necrosis. Polymerase chain reaction analysis was positive for *Mycobacterium tuberculosis* complex. There were no signs of malignancy. Antitubercular medication was initiated and nivolumab was discontinued. When asked, the patient stated that he had previously visited TB endemic areas.

Discussion

To our knowledge, only two comparable cases have been published. One [2] describes an elderly Chinese patient with relapsed Hodgkin's lymphoma who developed symptomatic TB after five cycles of pembrolizumab. In the other case report [3], development of TB was detected in a Japanese patient with NSCLC following eight cycles of third-line nivolumab.

The mechanism of TB development following treatment with immunotherapeutic agents remains to be properly understood. Investigations in mice have demonstrated a possible protective effect of the PD1/PD-L1 interaction. One study [4] reported how PD-1 knockout (PD-1$^{-/-}$) mice had increased susceptibility when exposed to TB, perhaps because of defective lymphocyte proliferation. Another report [5] describes how PD-1 knockout mice rapidly succumbed to TB infection possibly due to increased CD4 T cell-mediated pathology. Thus, the PD1/PD-L1 interaction may contain a protective role under certain circumstances.

Development or reactivation of TB during treatment with immunotherapeutic agents remains a rare phenomenon, but ought to be kept in mind when treating patients with known latent infection or relevant previous exposure. The present case also emphasizes the importance of reevaluation and re-biopsy when progression is suspected.

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LETTER TO THE EDITOR

Interim FDG-PET/CT in Hodgkin lymphoma: what are we actually looking at?

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Recently, a study by Borchmann et al. [1] published in the Lancet Oncology included 440 patients with advanced-stage Hodgkin lymphoma who were positive (i.e., Deauville criteria score of 3-5) at interim ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) after two cycles of BEACOPP$_{escalated}$. These patients with positive interim FDG-PET/CT results were randomized to either six additional cycles of BEACOPP$_{escalated}$ ($N = 220$) or six additional cycles of rituximab-BEACOPP$_{escalated}$ ($N = 220$). Interestingly, interim FDG-PET/CT failed to identify a group of patients at high risk of treatment failure, with a high 3-year progression-free survival (PFS) of 91.4% (87.0–95.7%) for interim FDG-PET/CT positive patients who continued BEACOPP$_{escalated}$ and a 3-year PFS of 93.0% (89.4–96.6%) for those additionally treated with rituximab (risk difference 1.6%, log rank $p = .99$). Borchmann et al. [1] concluded interim FDG-PET/CT to be unable to identify patients at high-risk for treatment failure due to the very effective German Hodgkin Lymphoma Study group treatment (BEACOPP$_{escalated}$/rituximab-BEACOPP$_{escalated}$), which may overcome the adverse impact of the positive interim FDG-PET/CT result on patient outcome. In an accompanying editorial, Crump [2] speculated the relatively early timing of interim FDG-PET/CT with possible effects of G-CSF and prednisone, the use of a Deauville score of 3 as a

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Table 1. Current evidence on the proportion of false-positives on interim FDG-PET/CT in lymphoma.

Study	FDG-PET/CT criteria for positivity	Lymphoma subtype	Prior treatment before FDG-PET/CT acquisition	No. of interim FDG-PET/CT positive	Proportion of patients biopsied	Proportion of false-positive results	Histological findings of false-positive cases
Lazarovici et al. [18]	Non-specified criteria	PMBCL	4× R-ACVBP or 4× R-CHOP or 4× R-COPADEM	17/36 (47.2%) (2× DS of 2, 1× DS of 3 and 14× DS of 4)*	17/17 (100%)	16/17 (94.1%)	15× inflammatory necrosis/fibrosis 1× silicosis
Casasnovas et al. [19]	DS 3–5	DLBCL: 98	4× R-CHOP 4× R-ACVBP	42/98 (42.9%)	10/42 (23.8%)	8/10 (80%)	8× 'no evidence of lymphoma'
Cox et al. [20]	DS 3–5	DLBCL: 73 PMBCL: 12	3× R-CHOP or 6× R-MACOP-B	24/85 (28.2%)	7/24 (29.2%)	4/7 (57.1%)	4× inflammation/reactive
Moskowitz et al. [21]	>local background activity with corresponding abnormality at CT	DLBCL: 98	4× R-CHOP	38/98 (38.8%)	38/38 (100%)	33/38 (86.8%)	33× inflammation
Schoder et al. [22]	DS 4–5	DLBCL: 51 PMBCL: 13 FL grade 3B: 1	4× R-CHOP	21/65 (32.3%)	21/21 (100%)	19/21 (90.5%)	19× inflammation

ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL: diffuse large B-cell lymphoma; DS: Deauville score; FL: follicular lymphoma; MACOP-B: methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; PMBCL: primary mediastinal B-cell lymphoma; R: rituximab.
*A retrospective classification according to the Deauville criteria was performed in this study.

relatively low threshold for interim FDG-PET/CT positivity (patients with Deauville scores of 4 and 5 still had a very good 3-year PFS of 90.5%) [1], and the fact that this was the first randomized interim FDG-PET/CT adapted trial with a control arm that did not use less reliable historical data to be possible explanations why the outcomes in this HD18 study were so different from what earlier observational studies of interim FDG-PET/CT suggested they would be.

We would like to add some important comments to this discussion. Surprisingly, the histopathological substrate of a residual FDG-avid 'lesion' on interim FDG-PET/CT in Hodgkin lymphoma is still unknown. Interestingly, multiple studies reported staggeringly high numbers of false-positive interim FDG-PET/CT scans in non-Hodgkin lymphoma, the vast majority due to inflammatory changes, and with false-positive proportions ranging between 57.1% and 94.1% (Table 1). It is not unlikely that these data can be extrapolated to Hodgkin lymphoma as well. Note that Hodgkin lymphoma comprises only 0.1–1.0% of malignant Reed–Sternberg tumor cells, and that consequently virtually all FDG avidity is caused by surrounding inflammatory cells, even before treatment has been initiated. As correctly mentioned by Crump [2] few other studies have shown such dismal outcomes for interim FDG-PET/CT positive Hodgkin lymphoma patients as those reported by Gallamini et al. [3,4], who reported 2-year PFS rates of 12.8% and 28%, respectively. Importantly, in Gallamini et al.'s work, disease recurrence was not histologically confirmed but determined by means of follow-up imaging in the majority of cases [3,4]. However, follow-up FDG-PET/CT also suffers from a strikingly high number of false-positives [5]. Therefore, Gallamini et al.'s results [3,4] have been seriously biased. In other studies on the value of interim FDG-PET/CT in patients with advanced-stage Hodgkin lymphoma treated with ABVD, the predictive value was less strong, with PFS rates ranging between 28.8% and 43% for those with positive interim FDG-PET/CT results [6–8]. Of note, in two recent studies including an ABVD treated cohort of early- and advanced-stage Hodgkin lymphoma patients, interim FDG-PET/CT had minor or no predictive value at all, with interim FDG-PET/CT positive patients having PFS of 56.3% [9] and 100% [10], respectively. In patients treated with BEACOPP, the prognostic value of interim FDG-PET/CT diminishes drastically. Patients with positive interim FDG-PET/CT results after two cycles of BEACOPP have a generally good PFS ranging between 60% and 91.4% [1,11,12] after the entire regimen, as reported by several studies. Meanwhile, patients with persistent FDG-avid lesions at interim PET/CT after two cycles of ABVD whose therapy is escalated to BEACOPP have been reported to have a somewhat less favorable PFS ranging between 60% and 76% [13–16] than patient who start and continue with BEACOPP chemotherapy after positive interim FDG-PET/CT. Finally, and of particular interest, are the results of the HD 15 trial [17] which included 182 patients with FDG-avid lesions at PET/CT after the entire regimen of 6× or 8× BEACOPP and who received only radiation therapy as additional treatment. These patients had an excellent 5-year PFS of 86.1%, which strongly suggest false-positive results to occur in a considerable proportion of cases.

In conclusion, we believe false-positives to be a very plausible reason for the failure of interim FDG-PET/CT to identify patients with a worse outcome. Furthermore, FDG-PET/CT results after treatment suffer from a high false--positive rate as well, and using these results as outcome measure may be unjustified and explain the heterogeneity among study results as discussed above. Well-designed studies which apply histological verification of treatment failure are needed to determine the value of interim FDG-PET/CT in predicting outcome before further studies on treatment escalation are justified.

Disclosure statement

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