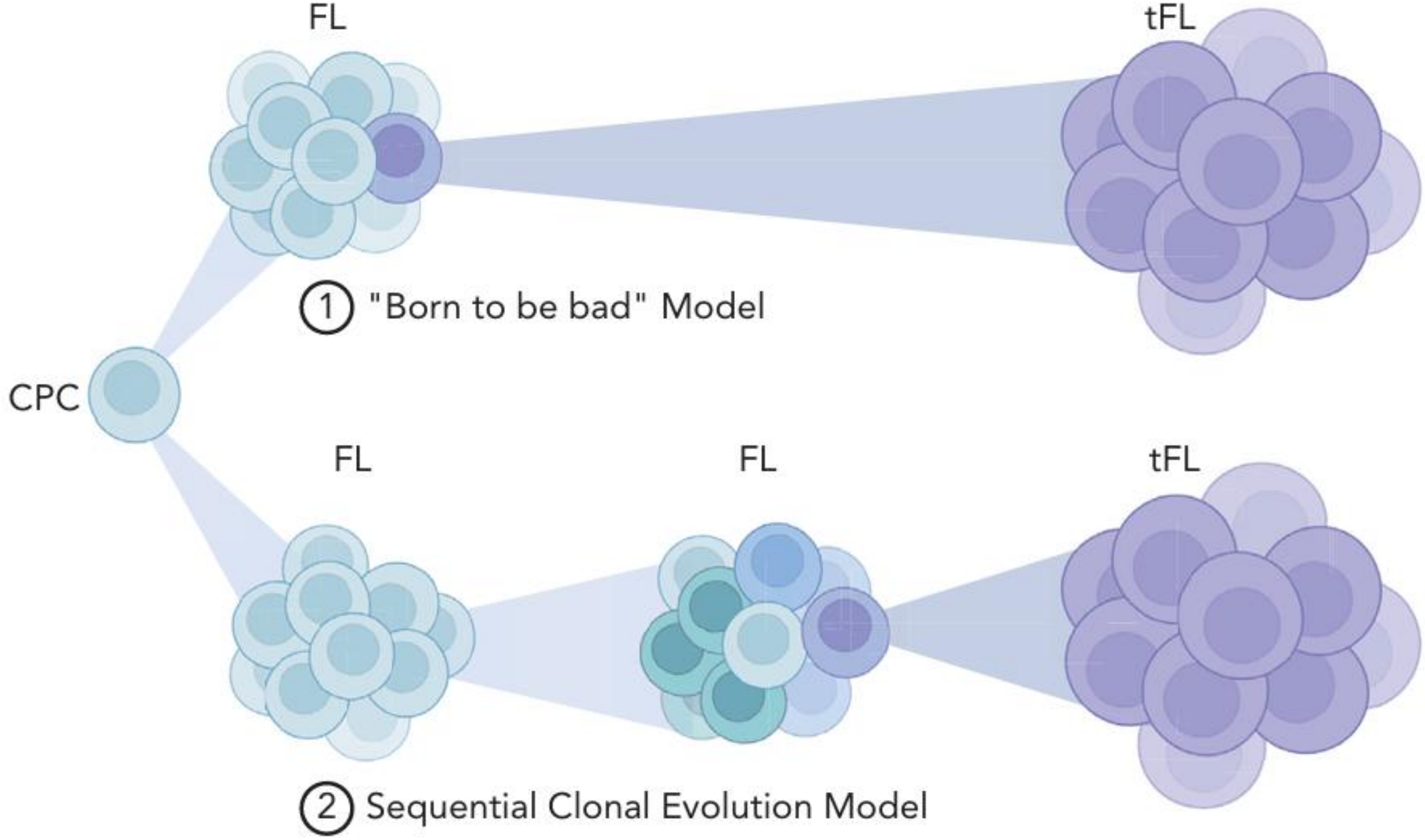


CPC

PROGRESSED FL

Adapted from Kridel et al, *Plos Med* 2016

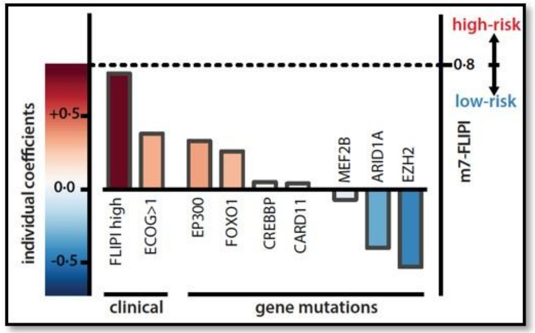
Hypothesised genetic models of tFL development



Parry, Okosun, *Blood* 2025

Incorporating ***tumour genotype*** and ***TME*** into prognostic tools

m7-FLIPI

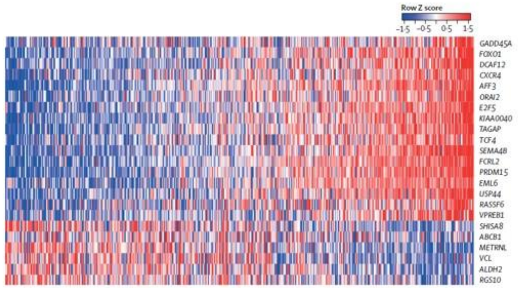


Model: **7 genes** + **PS** + **FLIPI** score

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

Pastore et al, *Lancet Oncol* 2015

PRIMA 23-Gene expression



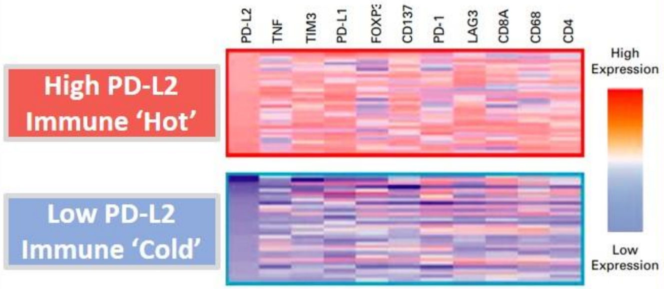
N = 134 patients (Training cohort)
Confirmed in 3 validation cohorts

