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LETTER TO THE EDITOR

Treatment of therapy-related acute myeloid leukemia and underlying multiple myeloma with decitabine/venetoclax and daratumumab

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Dear Editor,

With increased survival of patients with multiple myeloma (MM), therapy-related myelodysplastic syndrome (t-MDS) and t-acute myeloid leukemia (AML) may occur more frequently [1, 2]. We present here a patient with high-risk (HR) MM, who developed t-MDS and subsequent t-AML. AML treatment with decitabine/venetoclax resulted in complete remission (CR) of the t-AML, while progressive disease of MM was treated with daratumumab. We hypothesize that upregulation of CD38 in bone marrow plasma cells (BMPCs) after decitabine/venetoclax may have enhanced MM response. Additionally, we performed a review of the literature (Suppl. Table 1).

In June 2015, a 64-year-old female was diagnosed with IgG kappa (κ) MM. IgG levels were 46g/L, κ-serum-free light chains (SFLC) 75.4mg/L and ß2-microglobulin 8.2mg/L (Fig. 1A). Anemia with a hemoglobin (Hb) of 8.4g/dL and osteolytic lesions were present. BMPC infiltration was 90%, and fluorescence in situ hybridization (FISH) revealed hyperdiploidy and del17p13 (Fig. 1B (a) and C). The MM was classified as International Staging System (ISS) III, R-ISS III, with 2/4 CRAB criteria. The patient's revised myeloma comorbidity index was intermediate-fit [3].

First-line therapy with bortezomib, cyclophosphamide, and dexamethasone was followed by autologous stem cell transplantation and maintenance therapy with lenalidomide (Fig. 1A). After 1½ years (11/2017), lenalidomide was discontinued due to worsening anemia (Hb 10g/dL) and leukopenia ($2.8x10^6$/L). BM assessment did not reveal increased PCs or MDS, and serological parameters indicated stable disease.

In January 2019, pancytopenia worsened (Hb 8.4g/dL, leukocytes $0.59x10^6$/L, platelets $12x10^6$/L) and κ-SFLCs increased (Fig. 1A). Another BM biopsy revealed BMPCs of 50% and myeloid blasts of 22% (Fig. 1B (b)). Molecular analyses identified mutations in *DNMT3A* and *IDH1* (Fig. 1C). Coexistence of MM and t-AML (Fig. 1D, left) was confirmed by 10-color multiparameter flow cytometry (MFC) analysis of the BM [4].

Due to frailty at that time, she was ineligible for intensive AML induction therapy. Therefore, treatment with decitabine/venetoclax was started in February 2019. A BM biopsy in March 2019 confirmed CR of the t-AML (Fig. 1B (c)). However, PCs assessed by immunohistochemistry for CD38 had increased to 90%, and MFC confirmed aberrant PCs (aPCs) (Fig. 1D, right); therefore 2nd line daratumumab treatment was initiated (Fig. 1A). This induced VGPR and peripheral blood (PB) counts improved (Hb 10.2g/dL, leukocytes $3.2x10^6$/L, platelets $94x10^6$/L).

In June 2019, after worsening pancytopenia re-emerged and myeloid blasts were detectable in PB smears, decitabine/venetoclax was re-initiated. The BM biopsy in August 2019 showed persisting (30%) immature myeloid blasts (Fig. 1B (d)), upon which melphalan per os was started [5]. The patient died 2 months later of t-AML/MM progression, 50 months after the diagnosis of HR MM, and 9 months after t-AML.

