

## PET-guided, BEACOPP<sup>escalated</sup> therapy in advanced Hodgkin lymphoma

### Authors' reply

We are delighted that Anthony Perissinotti and colleagues acknowledge in our AHL2011 study<sup>1</sup> that BEACOPP<sup>escalated</sup> exposure can be reduced in 346 (84%) of 410 patients with negative PET assessment after two cycles of treatment (PET2) without loss of lymphoma control. However, they criticise exposing all patients to at least two cycles of BEACOPP<sup>escalated</sup> instead of PET-driven upfront ABVD treatments and conclude that starting treatment with the more toxic BEACOPP<sup>escalated</sup> regimen is useless. This assertion is questionable: haematological immediate toxicity of the first two cycles of BEACOPP is manageable and only two patients (0.4%) died from adverse events in the AHL2011 PET-driven group; secondary primary malignancies frequency was also low (five [1.2%]), even if we acknowledge that a longer follow-up is warranted; and the increased risk of gonadal toxic effects related to BEACOPP compared with ABVD was shown only beyond two cycles.<sup>2</sup> They minimise the fact that starting with BEACOPP<sup>escalated</sup> provides better disease control in both patients who are PET2 negative or positive, even if no direct, randomised comparison of these approaches is available. Fewer patients were required to be exposed to salvage therapy and transplantation, and also encumbered an increased risk of immediate and long-term toxicity. Perissinotti and colleagues did not mention that most patients chose to receive treatment with curative intent as first-line treatment,<sup>3</sup> which places lymphoma control as a major endpoint for patients, haematologists, and oncologists. Because patients with low international prognosis score also benefit from BEACOPP<sup>escalated</sup><sup>4</sup> and the biological characteristics of the tumour<sup>5</sup> did not identify which patients

require more intense treatment than ABVD, no baseline factor helps in making individual decisions for upfront chemotherapy. Therefore, we estimate that AHL2011's strategy offers a better balance between disease control and treatment toxicity than upfront ABVD PET-adapted treatments in advanced Hodgkin lymphoma.

We agree with Charles Mesguish and colleagues that PET2 assessment alone is insufficient to accurately stratify patients with different outcomes, and to our knowledge, AHL2011 is the first study showing prospectively the added prognosis value of PET4, which improved patients' stratification independently of their PET2 results. Indeed, in a multivariate analysis, the tandem interim PET evaluation after two and four cycles of chemotherapy overcomes the prognosis value of the international prognosis score. On the basis of the available data, it is difficult to affirm that end of treatment could still refine the interim PET-based prognosis assessment in a substantial subset of patients. In the GHSG HD18 study,<sup>6</sup> 188 (13%) of 1439 treated patients had a hypermetabolic residual mass of 2.5 cm or greater, including 155 (35%) of 434 patients in the positive PET2 group and 33 (3%) of 1005 in the negative PET2 group, and received radiation therapy. However, we do not know how many of these patients would have had positive PET4. In AHL2011, all relapses in the PET2 and PET4 negative group except one and 12 (80%) of the 15 relapses in the PET2 positive and PET4 negative group occurred after the end of treatment evaluation so were not identified at the end of treatment PET. Altogether, these results suggest that PET4 is probably more suitable than end of treatment PET for the management of patients and early identification of patients who need salvage therapy.

R-OC received grants, personal fees and non-financial support from Gilead, Roche, and Takeda, personal fees and non-financial support from Bristol-Myers Squibb, Cellegue, and Merck Sharpe & Dohme, and personal fees from Abbvie. PB received personal fees from Bristol-Myers Squibb, Merck Sharpe & Dohme, and Takeda, grants from Takeda Millennium,

and non-financial support from Roche. AS received personal fees from Takeda. MM received personal fees from Roche China. All other authors declare no competing interests.

\*René-Olivier Casasnovas, Reda Bouabdallah, Pauline Brice, Julien Lazarovici, Hervé Ghesquieres, Aspasia Stamatoullas, Alina Berriolo-Riedinger, Luc-Matthieu Fornecker, Marc André, Michel Meignan  
oliver.casnovas@chu-dijon.fr

Department of Hematology, University Hospital F Mitterrand and Inserm UMR 1231, Dijon 21000, France (R-OC); Department of Hematology, Institut P Calmette, Marseille, France (RB); Department of Hematology, APHP, Hôpital Saint Louis, Université Paris Diderot, Paris, France (PB); Department of Hematology, Gustave Roussy, Université Paris-Saclay, Villejuif, France (JL); Department of Hematology, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud and Université Claude Bernard Lyon-1, Pierre Bénite, France (HG); Department of Hematology, Centre H Becquerel, Rouen, France (AS); Department of Nuclear Medicine, Centre G F Leclerc, Dijon, France (AB-R); Department of Hematology, University Hospital of Strasbourg, Strasbourg, France (L-MF); Department of Hematology, CHU UCL Namur, Université Catholique de Louvain, Yvoir, Belgium (MA); and LYSA Imaging, University Hospital H Mondor, Creteil, France (MM)

- 1 Casasnovas R-O, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol* 2019; **20**: 202–15.
- 2 Behringer K, Mueller H, Goergen H, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J Clin Oncol* 2013; **31**: 231–39.
- 3 Kreissl S, Goergen H, Müller H, et al. Survivors' perspectives on risks and benefits of Hodgkin lymphoma treatment: results of a survey by the German Hodgkin Study Group. *Leuk Lymphoma* 2018; **3**: 1–10.
- 4 Mounier N, Brice P, Bologna S, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol Off J Eur Soc Med Oncol ESMO* 2014; **25**: 1622–28.
- 5 Scott DW, Li H, Chan F, et al. The 23 Gene expression-based assay does not predict interim PET scan results after ABVD in advance stage classical Hodgkin lymphoma in the US intergroup S0816 trial. *Hematol Oncol* 2017; **35**: 92–93.
- 6 Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet* 2018; **390**: 2790–802.
- 7 Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32**: 3059–68.