	5 yr PFS
High risk	26%
Low risk	73%

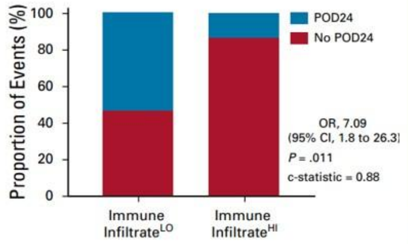
No effect on OS

Huet *et al*, Lancet Oncol 2018

PD-L2 expression



Immune 'cold' = higher POD24

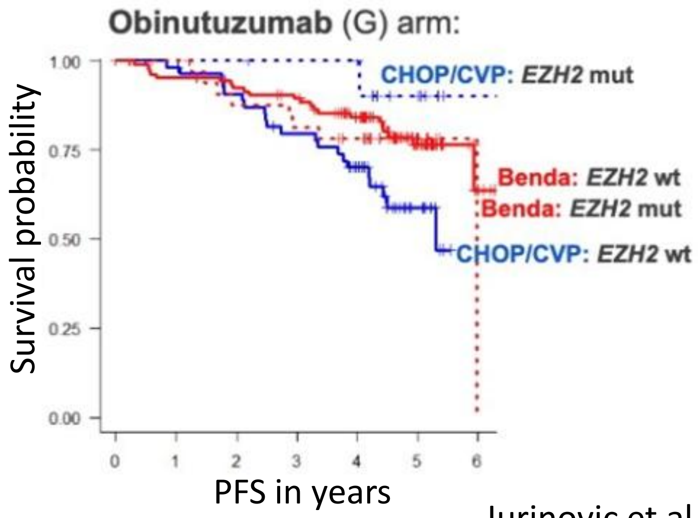


Tobin et al, *JCO* 2019

Challenges: Validity of prognostic tools with differing treatments

m7-FLIPI not prognostic in specific cohorts

- Chemo-free regimens: Rituximab only
- GALLIUM study, m7-FLIPI *not prognostic* for PFS in *Ritux-/Obi-Bendamustine* cohort

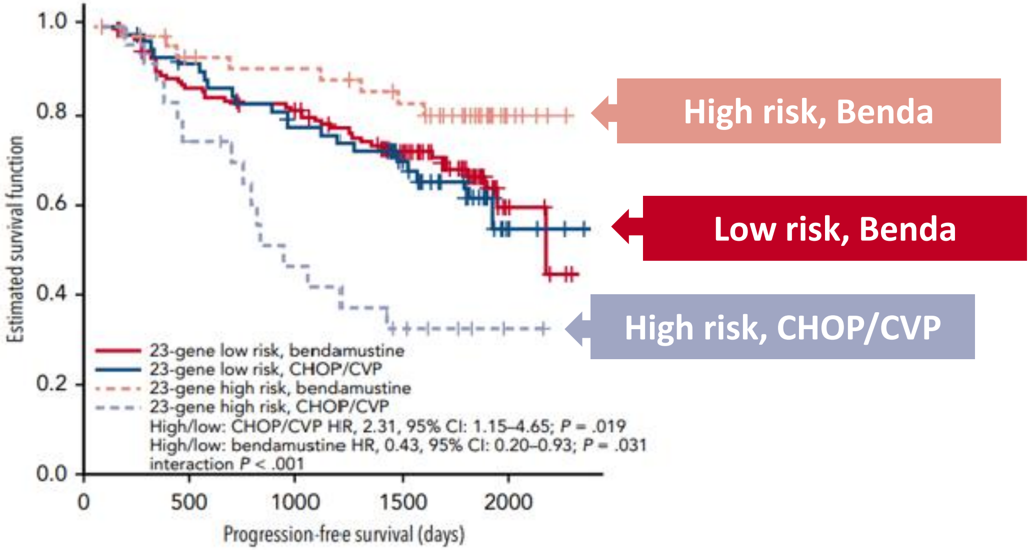


'Effect of EZH2 mutations'

Jurinovic et al, *ASH annual meeting* 2019

PRIMA 23-gene and impact of treatment

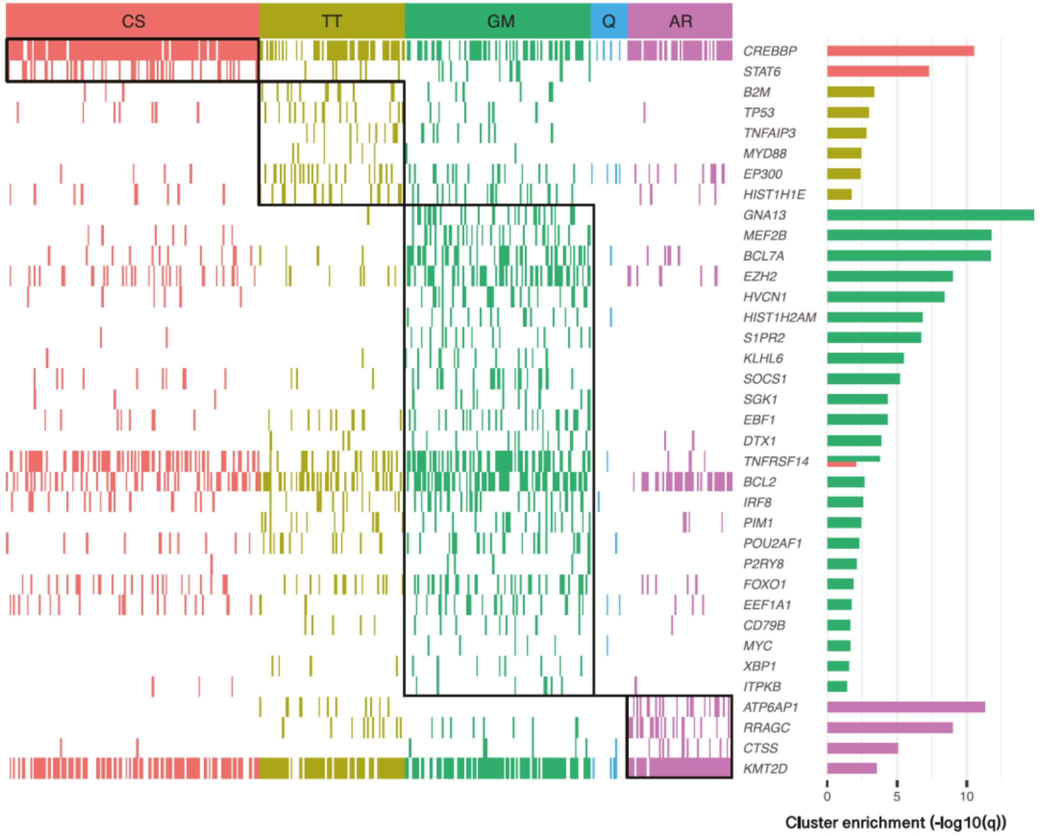
- Bendamustine-treated: 23-gene$^{\text{high risk}}$ better outcomes than 23-gene$^{\text{low risk}}$



Bolen et al, *Blood* 2021

Biological Heterogeneity: Are there distinct FL molecular subtypes?

