Original Article

Anti-CD38 Therapy with Daratumumab for Relapsed/ Refractory CD20-Negative Diffuse Large B-Cell Lymphoma

(Non-Hodgkin lymphomas / CD38 / daratumumab / patient-derived xenograft)

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Abstract. Diffuse large B-cell lymphoma (DLBCL) is the most common and one of the most aggressive subtypes of non-Hodgkin's lymphomas. Front-line therapy consists of chemotherapy in combination with anti-CD20 monoclonal antibody rituximab. Relapses after rituximab-based regimen have poor prognosis and call for new treatment options. Immunohistochemistry analysis of relapsed DLBCL often reveal CD20-negative lymphoma, which limits repeated use of rituximab in combination with salvage chemotherapy. CD38 is a surface antigen that binds to CD38, CD31/PECAM-1 and hyaluronic acid. CD38 is an important mediator of signal transmission from the microenvironment into the cell. Anti-CD38 monoclonal antibody daratumumab has been approved for the treatment of multiple myeloma. Expression of CD38 on the surface of DLBCL is highly variable (compared to strong expression on myeloma cells), but can be easily assessed by flow cytometry or immunohistochemistry. A patient-derived xenograft (PDX) model of CD20-negative, CD38-positive DLBCL derived from a patient with rituximab-refractory DLBCL was used for *in vivo* experiments. We demonstrated that daratumumab suppressed growth of subcutaneous PDX tumours significantly more effectively than rituximab. Analysis of tumours obtained from mice treated with daratumumab revealed down-regulation of surface CD38, suggesting endocytosis of CD38-daratumumab complexes. The results suggest a potential clinical use of daratumumab in combination with salvage chemotherapy in patients with relapses of CD20-negative DLBCL. In addition, daratumumab might potentially serve as a suitable antibody moiety for derivation of antibody-drug conjugates for the targeted delivery of toxic payloads to the lymphoma cells.

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Abbreviations: ABC – activated B-cell-like, ADCs – antibody-drug conjugates, B-NH – B-non-Hodgkin lymphoma, CNV – copy number variant, CR – complete remission, DLBCL – diffuse large B-cell lymphoma, FCM – flow cytometry, FL – follicular lymphoma, GCB – germinal centre B-cell-like, mAb – monoclonal antibody, MCL – mantle cell lymphoma, NGS – next-generation sequencing, NSG mice – NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice, PBS – phosphate-buffered saline, PDX – patient-derived xenograft, PFS – progression-free survival, PMBL – primary mediastinal B-cell lymphoma.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common and one of the most aggressive subtypes of B-non-Hodgkin's lymphomas (Armitage, 1997). The median age of patients with newly diagnosed DLBCL is in the 7th decade, with a slight male predominance (Perry et al., 2016). Gene expression profiling divides DLBCLs into three basic subgroups according to the cell-of-ori-

gin: germinal centre B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (PMBL) (Alizadeh et al., 2000; Rosenwald et al., 2002). These DLBCL subtypes have significantly different overall survival after immunochemotherapy (Alizadeh et al., 2000; Rosenwald et al., 2002, 2003).

In DLBCL, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or similar regimens are used for front-line therapy. In elderly patients, the use of anti-CD20 monoclonal antibody (mAb) rituximab with cytostatics (cyclophosphamide, doxorubicin/hydroxydaunorubicin, vincristine/oncovine) and prednisone (so-called R-CHOP regime) induces complete remission (CR) in 75–80 % patients and 5-year progression-free survival (PFS) in 50–60 % cases (Coiffier et al., 2002).

The patients with relapsed DLBCL are usually treated with salvage therapy containing different cytostatics, most commonly platinum derivatives and high-dose cytarabine, but the same mAb, rituximab, due to the lack of alternative therapeutical mAbs. Daratumumab is a human mAb against CD38 approved (2016) for the therapy of multiple myeloma. Daratumumab induces death of CD38-expressing cells by a wide spectrum of mechanisms – antibody-dependent cellular phagocytosis, complement-dependent cellular toxicity, direct induction of apoptosis, and modulation of CD38 enzymatic activity (de Weers et al., 2011; Overdijk et al., 2015, 2016).

