

Follicular Lymphoma

Are We Ready for Precision Medicine?

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Professor of Medicine

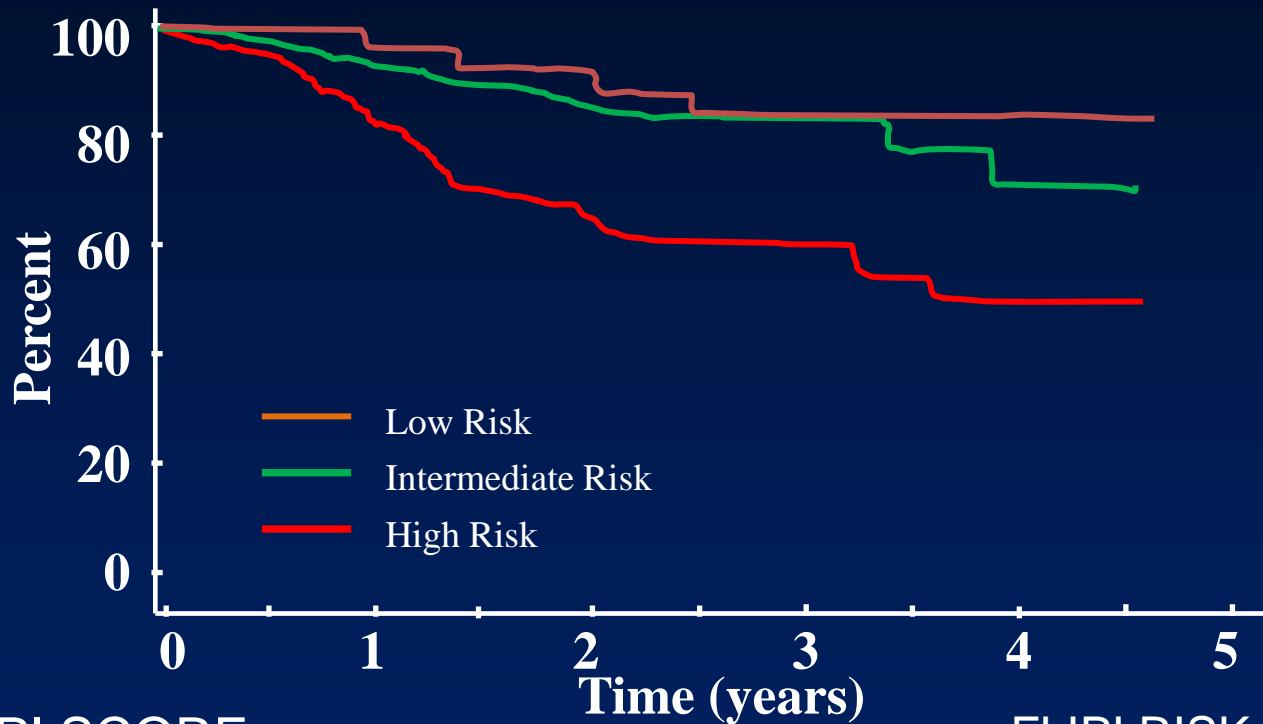
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Disclosures

- Grants: Roche, Celgene, TG Therapeutics
- Advisory Board: Roche, TG Therapeutics, BMS, Novartis
- Employment: BostonGene

FLIPI Predicts Overall Survival

Overall Survival Following R-CHOP



FLIPI	10yr OS
Good	71%
Inter	51%
Poor	36%

FLIPI SCORE

- Age \geq 60
- Serum LDH > ULN
- Stage III-IV
- Nodal Site > 4
- Hemoglobin < 12

FLIPI RISK GROUPS

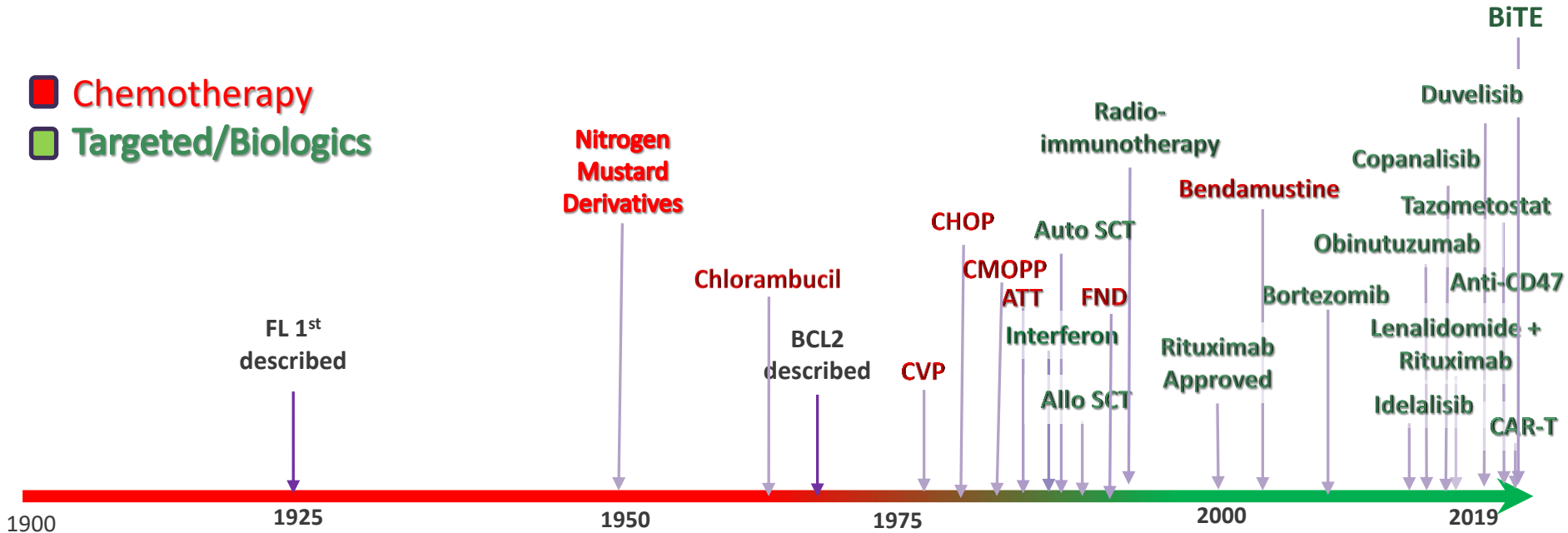
- Low Risk 0-1
- Intermediate Risk 2
- High Risk 3-5

Risk-Adapted Approach in Follicular Lymphoma is Essential

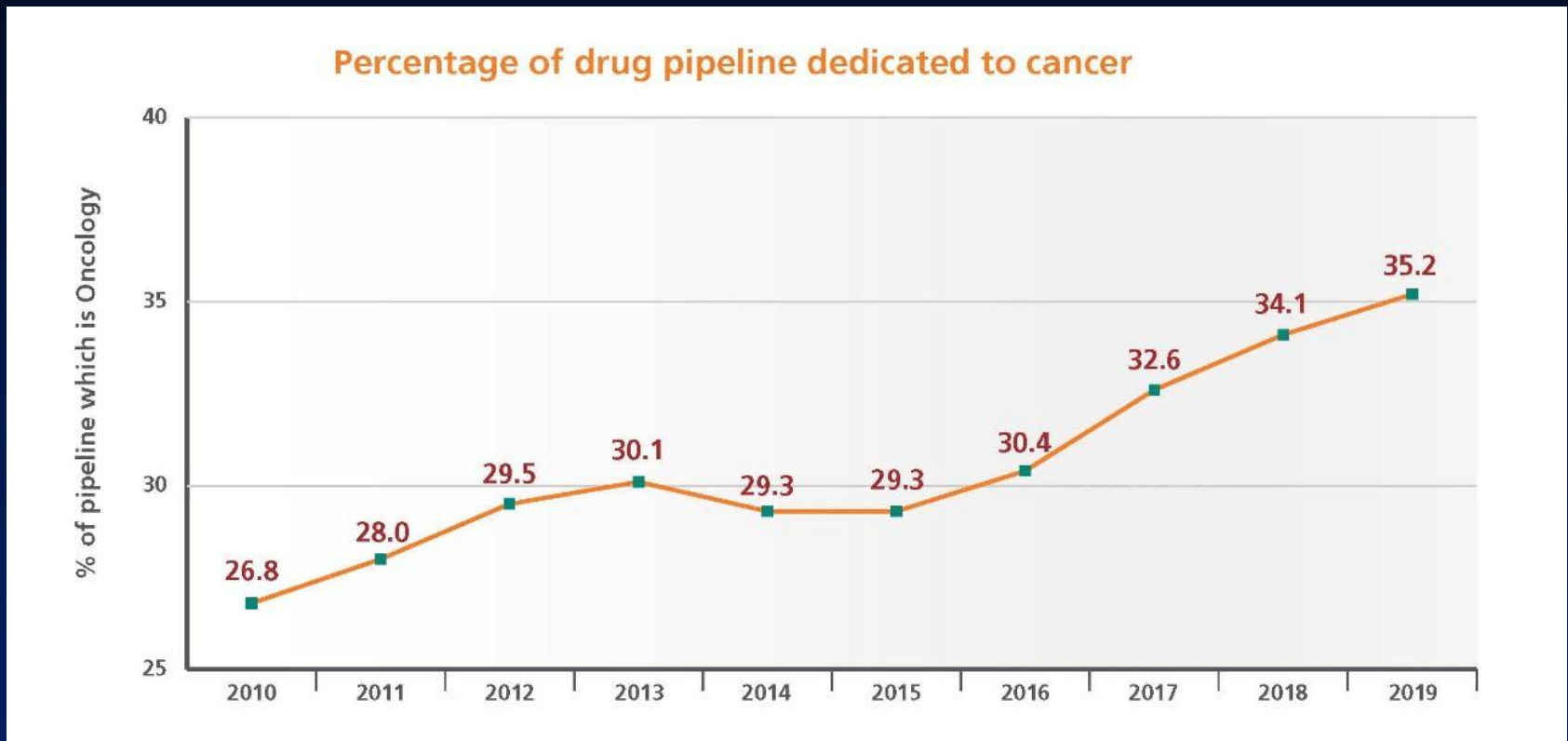
- Survival outcomes are improving in follicular lymphoma.
- Patients can have dramatically different outcomes with the SAME (or no) therapy.
- Treatment landscape is rapidly changing in FL
 - Many new agents are associated with rare, but serious adverse events.
 - >1500 oncology drugs currently in clinical development
- **New (and old) drugs still fail to achieve cure in the majority of patients**

