19th International Ultmann Chicago Lymphoma Symposium

LIVE Symposium

APRIL 29-30
2022

19TH ULTMANN

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Biology of Follicular Lymphoma

R. Kridel, Princess Margaret Cancer Centre, Toronto

Disclosures

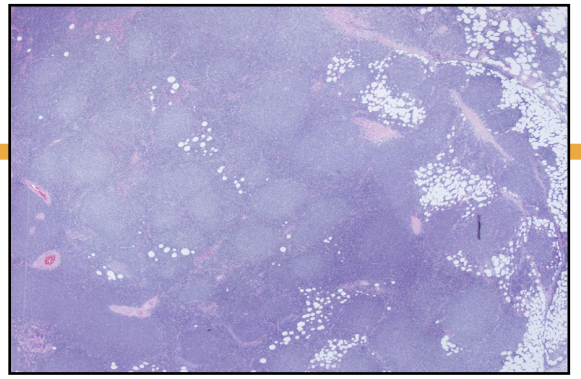
- Research funding from Roche and Abbvie.

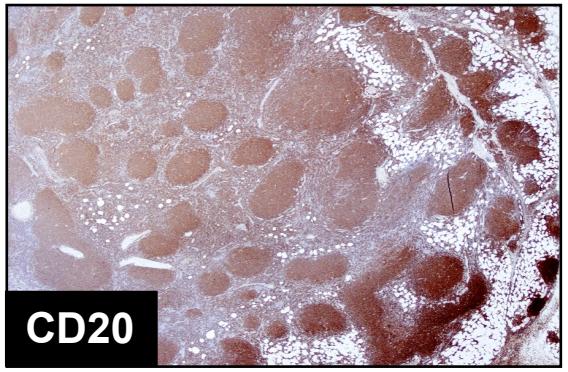
Pathology

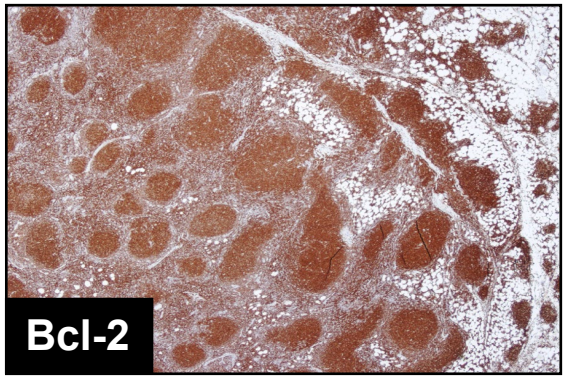
- FL grade 1-3A -> classic FL (cFL)
- FL grade 3B -> follicular large B-cell lymphoma (FLBCL)

- t(14;18) in ~85% of cases

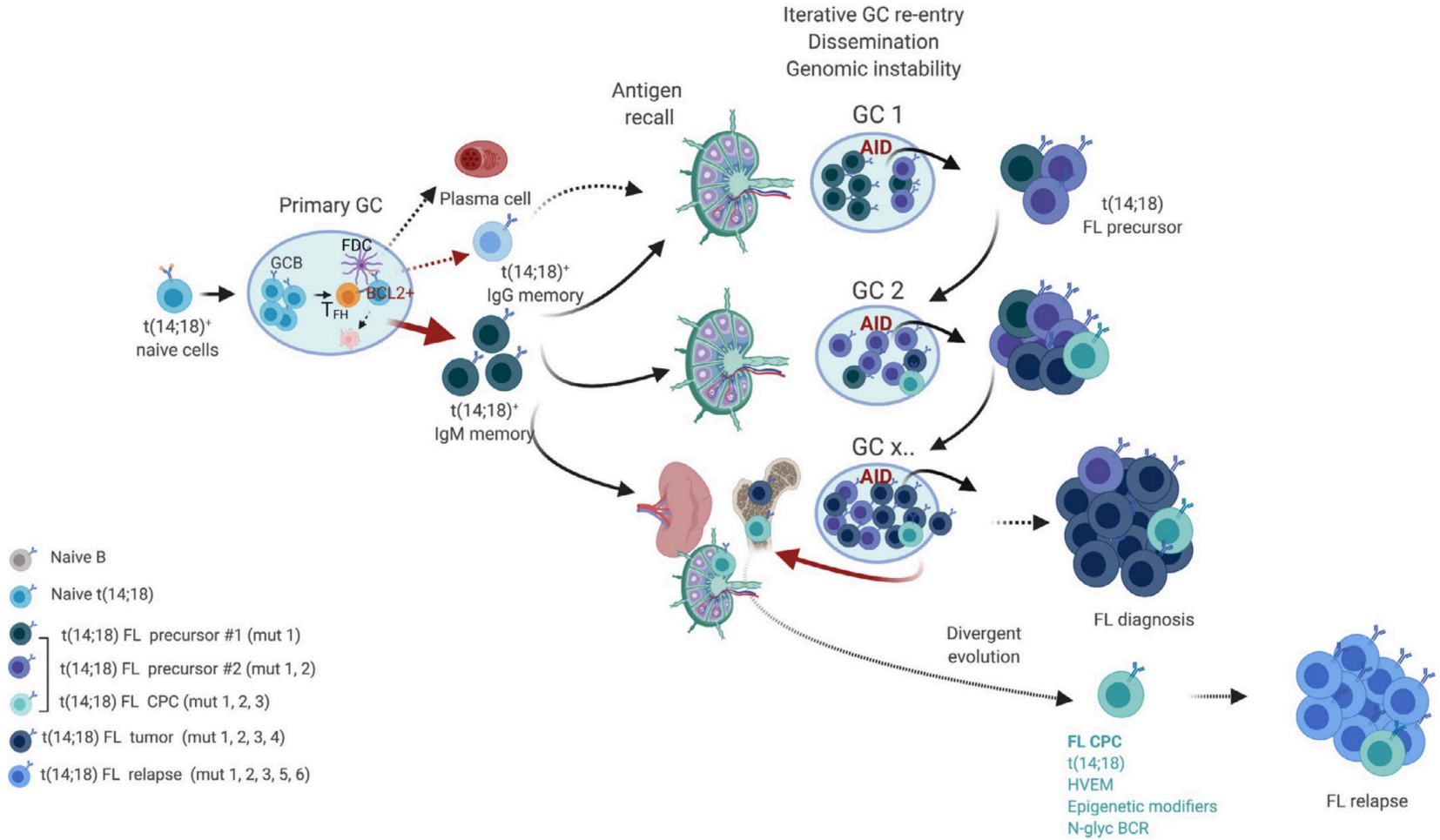
- Variations:
  - In-situ follicular B-cell neoplasm
  - Paediatric-type follicular lymphoma
  - Duodenal-type follicular lymphoma
  - Primary cutaneous follicle centre lymphoma