In this study we evaluated the preclinical activity of daratumumab *in vivo* in a patient-derived lymphoma xenograft established from a patient with CD20-negative, CD38-positive relapsed/refractory DLBCL. In addition, we analysed the molecular mechanisms associated with acquired resistance of lymphoma cells to daratumumab.

Material and Methods

Whole-exome sequencing by next-generation sequencing (NGS)

Samples were sequenced by our facility in the NextSeq 500 (Illumina, San Diego, CA) instrument according to the manufacturer‘s protocols with sequencing libraries prepared using a SureSelectXT Human All Exon V6+UTR kit (Agilent Technologies, Santa Clara, CA). Detailed description of the data processing is provided in Supplemental Methods (https://lymphoma-lab.lf1.cuni.cz/vockova-et-al-supplemental-data).

Reagents

Rituximab (MabThera) and daratumumab (Darzalex) were purchased from the General University Hospital in Prague pharmacy, Czech Republic.

PDX model establishment and in vivo therapy

The PDX model of treatment-refractory CD20-negative, CD38-positive DLBCL, designated VFN-D5, was derived from a core-needle lymph node biopsy of a patient with DLBCL relapse after signing an informed consent as previously described (Klanova et al., 2014; Lemm et al., 2019; Prukova et al., 2019).

The experimental design was approved by the Institutional Animal Care and Use Committee (MSMT-32441/2018-6). NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice (referred to as NSG mice) were purchased from The Jackson Laboratory (Bar Harbor, ME). All animals were maintained in a pathogen-free environment in individually ventilated cages and provided with sterilized food and water. Adult female NSG mice were used for all experiments. NSG mice were subcutaneously inoculated with 10 million PDX cells. Therapy was initiated when all mice developed palpable tumours (= day 1, D1). At D1, all mice were stratified so that all cohorts contained mice with comparable calculated tumour volumes. The treatments (rituximab or daratumumab) were administered intraperitoneally at a dose of 10 mg/kg twice weekly in phosphate-buffered saline (PBS) (0.3 ml per mouse) for two weeks. Tumour growth was recorded daily using three perpendicular dimensions (in millimetres) with a digital calliper. Tumour volumes were calculated using the following formula: $\pi/6 \times$ length $\times$ width $\times$ height. Observation was terminated (and experimental mice euthanized) when subcutaneously grown tumours exceeded 2 cm in the largest diameter. Tumours were excised and weighed, and the euthanized mice were dissected in search for any signs of advanced (disseminated) lymphoma (splenomegaly, abdominal lymphoma spread, etc.).

Flow cytometry (FCM) and QuantiBRITE analysis

Cell samples from the tumours were obtained by tissue homogenization using a 40 μM cell strainer (Falcon, Corning, NY). After washing in PBS, the cells were used directly for flow cytometry, and the cell pellets were stored at –80 °C. The samples used for flow cytometry were obtained from SC tumours of non-treated or treated mice. The samples were washed in PBS and stained with antibodies for 15 min at room temperature in the dark and twice washed with PBS. The following fluorochrome-conjugated mAb were used: CD20 PE (clone 2H7, BD Biosciences, Franklin Lakes, NJ), CD38 PE (clone HIT2, BD Biosciences). Samples were analysed by FACSCanto (Becton Dickinson, San Jose, CA). For quantification of surface antigens, we used BD QuantiBRITE Beads (BD Bioscience) according to the manufacturer’s instructions.

FCM results were processed with Kaluza software, version 1.5 (Beckman Coulter, Brea, CA). Isotype-matched negative controls were used in all the assays to distinguish positive from negative cells. All the measurements were performed in biological duplicates.