Using targeted sequencing: 57 genes



N = 713 pre-treatment FL

5 GENETIC SUBTYPES:

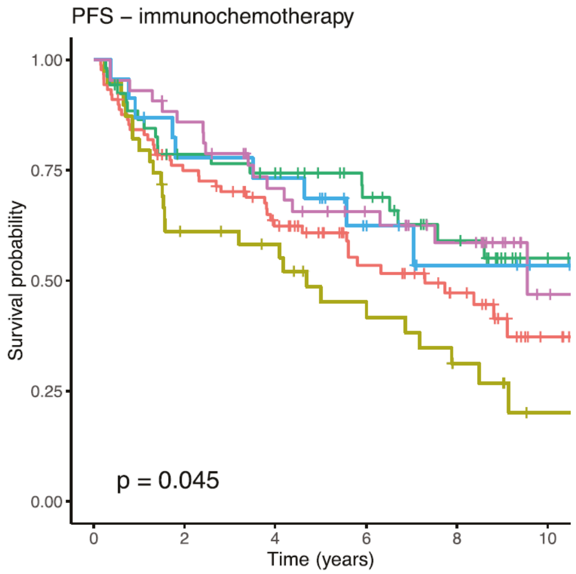
CS = CREBBP and STAT6

TT = TNFAIP3 and TP53

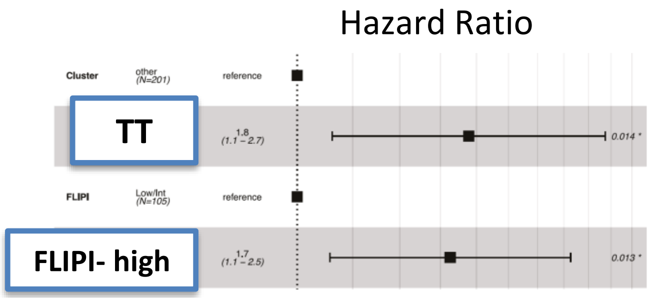
GM = GNA13 and MEF2B

Q = quiescent, for low mutation burden

AR = mutations of mTOR pathway-related genes



TT – worse prognosis



Shelton et al, *Blood Cancer Journal* 2024

Can the FL genetic pattern predict the risk of transformation ?

Using WGS: increases the power of discovery

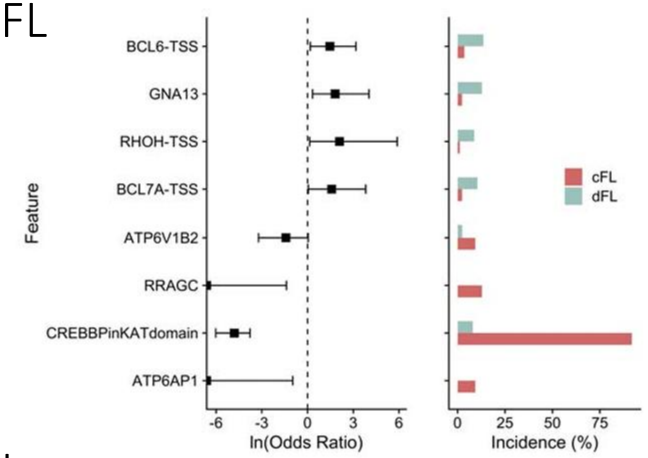
Classifier trained on genetic features enriched in FL relative to DLBCL – separates FL into 2 groups

- DLBCL-like FL (dFL)
- “constrained” FL (cFL)

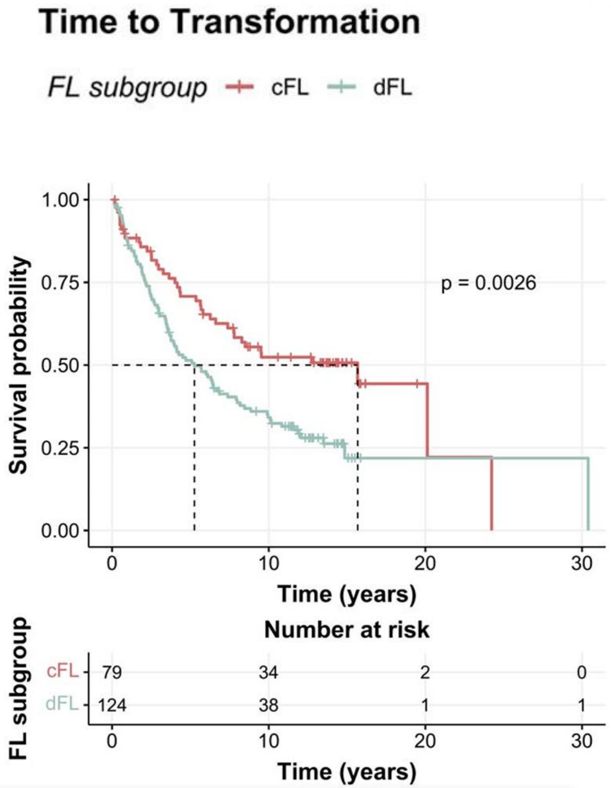
Most prominent genetic feature of cFL:

- *CREBBP* KAT domain mutation
- Lower mutation burden in cFL across the most common sites affected by aSHM in DLBCL

Constrained FL (cFL) vs DLBCL-like FL (dFL)



cFL highly enriched for *CREBBP* KAT mutations



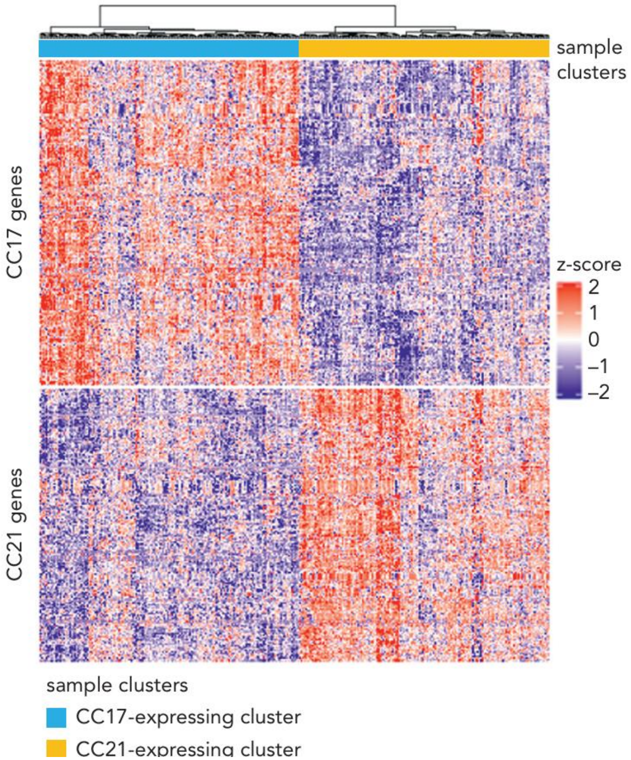
Genetics of cFL may constrain its evolutionary trajectory to transformation