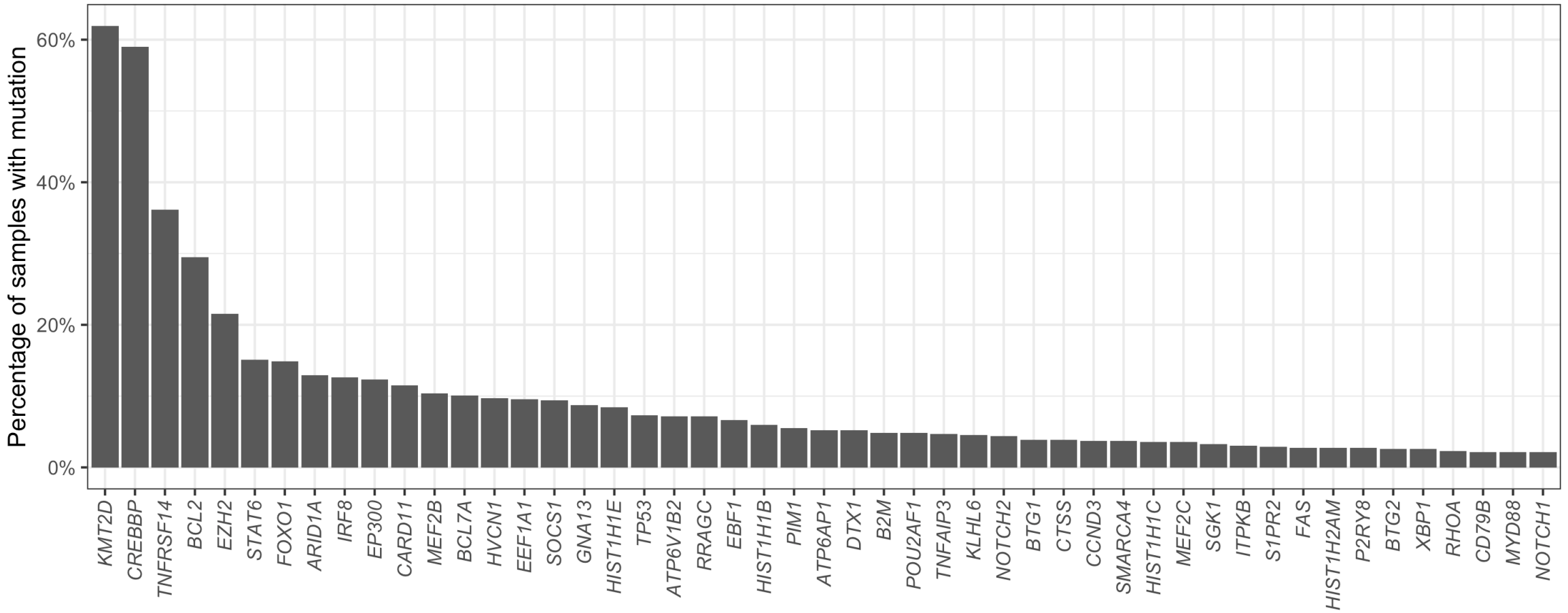


Stepwise model of follicular lymphoma pathogenesis



Milpied et al. Advances in Immunology, 2021

Mutational landscape



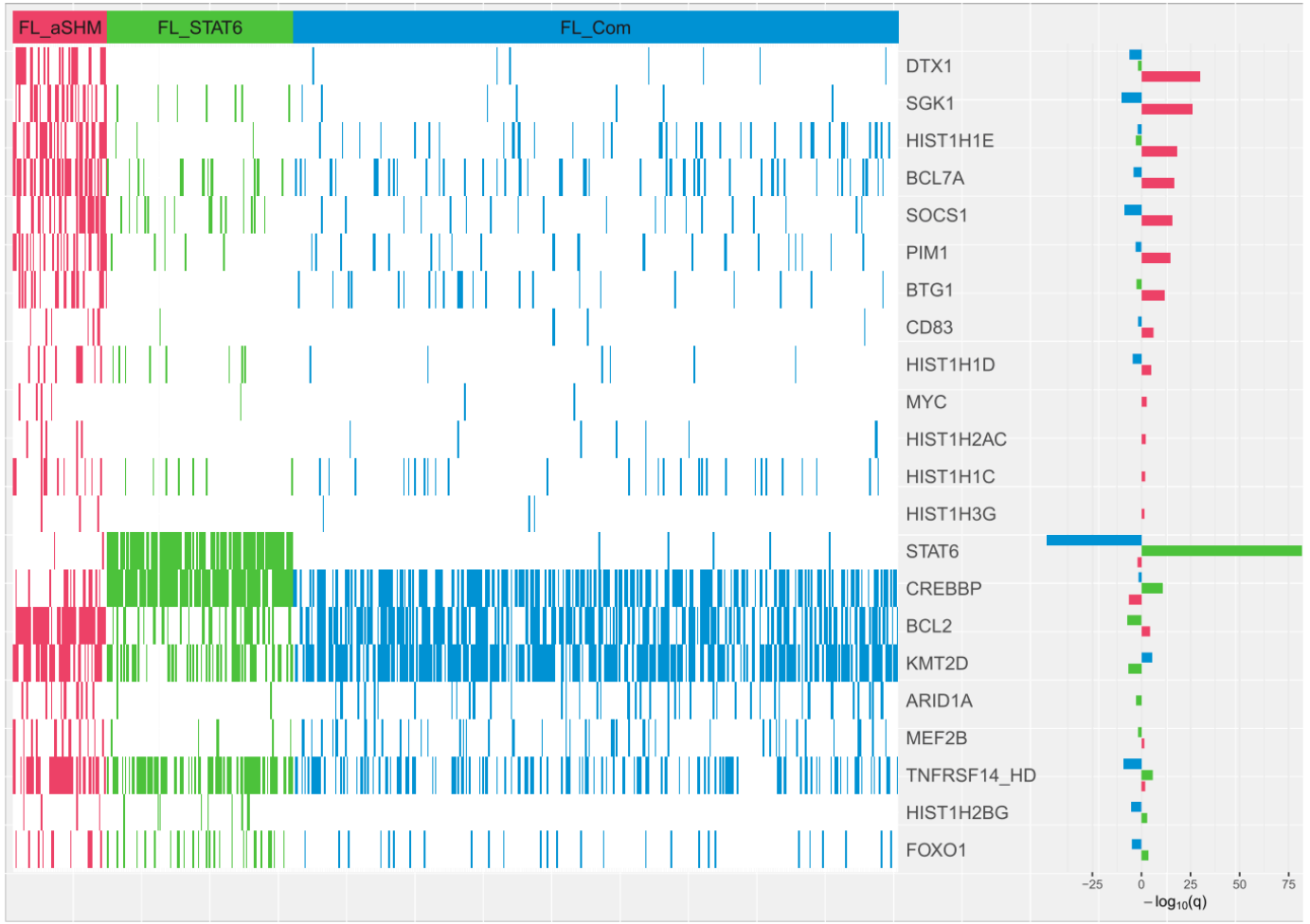
Genetic subtypes in FL

UK Haematological Malignancy Research Network

548 pts

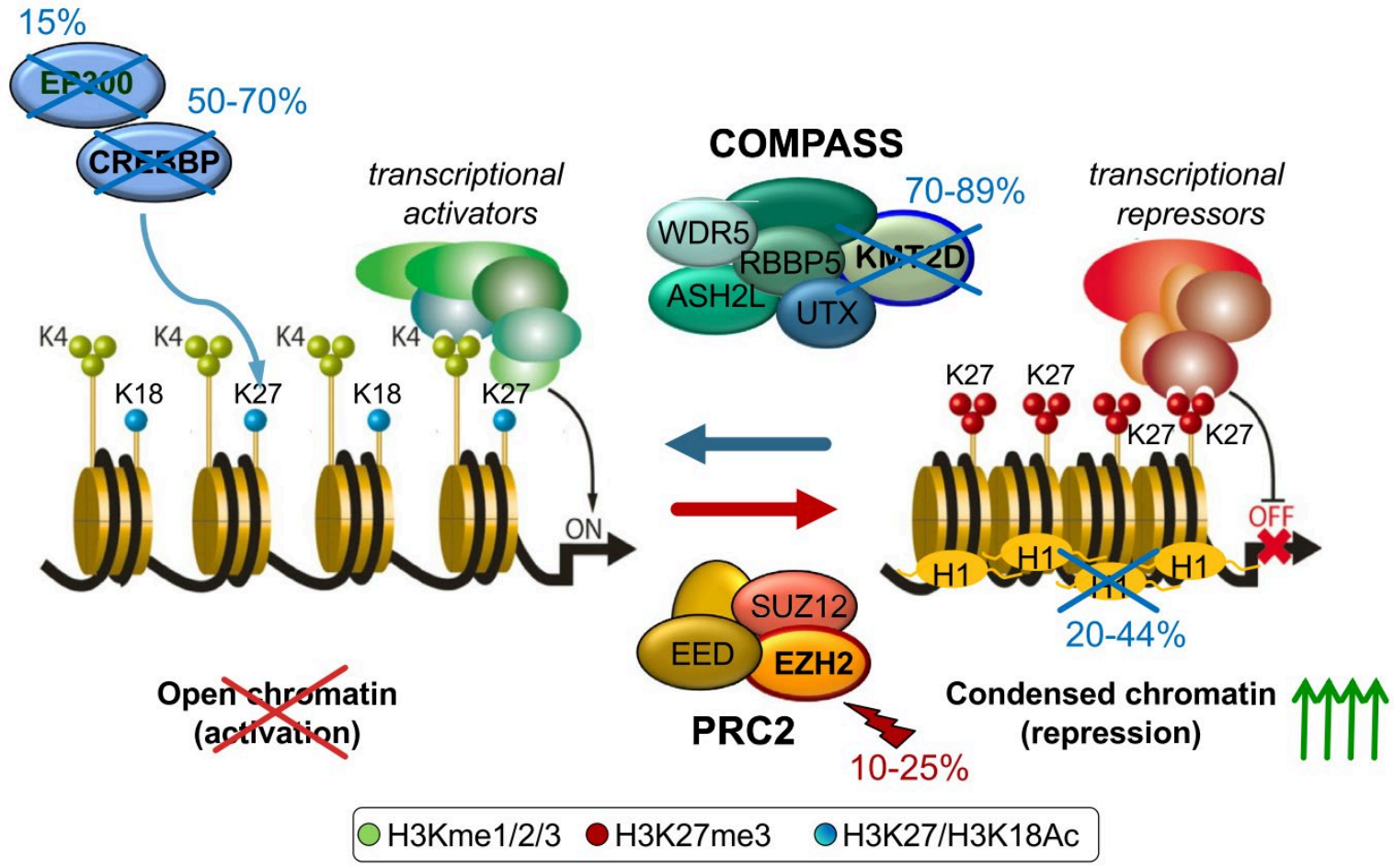
Targeted DNA sequencing (293-gene panel)

aSHM subgroup associated with inferior outcome (older age)