Results

Establishment and characterization of VFN-D5, a PDX model of CD20-negative, CD38-positive treatment-refractory DLBCL

The PDX model designated VFN-D5 was derived from an infiltrated lymph node of a patient with treatment-refractory DLBCL. Immunohistochemistry analysis of the lymph node biopsy revealed CD20 negativity of the relapsed lymphoma cells. Mutational analysis by NGS confirmed that VFN-D5 cells harboured mutations recurrently found in patients with DLBCL (Fig. 1A, B, Supplemental Table 1 (https://lymphoma-lab.lf1.cuni.cz/vockova-et-al-supplemental-data)). Similarly, the copy number variant (CNV) analysis demonstrated a similar

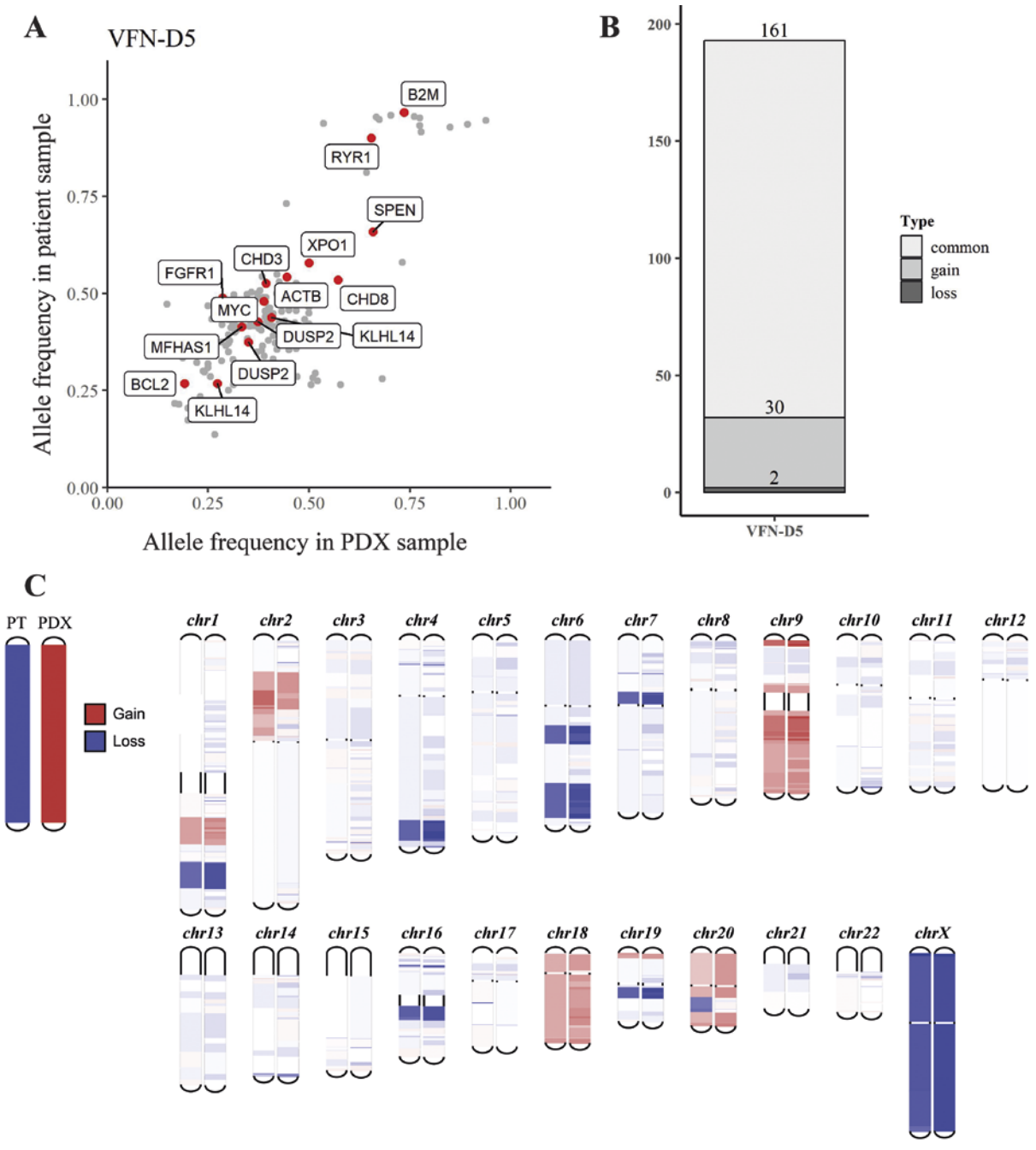

Fig. 1. **A -** Scatter plot showing the allele frequency of common protein-coding variants in a PDX model sample compared to the sample from which it was derived. Variants in genes of special interest based on a list of frequently mutated genes described in the Methods are highlighted in red and all remaining variants are grey. **B -** Stacked bar chart showing numbers of common protein-coding variants in both samples and those gained or lost in the derivation of the PDX model. **C -** Karyotype diagram chart showing the copy number variation (CNV) as calculated by CNVkit in the patient's sample (left chromosomes) and the PDX model derived from this sample (right chromosomes). Inferred segmental changes are marked in shades of blue (loss) and red (gain). Y chromosome has been removed from the chart.

Supplemental Table 1. legend

A complete list of protein-coding variants that passed filtering described in Supplemental Methods and were found in both the PDX model sample and the patient's sample from which it was derived (S1A), and variants that were gained (S1B) or lost (S1C) during the PDX model derivation. Variants in genes of special interest based on a list of frequently mutated genes described in the Methods are highlighted in red. The gene list is included in the Table (S1D).

