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Predictive modeling of treatment outcomes in chronic lymphocytic leukemia based on functional profiles at baseline

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1. INTRODUCTION

Although targeted therapies have revolutionized the management of chronic lymphocytic leukemia (CLL), treatment efficacy varies from patient to patient and no treatment is given with curative intent. To avoid short treatment durations or toxicities of therapy, there is a need to identify biomarkers that can guide optimal treatment decisions for the individual patient.

2. AIM

To develop computational models that predict treatment outcomes in CLL patients based on functional analyses performed on primary CLL cells sampled before treatment start.

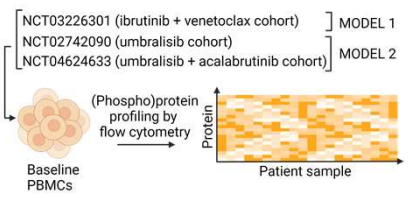
3.METHODS

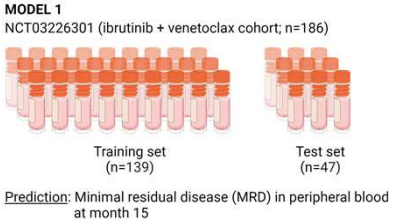
Peripheral blood mononuclear cells (PBMCs) were collected at baseline from relapsed/refractory CLL patients enrolled in three phase 2 clinical trials [NCT03226301 (ibrutinib + venetoclax cohort; n=186), NCT02742090 (umbralisib cohort; n=55), and NCT04624633 (umbralisib + acalabrutinib cohort; n=12)]. Multi-color flow cytometry with fluorescent cell barcoding was applied to the PBMCs for (phospho)protein profiling (31 proteins) of resting CLL cells.

Two computational models were developed to predict treatment outcomes on the clinical trials. Model 1 used (phospho)protein profiles from the ibrutinib + venetoclax cohort to predict MRD level in peripheral blood at cycle 15. The cohort was divided into a training set (n=139; 75%) and a test set (n=47; 25%), stratified based on MRD level, IGHV mutational status, and *TP53* aberration status. After 15 cycles of ibrutinib + venetoclax treatment, 63, 44, and 7 patients in the training set had obtained an undetectable ($<10^{-4}$, i.e. less than 1 CLL cell detected in 10000 leukocytes by flow cytometry), intermediate (10^{-4} to 10^{-2}), or high MRD ($>10^{-2}$) status, respectively. MRD sample or (phospho)protein profile was missing for the remaining 25 patients.

Model 2 used (phospho)protein profiles from the umbralisib cohort (training set) to predict tumor objective response rate (ORR). The umbralisib + acalabrutinib cohort was used as an independent test set. Patients who achieved partial response (PR) or complete response (CR) to umbralisib were classified as responders (n=15). Patients who achieved stable disease (SD) or progressive disease (PD) were classified as non-responders (n=40).

Statistical associations between the (phospho)protein profiles and treatment outcomes were assessed with Wilcoxon non-parametric test.

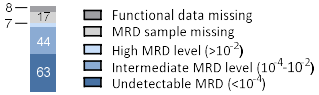




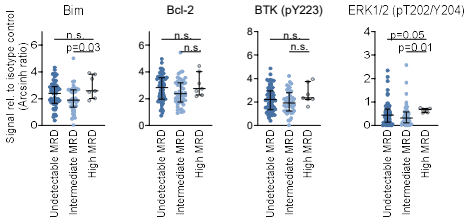
4. RESULTS

MODEL 1

| MRD in ibrutinib + venetoclax cohort at cycle 15 (training set)

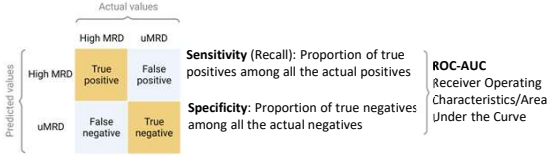


| (Phospho)protein profiles in training set

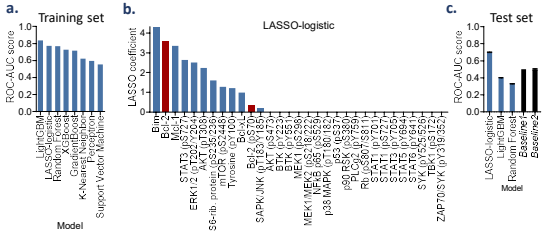


Patients with high MRD after 15 cycles of ibrutinib + venetoclax therapy showed significantly higher (phospho)protein levels than patients with intermediate or undetectable MRD for 8 proteins in the training set ($p<0.05$), including Bim and ERK1/2 (pT202/Y204). There were no significant differences in (phospho)protein profiles between intermediate and undetectable MRD groups.

| Predictive modeling of MRD status using machine learning



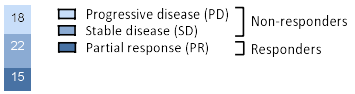
| Model performance and feature importance



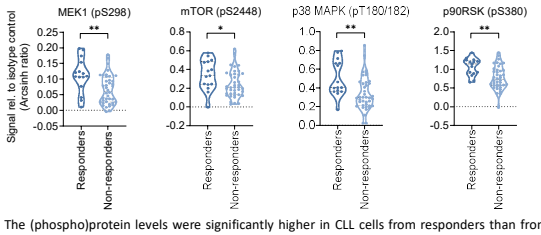
a | ROC-AUC scores for eight different models on the training set. **b |** Feature importance in the LASSO-logistic model. **c |** ROC-AUC scores for three models on the test set. Negative control models (Baseline 1 and 2) are shown in black.

MODEL 2

| ORR in umbralisib cohort (training set)

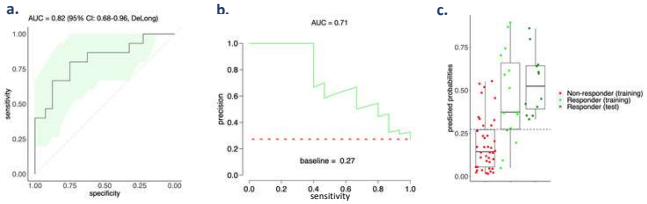


| (Phospho)protein profiles in training set



The (phospho)protein levels were significantly higher in CLL cells from responders than from non-responders for 8 proteins ($p<0.05$), including MEK1 (pS298), mTOR (pS2448), p38 MAPK (pT180/182), and p90 RSK (pS380).

| Model performance



a | A LASSO-logistic model with leave-one-out cross validation was developed to predict patients who responded to umbralisib treatment. The plot shows the ROC-AUC score for the training set. **b |** AUC-PRC score for the training set. **c |** The proportion of the responders in the training set (15/55 = 0.27) was used as cut-off for the probability to predict a responder. The model correctly predicted all patients in the test set (umbralisib + acalabrutinib cohort; n=12) to be responders.

5. CONCLUSION

We present a novel approach to model treatment outcomes for CLL patients based on functional analyses and show that baseline (phospho)protein profiles of CLL cells have predictive value in independent CLL cohorts treated with targeted therapies.

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