A functional prognostic model predicts progression free survival in patients with relapsed chronic lymphocytic leukemia treated with ibrutinib + venetoclax

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BACKGROUND

- Current prognostic models in CLL were developed to predict responses to chemoimmunotherapy
- These models have limited predictive value for newer combinations of targeted therapies

"Accurate prognostic models are needed to guide optimal treatment with targeted therapies

AIM

- To identify predictors of PFS in response to BTK + Bcl-2 inhibitor combination therapy

1 Material

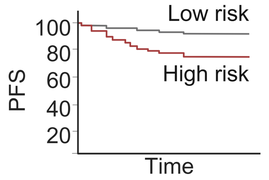
PBMCs from CLL patients (n=177) in the HO141/VISION trial (NCT03226301)

2 Measurements

- Genetic
  - IGHV, *TP53*, karyotype
- Functional
  - Ex vivo drug sensitivity
  - Cell signaling analysis
  - Immunophenotyping
- Clinical
  - Binet stage, MRD, PFS

3 Modeling

- Feature selection
- Machine learning

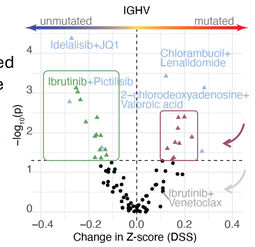


RESULTS

- IGHV and *TP53* do not predict ex vivo sensitivity to ibrutinib + venetoclax
- A functional biomarker predicts response to ibrutinib + venetoclax

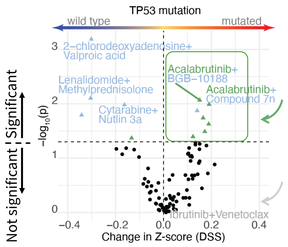
A IGHV and *TP53* do not predict sensitivity to ibrutinib + venetoclax

IGHV unmutated CLL is sensitive to BTKi-based treatments



IGHV mutated CLL is sensitive to Bcl-2i-based treatments

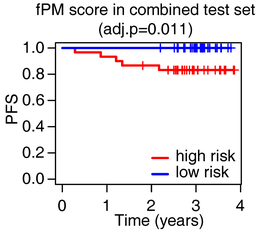
Ibrutinib + venetoclax sensitivity does not depend on IGHV status

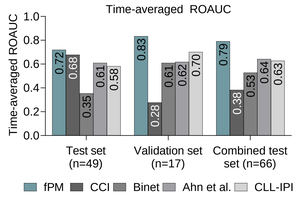


TP53 mutated CLL is sensitive to BTKi-based treatments

Ibrutinib + venetoclax sensitivity does not depend on *TP53* status

B A functional biomarker predicts response to ibrutinib + venetoclax





Variables	Coefficients	CoefficientstSD	95%CI	HR
Vandetanib	−0.466		(−0.486)–(−0.446)	0.628
Bcl-2 | Btk (pY223)	−0.435		(−0.451)–(−0.417)	0.647
p90 RSK (pS380) | PLCγ2 (pY759)	−0.324		(−0.341)–(−0.306)	0.723
Ruxolitinib + Venetoclax	−0.397		(−0.415)–(−0.380)	0.672
Acalabrutinib + ZSTK474	−0.259		(−0.276)–(−0.242)	0.772
$CD8^+$ T cells	0.402		0.385–0.419	1.495

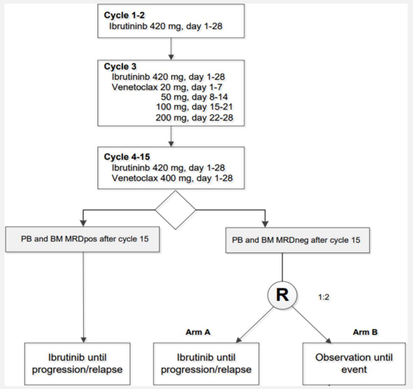
Negative coefficients correspond to low risk of progression and positive coefficients to high risk of progression

−0.5 −0.3 −0.1 0.1 0.3 0.5

Longer PFS time — Shorter PFS time

"A functional biomarker score including signaling pathway phosphorylation, drug sensitivity, and T cells predicts PFS for R/R CLL treated with ibrutinib + venetoclax

HO141/VISION TRIAL



NCT03226301; Levin et al, BMJ Open, 2020

GLOSSARY

Bcl-2	B-cell lymphoma-2
BTK	Bruton's tyrosine kinase
CCI	Charlson comorbidity index
CLL	Chronic lymphocytic leukemia
CLL-IPI	International prognostic index for CLL
fPM	Functional prognostic model
IGHV	Immunoglobulin heavy variable
MRD	Minimal residual disease
PBMC	Peripheral blood mononuclear cell
PFS	Progression free survival
R/R	Relapsed/refractory
ROAUC	Receiver operating area under the curve
TP53	Cellular tumor antigen p53

HOVON · Oslo University Hospital · Norwegian Cancer Society · The Research Council of Norway · ERA PerMed · CLL-CLUE

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