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Mind the gap: anti–PD-1 salvage before autologous transplantation in classical Hodgkin lymphoma

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Editorial Text
In this issue of *Haematologica*, Tharmaseelan and colleagues report a multicenter European real-world analysis of programmed cell death protein 1 (PD-1) inhibitor-based salvage therapy for relapsed or refractory classical Hodgkin lymphoma (cHL), largely delivered with curative intent, frequently followed by consolidative transplantation [1]. Their experience reflects a rapidly evolving clinical reality: PD-1 blockade, once positioned primarily as later-line therapy, is now increasingly deployed earlier to deepen responses before high-dose therapy and autologous stem cell transplantation (HD-ASCT). However, a transplant-eligible second-line indication remains off-label in many jurisdictions, including the absence of EMA approval for intent-to-transplant use, a gap the authors explicitly highlight.

The real-world results validate phase II efficacy while reflecting broader practice. In the present cohort, 47 patients were treated across eight academic centers, with an overall response rate (ORR) and complete response (CR) rates of 90.9% and 47.7%, respectively. Higher CR rates were observed for anti-PD-1 plus chemotherapy (with 88.2% receiving P-GVD) versus ICI monotherapy approaches (61.3% vs. 10%) [1]. While lower than the 86% to 95% CR rates reported in selected trials, these results likely reflect broader case mix and pragmatic response assessment (Table 1) [1–4].

Importantly, responses were frequently converted into durable disease control through consolidation: 91.5% of patients proceeded to transplant-based consolidation, most commonly HD-ASCT, and among evaluable patients after transplantation, 97% achieved CR. Importantly, seven of eight patients in PR after pre-transplant ICI monotherapy converted to CR after transplant. The reported 1-year progression-free survival (PFS) of 83.9% and overall survival of 95.6%

underscore that “imperfect” pre-transplant remission rates can still translate into excellent early outcomes when anti-PD-1-based salvage is integrated into an effective transplant pathway [1].

Why does this matter now? Because PD-1 blockade plus chemotherapy has repeatedly demonstrated the capacity to produce deep remissions quickly in patients for whom traditional platinum-based salvage delivered CR rates that were often only 40% to 50%. In the pivotal pembro-GVD experience, pembrolizumab combined with gemcitabine, vinorelbine, and liposomal doxorubicin produced an ORR of 100% with CR rates of 95% as second-line therapy, enabling most patients to proceed to ASCT [2]. Similarly, pembrolizumab plus ICE yielded a CR rate of 86.5% and a 2-year PFS exceeding 85% in a multi-institutional phase II study [3]. A response-adapted approach using nivolumab alone with selective intensification (nivolumab plus ICE) achieved an end-of-protocol ORR of 93% with a CR rate of 91%, with a 2-year PFS of 94% among those bridged directly to autologous transplantation [4]. Collectively, these studies suggest PD-1 blockade before autologous transplantation can deepen response and may improve long-term disease control versus chemotherapy alone.

However, the field should not overlook the regulatory paradox that Tharmaseelan et al. bring into focus. Even as guidelines and practice have shifted toward checkpoint inhibitor-based salvage in transplant-eligible second-line settings, licensing frameworks still largely reflect the earlier era in which PD-1 antibodies were developed for later-line, post-transplant relapse or transplant-ineligible populations. Lack of an on-label indication complicates access, reimbursement, and uniform adoption, and it disincentivizes the randomized trials that would most cleanly define when immunotherapy should be paired with HD-ASCT, and when it even might safely replace it [5-7].

That replacement question is no longer theoretical. If anti-PD-1-based salvage can generate deep remissions, do all such patients still require HD-ASCT? The current real-world analysis cannot answer this because transplantation was integral to the observed outcomes and only a minority did not proceed to consolidation [1]. Yet the question is increasingly important given both short-term and delayed toxicities of HD-ASCT. However, transplant-related inflammatory complications after recent anti-PD-1 exposure remain a concern. Following pembrolizumab-based salvage therapy prior to ASCT, phase II studies reported high rates of engraftment syndrome (e.g., 68% with pembrolizumab-GVD, and one fatal case among 42 patients treated with pembrolizumab-ICE), and larger lymphoma cohorts similarly showed substantially higher engraftment syndrome rates in patients with prior anti-PD-1 exposure compared with those without prior PD-1 therapy [2,3]. In the present series, severe immune-related adverse events were uncommon (10.6%), pneumonitis was reported in 4.3%, and engraftment syndrome occurred in 4.6% of transplanted patients. These rates are reassuring, but vigilance for inflammatory syndromes remains essential whenever PD-1 blockade precedes stem cell reinfusion.

