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

POSTER #16

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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, retrospective 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.

MATERIAL

A cohort of 47 DLBCL patients from the Study were selected and used for analysis based on tissue expression of CD20 and CD37, and availability of CD20/CD37 IHC staining.

Patient characteristics of the analyzed cohort were similar to those of the full study cohort. Overall response rate (ORR) of the analyzed 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.

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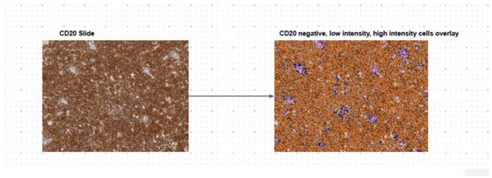
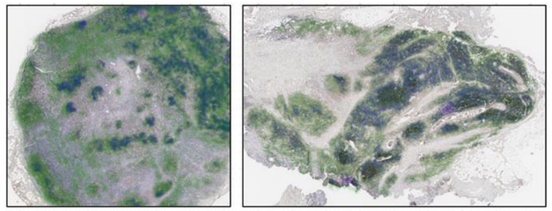
METHODS

Over 140 features were pre-defined based on biological hypotheses and were calculated for each patient based on cell and CD20/CD37 receptor spatial distribution, using image alignment prediction.

Due to the small cohort size, a repeated 5-fold cross-validation analysis was performed to identify features predictive of objective response.





Blue: Density of positively stained CD37 cells

Green: Density of positively stained CD20 cells

Purple: Co-expression of CD37 and CD20 positive cells

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

RESULTS

Two spatial features related to the proximity of CD37 and CD20 positive cells, demonstrated a significant correlation with clinical outcome in patients treated with naratuximab emtansine and rituximab.
Each feature identified patients in the analysed cohort as having either a positive or a negative response. On average 21% of patients were classified as positive for feature 1 (Model 1) and 35% for feature 2 (Model 2).
A significant increase in ORR was observed in the positive patient subpopulation for each feature.

	Full study cohort ORR	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 increased value by		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<=ULN	LDH>ULN	IPI<2	IPI>2
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

In a retrospective analysis, using deep learning analysis of the co-expression and spatial arrangement of CD37 and CD20 in pre-treatment biopsies we were able to identify features that could improve ORR in patients with R/R DLBCL treated with naratuximab emtansine and rituximab. These features could potentially be used as predictive biomarkers and drive patient selection in future clinical trials.

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