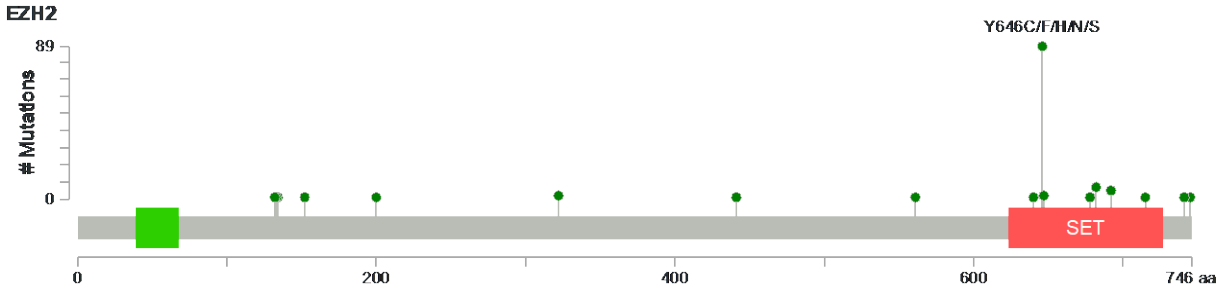
Crouch et al. Blood Advances, 2022

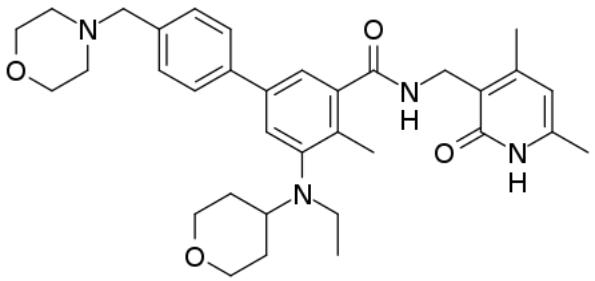
Remodeling of epigenetic machinery

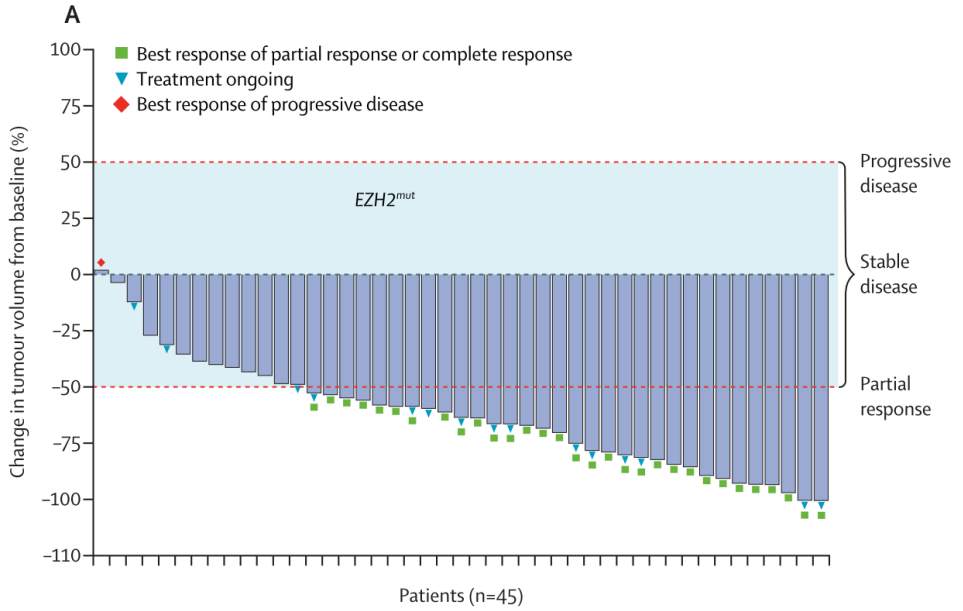


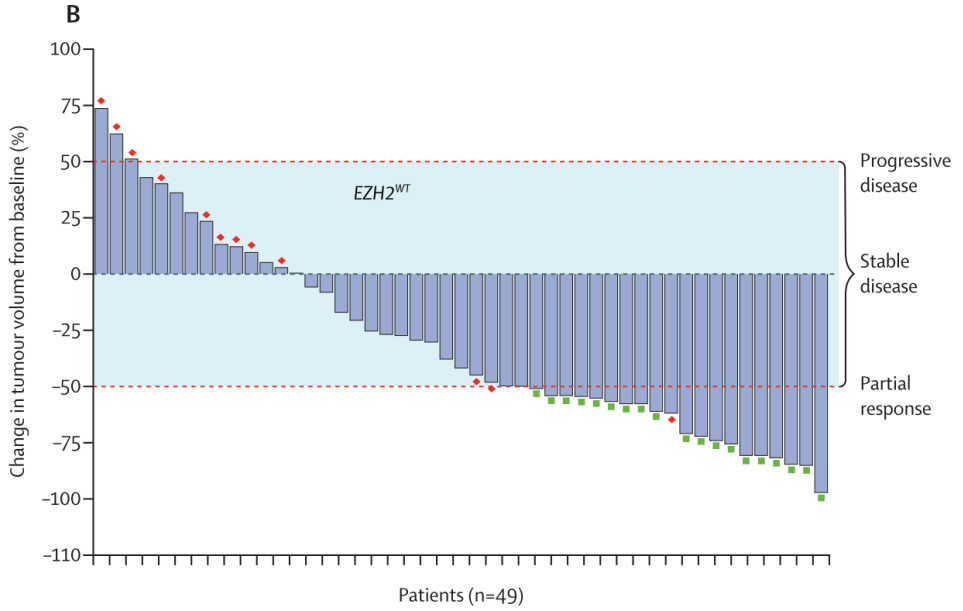
Milpied et al. Advances in Immunology, 2021

EZH2 – target for therapy







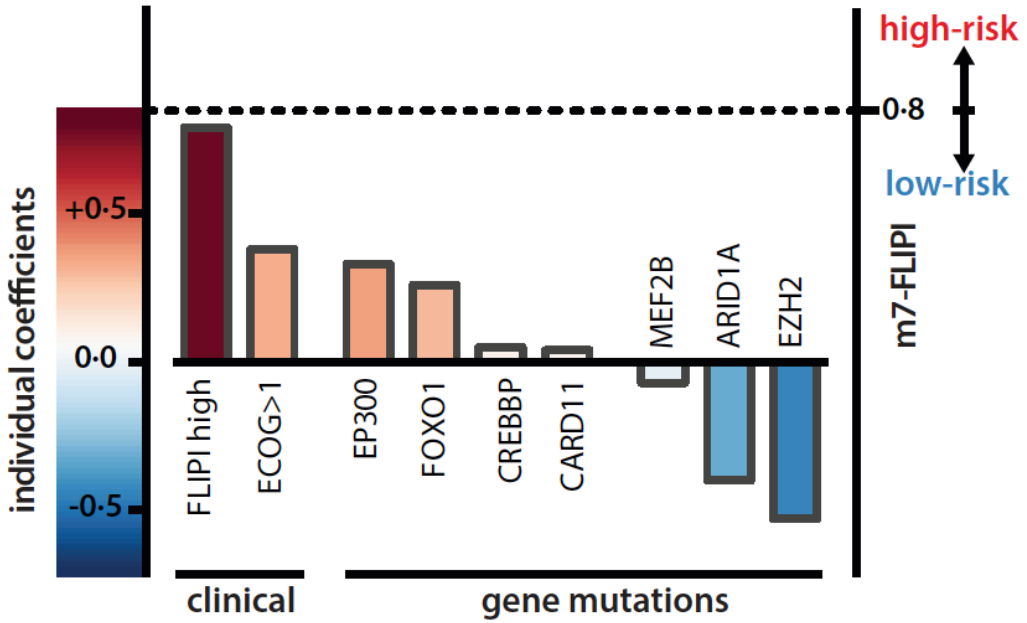


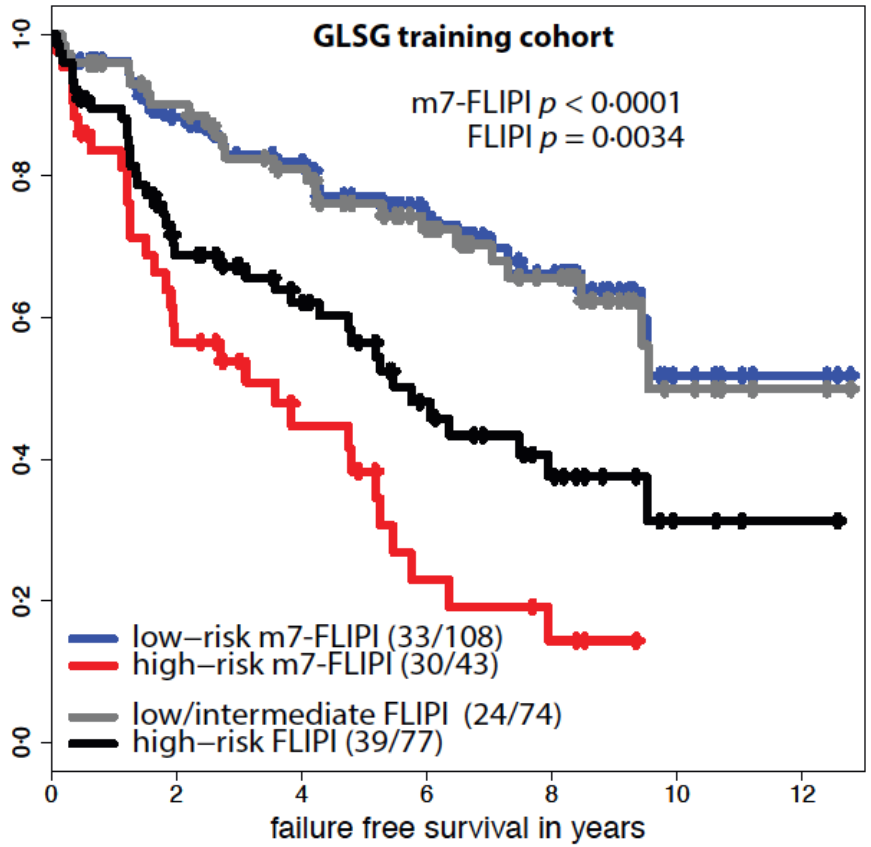
Morschhauser et al. Lancet Oncology, 2020