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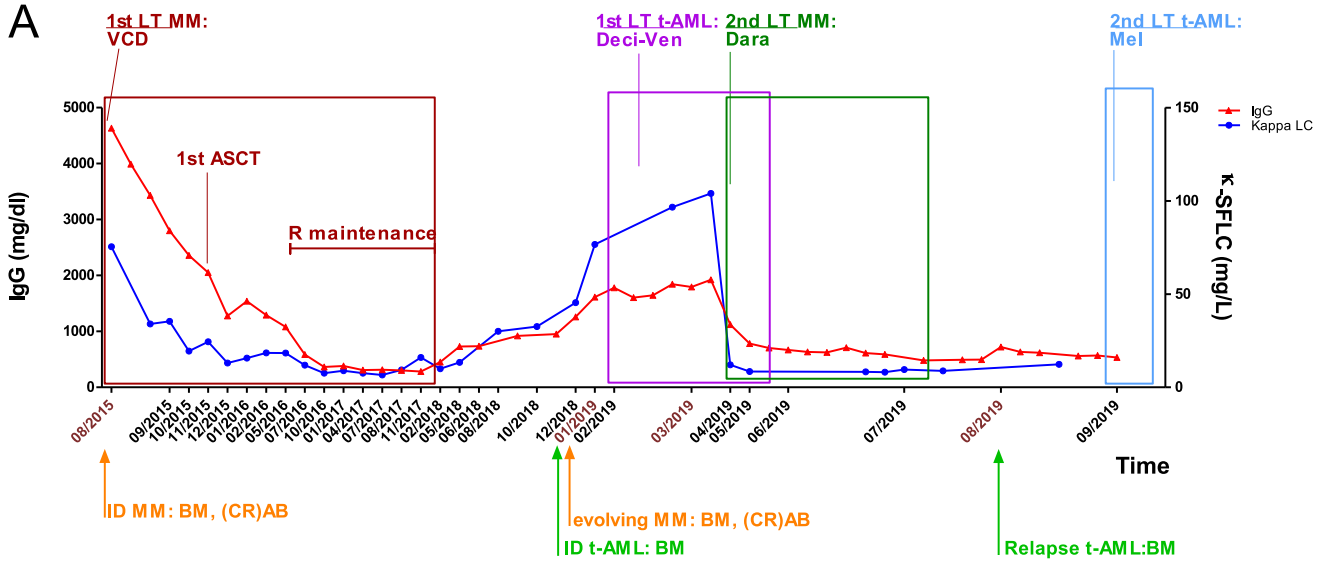
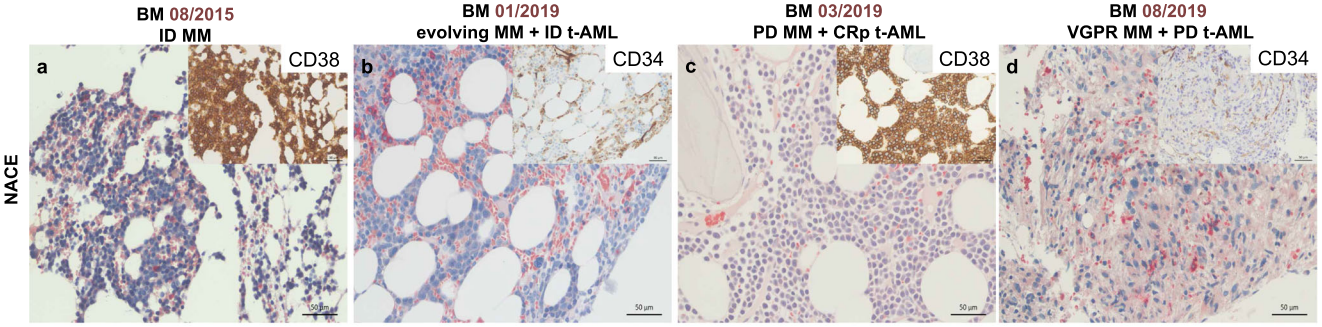
A



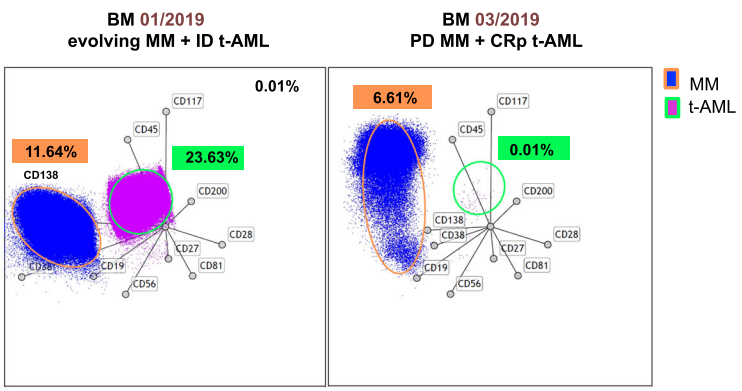
B



C

Date	08/2015	01/2019	03/2019	08/2019
Disease Stage	ID MM -	evolving MM ID t-AML	PD MM CRp t-AML	VGPR MM Relapse t-AML
FISH	Hyperdiploidy/del 17p13 (60%)	Hyperdiploidy/del 17p13 (30%)	Hyperdiploidy/del 17p13 (60%)	No Hyperdiploidy/del 17p13
MA	not done	IDH1 (30%)	IDH1 (20%)	IDH1 (20%)

D



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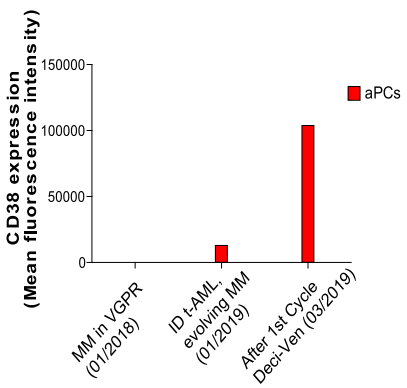

