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LETTER TO THE EDITOR

Combined PD-1 and JAK1/2 inhibition in refractory primary mediastinal B-cell lymphoma

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Dear Editor,

Primary mediastinal large B-cell lymphoma (PMBL) represents 2–4% of all B-cell non-Hodgkin lymphoma [1]. It shares clinical and molecular features with classical Hodgkin lymphoma [2]. Amplification or gain of 9p24.1 is observed in more than half of PMBL cases, resulting in overexpression of the immune checkpoints programmed cell-death ligand 1 and 2 (PD-L1 and PD-L2) and the cytokine receptor signaling kinase Janus kinase 2 (JAK2) [3, 4]. Besides increased growth signaling through the JAK-STAT pathway, JAK2 overexpression enhances PD-L1 transcription and expression [3]. Although recent studies indicate a favorable outcome of PMBL patients treated with dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisone plus rituximab in first line [5], outcome of relapsed large B-cell lymphoma remains poor.

Herein, we describe a 39-year-old Caucasian female with a refractory PMBL who was treated with a novel combination of PD-1 and JAK2 inhibition. PMBL had progressed after R-CHOP. Subsequent treatments consisted of dexamethasone, cytarabine, and cisplatinum (DHAP), brentuximab vedotin, and radiotherapy. Progression was histologically confirmed (Fig. 1a). Fluorescence in situ hybridization revealed 9p24.1 amplification (Fig. 1b) and polysomy (Fig. 1c). However, PD-L1 or pSTAT3 (as a measure of increased JAK2 activity) expression could not be observed (Fig. 1d, e). PD-1 staining of T-cells (Fig. 1f) was limited. The patient had a life threatening vena cava superior syndrome (VCSS). In the absence of a clinical trial, with the patient's consent, she was treated with off-label ruxolitinib at a dose of 10 mg bid. Off-label pembrolizumab was initiated 2 weeks later at 2 mg per kilogram in 3-week cycles (Fig. 2a). Four weeks after start of ruxolitinib the VCSS had resolved. Staging and response evaluation were performed with combined fluorodeoxyglucose positron emission tomography and computerized tomography scans according to the Lugano classification [6]. A complete metabolic remission was documented 10 weeks after start of ruxolitinib (Fig. 2b). The patient continued treatment until an allogeneic hematopoietic cell transplantation (HCT) after non-myeloablative conditioning with

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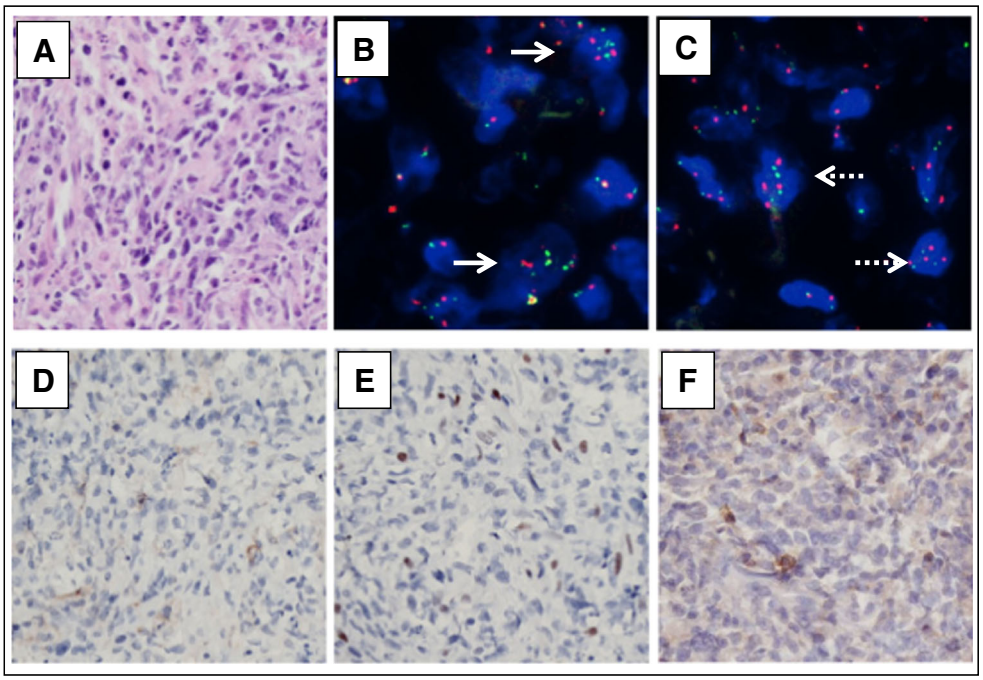

Fig. 1 Immunohistochemical staining and fluorescence in situ hybridization of formalin-fixed paraffin-embedded refractory primary mediastinal B-cell lymphoma tissue for PDL-1, pSTAT3, and PD-1. **a**. Hematoxylin and eosin staining of the paraffin-embedded mediastinal needle biopsy at progression (40×). **b**, **c** Fluorescence in situ hybridization with a CD274 (green)/CEN9 (red) dual color probe showed amplification (solid arrows) and polysomy (dashed arrow) both in 10% of tumor cells. **d**, **e** Immunostaining with anti-PD-L1 and anti-pSTAT3 of paraffin-embedded tumor biopsy revealed no staining of tumor cells (40×). **f** Immunostaining with anti-PD-1 showed modest PD-1 expression on infiltrating T-cells (40×)