Short (ish) History of Selected Therapy Development of Follicular Lymphoma

- Chemotherapy
- Targeted/Biologics



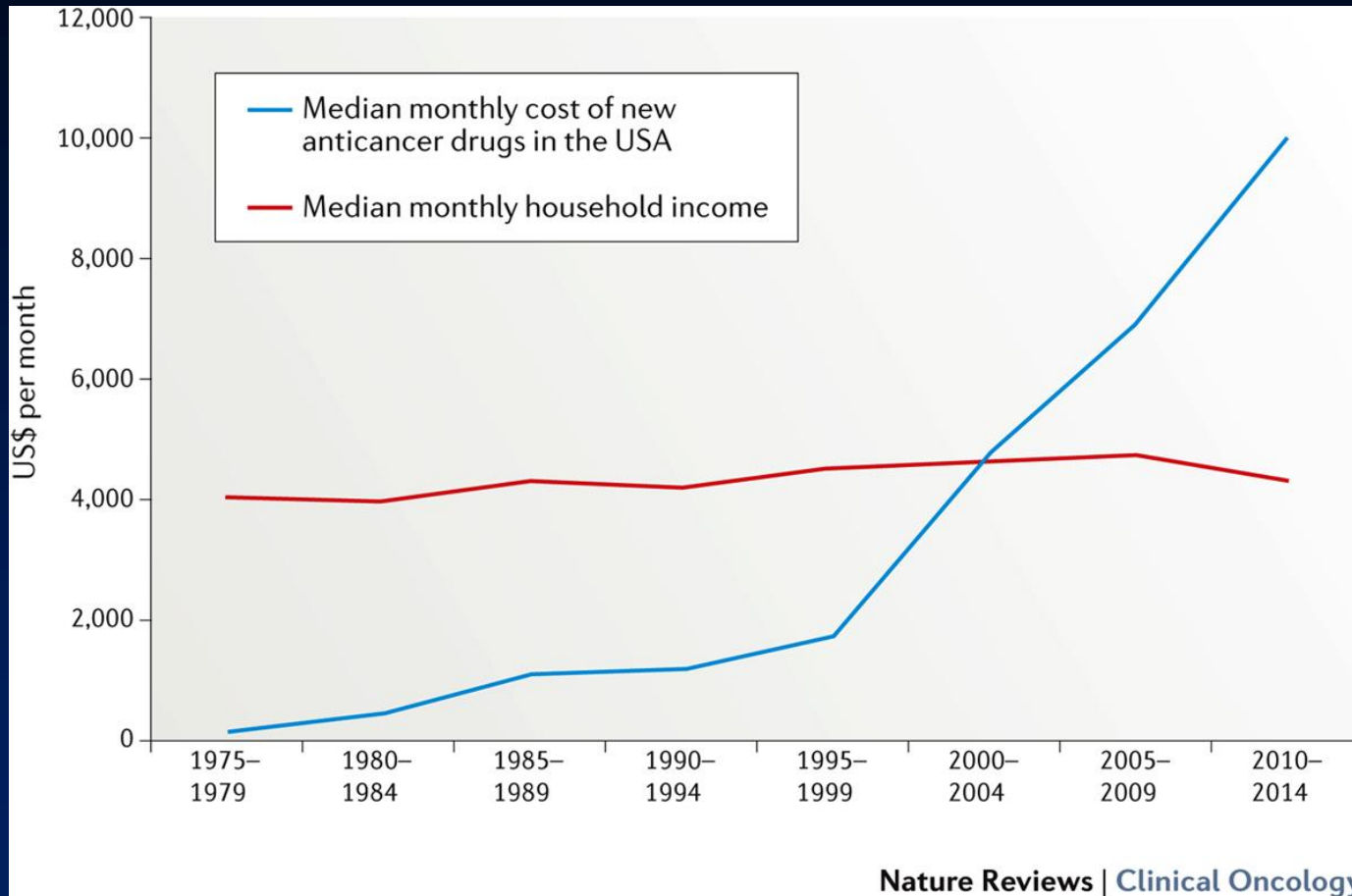
Pipeline Development of Oncology Drugs by Pharma



<https://www.optum.com/business/resources/library/oncology-drugs.html#>

Source: Informa. R&D Review 2019

Monthly launch price of a new anticancer drug, compared with median monthly household income in the USA



EFS12

Event Free Survival at 12 mo following *Diagnosis*

Fig 1a. OS from EFS12 for patients achieving EFS12
MER

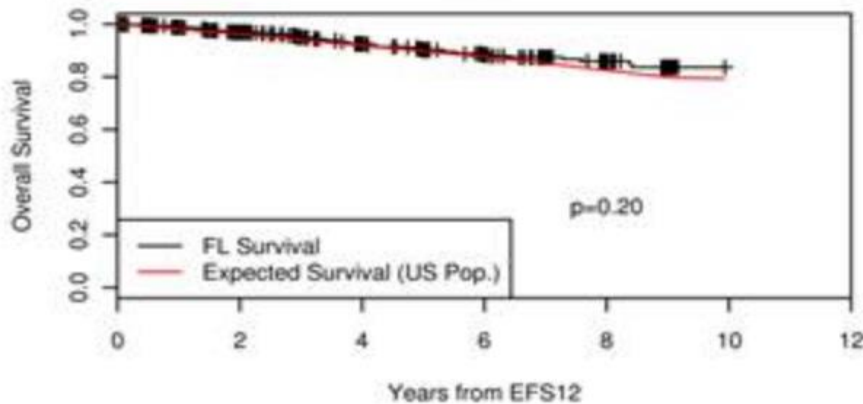


Fig 1b. OS from event for pts who fail to achieve EFS12
MER

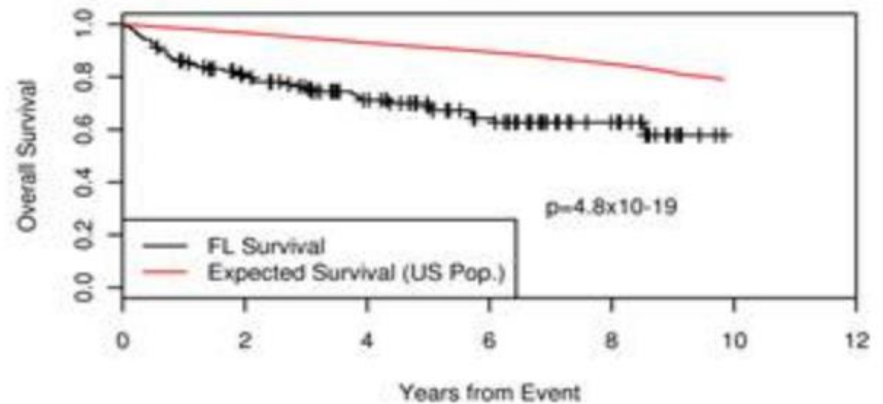


Fig 1c. OS from EFS12 for patients achieving EFS12
Lyon

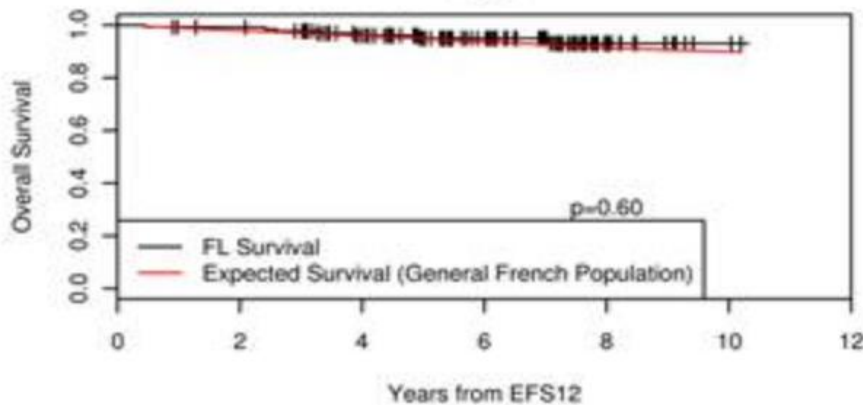
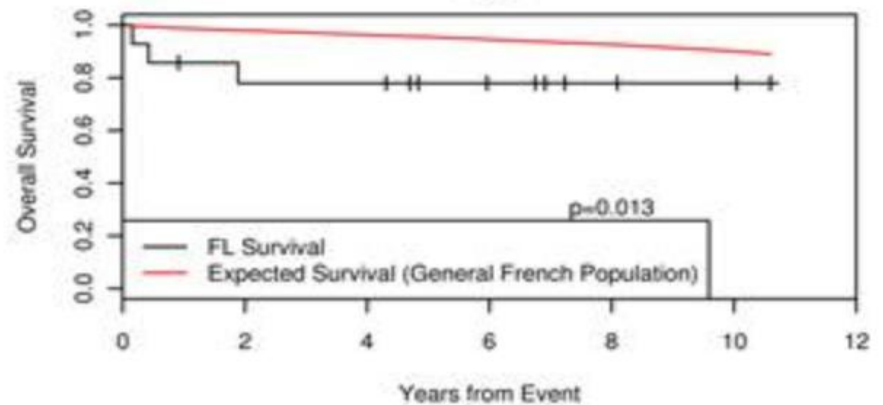