Dreval et al, *Blood* 2023

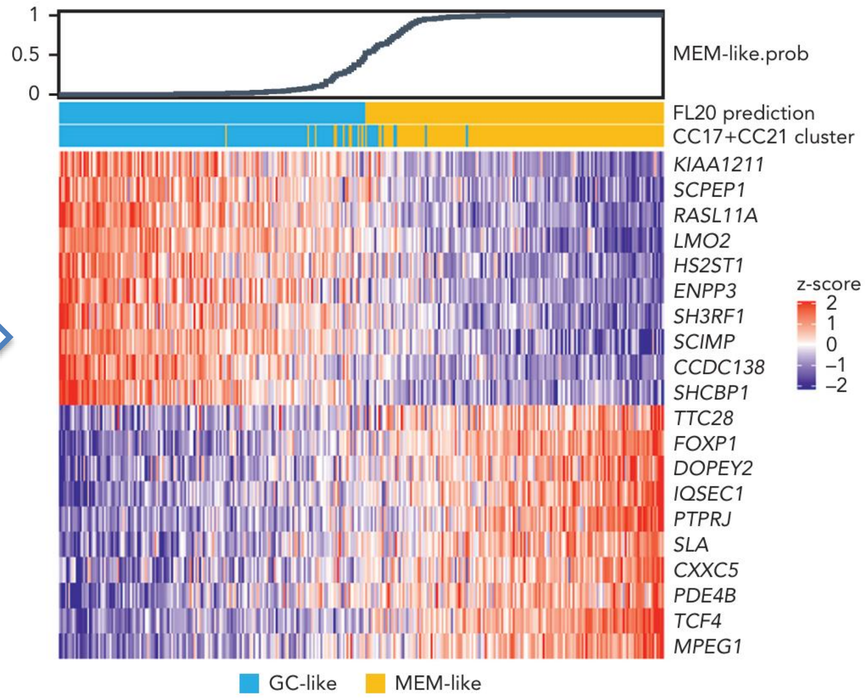
Cell-Of-Origin based molecular FL subgroups

Gene expression signature derived from the RELEVANCE trial divides FL into two molecular ‘cell of origin’ subgroups

- **MEM-like FL**
- **GC-like FL**



FL20



Laurent et al, *Blood* 2024

Cell-Of-Origin based molecular FL subgroups

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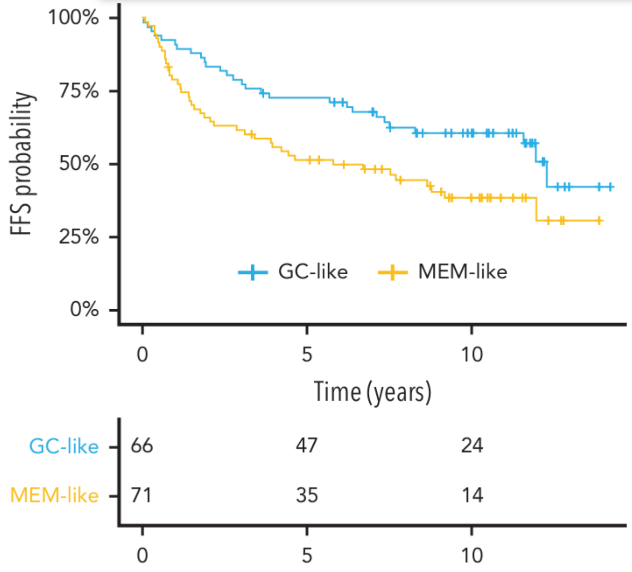
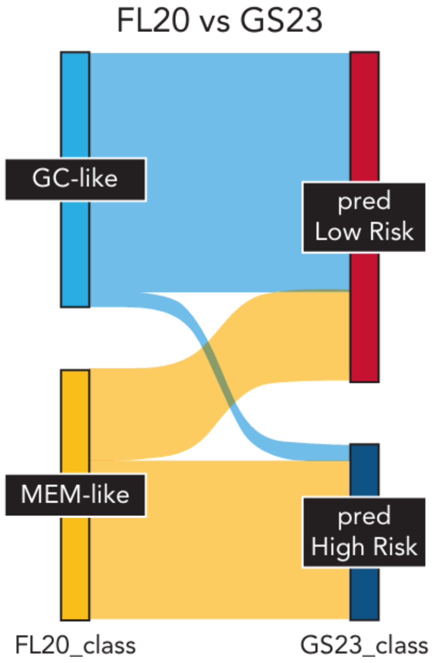
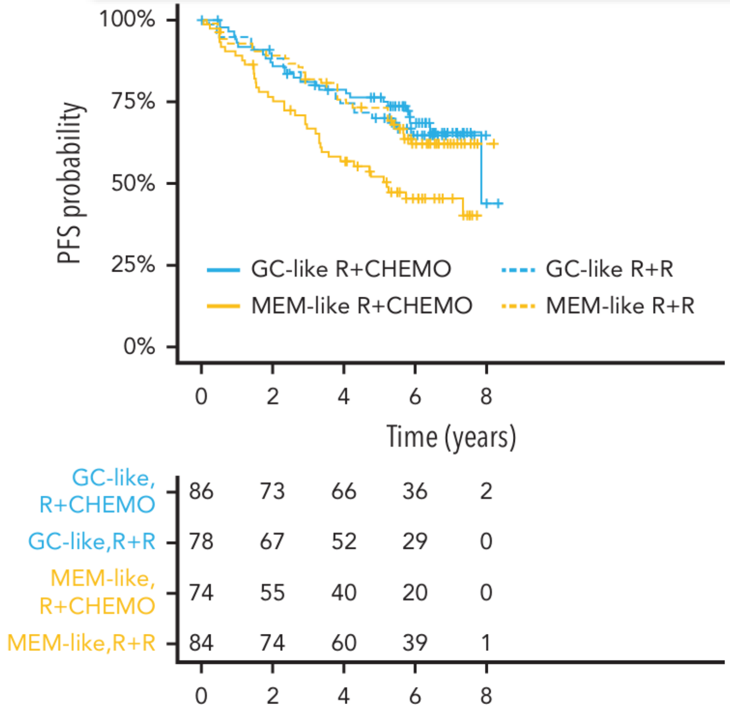
- ○ **MEM-like FL**
- ○ **GC-like FL**

R-chemo patients





MEM-like overcome by R2?