m7-FLIPI

151 patients GLSG – R-CHOP

107 patients BC Cancer – R-CVP +/- maintenance





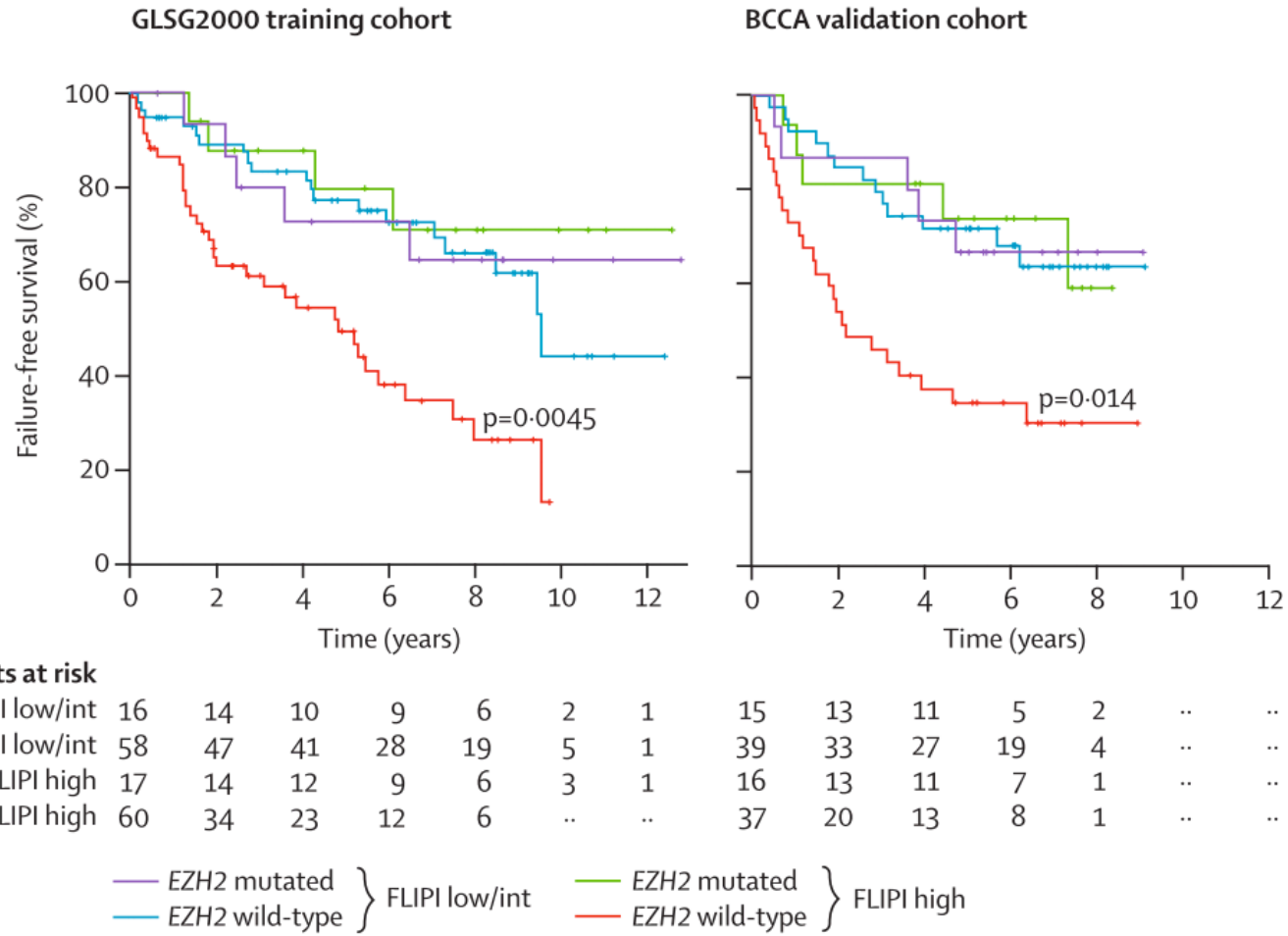
Pastore et al. Lancet Oncol 2015

EZH2 mutations – predictive and prognostic implications

~20% of all FLs

Predictive biomarker for response to tazemetostat

Prognostic biomarker for immunochemotherapy

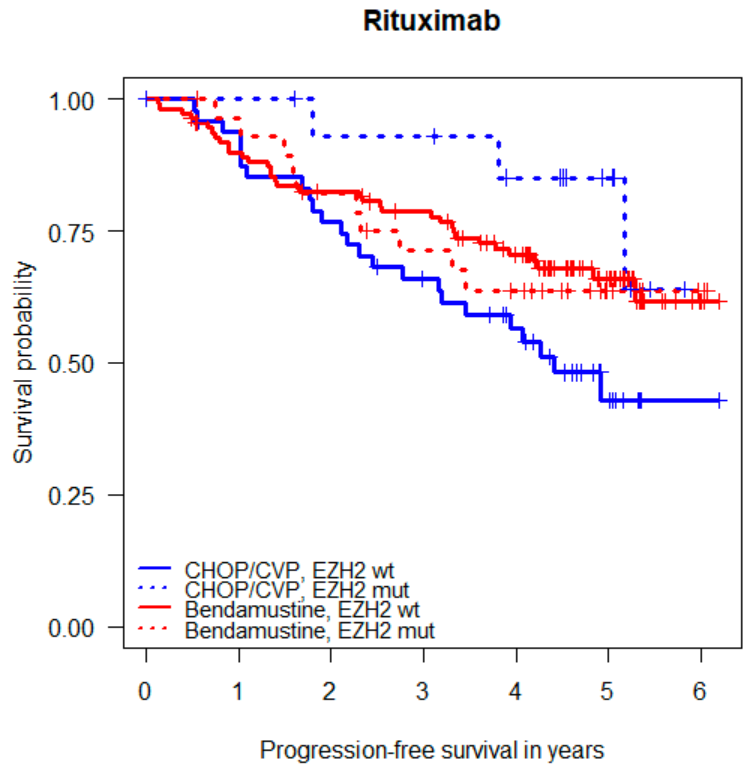


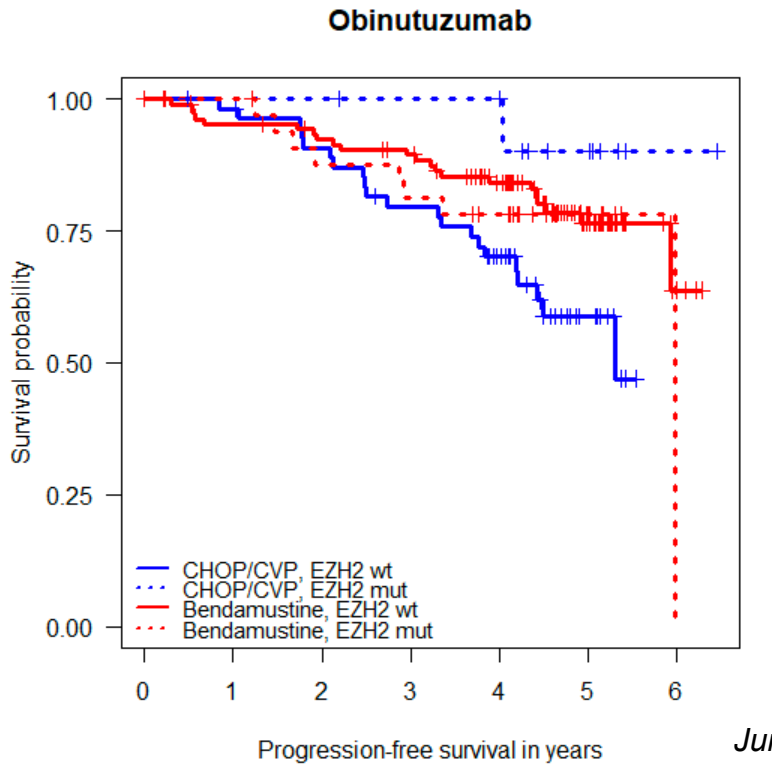
Pastore et al. Lancet Oncol 2015

EZH2 mutations – prognostic implications based on chemo

EZH2 mutated FL: better outcome with CVP/CHOP backbone

EZH2 wild-type FL: better outcome with bendamustine backbone





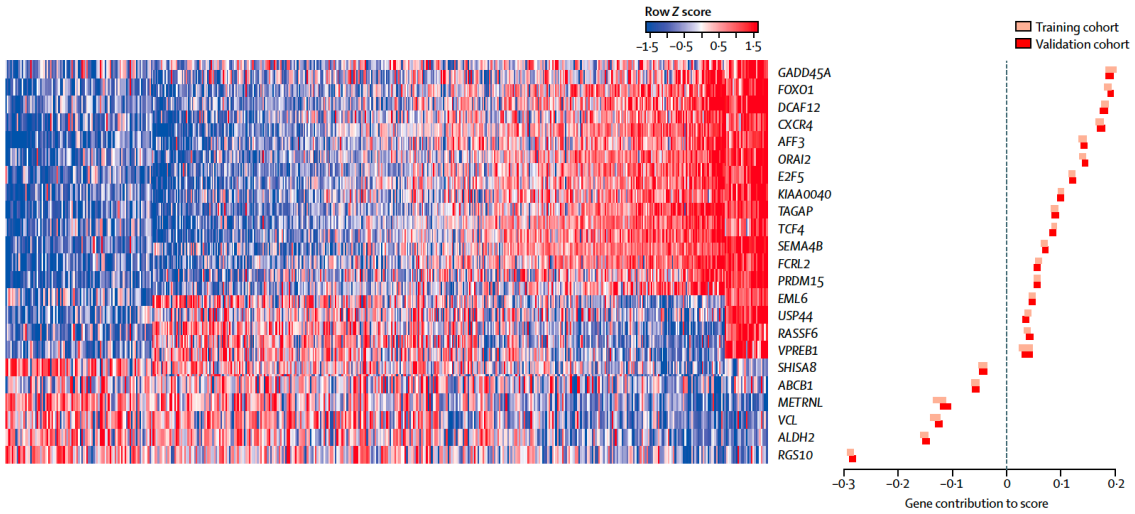
Jurinovic et al, ASH, 2019

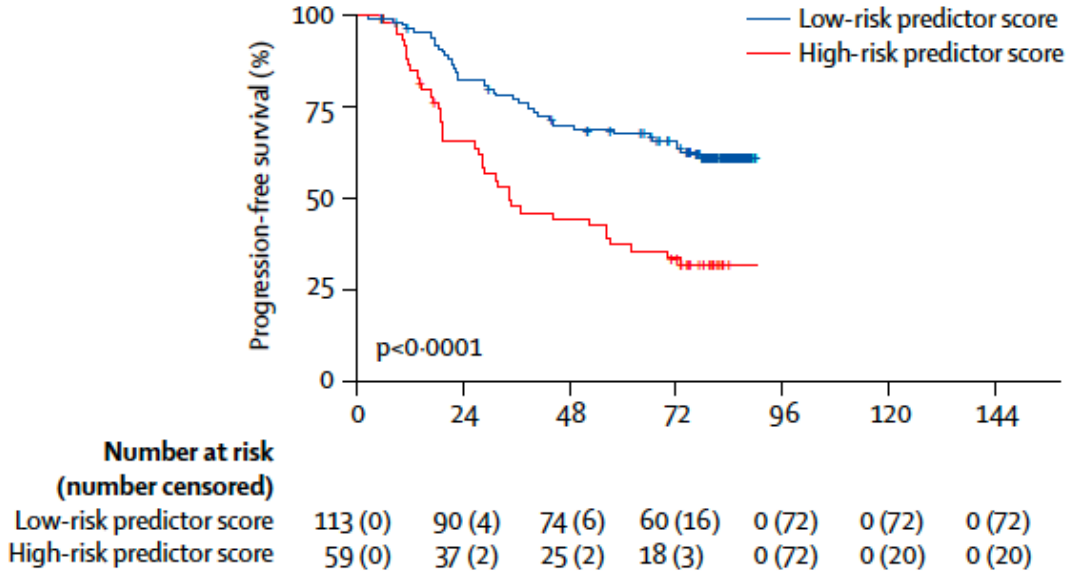
23 gene signature

Trained in samples from PRIMA trial.

Genes associated with outcome identified initially using Affymetrix microarrays.

Transposed to NanoString platform.