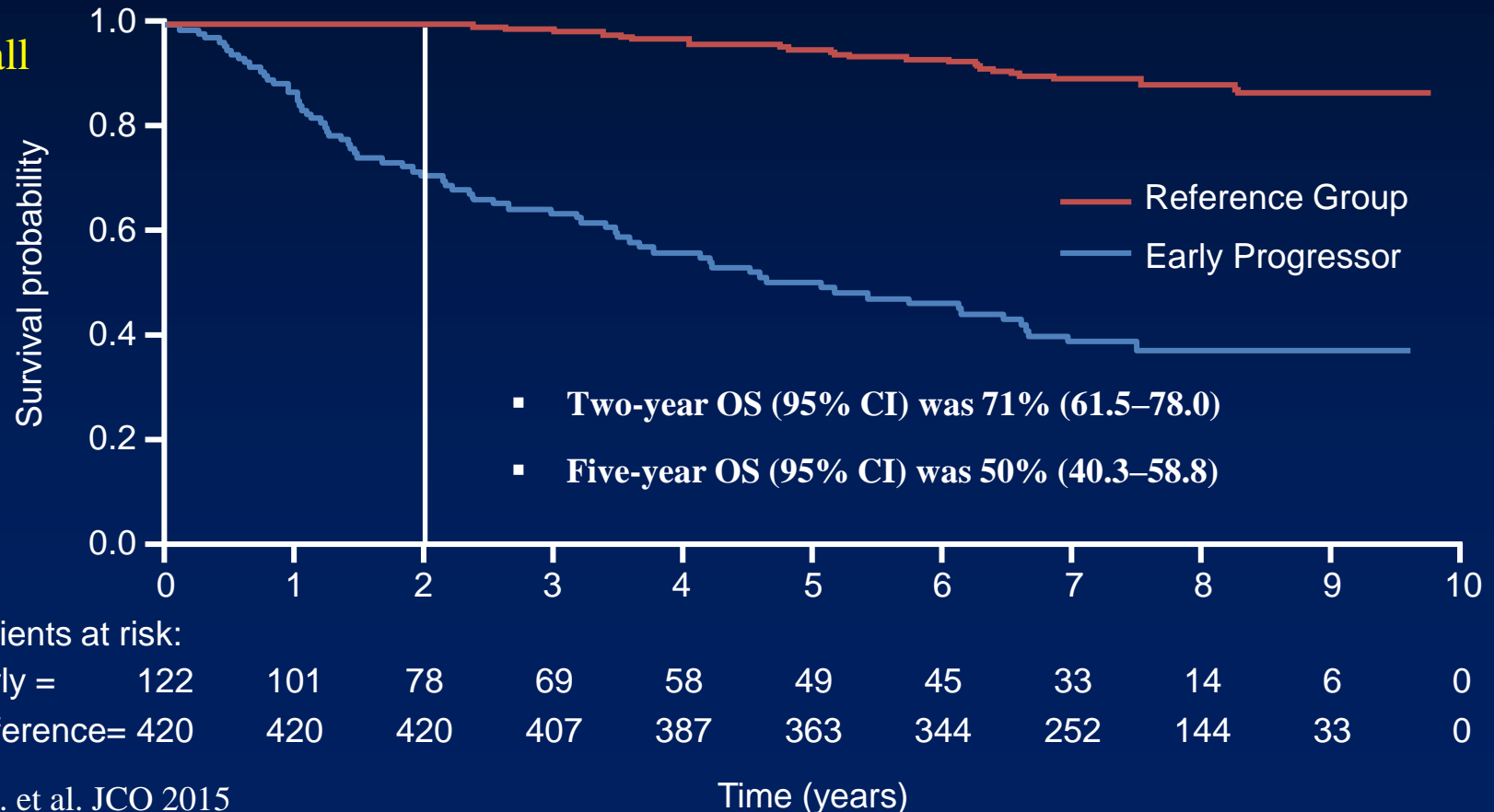
Fig 1d. OS from event for pts who fail to achieve EFS12
Lyon



OS of Patients With FL Who Relapsed Within 2 Years of R-CHOP (“Early POD”)

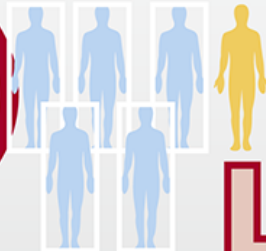
- 122 patients were classified as early progressors (n=110 POD and n=12 non-POD death within 2 years)

2/3 of all deaths

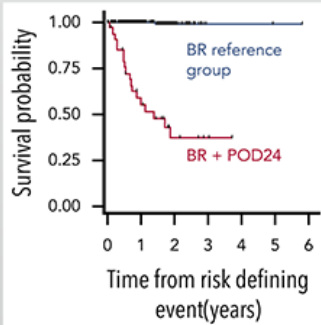
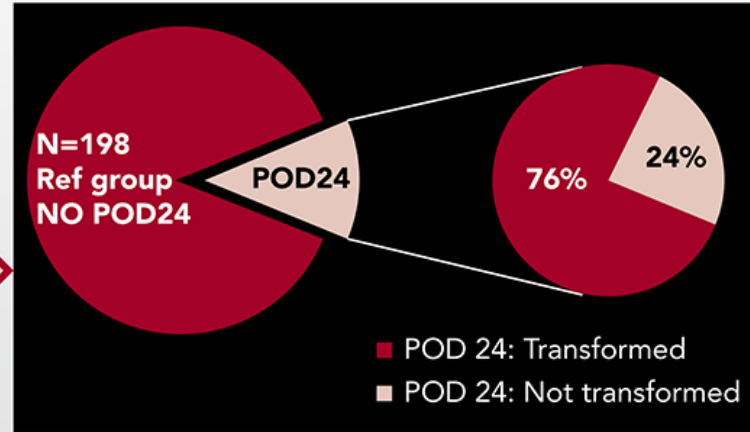
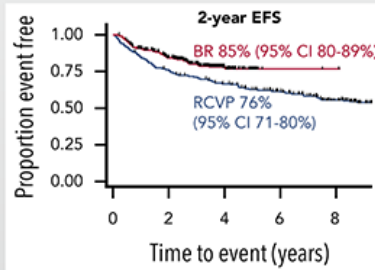


Early progression after BR is associated with high risk of transformation in advanced stage follicular lymphoma