Chr – chromosome, REF – reference allele (patient), ALT – alternative allele, AA change – amino acid change, Patient AF – allele frequency in patient's sample, Patient Depth – read depth in patient's sample, PDX AF – allele frequency in PDX model sample, PDX Depth – read depth in PDX sample.

extent of gain or loss of genetic material in PDX compared to primary lymphoma cells (Fig. 1C). Flow cytometry analysis of VFN-D5 cells confirmed CD20 negativity and high CD38 positivity of PDX cells (Fig. 2).

Anti-CD38 therapy with daratumumab significantly suppressed growth of subcutaneous VFN-D5 tumours in vivo

When immunodeficient mice subcutaneously injected with VFN-D5 cells developed palpable tumours, the mice were stratified into three cohorts and subjected to therapy with daratumumab, rituximab and no therapy. Daratumumab significantly suppressed growth of SC tumours compared to both rituximab-treated and untreated mice (Fig. 3).

Molecular mechanisms of resistance to anti-CD38 therapy include CD38 down-regulation as revealed by flow cytometry analysis of PDX tumours obtained from the treated and untreated mice

To evaluate the possible mechanism of overcoming anti-CD38 therapy, we performed flow cytometry analysis of cells obtained from the daratumumab-treated and untreated mice. The daratumumab-treated tumours had significantly lower CD38 expression compared to untreated controls (Fig. 4).

Discussion

Relapses of DLBCL after failure of R-CHOP-based front-line therapy remains a therapeutic challenge and unmet medical need. While patients with relapsed DLBCL are treated with different cytostatic agents, they usually receive the same mAb, rituximab. However, at least part of the relapsed DLBCL are associated with decreased or absent CD20 expression. In this study, we provided a preclinical proof-of-concept demonstrating that CD20-negative, CD38-positive DLBCL can respond to single-agent anti-CD38 daratumumab (but not to anti-CD20 rituximab).

