Reply to T. Vassilakopoulos et al

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Reply to T. Vassilakopoulos et al

We appreciate the interest of Vassilakopoulos et al[1] in our recent report on the long-term outcome of patients enrolled in the EORTC/LYSA/FIL H10 trial for early-stage Hodgkin lymphoma.[2] Here, we would like to comment on their remarks and try to address all the issues they raised.

We agree with Vassilopoulos et al[1] that the International Harmonization Project (IHP) criteria adopted for the assessment of interim positron emission tomography (PET) in the H10 trial[3] are today considered outdated and are therefore no longer used. However, we must state that the use of IHP criteria did not influence the results of the H10 study at all.

According to the protocol, a PET scan was considered negative if uptake was below the mediastinum, which currently corresponds to Deauville scores (DS) 1 (no uptake) and 2 (uptake ≤ mediastinum) on the 5-point Deauville scale, as mentioned in the first report of the trial.[4] When we designed the study, we chose a conservative threshold to define negative PET findings, as in the RAPID and HD17 studies, which both investigated the omission of radiotherapy after a negative PET, using IHP criteria or DS 1 or 2 as PET negative.[5,6]

A closer look at the definition of PET-2 positivity was, and still is, out of the aims of the H10 trial and, in fact, no concern for the interpretation of interim PET results in the H10 trial (using the IHP criteria) or in the RAPID and HD17 trials (where only scores 1 and 2 indicated negative findings on the 5-point DS) has ever been expressed since the publication of these studies.[4-7] Vassilakopoulos et al[1] conclude that our reporting of the long-term results of the H10 trial using the IHP criteria was inadequate, basing this statement on the results of an abstract presented at the 2018 Menton PILM (PET-scan in Lymphoma and Myeloma) meeting.[8]

That study was an interesting retrospective analysis of PET/computed tomography from interim positron emission tomography (iPET)-positive patients restricted to LYSA centers in the H10 trial and graded according to the DS. The aims of that study were to reanalyze all the iPET-positive scans using the DS with the liver as reference for positivity (DS ≥4) and to compare the prognostic value of DS 1-3 versus DS ≥4 in the two treatments arms. We underline that this exploratory analysis focused on whether considering DS3 as negative was opportune and not on comparing cases classified as negative using DS and positive using IHP criteria.

The conclusion that DS3 cases should be considered negative was arbitrary; in our study, as in the RAPID and HD17 trials, a conservative threshold was chosen to define negative PET findings, thus limiting the risk of undertreatment of patients with a negative PET2. We acknowledge that applying a different cutoff to define PET positivity would have resulted in a different outcome mainly for PET-positive patients. Most likely, the benefit of escalating to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) might have been clearer when selecting patients at higher risk of relapse using a higher cutoff. Again, subgroup analysis on a different cutoff was not within the scope of the trial, where a conservative cutoff was chosen to prevent undertreatment in the PET-negative subgroup.

We agree with the comment that in general, a blinded central review would have been optimal to confirm local PET reports. As stated in the primary paper, a second blinded review barely affected the results regarding patients with a negative PET2 and did not change the recommendations of the Independent Data Monitoring Committee to amend the study for PET2-negative patients. As extensively summarized by Vassilakopoulos et al,[1] with all the technical issues, including advances in PET techniques and acquisition methods over the years, efforts have been made for such a retrospective review in the PET-positive subgroup. Finally, regarding their concern that the H10 update excludes any benefit of BEACOPP intensification in patients with a positive PET2, had the scans been interpreted according to the DS, the results would have been the same. Our protocol clearly outlined that DS3 were to be considered positive, not negative, as proposed by Vassilakopoulos et al.[1]

As a result, we uphold our conclusion that this long-term analysis confirmed the previous findings: Interim PET positivity after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine using the criteria mentioned in the primary paper is associated with a worse outcome, unfortunately not completely corrected by intensification with two cycles of BEACOPPescalated. Indeed, current interpretation methods that have evolved over time to define interim PET positivity might have been able to better select patients who would have benefitted the most from intensification to BEACOPPescalated.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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