Huet et al, Lancet Oncol, 2018

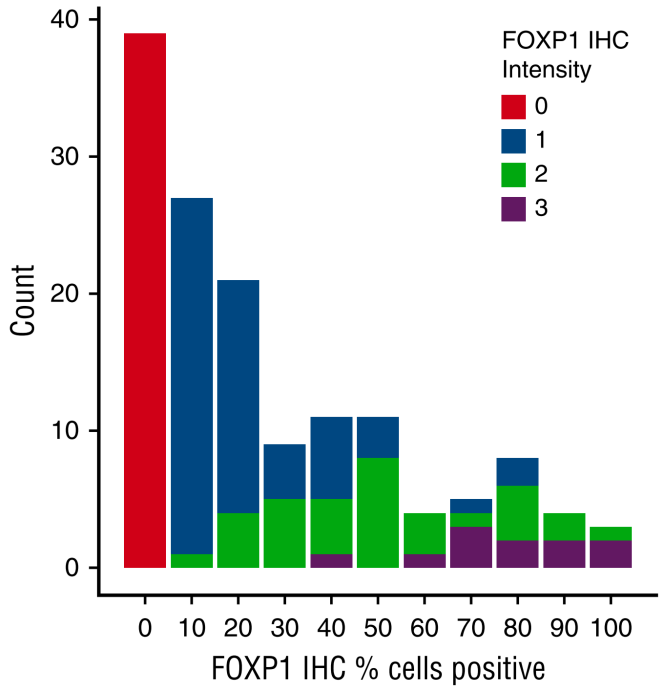
FOXP1 expression

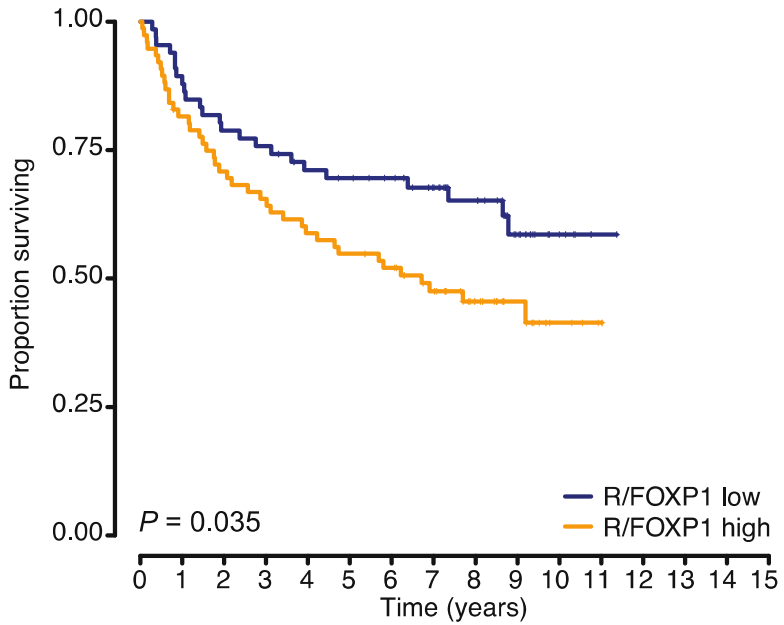
FOXP1 expression downregulated in *EZH2* and *MEF2B*-mutated FL

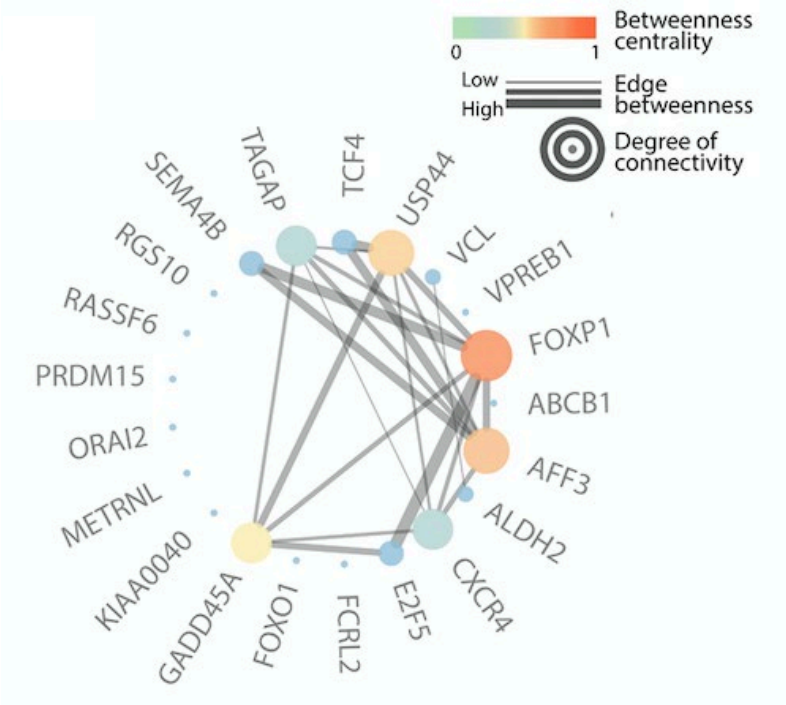
FOXP1 expression high in a subset of FL cases (*EZH2* and/or *MEF2B*-wildtype FL)

High FOXP1 expression associated with shorter FFS

High FOXP1 expression associated with 23 genes signature







Mottok et al, Blood, 2018
Silva et al, Haematologica, 2019

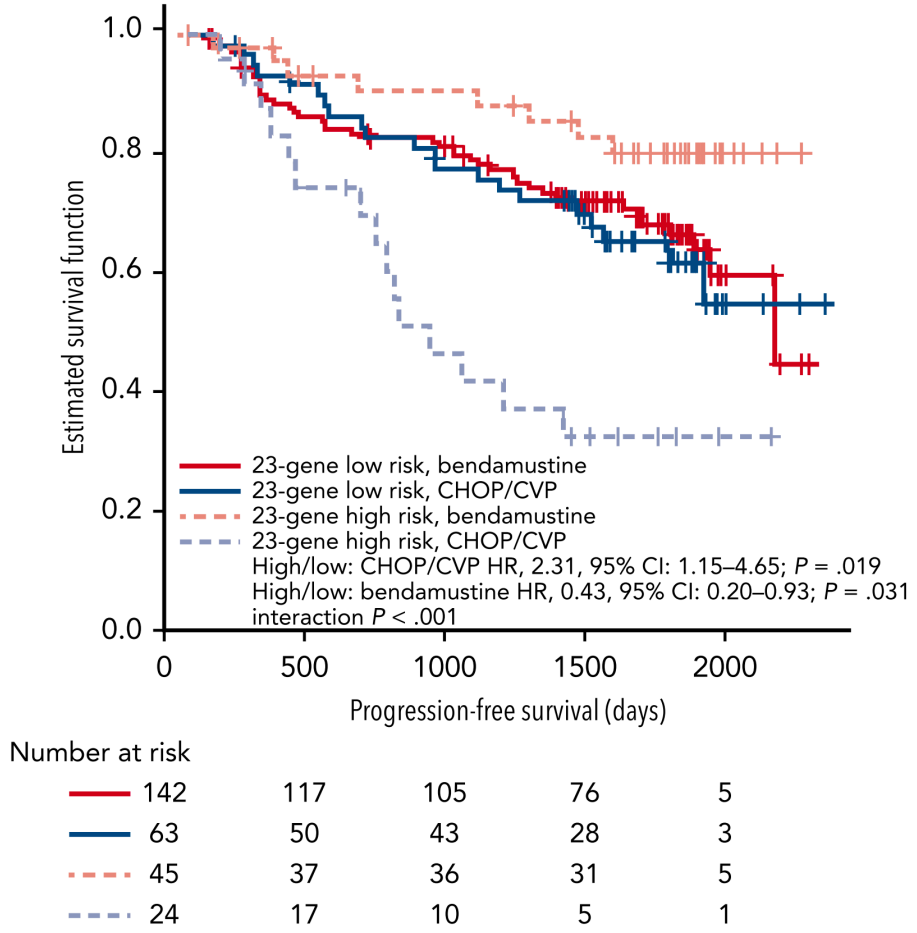
Treatment dependence of 23 gene score

GALLIUM trial

274 samples with RNAseq

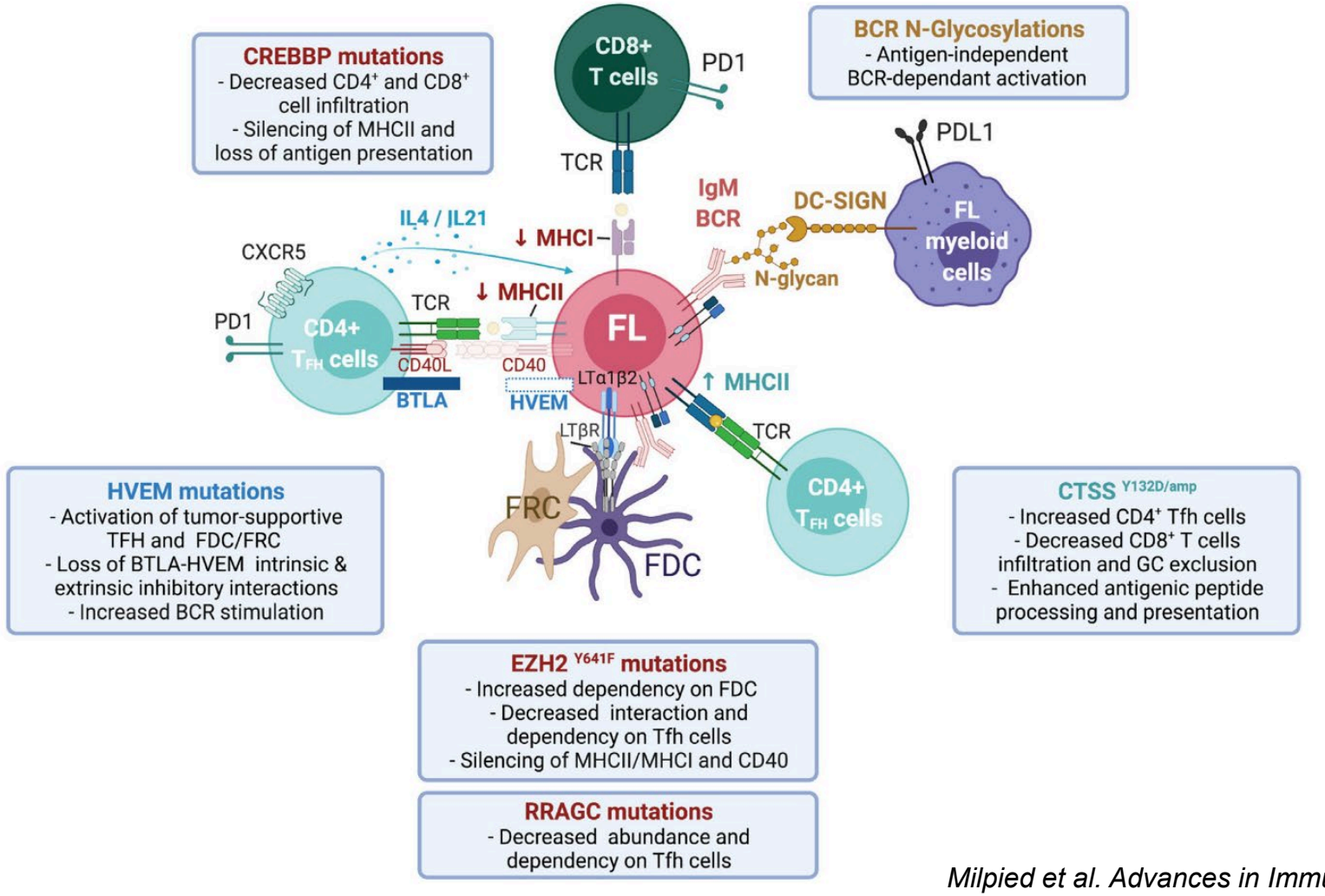
High expression of 23 gene predictor:

