Predicting response to naratuximab emtansine, an anti-CD37 antibody-drug conjugate (ADC), in combination with rituximab in Diffuse Large B Cell Lymphoma (DLBCL), by analyzing the spatial arrangement of CD37 and CD20 positive cells using deep learning

Anna Pokorska-Bocci[1], Sandrine Micallef[1], Mariola Dymkowska[1], Yuval Gabay[2], Roman Gluskin[2], Avi Laniado[2], Efrat Dicker[2], Amit Bart[2], Tomer Dicker[2], Ifat Rotbein[2], Albert Achtenberg[2], Ori Zelichov[2]

[1]Debiopharm International SA, Lausanne, Switzerland [2]Nucleai, Tel Aviv, Israel

INTRODUCTION

- DLBCL is the most common type of Non-Hodgkin's lymphoma, accounting for 30-40% of cases.
- Despite improvements in survival with standard of care treatment, up to 40% of patients have relapsed and/or refractory (R/R) disease.
- A phase 2 study (NCT02564744) evaluated the efficacy of naratuximab emtansine, an anti-CD37 ADC, in combination with rituximab, in 80 patients with R/R DLBCL.
- We performed an exploratory analysis of the study to find pathology-based biomarkers predictive of response.
- Deep learning (DL) models were used to extract spatial features from whole slide images (WSI) stained with CD37 and CD20 and their predictive role was evaluated.

METHODS

- A cohort of 47 DLBCL patients from the study were selected based on availability of CD20/CD37 IHC staining and were used for analysis.
- Patient characteristics of the analyzed cohort were similar to those of the full study cohort. Overall response rate (ORR) of the cohort was 44.7%, similar to the ORR of the full study cohort.
- For each patient, two WSI from a pre-treatment biopsy, one stained for CD20 and one for CD37, were analyzed.
- DL models were used to classify cells as positive or negative to the two markers and CD20+/CD37+ co-expression was assessed using an image alignment model to better predict potential synergy of the drug combination.

METHODS

- Over 140 spatial features were pre-defined based on biological hypotheses and were calculated for each patient based on cell classifications.
- Due to the small cohort size, a repeated 5-fold cross-validation analysis was performed to identify features predictive of objective response.

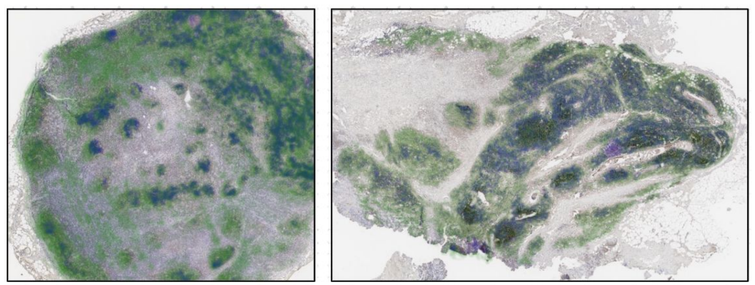

Image alignment used to overlay slides and generate virtual co-expression maps of two markers

Blue: Density of positively stained CD37 cells
Green: Density of positively stained CD20 cells
Purple: Coexpression of CD37 and CD20 positive cells

RESULTS

- Two spatial features related to the proximity of CD37 and CD20 positive cells, demonstrated a significant correlation with clinical outcome.
- Each feature identified patients in the cohort as having either a positive or a negative response.

	Retrospective Data Set	Model 1 ORR	Model 2 ORR
Responders	**44.7%**	**78%**	**67%**
Non-Responders	**55.3%**	**22%**	**33%**
95% Confidence Interval		**0.64-0.82**	**0.62-0.71**
ORR increase		**34%**	**23%**
P-Value		**<0.05**	**<0.05**

ORR of patients in sub-populations positive to predictive spatial features compared with ORR in the original trial

- In a covariate analysis, the spatial features remained predictive after stratification to prognostic factors including LDH and IPI score.

Median RR	LDH+	LDH-	IPI+	IPI-
Feature 1	75%	50%	75%	56%
Feature 2	83%	67%	80%	75%
ORR	62%	25%	50%	36%

ORR of patients with positive or negative known prognostic factors stratified by spatial features

CONCLUSIONS

- DL analysis of the co-expression and spatial arrangement of CD37 and CD20 in pre-treatment biopsies of DLBCL patients could potentially be used as a predictive biomarker for a response to a combination treatment of anti-CD37 and anti-CD20 drugs in DLBCL.
- This biomarker may improve patient stratification and be used for further clinical trials.

Corresponding Authors: anna.pokorskabocci@debiopharm.com