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The gap narrows but shifts. Response to Comment on: "Mind the gap: anti–PD-1 salvage before autologous transplantation in classical Hodgkin lymphoma"

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Tharmaseelan and von Tresckow provide a valuable update to the discussion around anti–PD-1-based salvage in classical Hodgkin lymphoma (cHL).[1-3] The European Commission approval of nivolumab plus brentuximab vedotin (BV) for patients aged 5–30 years with relapsed or refractory cHL after one prior therapy line, based on CheckMate-744, is the first immunotherapy-based salvage regimen licensed in Europe for this setting and directly addresses the regulatory gap identified in both the original analysis and the editorial.[4]

Notably, CheckMate-744 excluded patients with prior exposure to anti–PD-1 antibodies or BV.[3] This exclusion has growing practical relevance as frontline regimens increasingly incorporate these agents. In Europe, BrECADD is emerging as a preferred advanced-stage option, particularly in German-speaking countries, replacing escalated BEACOPP and introducing BV into first-line treatment.[5] In the United States, the recent FDA approval of nivolumab plus AVD based on the SWOG S1826 trial shifts frontline exposure toward anti–PD-1 therapy.[6] Whether patients relapsing after BV- or anti–PD-1-containing frontline regimens respond to nivolumab plus BV with comparable efficacy is unknown, and such patients may not clearly fall within the scope of the current approval. The practical window in which the CheckMate-744-based indication applies, that is, patients within the age range who relapse after frontline therapy without BV or anti–PD-1 exposure, remains sizable today, particularly after limited-stage treatment with ABVD or AVD, but will narrow as frontline practice continues to evolve.

At the same time, the anti–PD-1 plus chemotherapy combinations that dominate salvage practice in adults beyond the approved age range and that produced CR rates exceeding 85% in phase II studies remain unapproved in the second-line transplant-eligible setting.[7–9] The post-

consolidation data from the original multicenter analysis by Tharmaseelan et al. add a useful nuance here: the pre-transplant CR rate was 47.7%, yet 97% of evaluable patients achieved CR after transplant consolidation, including seven of eight patients who had only a partial remission after anti–PD-1 monotherapy.[1] This does not diminish the value of achieving deep remissions before transplant, but it suggests that the post-consolidation outcome, rather than the induction CR rate alone, may be the more appropriate benchmark when comparing salvage regimens. If confirmed in larger cohorts, this perspective could temper cross-trial comparisons of induction CR rates between approaches such as nivolumab plus BV and anti–PD-1 plus multi-agent chemotherapy, provided transplant consolidation remains part of the strategy. For patients in whom transplant is not intended, the CheckMate-744 low-risk cohort offers preliminary evidence that nivolumab plus BV followed by involved-site radiotherapy can achieve durable remissions without high-dose chemotherapy, though the small sample size and the restriction to a younger, lower-risk population limit generalizability.[10]

Closing the remaining gap will require randomized trials comparing anti–PD-1-based salvage against standard platinum-based regimens in transplant-eligible adults without age restriction, ideally stratified by prior frontline exposure.

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