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by Hishan Tharmaseelan and Bastian von Tresckow

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On closing the gap: anti-PD-1-based salvage in relapsed/refractory classical Hodgkin lymphoma. Comment on: "Mind the gap: anti-PD-1 salvage before autologous transplantation in classical Hodgkin lymphoma"

Hishan Tharmaseelan[1], Bastian von Tresckow[1,2]

[1] *University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department I of Internal Medicine; Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD); and German Hodgkin Study Group (GHSG), Cologne, Germany*

[2] *Department of Hematology and Stem Cell Transplantation, West German Cancer Center and German Cancer Consortium (DKTK partner site Essen), University Duisburg-Essen, University Hospital Essen, Essen, Germany*

Corresponding author: Bastian von Tresckow, Department of Hematology and Stem Cell Transplantation, University Hospital Essen, Hufelandstraße 55, 45147 Essen, Germany. E-mail: bastian.vonTresckow@uk-essen.de

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In a recent issue of *Haematologica*, we reported a multicenter real-world analysis of anti-PD-1-based salvage therapy in 47 patients with relapsed or refractory classical Hodgkin lymphoma (cHL) in a European treatment context with heavily pretreated patients, demonstrating an overall response rate of 90.9%, a complete response (CR) rate of 47.7%, and a 1-year progression-free survival (PFS) of 83.9%.[1] In an accompanying editorial, Noerenberg, MD provided a comprehensive appraisal of the evolving role of PD-1 blockade before autologous stem cell transplantation (HD-ASCT), underlining both the transformative efficacy of anti-PD-1-based salvage and the regulatory paradox that checkpoint inhibitors remain largely off-label in the transplant-eligible second-line setting in Europe.[2] While these contributions capture the current evidence landscape with considerable nuance, a development further reshapes this discussion: the CheckMate-744 trial and, consequently, the recent European Commission (EC) approval of nivolumab plus brentuximab vedotin (BV) for relapsed or refractory cHL.

The CheckMate-744 study (NCT02927769) was an international phase II trial evaluating a risk-stratified, response-adapted salvage strategy using nivolumab plus BV in children, adolescents, and young adults (aged 5-30 years) with relapsed or refractory cHL after one prior line of therapy.[3] In the standard-risk cohort (R2), 43 patients received four induction cycles of nivolumab plus BV; those without complete metabolic response (CMR)

subsequently received BV plus bendamustine intensification. The CMR rate after induction was 59%, rising to a best overall response of 94% before consolidation with high-dose chemotherapy and auto-HCT, and the 1-year PFS rate was 91%.[3] Notably, most patients achieved CMR without requiring additional chemotherapy beyond BV. In the low-risk cohort (R1), 28 patients received nivolumab plus BV followed by involved-site radiotherapy without auto-HCT, achieving a CMR rate of 93% and a 3-year PFS rate of 87%.[4] With the limitations of low patient numbers and a phase II design, these results demonstrate that a chemotherapy-free induction combining PD-1 blockade with an antibody-drug conjugate can produce deep remissions in a younger low-risk population, with a favorable toxicity profile and the potential to spare patients from conventional cytotoxic salvage. With trials already published and additional studies underway (e.g., Pembro-CORE, NCT04838652), transplant-free approaches based on PD-1 blockade continue to be investigated in adult settings.[5] However, preliminary data from these trials indicate relapse rates of approximately 50% without high-dose chemotherapy consolidation, underscoring the need for further investigation before transplant-free approaches can be adopted in routine clinical care.

The European regulatory landscape has evolved substantially since our analysis was drafted. In March 2026, the EC approved nivolumab in combination with BV for the treatment of patients aged 5-30 years with relapsed or refractory cHL after one prior line of therapy, based on the CheckMate-744 data.[6] This represents the first immunotherapy combination approved in Europe for second-line cHL and directly addresses the regulatory gap that both our analysis and the editorial by Noerenberg, *MD* identified as a major barrier to uniform adoption. For patients within the approved age range, anti-PD-1-based salvage is no longer off-label in the European Union, removing a key obstacle to access and reimbursement. Concurrently, the FDA approved nivolumab plus doxorubicin, vinblastine, and dacarbazine (AVD) for previously untreated stage III-IV cHL based on the phase III SWOG S1826 trial[7], while the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending approval of nivolumab in combination with AVD for the same indication.[8] These regulatory milestones signal a broader institutional recognition of PD-1 blockade across multiple treatment lines in cHL.

However, important gaps remain. The EC approval of nivolumab plus BV is restricted to patients aged 5-30 years, leaving the majority of adults with relapsed or refractory cHL without an in-label anti-PD-1-based salvage option in Europe. The anti-PD-1 plus chemotherapy combinations (e.g., pembrolizumab-GVD[9], or nivolumab-ICE[10]) that dominate clinical practice and that produced the highest CR rates in phase II studies remain unapproved in the second-line transplant-eligible setting in most jurisdictions.

In conclusion, the CheckMate-744 results and the subsequent EC approval of nivolumab plus BV represent a meaningful step toward closing the gap between evidence and practice in second-line cHL. They validate the concept that immunotherapy-based, chemotherapy-sparing salvage can achieve high remission rates and favorable early outcomes, and they provide a regulatory framework for one such approach in younger patients. Nevertheless, broader approval of anti-PD-1-based salvage strategies across age groups and the generation of randomized evidence to define optimal regimens, transplant timing, and the potential to safely omit HD-ASCT in selected patients remain critical priorities for the field.

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