- Worse EFS with CHOP/CVP backbone
- Better EFS with bendamustine backbone



Bolen et al, Blood, 2021

Immune microenvironment



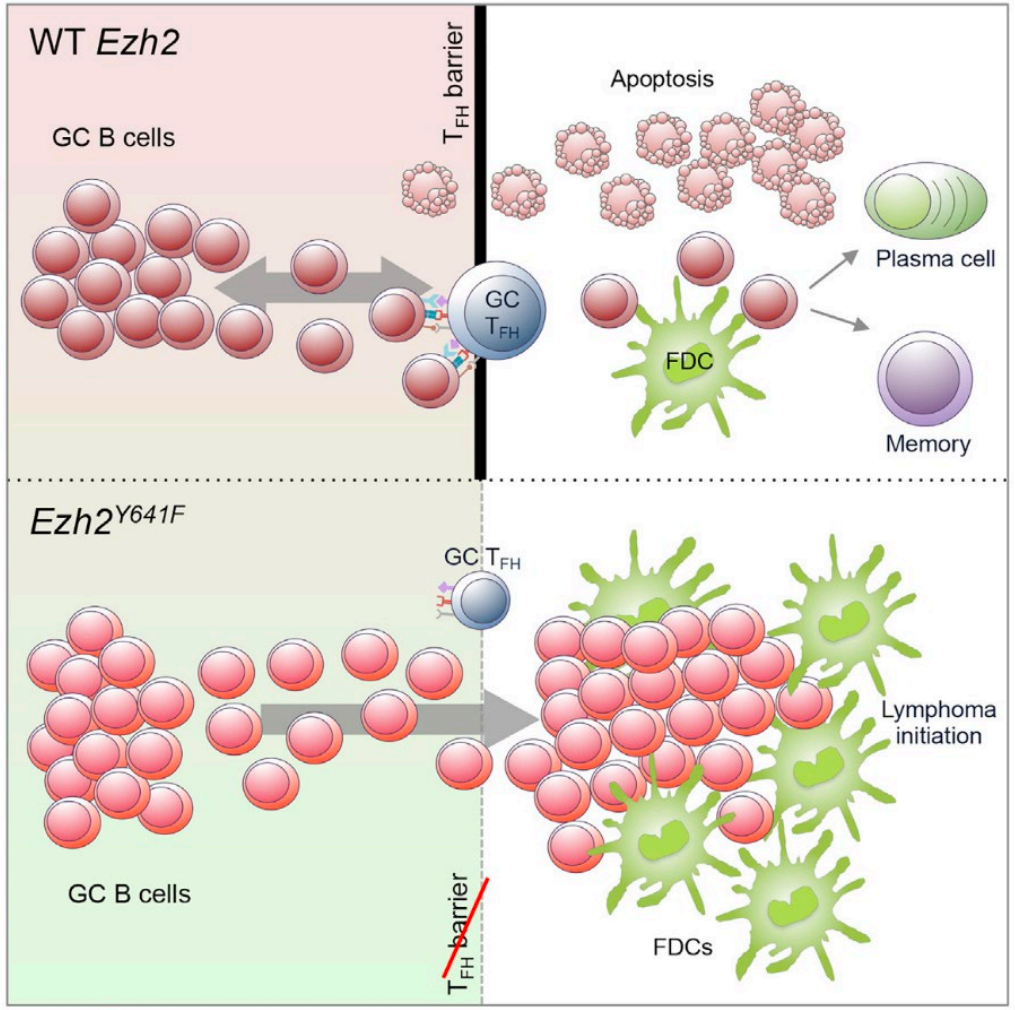
Milpied et al. Advances in Immunology, 2021