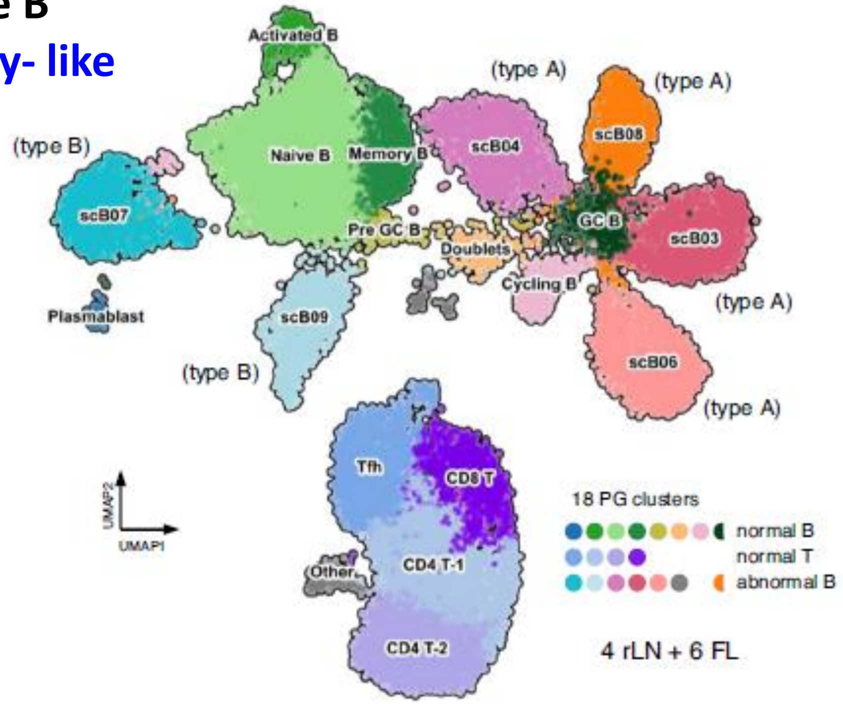


Laurent et al, *Blood* 2024

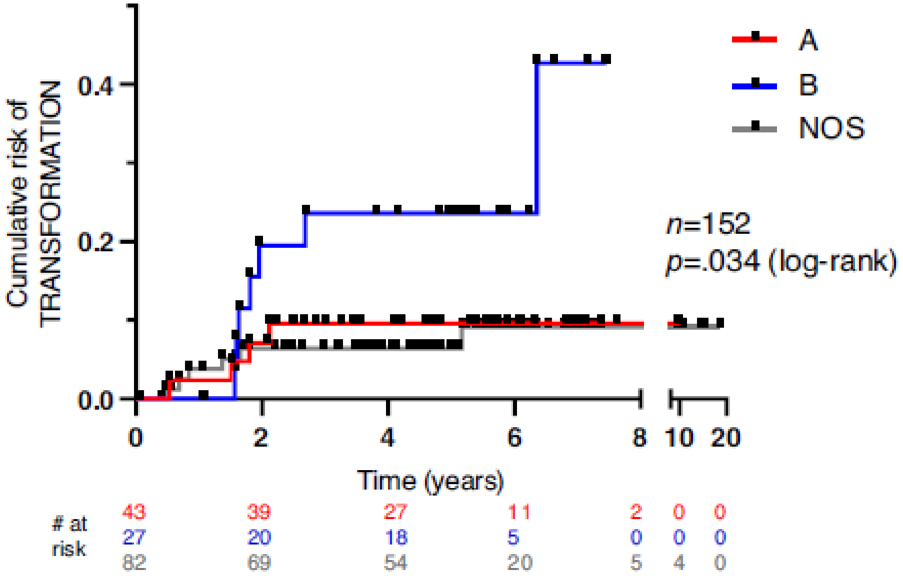
Memory B-cell like subtype of FL associated with increased tFL risk

