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Blocking the CD39/CD73 pathway synergizes with anti-CD20 bispecific antibody in nodal B-cell lymphoma

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ABSTRACT

Bispecific antibodies (BsAb) have emerged as a leading treatment modality in patients suffering from B-cell non-Hodgkin's lymphoma (B-NHL). However, treatment failure is common and may potentially be attributed to pre-existing or emerging T-cell exhaustion. CD39 catalyzes—together with CD73—the hydrolysis of immunogenic ATP into immunosuppressive adenosine and thus actively promotes an immunosuppressive micromilieu. Previously, we and others demonstrated that CD39$^+$ T-cell subsets may have an adverse impact on the efficacy of T-cell-engaging immunotherapies. In this study, we applied an autologous ex vivo culture model of primary lymph node-derived T cells to investigate the potential of anti-CD39 or anti-CD73 blocking antibodies as T-cell enhancing combination partners of an anti-CD20 BsAb. Existing single-cell data of patient samples examined in this study were used to detect potential biomarkers predicting combination benefits. Combining anti-CD20 BsAb with anti-CD39 or anti-CD73 blocking antibodies induced synergistic effects on tumor cell killing, T-cell expansion and secretion of cytokines, including granzyme B, perforin, interleukin-10, interferon-γ, and tumor necrosis factor-α. We discovered that blockade of the CD39/CD73 pathway was particularly effective in patients with a high proportion of Programmed cell death protein 1 (PD-1)$^+$ T-cell immunoglobulin and mucin-domain containing-3 (TIM3)$^+$ exhausted T cells. Also, expression of CD39 in effector memory T cells indicated superior treatment benefit ex vivo. In summary, our study holds significant relevance as it introduces the combination of bispecific and anti-CD39 or anti-CD73 antibodies as a synergistic treatment approach in B-NHL, while also suggesting potential indicators to identify patients that might benefit from this treatment.

INTRODUCTION

Nodal B-cell non-Hodgkin's lymphomas (B-NHL) represent a heterogeneous group of hematological malignancies that originate mainly from the lymphoid compartment. While immunochemotherapy represents a powerful first-line treatment for most B-NHL entities,[1 2] a substantial number of patients become refractory to chemotherapy[3 4] and require further treatment approaches. Bispecific antibodies (BsAb) have risen as an important treatment modality for patients with refractory and relapsed B-NHL, as they represent an off-the-shelf solution to redirect T cells against malignant B cells by simultaneously binding to both CD3 and a B-cell epitope.[5] Recent data report response rates between 50% and 60% for refractory and relapsed patients, with a small subset of patients benefiting in the long-term.[6 7] Failure of BsAb is commonly attributed to dysfunctional Tcells and an immunosuppressive microenvironment.[8] Aiming to improve the efficacy of BsAb, T-cell enhancing combinations, for instance with checkpoint inhibitors (eg, NCT03533283) or cereblon modulators (eg, NCT05169515), are increasingly being investigated.

Previously, we identified a lymph node-derived CD39$^+$ Helios$^+$ expressing regulatory T-cell (T_{REG}) phenotype that was associated with inferior ex vivo response to BsAb in B-NHL.[9] Beyond its expression in T_{REG} cells, we and others linked CD39 to advanced stages of T-cell exhaustion in solid tumors[10] and B-NHL.[11] However, CD39 is not only a marker of inhibitory cell states but actively promotes an immunosuppressive micromilieu, as it catalyzes—together with CD73—the hydrolysis of immunogenic ATP into immunosuppressive adenosine.[12 13] While local ATP and adenosine levels are precisely regulated in healthy states, cancer cells actively promote ATP depletion and adenosine accumulation, thereby evading immune response.[14] As CD39/CD73 blockade has previously been demonstrated to promote T-cell activation and antitumor immunity in models of solid cancers,[15–18] we evaluated combination treatments of anti-CD39 and anti-CD73 functional antibodies with anti-CD20 BsAb in B-NHL. Moreover, we harnessed existing single-cell data to identify potential indicators for the

efficacy of treatment involving anti-CD39 or anti-CD73 antibodies.