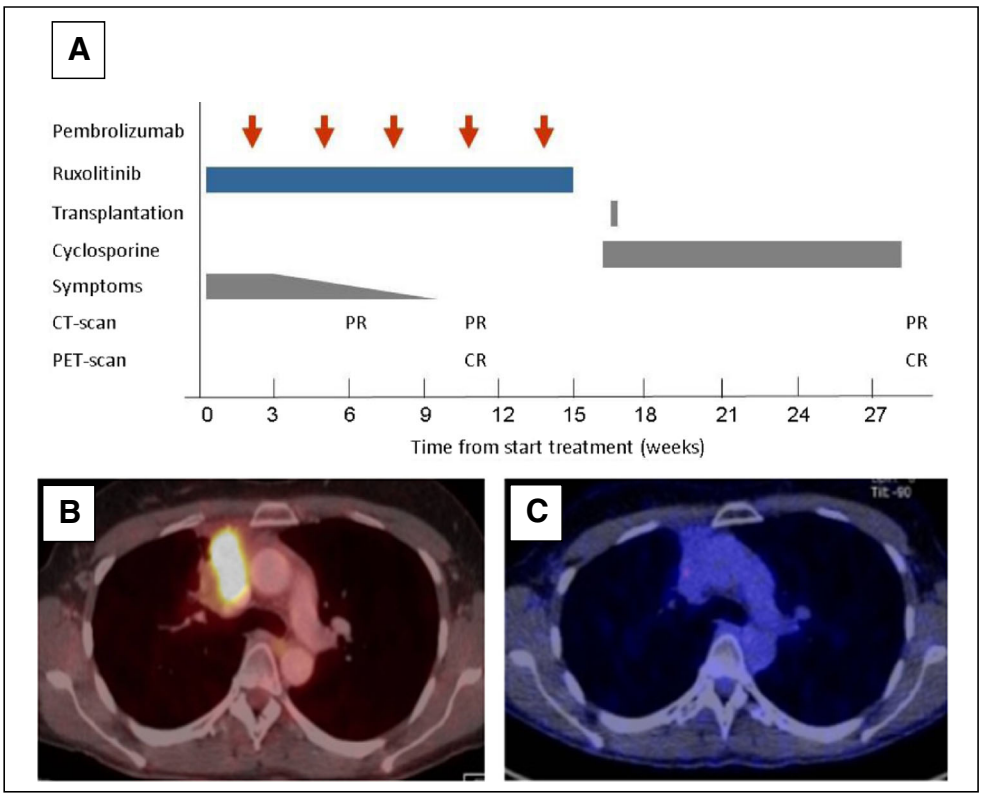

Fig. 2 Treatment and response assessment of patient with a refractory primary mediastinal B-cell lymphoma treated with PD-1 and JAK1/2 inhibition. **a** Treatment schedule and response assessments show a rapid clinical and complete metabolic response. The duration of response was sufficient to perform an allogeneic hematopoietic cell transplantation (HCT), with an ongoing remission 20 months after HCT. **b** Combined fluorodeoxyglucose (^{18}FDG) positron emission (PET) computed tomography (CT) scans before treatment showed a metabolic active tumor in the anterior superior mediastinum with encasement of the vena cava superior and brachiocephalic vein. **c** ^{18}FDG PET-CT scan 10 weeks after initiation of the combined pembrolizumab and ruxolitinib treatment showed a metabolic complete remission (Deauville 3) with a residual mass. PR, partial remission; CR, complete remission

fludarabine (30 mg/m2/day for 3 days) plus 2 Gy total body irradiation from an HLA identical matched unrelated donor. Besides anemia grade 1, no adverse events were observed over the course of treatment. The patient is in complete remission for 24 months, with excellent quality of life.

Optimal treatment of relapsed PMBL has not been defined. Despite CD30 expression in 80% of PMBL cases, the anti-CD30 antibody drug conjugate brentuximab vedotin showed an ORR of only 13% [7]. In a small pilot study, the JAK 1/2 inhibitor ruxolitinib showed limited activity as a single agent [8]. With an overall response rate of 41%, the efficacy of the anti-PD-1 antibody pembrolizumab in relapsed PMBL is encouraging [9]. However, complete remissions are observed infrequently and first responses are observed months after treatment initiation [9]. In contrast, the combined treatment with ruxolitinib and pembrolizumab in our patient resulted in a prompt clinical and metabolic remission. Accordingly, the addition of ruxolitinib to PD-1 blockade has been proposed to inhibit JAK-STAT proliferation and decrease PD-L1 expression on tumor cells [3]. Given the favorable toxicity profile, ruxolitinib can be applied in heavily pre-treated patients and is attractive for combination therapy [10].

Future studies are warranted to investigate the efficacy of combined PD-1 and JAK1/2 inhibition in relapsed PMBL.

Availability of data and material All data generated or analyzed are in the current report.

Authors' contributions MN designed the paper. MN, TM, and GH treated the patient. AD and RK provided pathological review. AS, LV, and AB performed FISH analysis. All authors contributed in writing the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Ethics approval and consent to participate The patient provided informed consent for all her sequential therapies.

Consent for publication Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interests The authors declare that they have no conflict interests.

Abbreviations HCT, hematopoietic cell transplantation; JAK2, Janus kinase 2; JAK-STAT, Janus kinase-signal transducer and activator of transcription; PD-L1/2, programmed cell-death ligand ½; PMBL, primary mediastinal B-cell lymphoma

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