296 BR treated FL pts



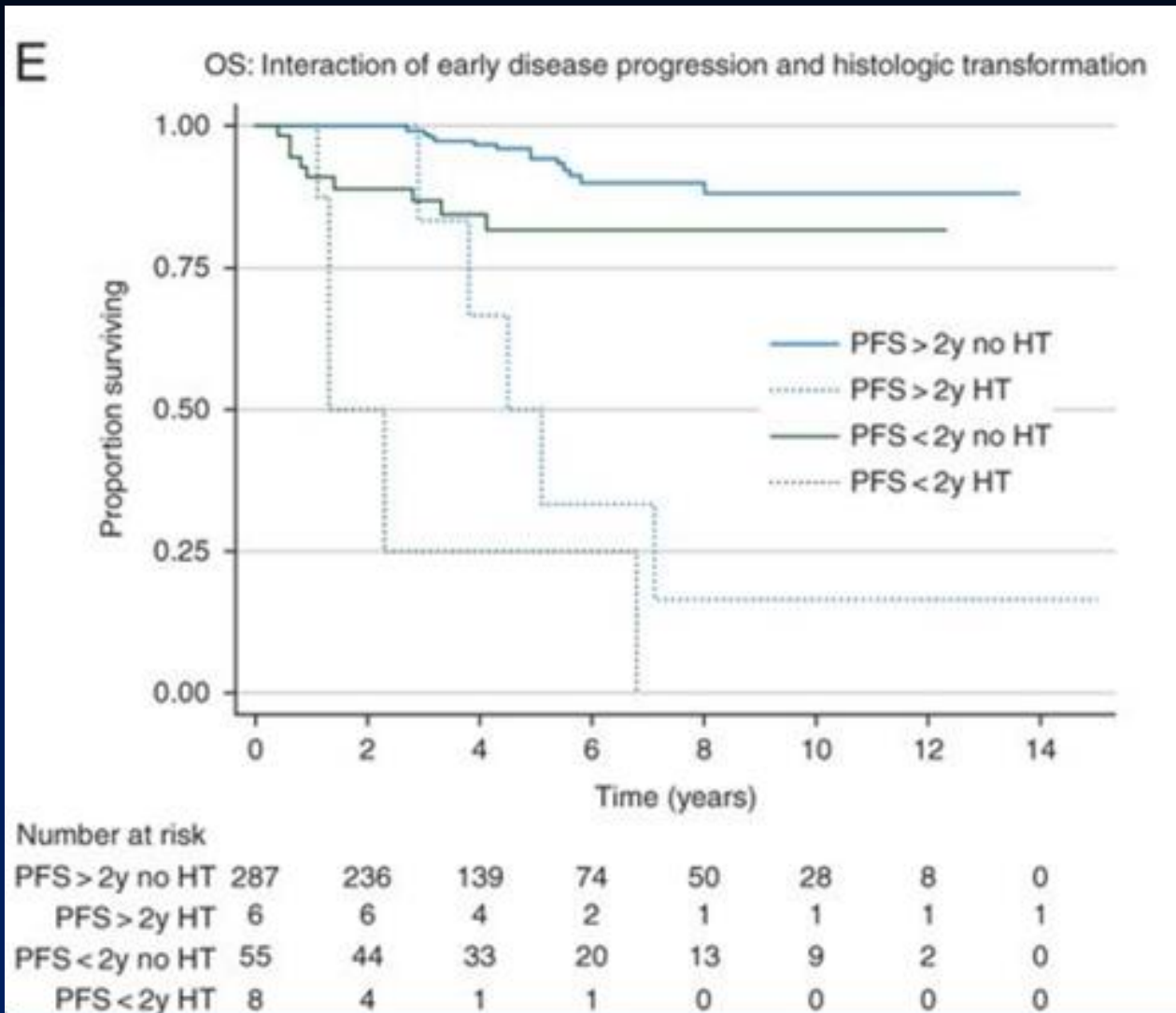
Good outcomes vs historical controls



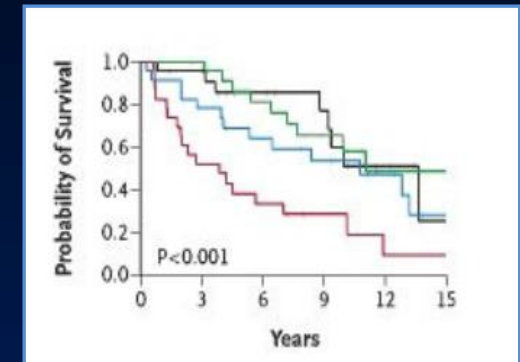
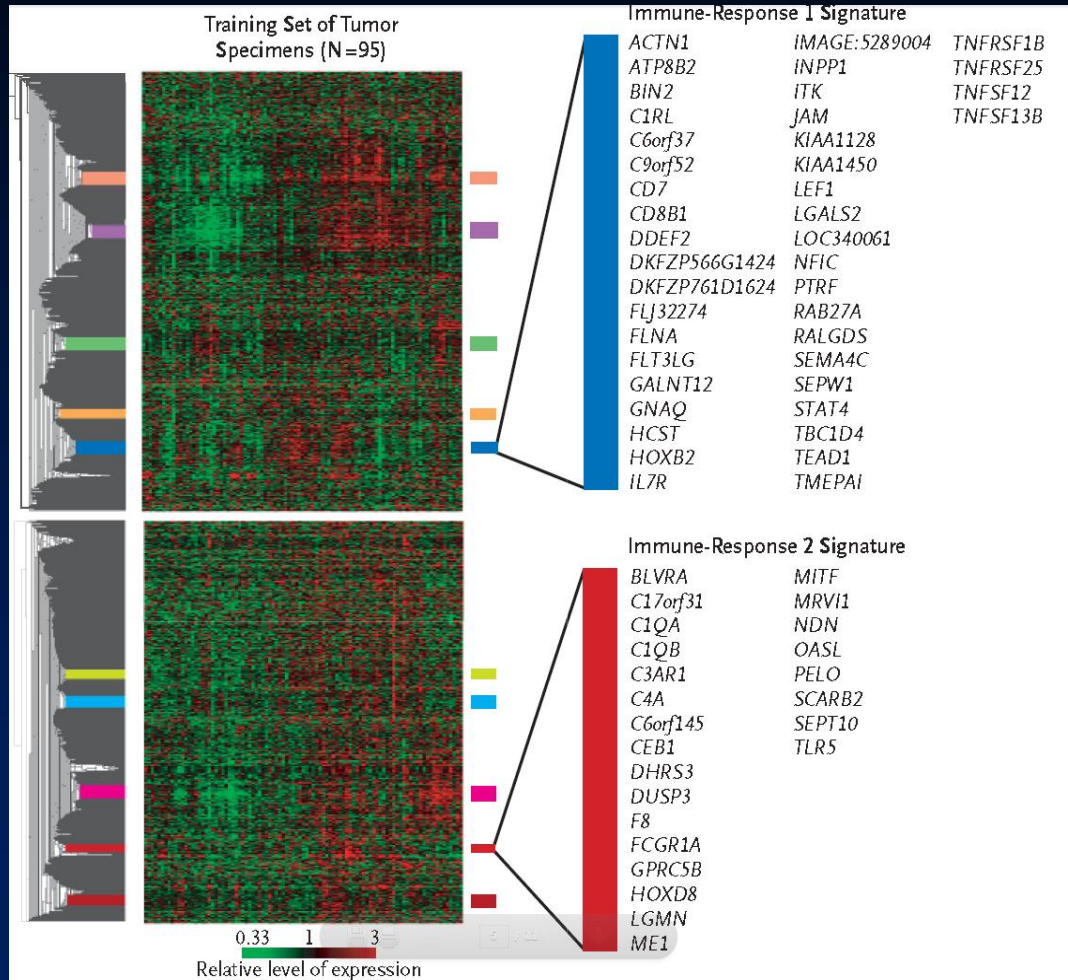
Poor OS in POD24 subgroup

The occurrence of early progression (POD24) may be decreasing following the introduction of BR, but the majority of POD24 patients have transformed lymphoma.

Transformation drives poor prognosis in POD24 Group



Genes Expression Predicts Survival

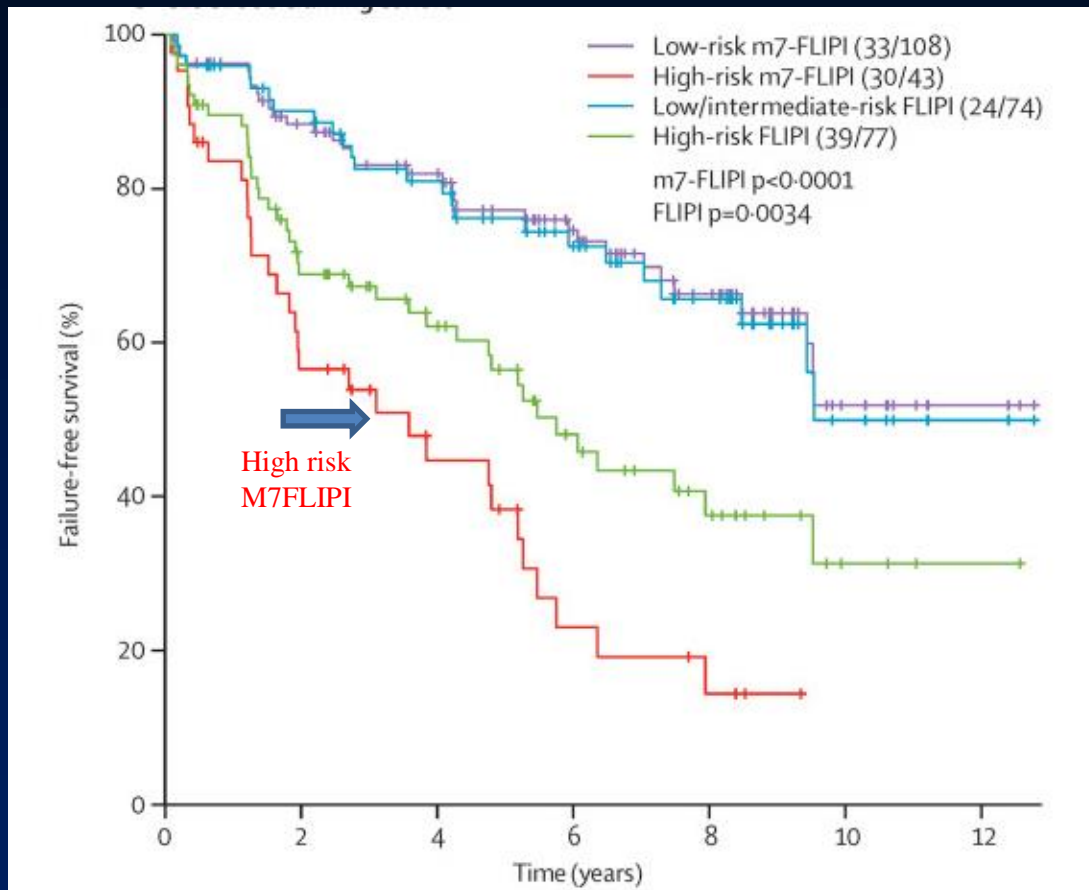


Quartile of SPS	Median Survival
1	13.6
2	11.1
3	10.8
4	3.9

M7 FLIPI

Clinicogenetic Risk Model

Deep sequencing of 74 mutations in 151 patients from biopsies of pts. Who got CHOP as frontline.