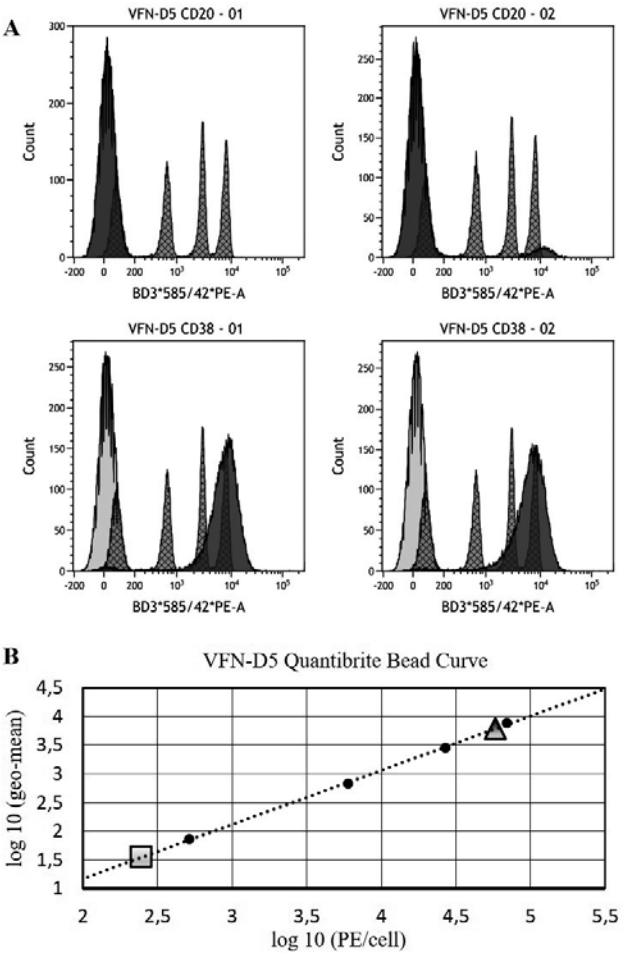

Fig. 2. Flow cytometry analysis of CD20 and CD38 surface antigens on VFN-D5 cells

A – Surface antigens CD20 and CD38 on the cell surface of VFN-D5 in comparison with isotype control for each antigen (negative control) and QuantiBRITE beads. Dark grey full histograms show fluorescence intensity of the measured antigen (type of antigen seen in the graph name), light grey full histograms show fluorescence of isotypes, and cross-hatched histograms represent fluorescence intensity of QuantiBRITE beads (four histograms – low, med-low, med-high, and high signal intensity). **B** – Difference in the CD20 and CD38 antigen expression per single cell. The dotted line shows a standard curve (four dark circles represent medians of each QuantiBRITE Beads group - low, med-low, med-high, and high signal intensity), CD20 antigen expression is marked by a square and that of CD38 by a triangle.

Recently, Salles et al. (2019) published results from phase II study evaluating potential anti-lymphoma efficacy of daratumumab monotherapy in patients with R/R DLBCL. In contrast to myeloma, anti-lymphoma efficacy of single-agent daratumumab was limited, which led to preliminary closure of the study (Salles et al. 2019). Despite the fact that we have demonstrated measurable single-agent activity of daratumumab *in vivo*, we are persuaded that the therapy of relapsed DLBCL can-

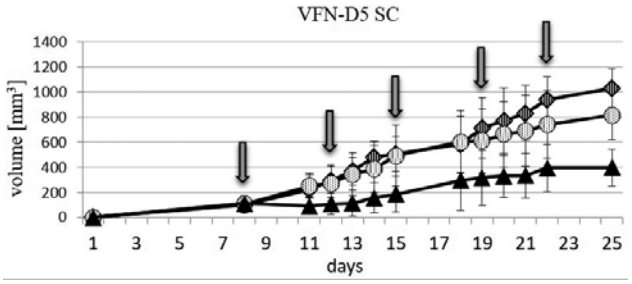

Fig. 3. Tumour growth curves compare means of the counted tumour volumes in the groups of untreated, rituximab-treated and daratumumab-treated mice, including standard deviations. There was no significant difference in growth between the untreated group (hatched rhombus) and the rituximab-treated group (dotted circles), but the daratumumab-treated group (dark trianglesd) showed significant tumour growth suppression.

not be based on monotherapies of any kind, but must be based on a combinatorial or sequential regimen. The main goal of this preclinical study was to provide an alternative mAb that might be used in combination with salvage chemotherapy in patients with CD20-negative relapses. In addition, CD38 positivity can be established by immunohistochemistry or flow cytometry, but requires re-biopsy.

Beside potential usage of daratumumab as part of combinatorial salvage therapy in DLBCL, other groups tested the anti-tumour efficacy of daratumumab as a maintenance therapy in other lymphoma subtypes, namely mantle cell lymphoma (MCL) and follicular lymphoma (FL). Vidal-Crespo et al. (2019) have shown that pre-emptive treatment prevented engraftment and growth of MCL and FL cell line-based xenografts in mice.