Mutant EZH2 reprograms the immune response

Mutant EZH2 impairs T-cell help

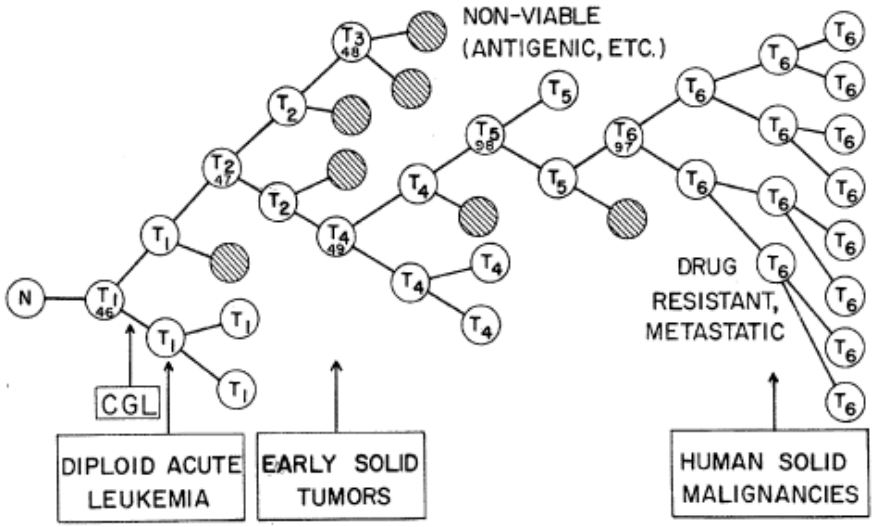
Drives slow expansion of centrocytes

Switch from T-cell to follicular dendritic cell dependency

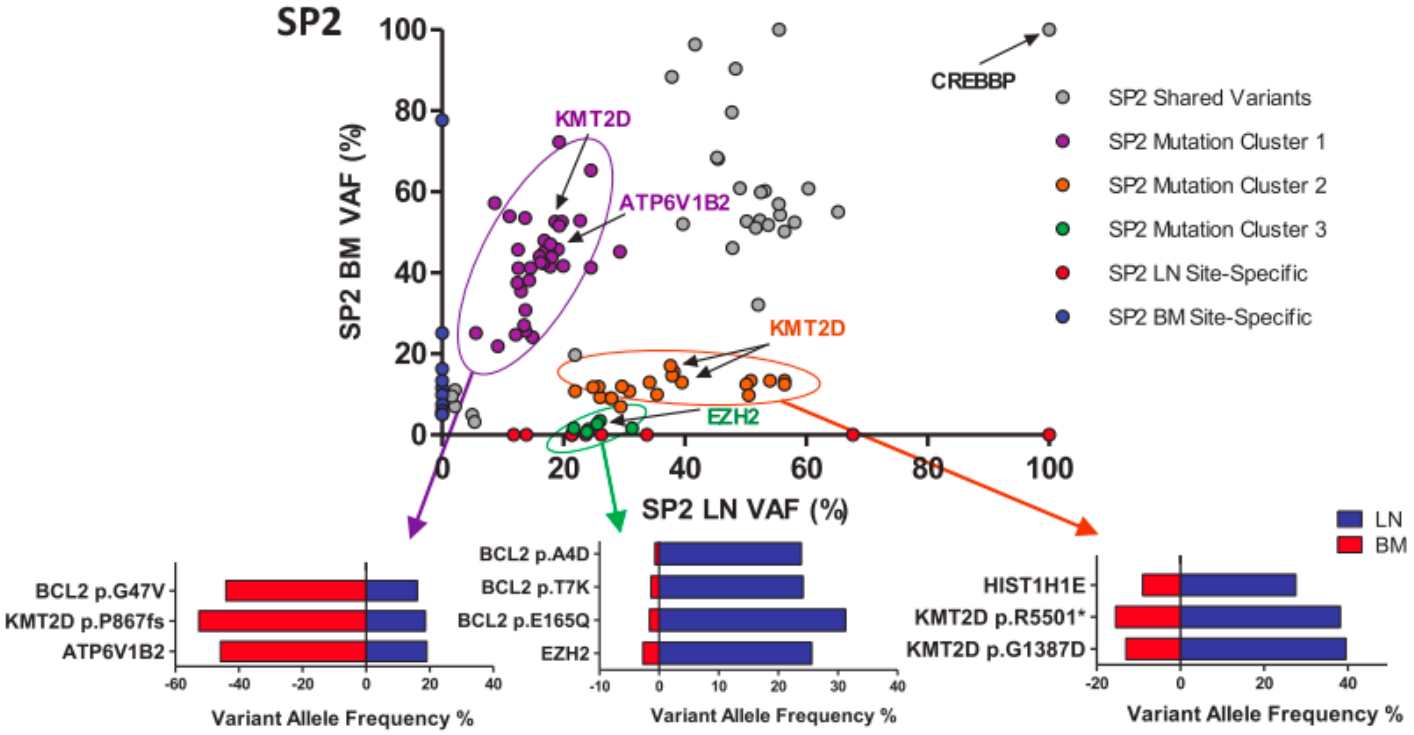


Beguelin et al. Cancer Cell 2020

Intratumoral heterogeneity

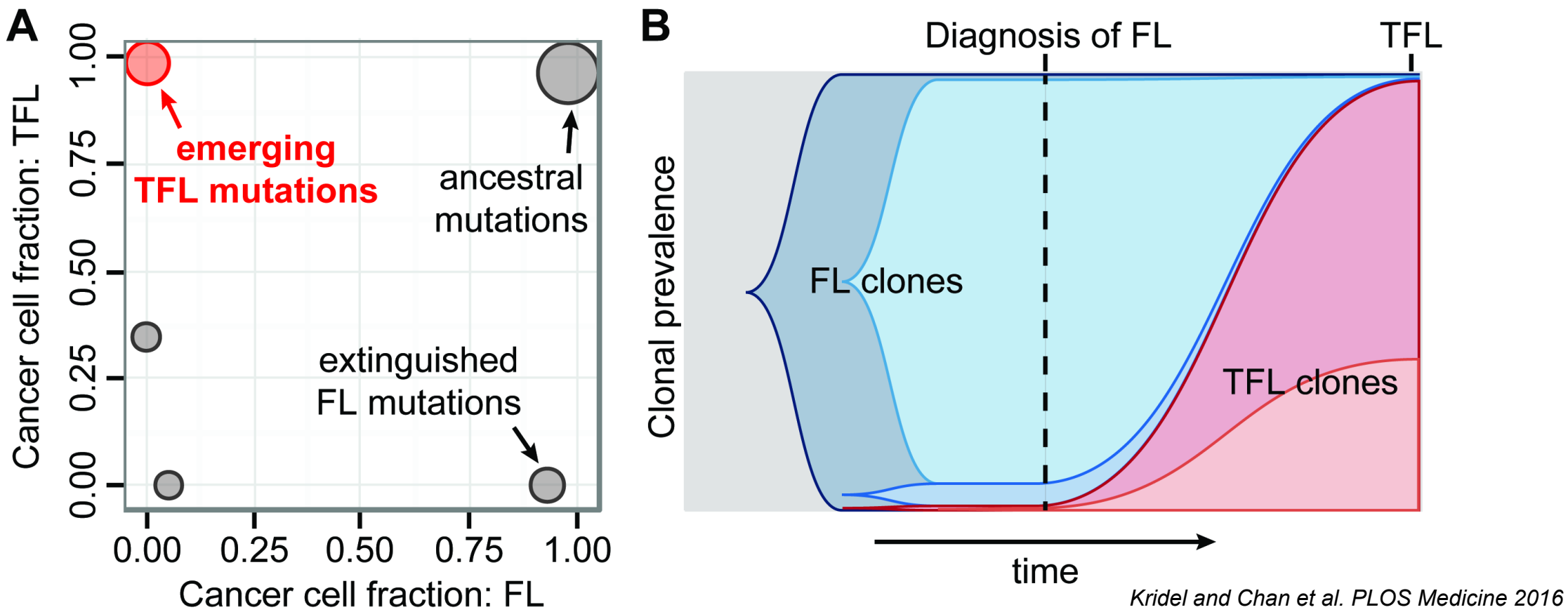


Peter Nowell, Science, 1976



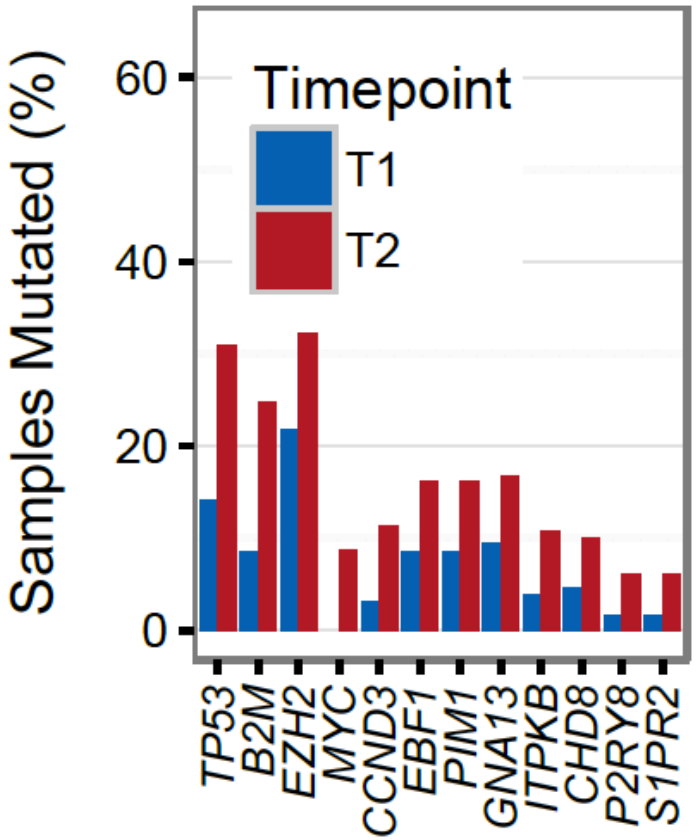
Araf et al, Leukemia, 2018

Clonal dynamics of transformation



Kridel and Chan et al. PLOS Medicine 2016

Gene mutations enriched in transformed FL



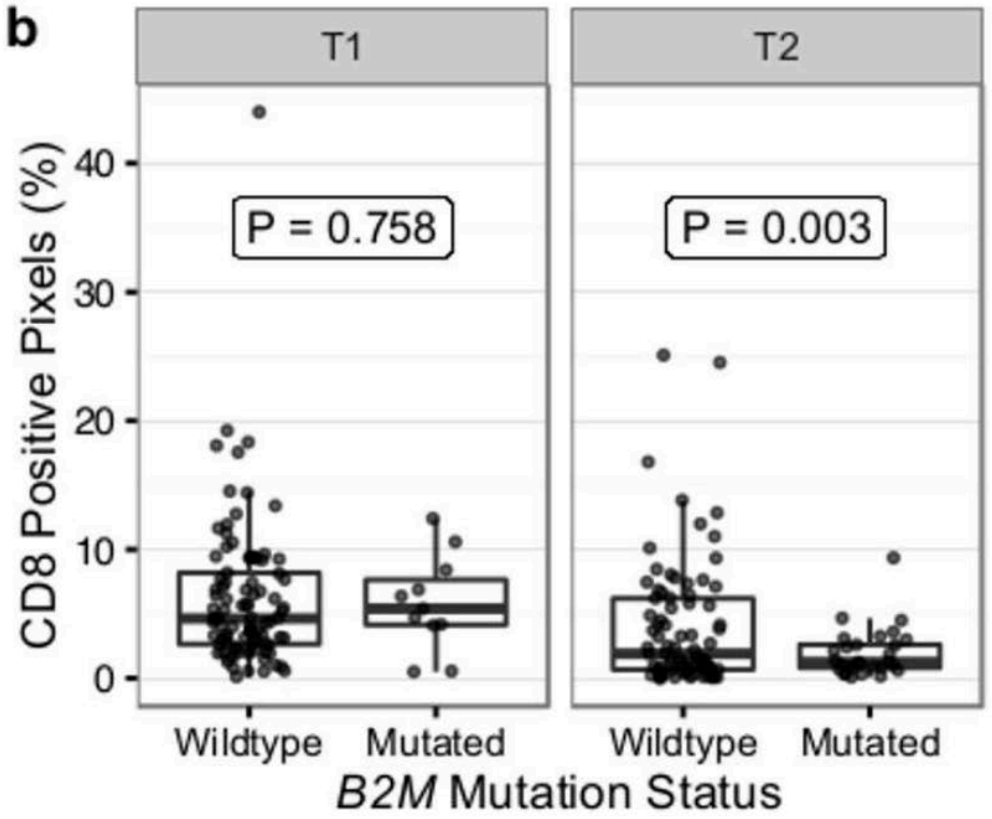
Kridel and Chan et al. PLOS Medicine 2016

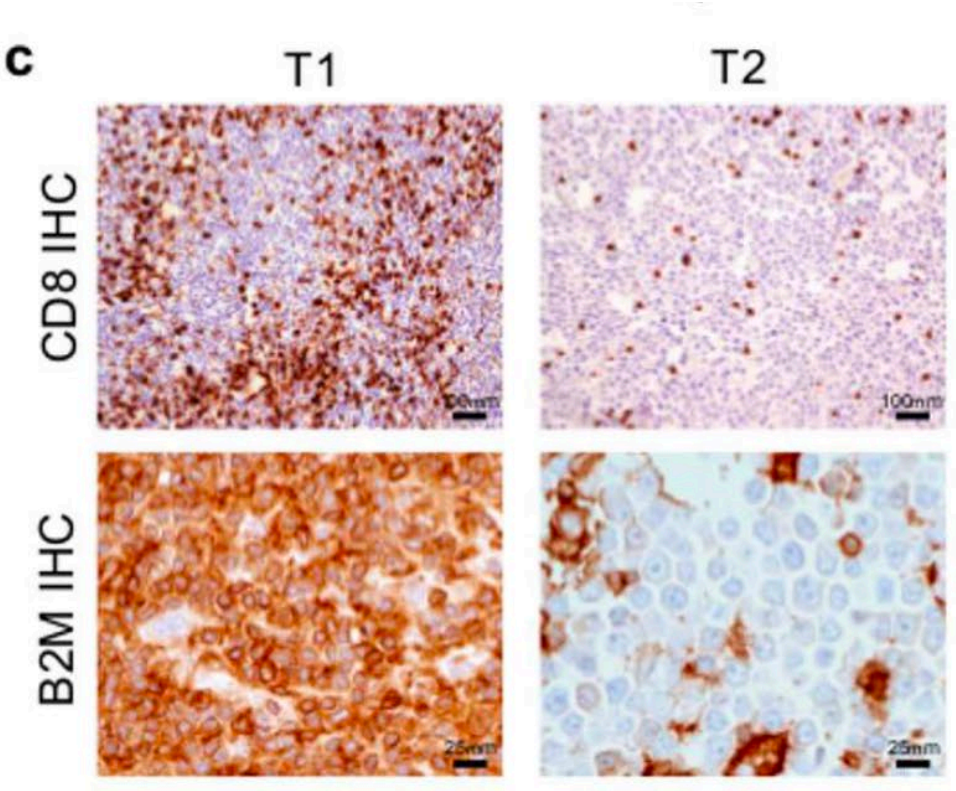
- Defective DNA damage response (*TP53*)
- Increased proliferation (*MYC* translocations, *CCND3*)
- Escape from immune surveillance (*B2M*)
- Loss of confinement within germinal centre (*GNA13*, *P2RY8*, *S1PR2*)