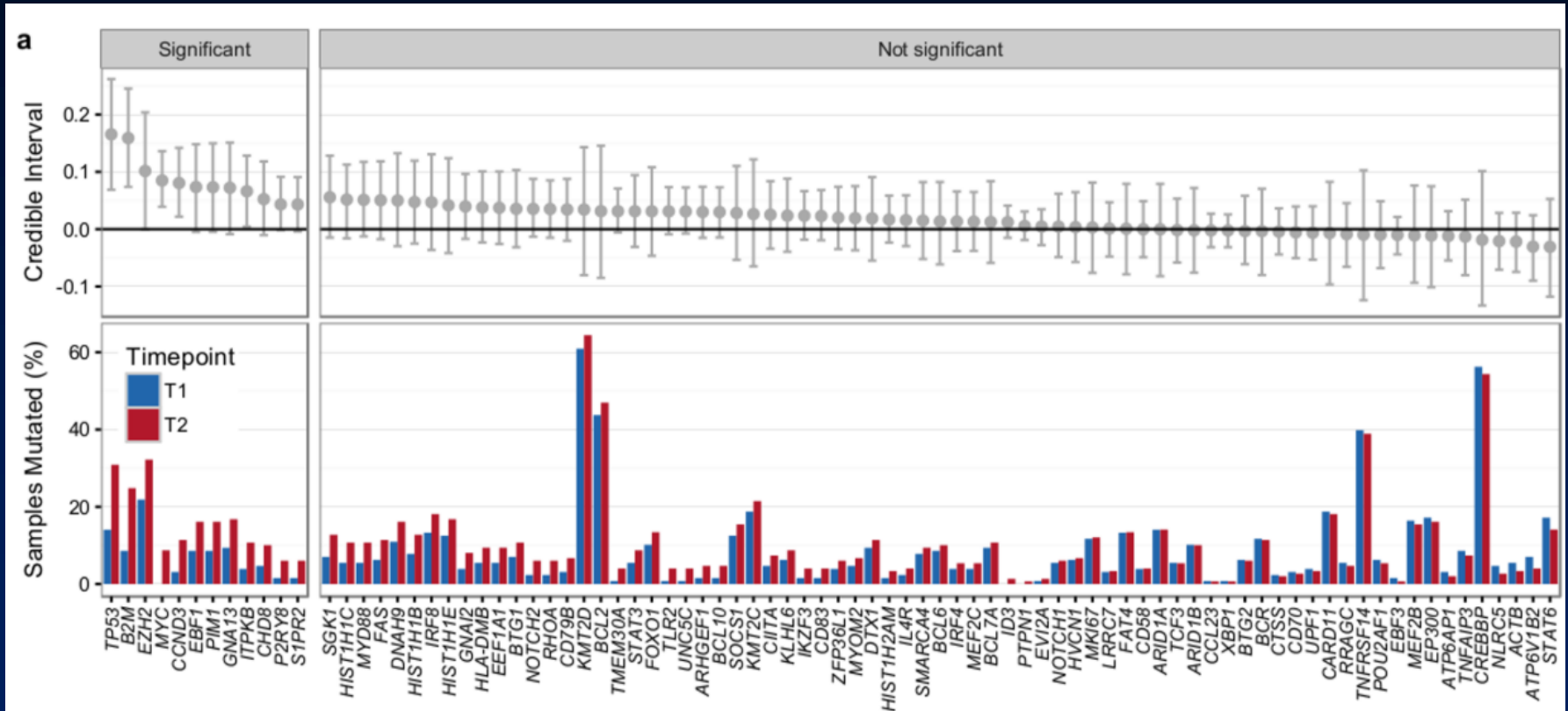


Risk Factors

Genes

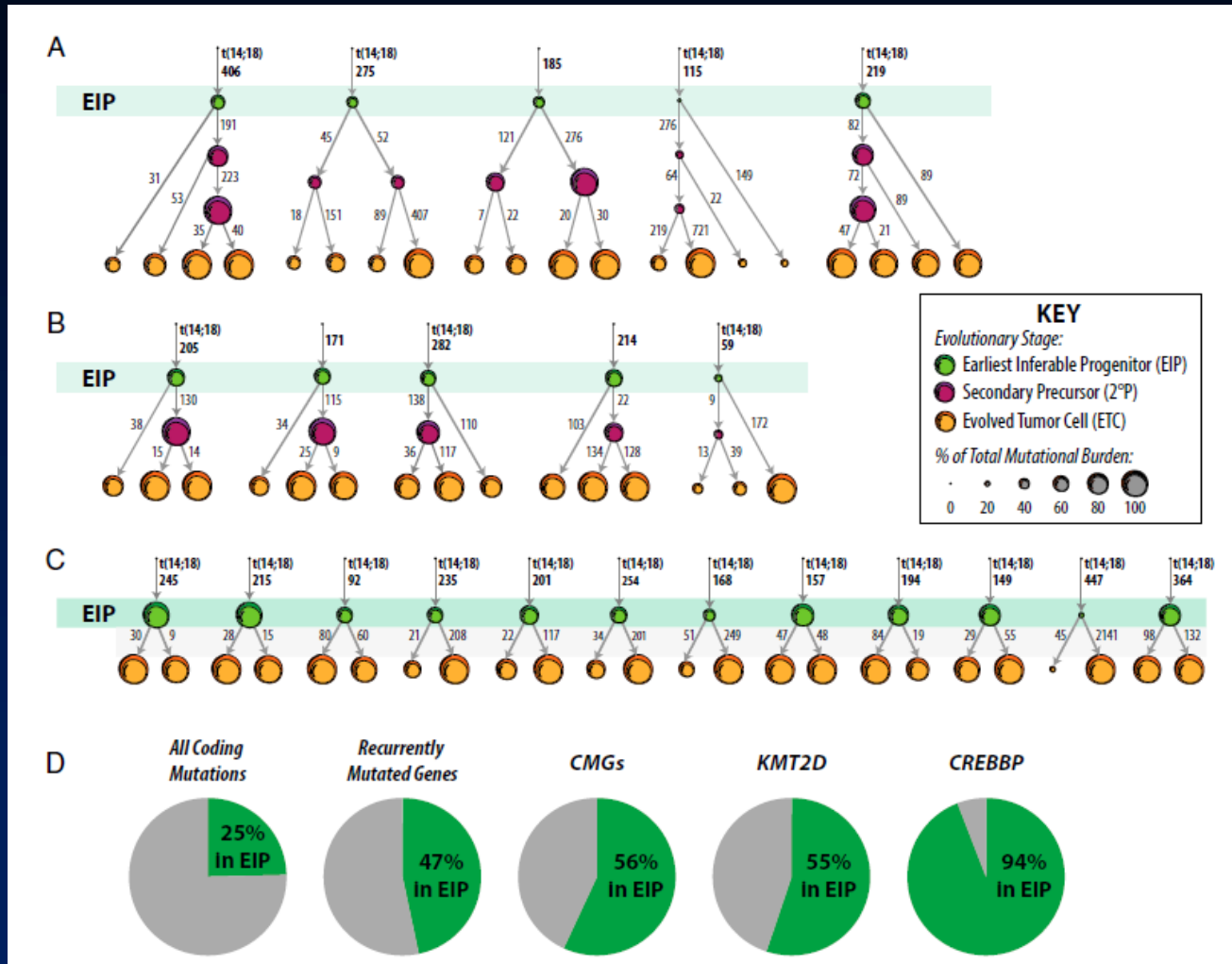
- EP300
- FOXO1
- CREBBP
- CARD11
- MEF2B
- ARID1A
- EZH2
- +
- FLIPI
- +
- ECOG PS

Mutations in FL



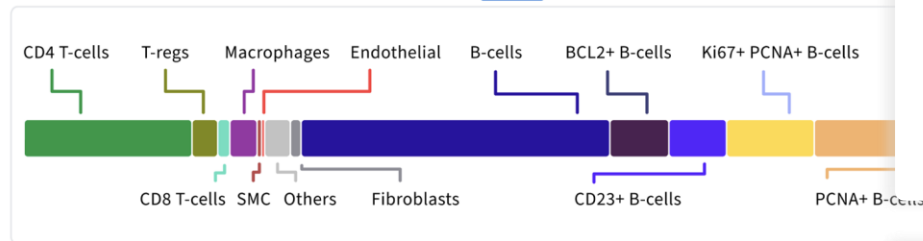
Targeted sequencing of 86 genes in samples from 159 transformed follicular lymphoma patients (128 T1 and 149 T2 samples)

Evolution of Mutational Burden in FL

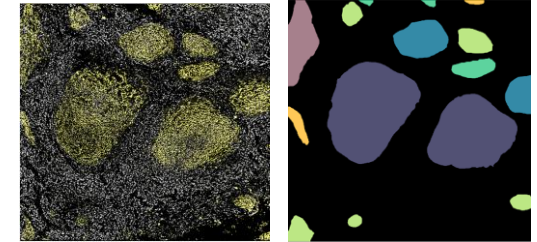


Intrafollicular cellular composition predicts patient outcome in follicular lymphoma. BioFLIPI Score