Type A
GCB like

Type B
Memory- like



Defined by CyTOF

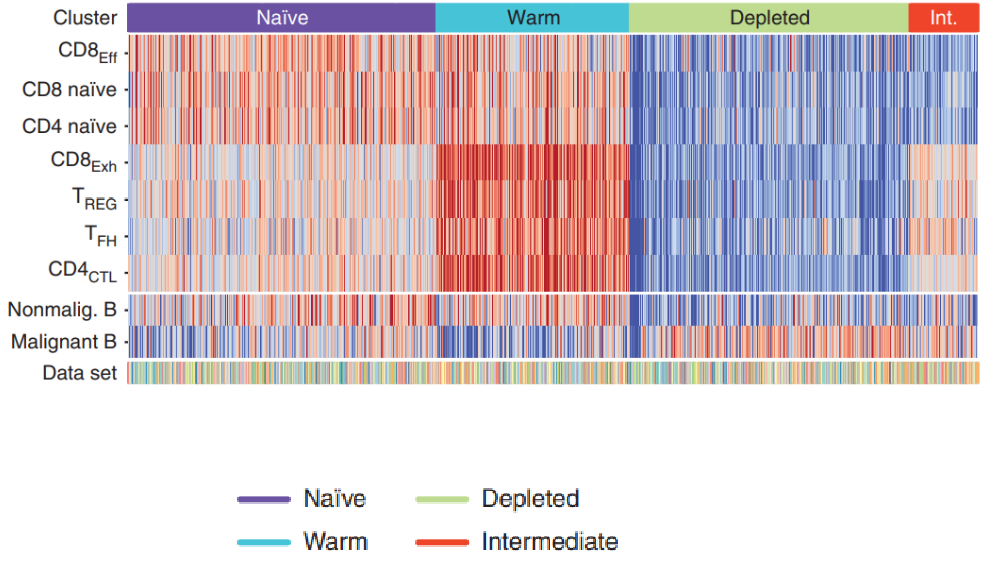


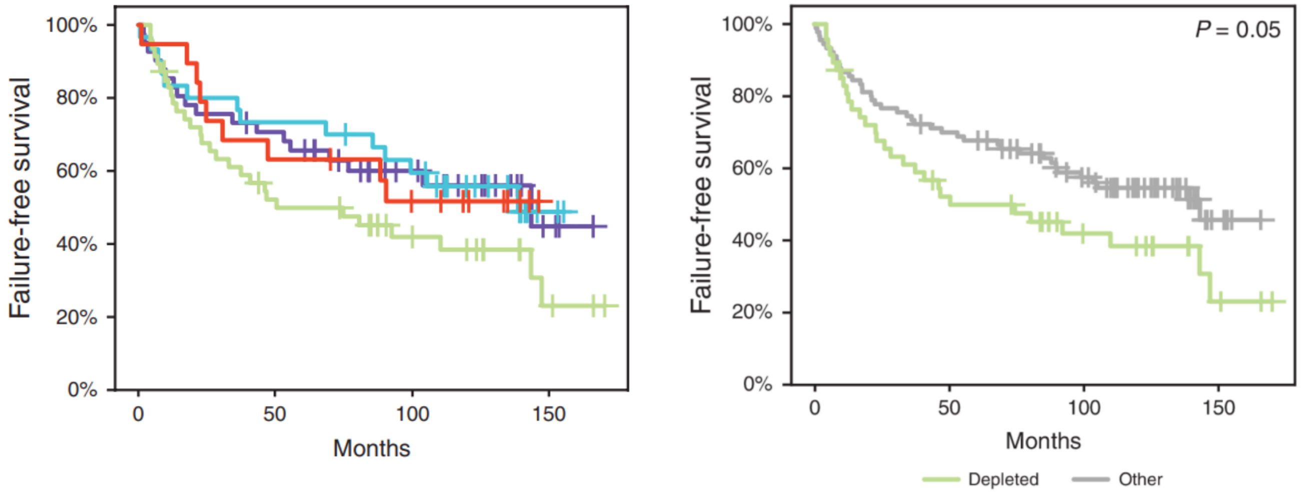
Wang et al, *Nature Comm* 2022

T-cell composition and states impact patient outcomes

Can the lymphoma microenvironment identify high-risk FL patients?

4 groups based on FL-infiltrating T-cells



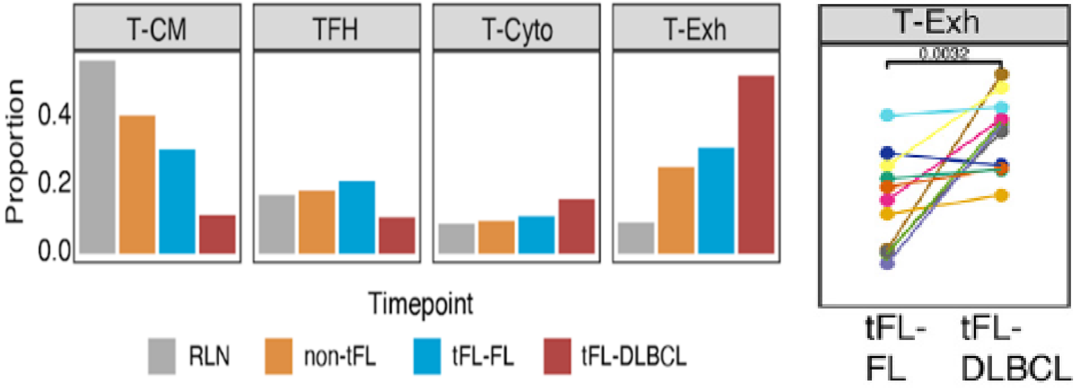


Major T-cell subtypes associated with differing outcomes

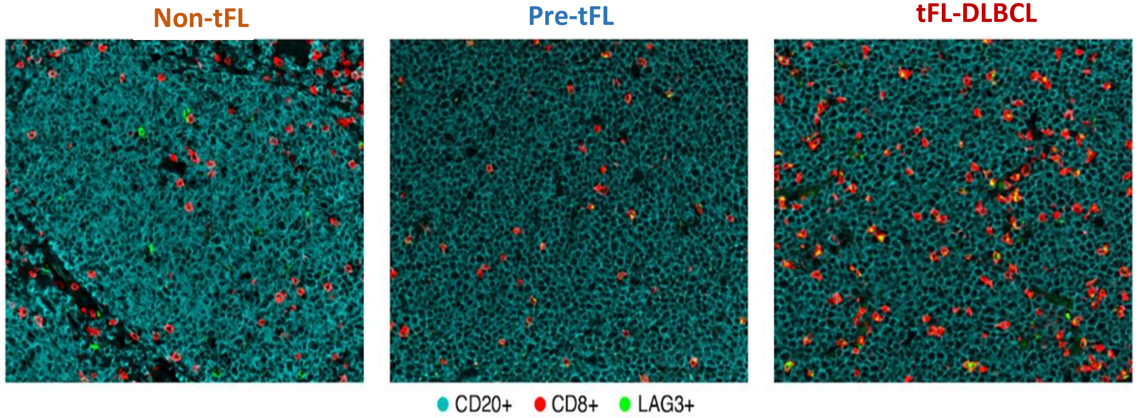
Han et al, *Blood Cancer Discovery* 2022

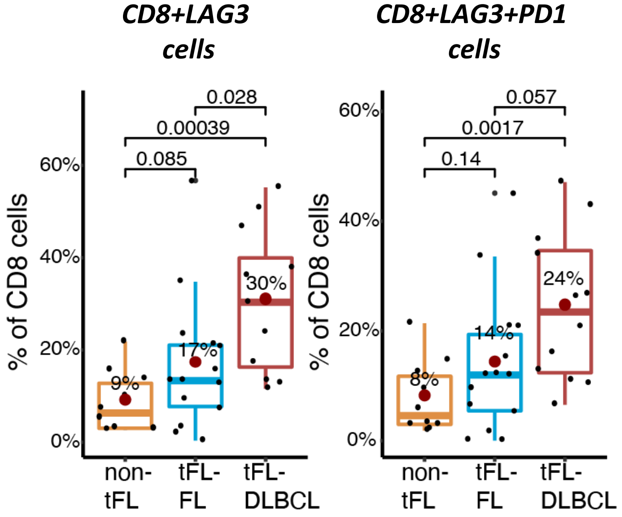
Immune microenvironment composition can predict transformation risk

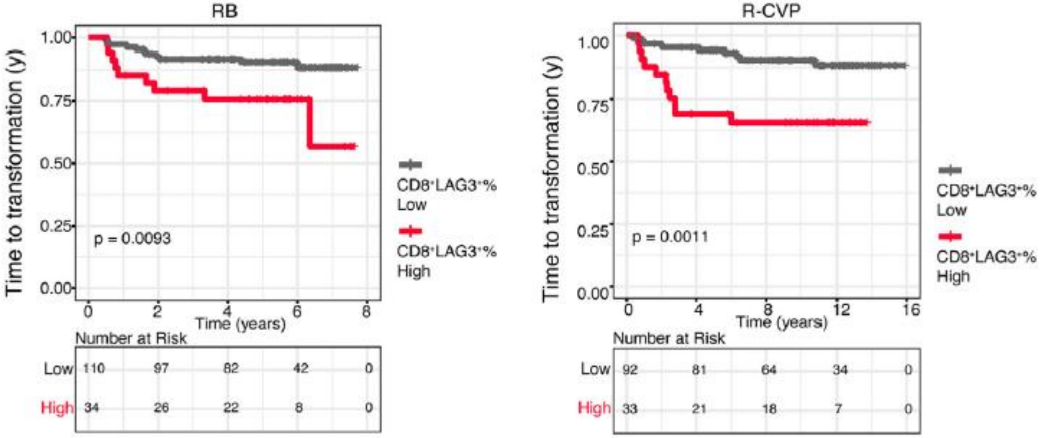
Increase in CD8+ exhausted T-cells in tFL