RESULTS

Using a flow cytometry-based autologous ex vivo model of BsAb treatment,[9] we quantified responses to anti-CD20 BsAb (figure 1A) in 27 primary lymph node samples from patients diagnosed with follicular (FL) or diffuse large B-cell lymphoma (DLBCL) (online supplemental table 1). As most patient samples were included in reference data sets of B-NHL,[11 19] detailed transcriptomic and epitope profiles at the single-cell level were available. Consistent with previous data,[9] anti-CD20 BsAb successfully induced concentration-dependent killing of B cells with a median reduction of 73.3% (figure 1B) and a median T-cell expansion of 13.6-fold at the highest concentration (figure 1C). Anti-CD39 or anti-CD73 blocking antibodies at two different concentrations (1 µg/mL, 10 µg/mL) were combined with anti-CD20 BsAb at 0.1 µg/mL. Blockade of CD39, CD73 or both significantly enhanced BsAb-induced lysis of B cells (figure 1D). To assess synergy statistically, we used the Bliss independence model which compares the observed effect of a combination treatment with the predicted effect of individual compounds.[20] All combinations tested induced a stronger effect as the Bliss model predicted, characterizing them as synergistic. Interestingly, we did not observe that simultaneous blockade of CD39 and CD73 further improved responses compared with the use of each agent individually. The combination treatments also dramatically augmented T-cell expansion in all tested conditions compared with single agent treatment (figure 1E). Using anti-CD39 blocking antibody as a representative example, we observed significantly higher levels of granzyme B, perforin, interleukin (IL)-10, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α secreted by primary lymph node cells compared with BsAb alone (figure 1F). Next, we incubated primary lymph node samples with anti-CD39 blocking antibody at a concentration of 1 µg/mL or 10 µg/mL and added ATP at 20 µM. Indeed, we found that the addition of anti-CD39 antibody significantly increases ATP levels (figure 1G), thereby confirming previous results.[15]

To identify potential indicators for the efficacy of anti-CD39 or anti-CD73 combination treatment, we quantified the extent to which individual samples benefited from combinations compared with BsAb monotherapy (see Method section). The benefit from adding anti-CD39, anti-CD73, or both to anti-CD20 BsAb was higher in DLBCL (figure 2A) and patients at initial diagnosis (figure 2B) compared with FL and patients at relapse, respectively. Moreover, we used single-cell data of these samples[11 19] to examine whether baseline data of T cells and B cells were associated with ex vivo response to combination treatment. In non-malignant B cells, we detected both CD39 and CD73, while malignant B cells spanning all investigated lymphoma entities exhibited a notably lower expression (figure 2C). Across 14 multimodally defined T-cell subsets,[11] we found the highest levels of CD39 in T_{REG} subsets and exhausted T cells (figure 2D). Likewise, we observed CD73 to be present in T cells at moderate, but—in contrast to CD39—relatively consistent levels across all cell types (figure 2C and E). Merging single-cell data with ex vivo responses to CD39/CD73 blocking antibodies revealed that a higher proportion of exhausted T cells (alias Programmed cell death protein 1 $(PD\text{-}1)^+$ T-cell immunoglobulin and mucin-domain containing-3 $(TIM3)^+$ effector memory T cells), as previously defined at single-cell level,[11] correlated with greater benefits of the anti-CD20 BsAb/anti-CD39 combination treatment (figure 2F). No such association was observed with other T-cell subsets or when using anti-CD73 blocking antibody (figure 2F). Furthermore, we examined the expression of various exhaustion markers, namely PD-1, TIM3, Lymphocyte-activation gene 3 (LAG3), CD43, T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and CD39 in lymph node-derived effector memory T cells. Interestingly, we noted increased levels of CD39 in effector T cells, including those displaying an exhaustion phenotype, were linked to pronounced benefits from the combination treatment of anti-CD39 and BsAb (figure 2G). In contrast, higher levels of PD-1 were associated with an inferior ex vivo response (figure 2G).

DISCUSSION

Our study demonstrates that blocking the CD39/CD73 pathway synergizes with BsAb by augmenting tumor cell killing, T-cell expansion, and cytokine secretion in B-NHL. Previously, we reported similar benefits when combining BsAb with cereblon modulators and checkpoint inhibitors,[9] which are currently being evaluated in clinical trials for nodal B-cell lymphoma. Clinical studies investigating blocking antibodies against CD39 and CD73 are limited to advanced stages of solid cancers (eg, NCT05742607). However, our data strongly suggest their application and evaluation in nodal B-cell lymphoma in combination with BsAb. Notably, CD39 has also been detected in dysfunctional CAR T cells,[21] implying that blocking the CD39/CD73 pathway could be valuable for T-cell-engaging approaches in general.