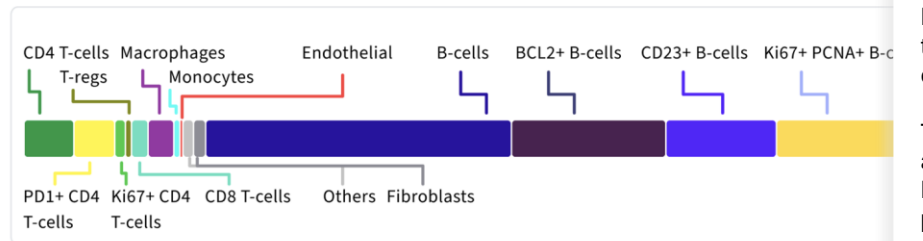
CD4 expression inside the follicle (BioFLIPI score) **18.7%**



Automated detection and recognition of follicles

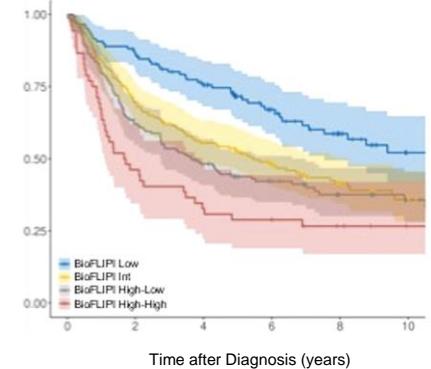


Normal Tonsil as a reference



BioFLIPI is a bio-clinical risk model that combined CD4 intrafollicular expression and FLIPI

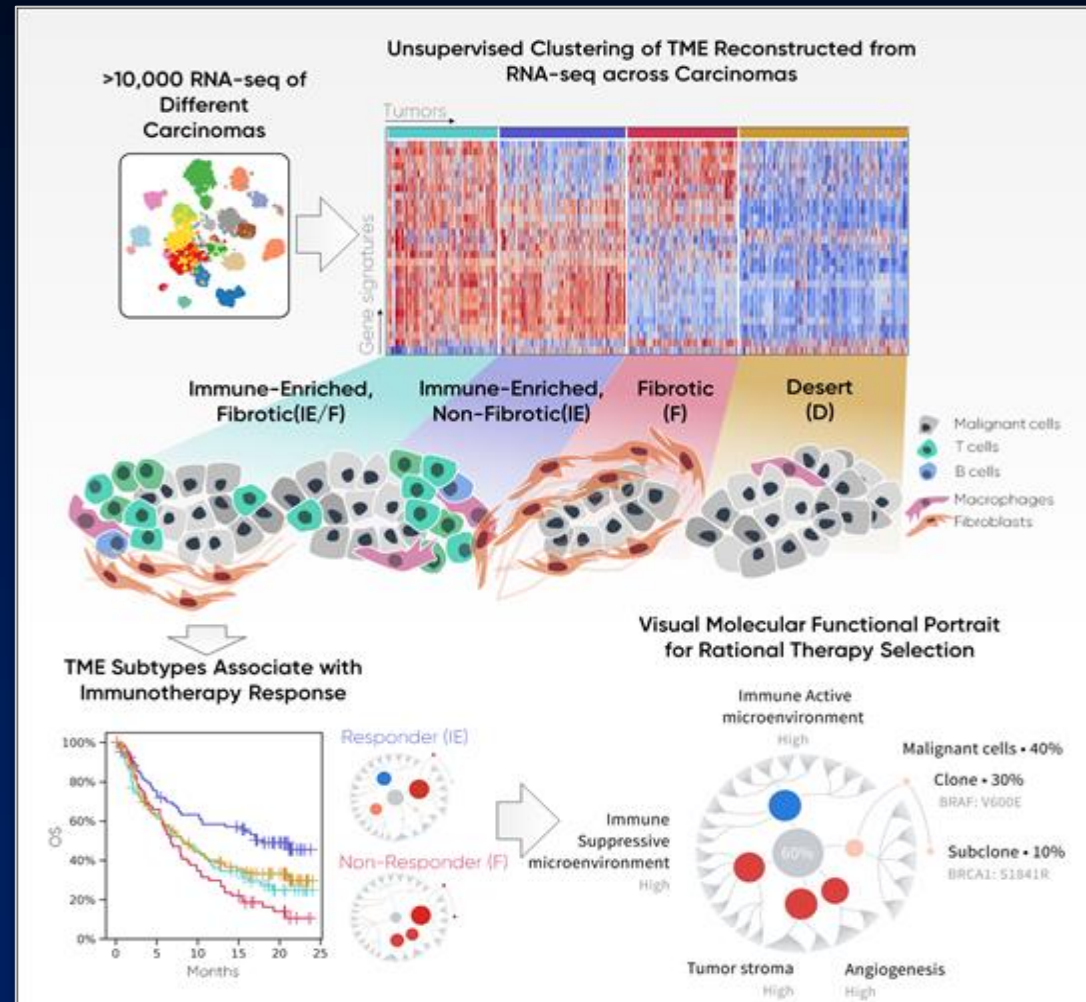
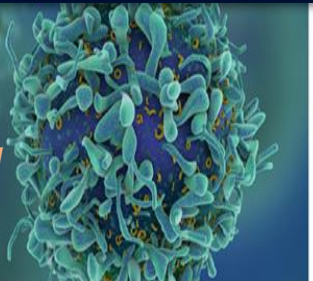
The BioFLIPI score was strongly associated with risk of early failure. BioFLIPI was also strongly predictive of continuous EFS, OS, and for EFS and EFS24 when restricted to IC-treated patients.



Unique Tumor Microenvironments Predict Response to Immunotherapy

cutting-edge
areas of cancer
research and
oncology in 2021

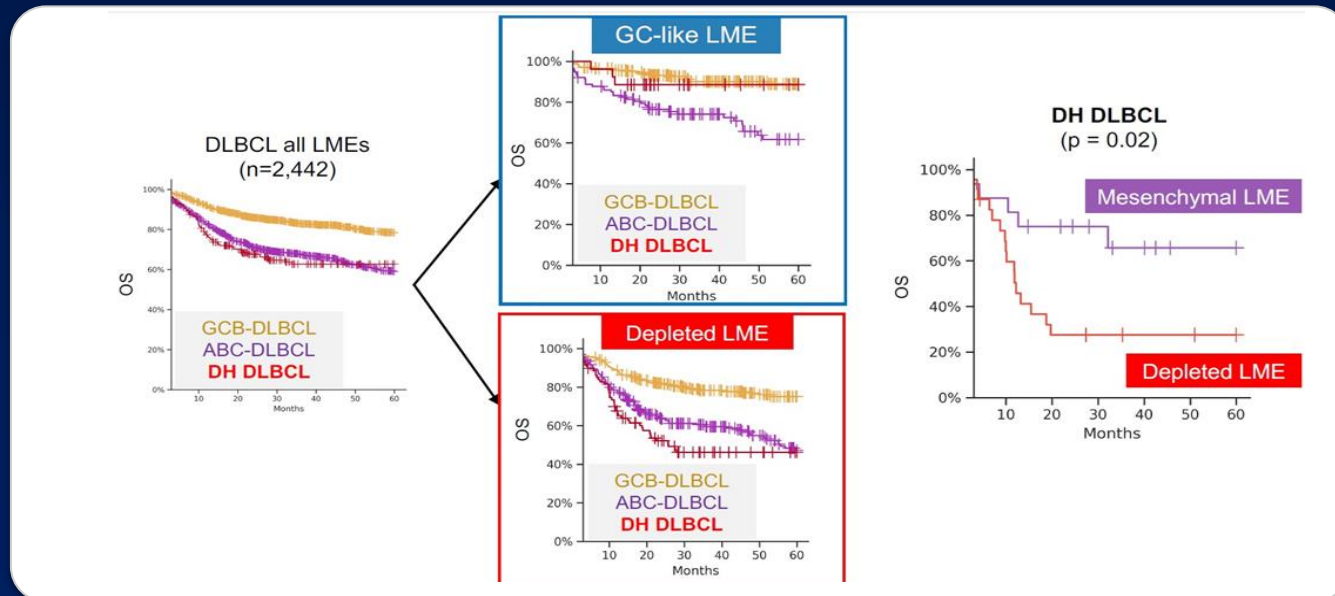
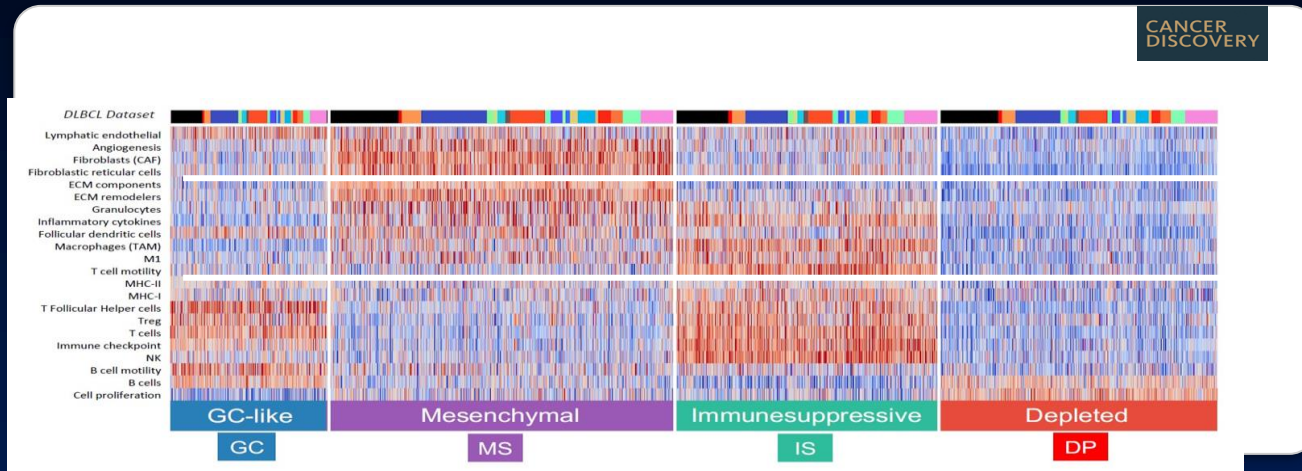
Editors' picks in 2021