The flow cytometry analysis of CD38 expression on lymphoma cells obtained from tumours of daratumumab-

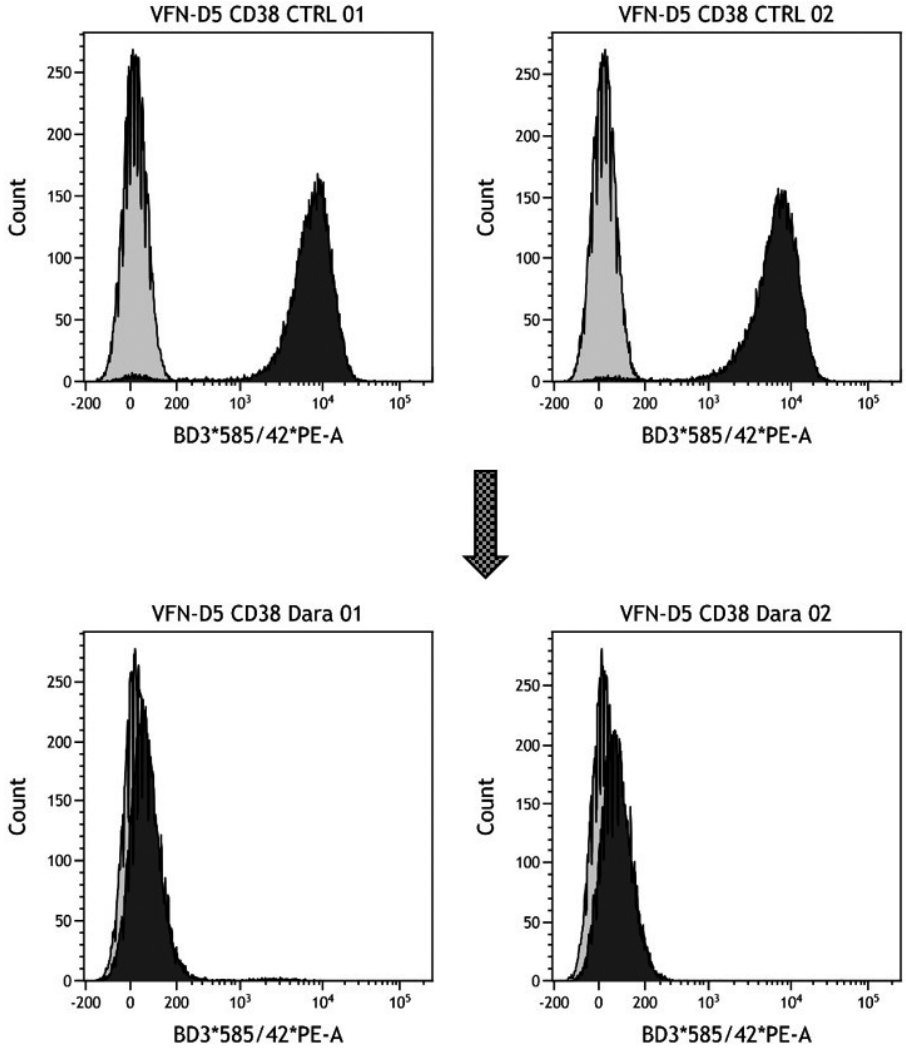

Fig. 4. Flow cytometry data shows significant CD38 down-regulation in VFN-D5 cells obtained from subcutaneous daratumumab-treated tumours (Dara 01, Dara 02) in comparison with VFN-D5 cells from untreated tumours (CTRL 01, CTRL 02). In each graph, dark grey full histograms represent fluorescence of CD38 antigen and light grey full histograms show fluorescence of the isotype control.

treated mice revealed marked down-regulation of CD38. The most plausible explanation for the observed CD38 knockdown as a result of anti-CD38 targeted therapy is endocytosis of CD38-daratumumab complexes. The results thus might suggest that daratumumab could serve as a suitable moiety for derivation of antibody-drug conjugates (ADCs) for targeted delivery of toxic payloads, e.g., monomethyl auristatin E. CD38-based ADCs might be significantly more effective even as monotherapies, in analogy to anti-CD30 antibody SGN-30 and ADC SGN-35 (Forero-Torres et al., 2009; Horwitz et al., 2019).

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