Furthermore, we have used the sample overlap with existing single-cell data to identify potential determinants of the ex vivo response to BsAb when combined with anti-CD39 or anti-CD73 blocking antibodies. We discovered that targeting CD39 or CD73 was particularly effective in patients with higher numbers of $PD\text{-}1^+$ $TIM3^+$ cytotoxic T cells, commonly referred to as exhausted T cells. Levels of CD39 in exhausted T cells exhibited significant heterogeneity and showed a correlation with the benefits obtained by combining BsAb with anti-CD39 or anti-CD73 blocking antibodies. In B-NHL, T-cell exhaustion is considered to contribute to treatment failure and early relapses in a subset of patients receiving BsAb.[22] Therefore, we speculate that these patients could benefit the most from antibodies targeting CD39 or CD73. While it may seem

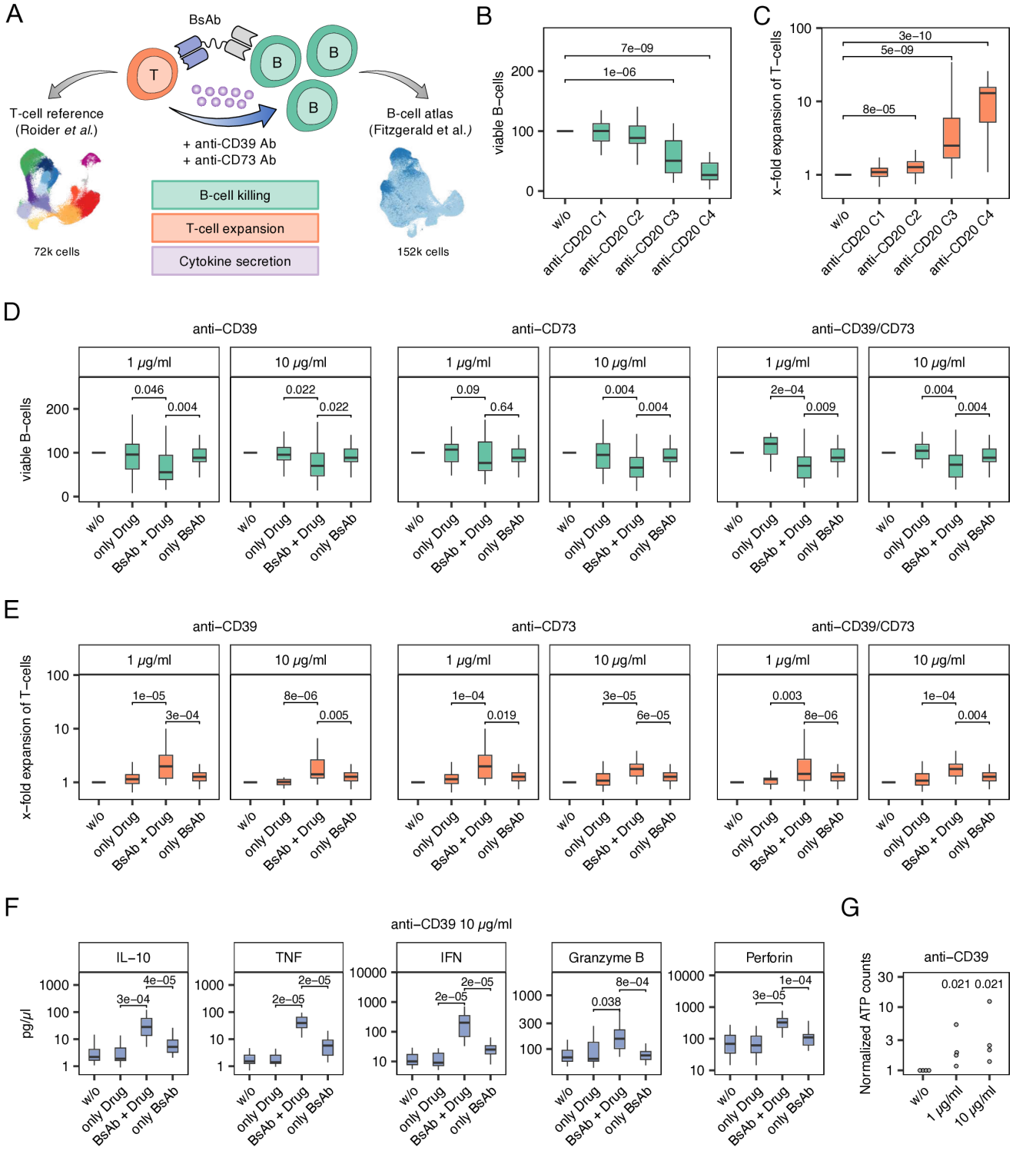

Figure 1 Blocking the CD39/CD73 pathway synergistically augments response to anti-CD20 BsAb. (A) Study overview. (B–F) Lymph node-derived lymphocytes were incubated with or without (w/o) a maximum of four concentrations of a CD20-BsAb (C1–C4) and/or a maximum of two concentrations of anti-CD39, anti-CD73, anti-CD39/CD73 blocking antibodies, as indicated. After 7 days, cells (B–E) or supernatants (F) were analyzed by quantitative flow cytometry or a bead-based immunoassay, respectively. Shown are the percentages based on the absolute numbers of viable B cells normalized to w/o (B, D), the x-fold expansion based on the absolute numbers of viable T cells normalized to w/o (C, E) or the cytokine levels in pg/μL (F) in n=27 biologically independent samples. (G) Lymph node-derived lymphocytes were incubated with or without the anti-CD39 blocking antibody at two different concentrations and then exposed to ATP at a concentration of 20 μM. Shown are ATP levels of n=4 biologically independent samples normalized to untreated control (w/o) after 60 min. (B–G) P values were calculated between w/o and every other condition using the two-sided Wilcoxon test and corrected for multiple testing using the Benjamini-Hochberg procedure. Only p values≤0.05 are shown. Box plots: center line, median; box limits, first and third quartile; whiskers, 1.5×IQR. BsAb, bispecific antibody; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