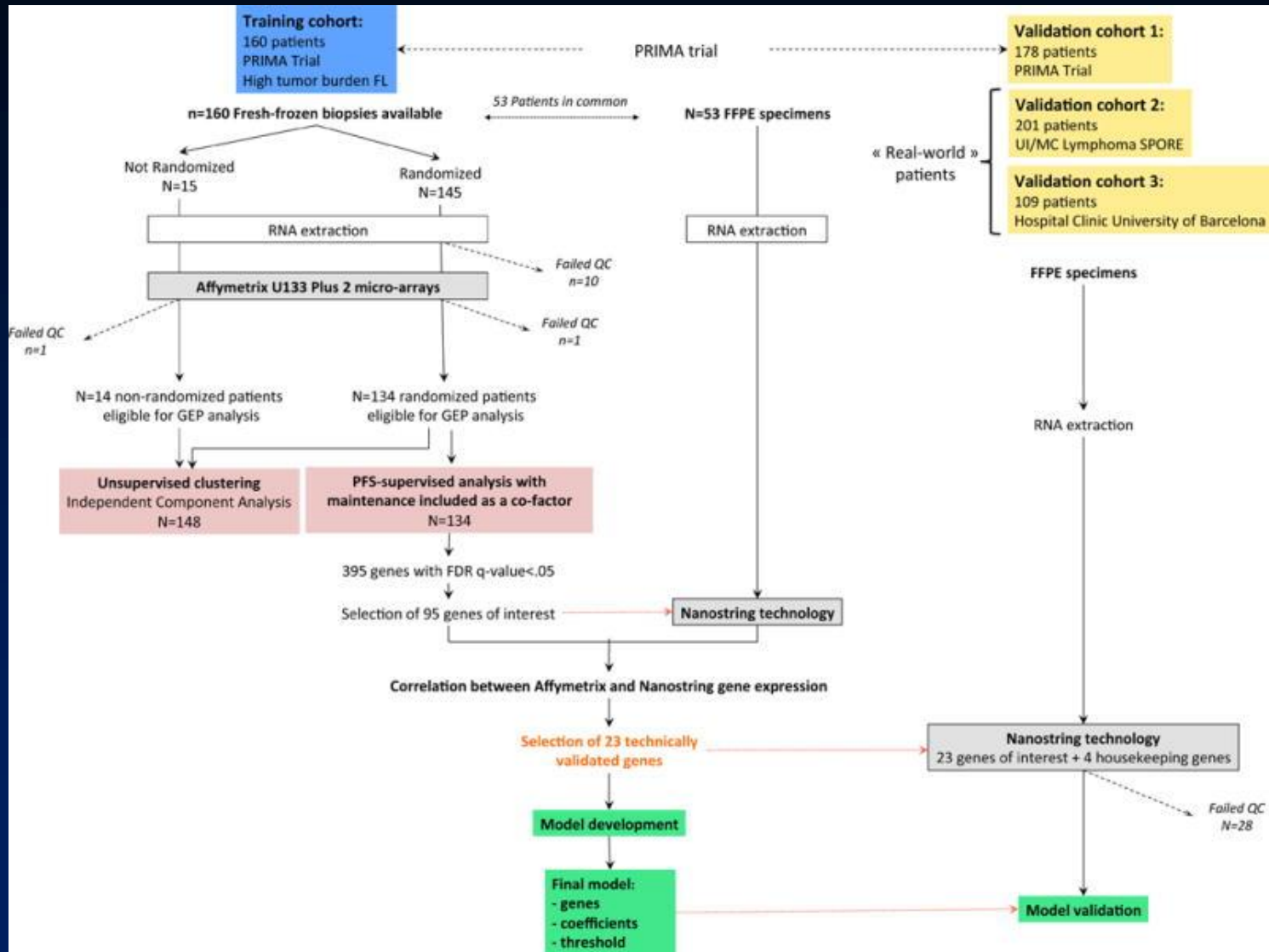
The LME subtype influences the prognosis of DH