Bouska et al, Blood, 2014
Okosun, Nature Genetics, 2014
Pasqualucci, Cell Reports, 2014
Bouska et al, Leukemia, 2016

Tumor microenvironment changes in transformed FL

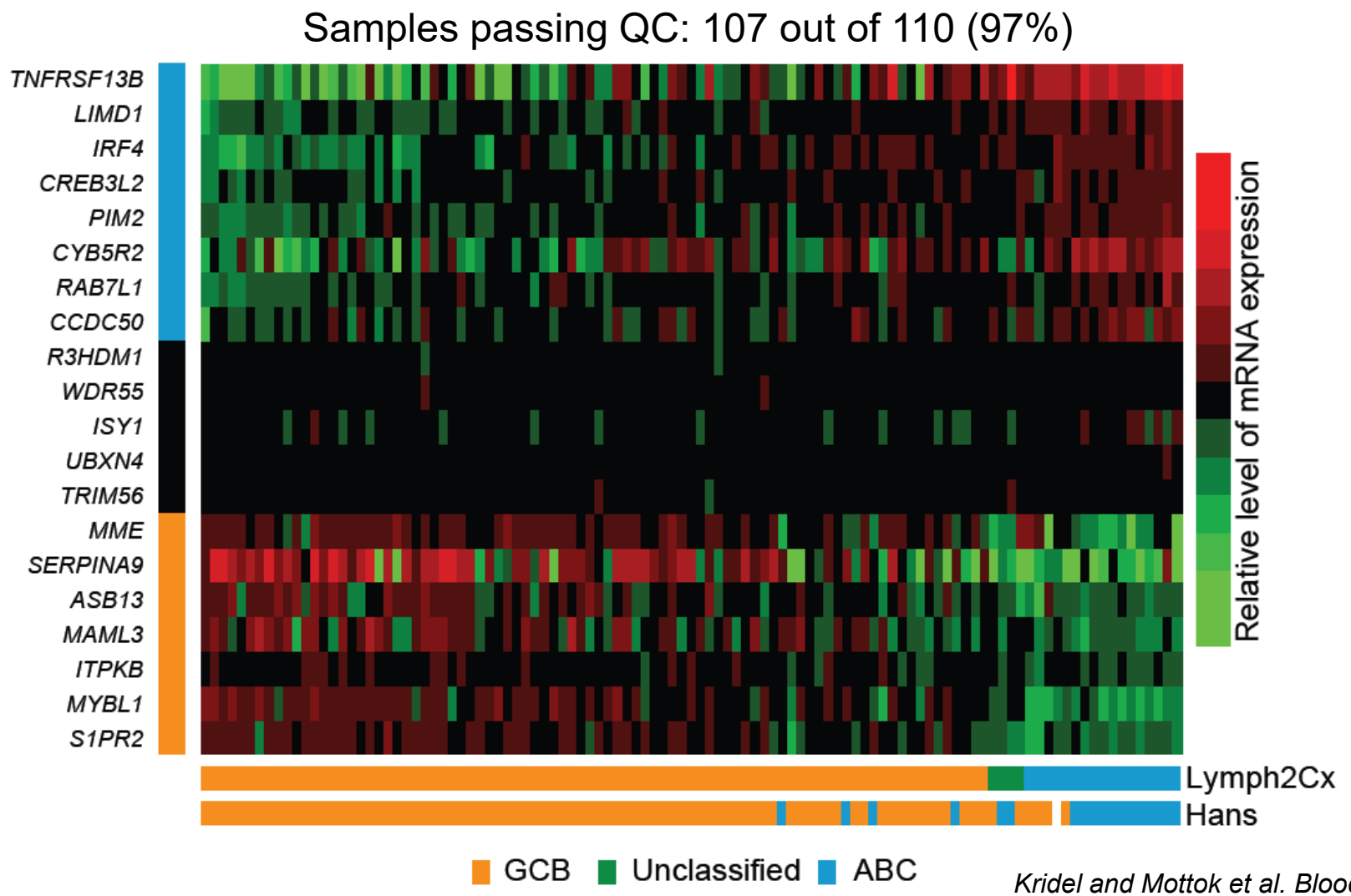
Reduced CD8+ T-cell infiltrate in transformed biopsies with *B2M* mutations





Kridel and Chan et al. PLOS Medicine 2016

Cell of origin of transformed FL

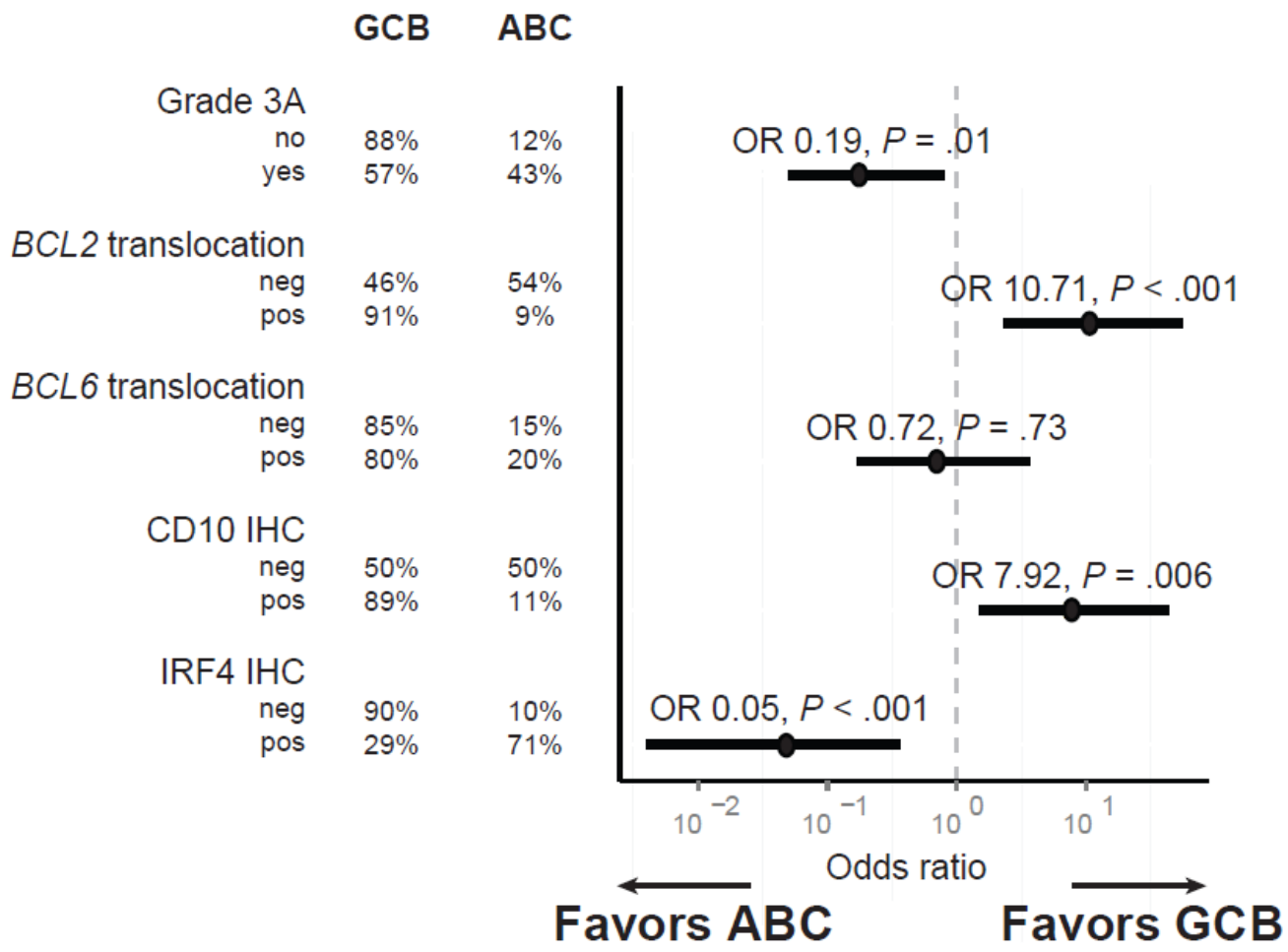


ABC-like
17/107 (16%)

GCB-like
86/107 (80%)

Kridel and Mottok et al. Blood 2015

FL ⟶ transformation into GCB or ABC



Kridel and Mottok et al. Blood 2015

Conclusions

- Epigenetic reprogramming is a hallmark of FL and has therapeutic implications:
  - Targeting EZH2 with small molecule inhibitors
  - EZH2 mutations may help select choice of frontline chemotherapy?
- Microenvironment remains insufficiently characterized
  - yet its composition is modulated by (epi)genetic alterations
  - predictive of response to immune therapies?
- Progression and transformation occur through branching evolution
- Molecular features of underlying FL are associated with phenotype of transformed FL

Audience response question

What are the prognostic implications of *EZH2* mutations for patients treated with frontline immunochemotherapy?

- EZH2 mutations predict response to tazemetostat but have no prognostic relevance for immunochemotherapy-treated patients
- *EZH2* mutations are associated with longer PFS in patients treated with R-CHOP/CVP
- *EZH2* mutations are associated with shorter PFS in patients treated with R-CHOP/CVP
- EZH2 regulates gene expression and has no impact on tumor-immune interactions

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