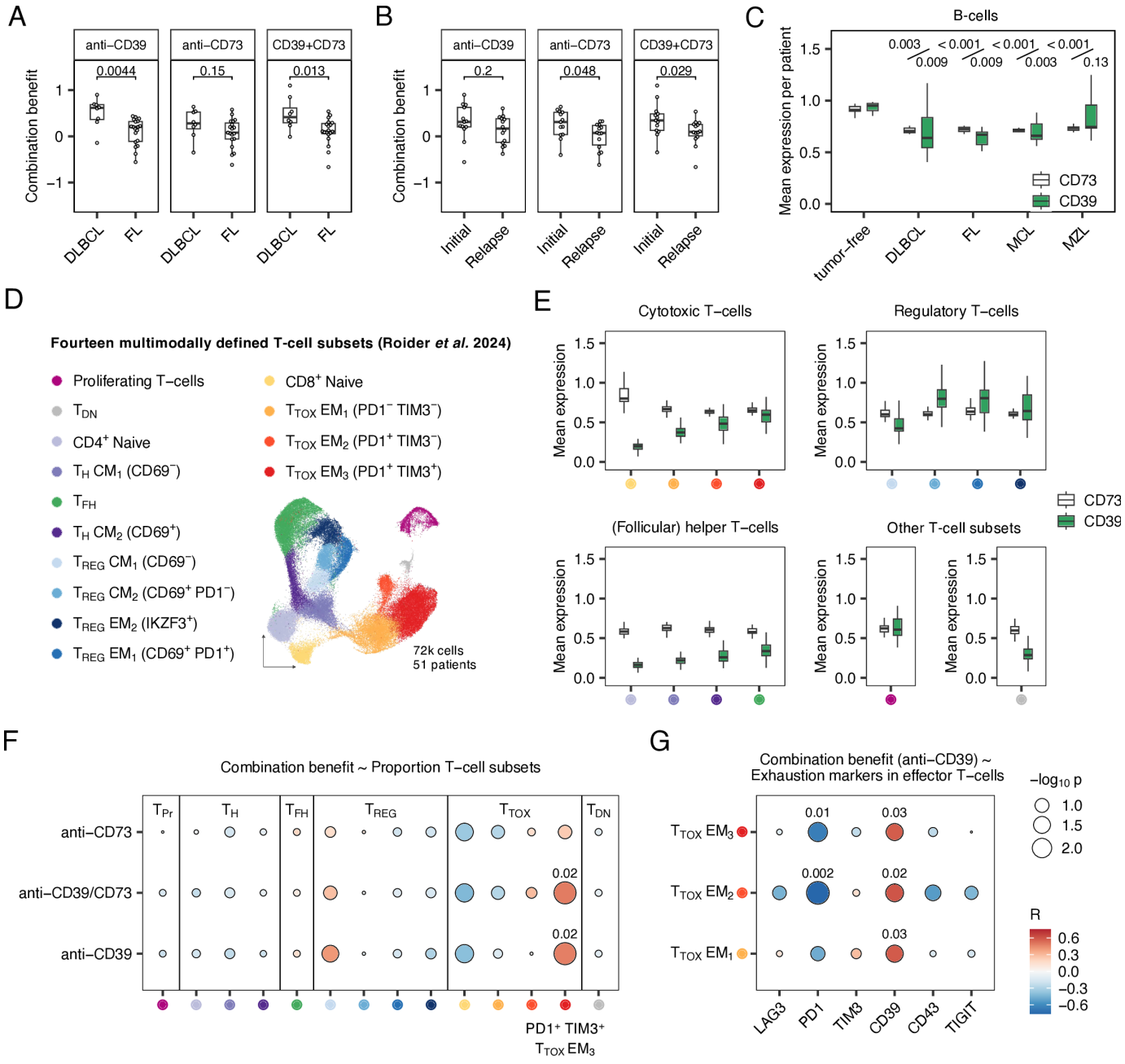

Figure 2 Benefit from anti-CD39/CD73 blockade is linked to the proportion of exhausted T cells and CD39 expression. (A–B) Box plots illustrating the associations of patient characteristics with benefits from three different combination treatments in n=27 biologically independent lymph node samples. P values were calculated using the Wilcoxon test. (C) Shown is the expression of CD39 and CD73 at the protein level based on publicly available single-cell data of in n=51 biologically independent lymph node samples. (D) Overview of 14 T-cell subsets defined by existing single-cell RNA and epitope sequencing in n=51 biologically independent lymph node samples. (E) Shown is the expression of CD39 and CD73 at the protein level based on previously mentioned T-cell reference data. (F) The proportion of fourteen specific T-cell subsets, defined in panel D (y axis), was correlated with the benefit from three different combination therapies (x axis) compared with BsAb monotherapy. Only p values≤0.05 are shown. High or low Pearson's R indicate direct or inverse associations of T-cell subset proportion and the extent of combination benefit. Only values ≤0.05 are shown. (G) The protein expression of six different exhaustion markers (x axis) across three effector memory T cells, defined in panel A, was correlated with the benefit when combining anti-CD39 blocking antibody with anti-CD20 BsAb compared with BsAb monotherapy. High or low Pearson's R indicates