DLBCL

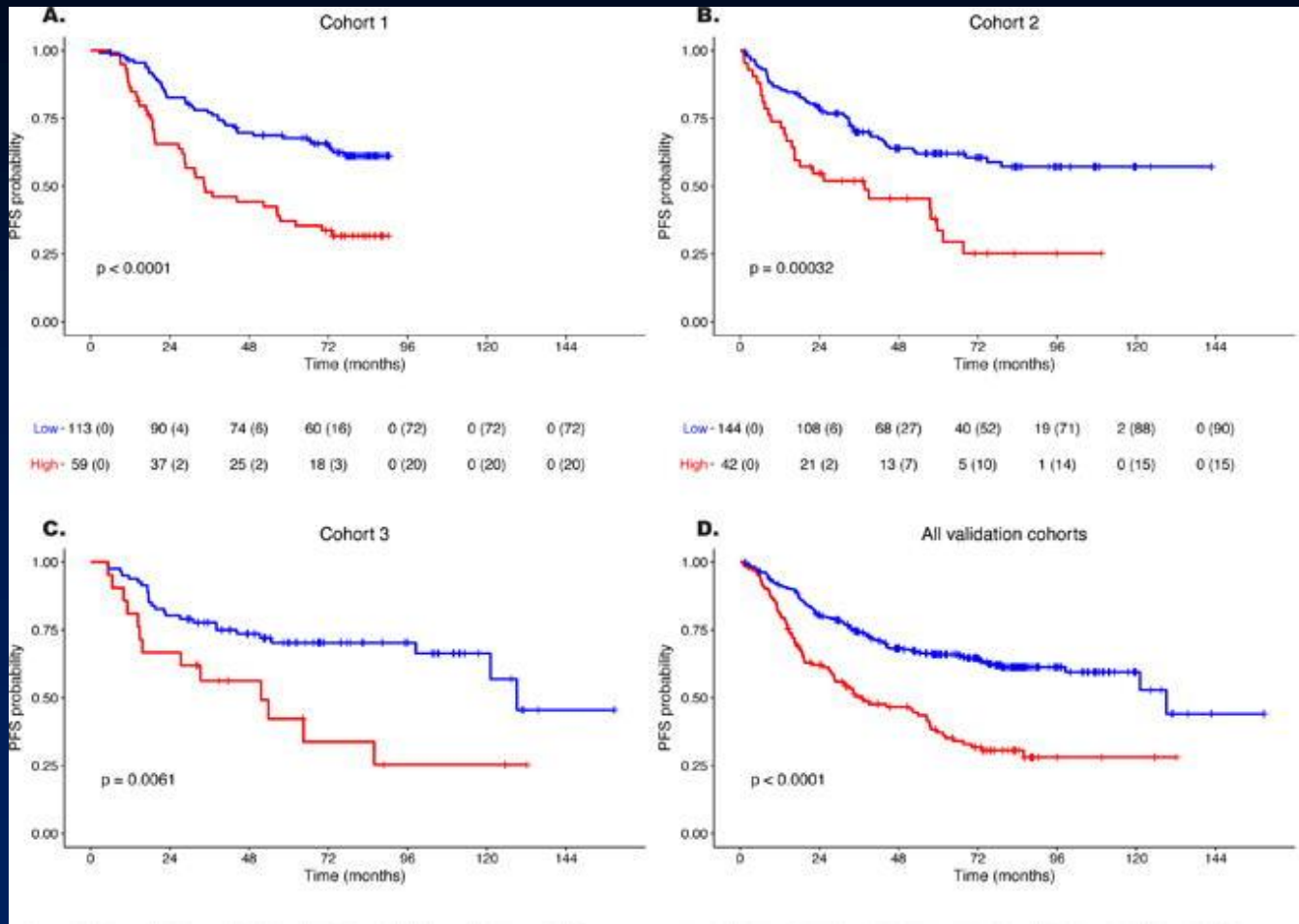
4,656 DLBCL GE Profiles



Developing Gene Based Scores in FL



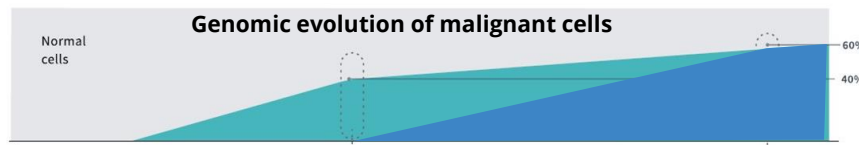
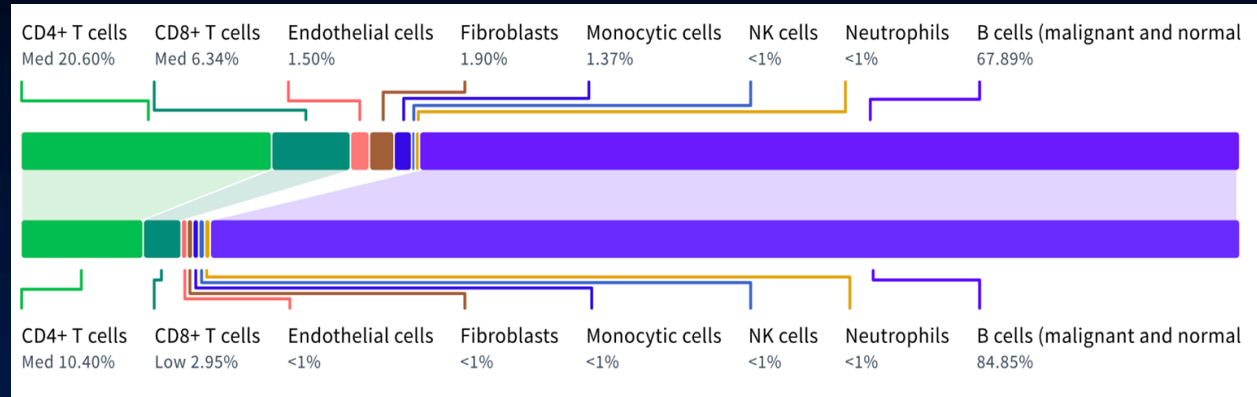
GEP Based Predictive Scores in FL



Tracking Dynamic Changes in Follicular Lymphoma

2014 Biopsy

2021 Biopsy



2014 Biopsy

2021 Biopsy

Summary: Genomic Dynamics

FFPE sample (2014) vs. FF sample (2021)

Two new CNA alterations

- *CDKN2A* loss (-2 copies)
- *CDKN2B* loss (-2 copies)

KMT2D E1067* nonsense, loss of function mutation

- (VAF 1% → VAF 53%).

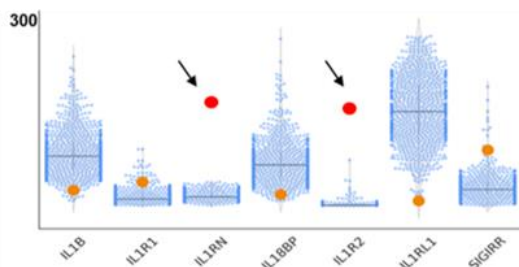
Two mutations of *BCL2* were detected.

- *BCL2* G36D mutation was outside of the limit of detection (VAF 1%) in the first biopsy and was detected in the new FF sample (VAF 35%).
- *BCL2* Y18F mutation in both, VAF increased from 18% to 33%.

Adaptive Immune Profiling

53 year old male with FL

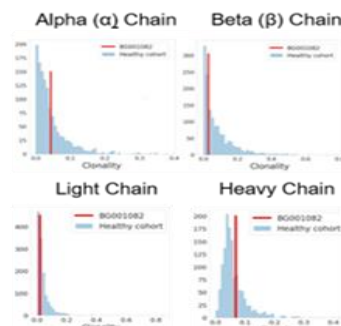
Cytokines/Chemokines/Growth Factors Receptor & Ligand Analysis



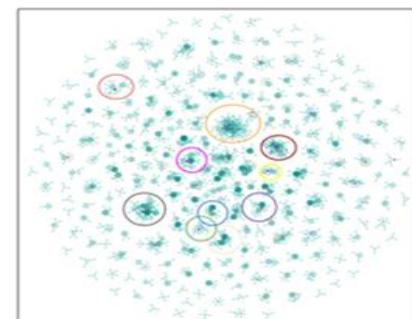
Significant Increases
(<3 S.D. over health cohort)

TNFRSF1A *TNFSF10*
TNFRSF10C *IL1RN*
RELT *IL1R2*
PGLYRP1 *CXCR2*
LTB *CXCR4*

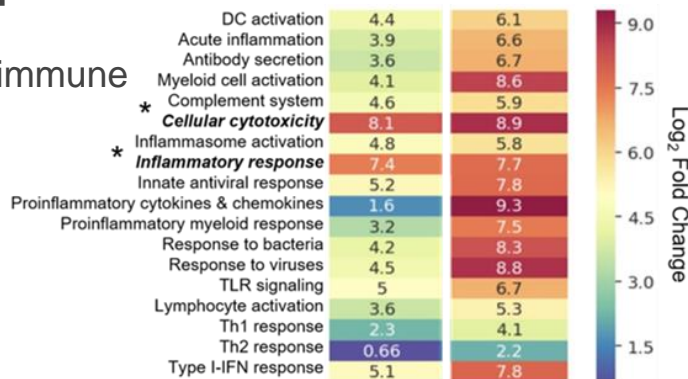
TCR/BCR Clonality



BCR hypermutation tree (Kappa)

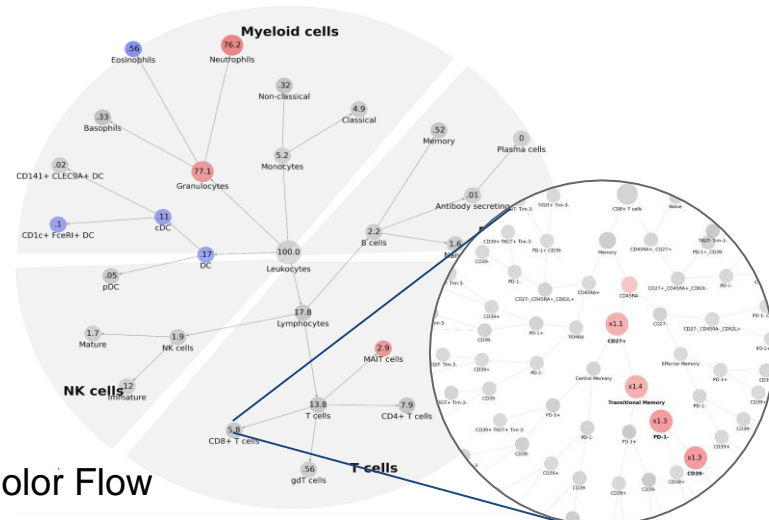


Bulk RNA-expression signatures for functional immune pathways



BG001082 (PL) Activated cohort

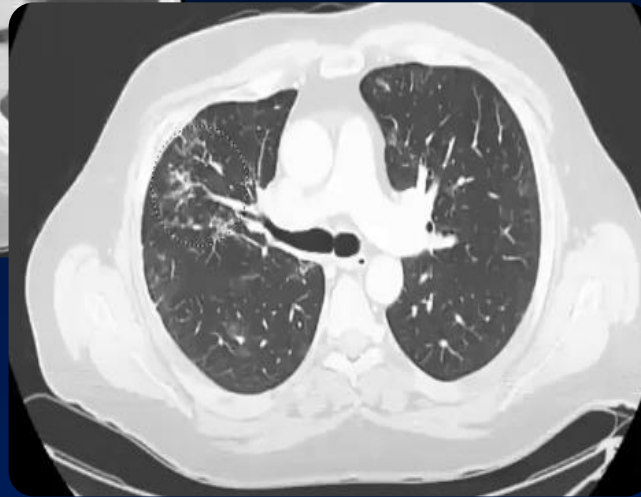
Immune Profiling in Peripheral blood



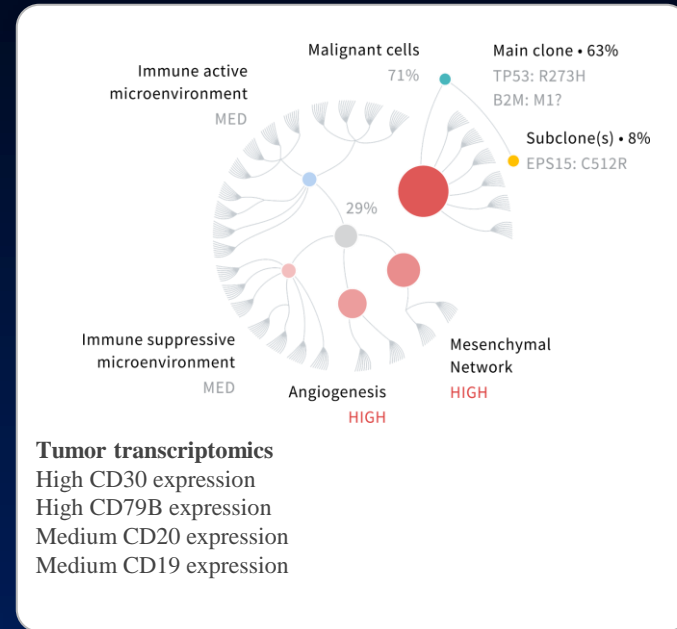
Unpublished work

30 Color Flow

Utilizing Precision Medicine Approaches in Lymphoma



Transformed
MZL



Conclusions

- Changes in treatment options have improved survival in most patients with follicular lymphoma.
- Today, Clinical models are used (FLIPI, GELF, remission duration, number of prior lines) to determine risk and help select appropriate treatment.
- Emerging biologic models combining genomic, molecular, and microenvironment signals have the potential to identify patients who will most likely response to more targeted treatment strategies.