MC-IF showing spatial distribution



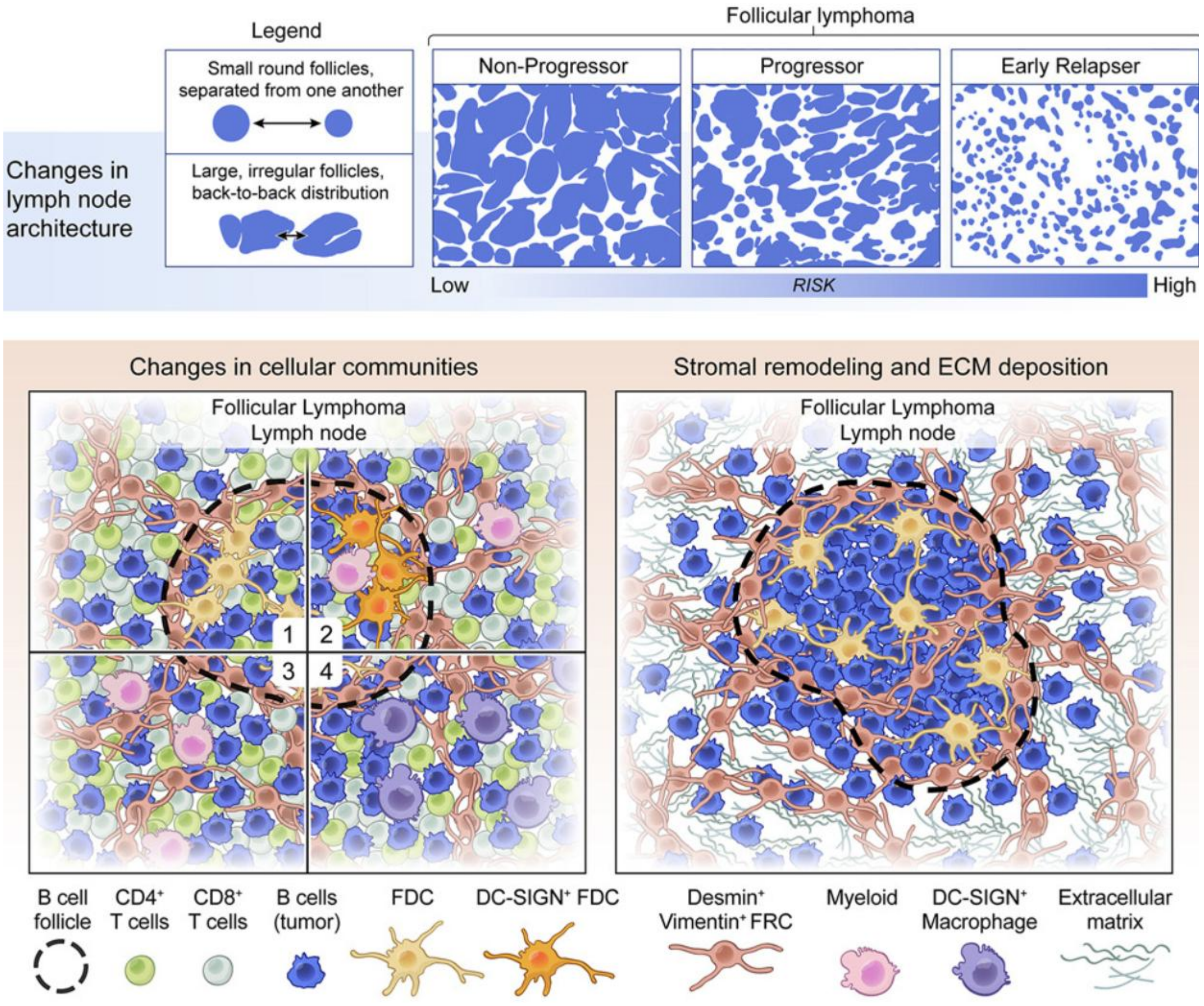




Sarkozy, Wu et al, *Cancer Cell, 2024*

Spatial architecture patterns in microenvironment linked with early relapse

Long Term Remission



Early Progressors

Radtke et al, *Cancer Cell* 2024

In 2026: Biological determinants of high-risk FL

Genetics

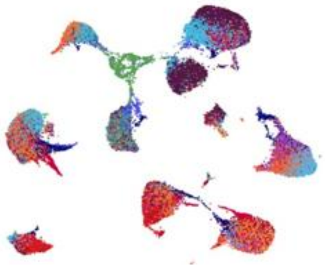
CPC 'backbone'

⬆ 'Baddies' – *MYC, TP53*

⬆ Mutations, CNAs, aSHM

B-cell States/ Cell-of-Origin

Memory-like > Germinal Centre-like

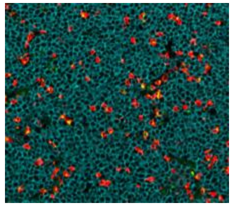


Microenvironment

T-cell composition

⬆ CD8 Exhausted phenotype

⬆ Stromal remodelling



Where could the biology weigh in for high-risk FL?

At diagnoses:

- Identify high risk patients (POD24, transformation) - *Prognostic*

  …..and Predictive tools

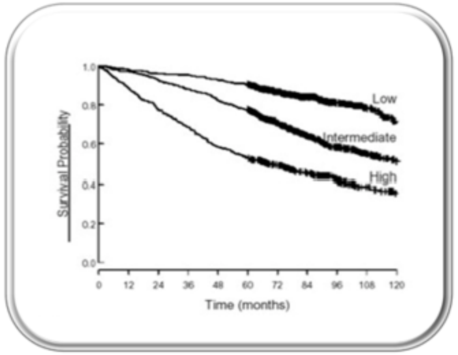
Post-induction:

- Define who might need post-induction therapy – *Prognostic and Dynamic tools*

At 2nd line and beyond:

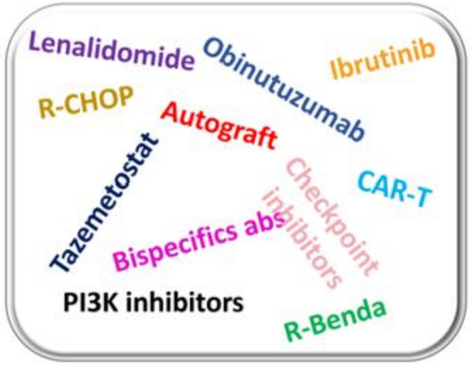
- Guide therapeutic decisions
  - who will respond best to bispecifics, CAR-T, X, Y, Z
  - who are likely to suffer adverse events from specific therapies – *Predictive and Dynamic tools*