direct or inverse associations of marker expression and the extent of combination benefit. Only values ≤0.05 are shown. Box plots: center line, median; box limits, first and third quartile; whiskers, 1.5×IQR. BsAb, bispecific antibody; CM, central memory; DLBCL, diffuse large B-cell lymphoma; EM, effector memory; FL, follicular; LAG3, lymphocyte-activation gene 3; LN, lymph node; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD-1, Programmed cell death protein 1; T_{DN}, double negative T-cells; TF, transcription factor; T_{FH}, follicular helper T-cells; T_H, helper T cells; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM3, T-cell immunoglobulin and mucin-domain containing-3; T_{Pr}, proliferating T-cells; T_{REG}, regulatory T cells; T_{TOX}, cytotoxic T-cells.

obvious that T cells play a significant role in the efficacy of anti-CD39 and anti-CD73 blocking antibodies, malignant or non-malignant B cells could be equally important. For example, Zhang *et al* and Bastid *et al* demonstrated in their studies that B cells can impair T-cell activity and expansion via the CD39/CD73 pathway.[23 24] Still, further research in the context of BsAb is necessary to clarify the exact role of each cell type.

In summary, our study is highly relevant as we introduce the combination of BsAb and anti-CD39 or anti-CD73 antibodies as a synergistic treatment approach in nodal B-cell lymphoma, while also suggesting potential biomarkers to identify patients eligible for this treatment.