◀ **Fig. 1** The patient's clinical, cytogenetic, and molecular results, describing both MM and t-AML clones. **A** Course of serological parameters (IgG and κ-SFLC) and disease state of MM (orange) and t-AML (green) between August 2015 and September 2019. Lines of treatment for each entity are depicted. **B** NACE and immunohistochemical stainings (CD34 or CD38) of BM biopsies from initial diagnosis of MM (a. August 2015), initial diagnosis of t-AML (b. January 2019), after the 1st cycle of decitabine/venetoclax (c. March 2019), and at t-AML relapse (d. August 2019). **C** Remission status (gray), fluorescence in situ hybridization (FISH) analyses (beige), and molecular diagnostics (blue) during the disease course. Percent of cells positive for hyperdiploidy and/or del17p13 as assessed by FISH at initial diagnosis of MM (August 2015), at initial diagnosis of t-AML (January 2019), and before treatment initiation with daratumumab (March 2019). Allele frequency of the *IDH1* mutation at initial diagnosis of t-AML (January 2019), after the 1st cycle decitabine/venetoclax (March 2019), and at t-AML relapse (August 2019). **D** Radar plot of the flow cytometry analysis with the 10-color MFC panel, showing the myeloma (dark blue/orange circle) and leukemia (pink/green circle) population at the initial diagnosis of t-AML (January 2019) and after the 1st cycle of decitabine/venetoclax (March 2019). **E** Mean fluorescence intensity of CD38 expression of aberrant plasma cells (aPCs) in the BM in January 2018, when the MM was in remission, at initial diagnosis of t-AML (January 2019) and after the 1st cycle of decitabine/venetoclax (March 2019). aPC, aberrant plasma cells; ASCT, autologous stem cell transplantation; BM, bone marrow; CRAB, hypercalcemia, renal impairment, anemia, bone lesions; CRp, complete remission with incomplete platelet recovery; Dara, daratumumab; Deci-Ven, decitabine/venetoclax; 1st LT MM, first-line treatment multiple myeloma; 1st LT t-AML, first-line treatment therapy-related acute myeloid leukemia; FISH, fluorescence in situ hybridization; ID, initial diagnosis; IDH1, isocitrate dehydrogenase 1; IgG, immunoglobulin G; LC, light chains; 2nd LT MM, second-line treatment multiple myeloma; Mel, melphalan; MA, molecular analysis; NACE, naphthol-AS-D-chloracetatesterase; PD, progressive disease; R, Lenalidomide; SFLC, serum-free light chains; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial remission

In summary, after decitabine/venetoclax induction and favorable t-AML-response, MM progression required 2nd line daratumumab treatment, resulting in VGPR and improvement of PB counts. Notably, decitabine/venetoclax may have resulted in upregulation of CD38 (Fig. 1 D and E), possibly augmenting the response to daratumumab, although single-cell CD38 expression on aPCs before and after decitabine/venetoclax was not performed. In line with this hypothesis, Choudhry et al. showed that treatment of MM cell lines and primary patient samples with the demethylating agent 5-azacytidine resulted in CD38 upregulation [6]. Moreover, ATRA and the pan-deacetylase-inhibitor panobinostat may increase expression of CD38 in MM [7, 8]. Similarly, Zhao et al. demonstrated upregulation of CD38 on CD8-positive T-cells of AML patients receiving decitabine [9]. Furthermore, daratumumab has been shown to be effective in targeting adult CD38-positive AML and T-cell acute lymphoblastic leukemia (T-ALL) as well as pediatric T-ALL blasts in a preclinical patient-derived xenograft mouse model, and a phase II study (NCT03384654) investigating the efficacy of daratumumab in relapsed and refractory T-ALL is currently ongoing [10, 11]. Recently, Berthon et al. reported about a patient with simultaneous AML and MM who concomitantly received 5-azacytidine and daratumumab during MM relapse (Suppl. Table 1) [12]. Clinical trials are currently under way to investigate whether pretreatment with demethylating agents enhances the efficacy of daratumumab.

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Author contribution K.S. designed the study, interpreted the data, and wrote the manuscript; J.J. and M.R. interpreted the data and wrote the manuscript; S.M.D. and V.R. performed FACS experiments and analyze and wrote the manuscript; M.P. performed cytogenetic analyses and provided information; G.H. provided patient data and wrote the manuscript; M.L., R.M. and R.W. helped with the conception and design of the study; M.E. designed the study, interpreted the data, and wrote the manuscript.

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Declarations

Ethics Informed consent was obtained from the patient for being included in this study.

Conflict of interest JJ, MR, SMD, VR, MP, GH, RM, ML have no financial or other relationships that might lead to a conflict of interest. KS has received travel support from Abbvie and consultancy fees from Novartis. RW has received research and travel support from Sanofi, Gilead, Jazz, Celgene, and Amgen and has received consultancy fees from Sanofi, Pfizer, Gilead, Novartis, Amgen, and Takeda. ME has received educational and trial support from Amgen, Takeda, BMS, Janssen, and Novartis, in all unrelated to this case.

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