Prognostication



Risk Stratification

Prediction

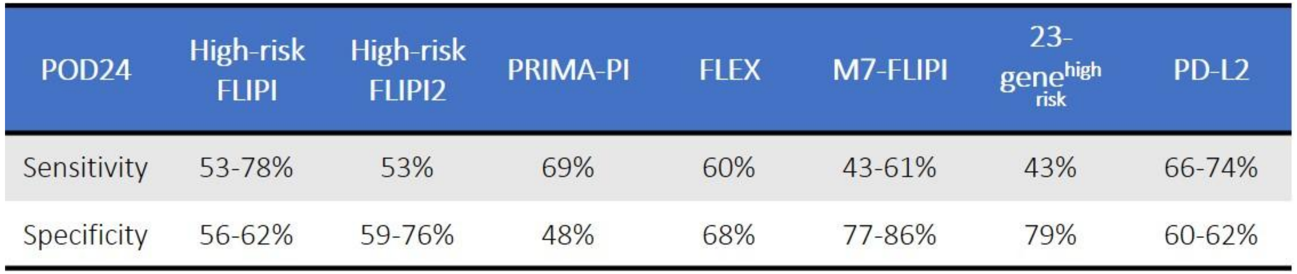


Tailoring Treatment

Requisites for tools/biomarkers to guide clinical decision-making

High prognostic or predictive ACCURACY →

ABILITY TO IDENTIFY POD24 PATIENTS?



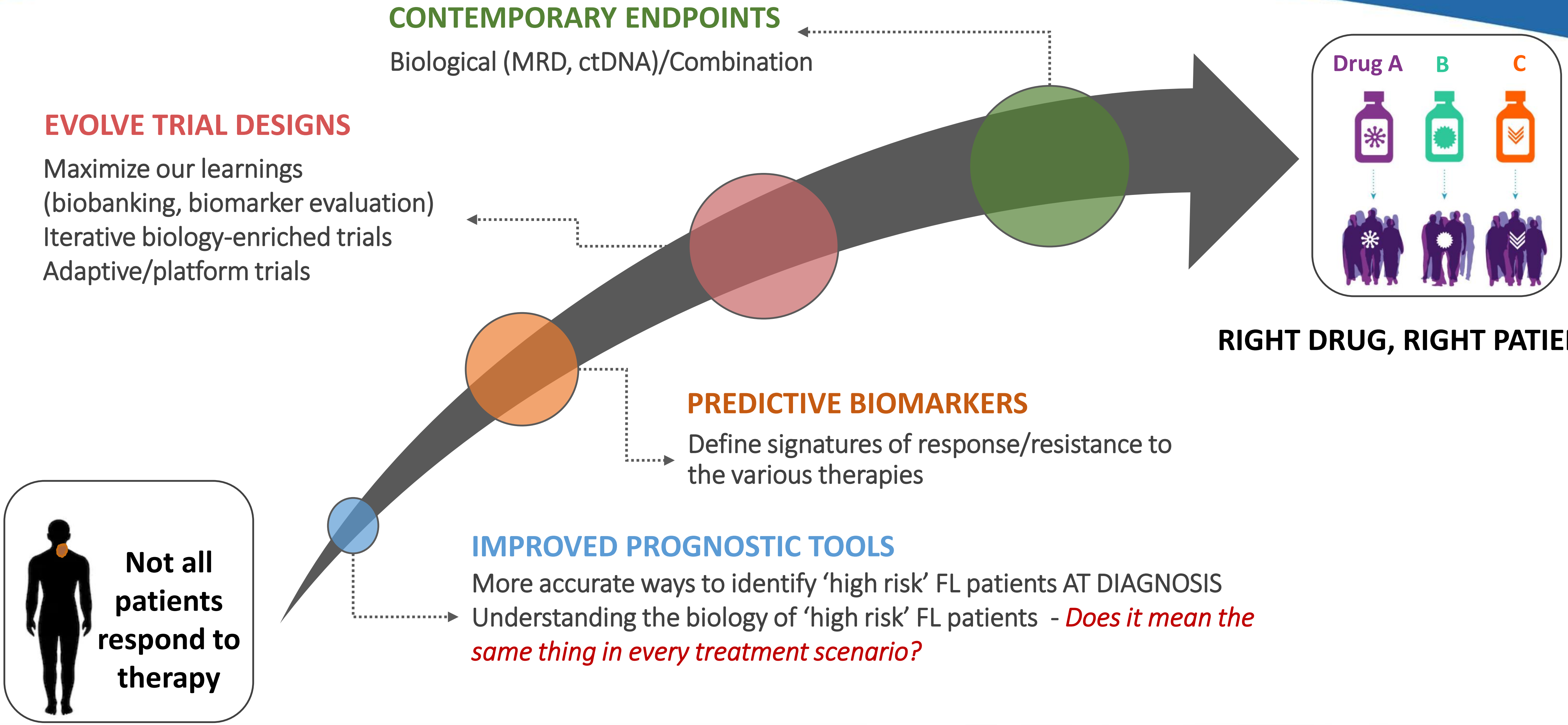
POD24	High-risk FLIPI	High-risk FLIPI2	PRIMA-PI	FLEX	M7-FLIPI	23-gene high risk	PD-L2
Sensitivity	53-78%	53%	69%	60%	43-61%	43%	66-74%
Specificity	56-62%	59-76%	48%	68%	77-86%	79%	60-62%

Is it ACTIONABLE - guides therapy selection → Need clear approach for ‘high risk’ patients

Widely ACCESSIBLE/AFFORDABLE →

- Clinical prognostic tools – straightforward
- Genotyping/gene expression/ctDNA - research tools

How can we continue to improve the precision of our choices?



CONTEMPORARY ENDPOINTS

Biological (MRD, ctDNA)/Combination

EVOLVE TRIAL DESIGNS

Maximize our learnings (biobanking, biomarker evaluation)
Iterative biology-enriched trials
Adaptive/platform trials

RIGHT DRUG, RIGHT PATIENT?

PREDICTIVE BIOMARKERS

Define signatures of response/resistance to the various therapies

IMPROVED PROGNOSTIC TOOLS

More accurate ways to identify ‘high risk’ FL patients AT DIAGNOSIS
Understanding the biology of ‘high risk’ FL patients - *Does it mean the same thing in every treatment scenario?*

Not all patients respond to therapy

Thank you