MATERIALS AND METHODS

Patient samples

The study was carried out according to the Helsinki protocol in its current version. Written informed consent was collected from all patients prior to sample processing. 29 consecutive patients undergoing lymph node biopsies that revealed B-NHL were included. The baseline clinical data of all patients is depicted in online supplemental table 1. Lymph node processing was performed as previously described by us.[25]

Flow cytometric ex vivo assays

Cryopreserved lymph node cell suspensions were thawed at 37°C using a water bath and resuspended in Roswell Park Memorial Institute (RPMI) 1640 cultural medium supplemented with 10% heat-inactivated human AB serum (Sigma Aldrich, St. Louis, Missouri, USA). To remove cell debris, the cell suspension was kept on a rotating mixer for 3 hours. Cells were strained using a 70 µm strainer. Unsorted cells were plated at 200,000 cells/well in a 96-well flat bottom plate containing 200 µL cell medium per well. The following antibodies were added: CD20×CD3 BsAb (BSFV-H226, Creative Biolabs, Shirley, New York, USA) at 10 ng/mL (C1), 100 ng/mL (C2), 1,000 ng/mL (C3), or 10,000 ng/mL (C4). The monoclonal anti-CD39 (clone: IPH5201) and anti-CD73 antibodies (clone: IPH5301, both Innate Pharma, Marseille, France, via material transfer agreement) were added at 1 µg/mL or 10 µg/mL. Cells were cultured at 37°C and 5% CO_2 for 7 days. Afterwards, cells were washed and stained for flow cytometric analysis. The following surface antibodies and viability dye were used: anti-CD3-APC/Cy7, anti-CD19-BV421, anti-CD4-PE/Dazzle, anti-CD8-FITC, anti-CD20-APC, anit-CD5-PE/Cy7 (all BioLegend), and fixable viability dye e506 (Thermo Fisher Scientific). Samples were analyzed using an FACSSymphony A3 (BD Biosciences, Heidelberg, Germany) and BD FACSDiva software (BD Biosciences).

Data analysis

Flow cytometric data was analyzed with FlowJo (BD Biosciences). Count Beads (BioLegend, San Diego, California, USA) were used to quantify absolute cell numbers. To evaluate synergy statistically, we used the Bliss independence model which compares the observed effect $y_{ab}$of a combination treatment with the predicted effect, alias Bliss score, $y_{ab}$of two separate compounds.[20] The calculation of the Bliss score is based on the formula:

$$\hat{y}_{ab} = y_a + y_b - y_a y_b$$

If the difference between the mean observed effect y_{ab} and the mean Bliss score across all patient samples is positive, alias excess over Bliss score, the combination treatment is considered synergistic.

The benefit from combination treatments for each individual patient was quantified by the difference in normalized number of B cells between monotherapy and combination therapy. Therefore, lower/negative numbers indicate stronger benefits from combinations.

Descriptive statistics were performed using R V.4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The correlation between continuous variables was calculated using Spearman's rank correlation. Means of independent variables were compared using the unpaired Wilcoxon signed-rank test. P values were adjusted for multiple tests using the Benjamini-Hochberg method.

Cytokine assays

Supernatants from primary human lymph node assays were analyzed. Granzyme B, perforin, IFN-γ, IL-10 and TNF-α levels were measured with a LEGENDplex assay kit as per manufacturer's protocol. Flow cytometric analysis was performed by using an LSRFortessa (BD Biosciences) and the LEGENDplex Data Analysis Software V.8.0 (BioLegend).

ATP assay

The effect of CD39 blockade on ATP levels in lymph node cell cultures was analyzed using the CellTiter Glo assay (Promega, Walldorf, Germany), as previously described.[15] Lymph node samples were processed as described above and incubated with anti-CD39 antibody at 10 µg/mL for 60 min. Next, ATP was added at a concentration of 20 µM. After 60 min, supernatants were analyzed using an EnSight multimode plate reader (PerkinElmer, Waltham, Massachusetts, USA). Inhibition of enzymatic activity was calculated as follows:

$$anti-CD39: \frac{(Cells+ATP+anti-CD39)-(Cells+ATP)}{(ATP)-(Cells+ATP)} \; x\,100$$

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Competing interests No, there are no competing interests.

Patient consent for publication Written informed consent was collected from all patients prior to sample processing.

Ethics approval The study was approved by the ethics committee of the University of Heidelberg (ID number S254/2016) and carried out according to the Helsinki protocol in its current version.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. Data generated specifically for this study will be provided upon request without further hurdles. Single-cell sequencing data used in this study have been previously published and are available for download as referenced in the original publications.[11 19]

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