An alternative strategy that can reduce chemotherapy exposure is the combination of brentuximab vedotin (BV) with PD-1 blockade. BV plus nivolumab as first salvage achieved an ORR of 85% and a CR of 67%, with an estimated 3-year PFS of 77%, and particularly favorable outcomes among patients who proceeded directly to ASCT [8]. While chemotherapy-free regimens may be appealing for selected patients with

cumulative toxicity concerns, neuropathy, cost, and the possibility of slightly lower CR rates than anti-PD-1 plus multi-agent chemotherapy remain practical tradeoffs [8]. The optimal approach is therefore not universal and should be guided by prior exposure, disease burden, clinical urgency, organ reserve, and the intended consolidative plan as well as shared decision-making with the patient (Figure 1).

A key next step is randomized confirmation that adding PD-1 blockade to second-line chemotherapy improves response depth and clinically meaningful endpoints. The phase III ORIENT-21 trial (sintilimab plus ICE vs placebo plus ICE) reported significantly higher complete remission rates with anti-PD-1 plus ICE (about 61% vs 32%), with a favorable PFS trend [9]. It is notable, however, that ASCT was not built into the ORIENT-21 strategy, which means the trial informs the benefit of immune checkpoint blockade but does not resolve the transplant versus no-transplant question [9].

In sum, Tharmaseelan and colleagues provide timely real-world confirmation that anti-PD-1-based salvage can be delivered at scale, can bridge most transplant-eligible patients to HD-ASCT, and can yield excellent early survival outcomes, despite lower response rates than in tightly controlled trials. The challenge now is to close the evidence-practice gap with randomized studies that define the best anti-PD-1-based regimen, establish the safest transplant timing, and identify the subset of patients for whom cure can be maintained with less toxicity, potentially even without HD-ASCT. Until then, anti-PD-1-based salvage before transplant represents both a transformative advance and a call for precision in how we deploy it.

References

1. Tharmaseelan H, Sgonina LM, Bühnen I, et al. Anti–programmed cell death protein 1–based salvage therapy for relapsed and refractory Hodgkin lymphoma: A multicenter real-world analysis. Haematologica. xxx
2. Moskowitz AJ, Shah G, Schöder H, et al. Pembro-GVD in relapsed/refractory cHL. J Clin Oncol. 2021;39(28):3109-3117.
3. Bryan LJ, Casulo C, Allen PB, et al. Pembrolizumab added to ifosafamide, carboplatin, and etoposide chemotherapy for relapsed or refractory classic Hodgkin lymphoma: a multi-institutional phase 2 investigator-initiated nonrandomized clinical trial. JAMA Oncol. 2023;9(5):683-691.
4. Mei MG, Lee HJ, Palmer JM, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. Blood. 2022;139(25):3605-3616.
5. Moskowitz A. Pembrolizumab maintenance instead of transplant for patients with r/r HL in CR after pembro-GVD. ISHL 2024 (presentation).
6. Ding K, Liu H, Ma J, et al. Tislelizumab with gemcitabine and oxaliplatin in patients with relapsed or refractory classic Hodgkin lymphoma: a multicenter phase II trial. Haematologica. 2023;108(8):2146-2154.
7. Spinner MA, Sica RA, Tamaresis JS, et al. Improved outcomes for relapsed/refractory Hodgkin lymphoma after autologous transplantation in the era of novel agents. Blood. 2023;141(22):2727-2737.
8. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. Blood. 2021;138(6):427-438.

9. Liu P, Li Z, Cen H, et al. Sintilimab (anti-PD-1) pluse ifosfamide, carboplatin, and etoposide (ICE) in second-line classical Hodgkin lymphoma (cHL): Results of a multicenter, randomized, controlled, double-blind phse 3 study (ORIENT-21). J Clin Oncol. 2025;43(16_suppl):7007.

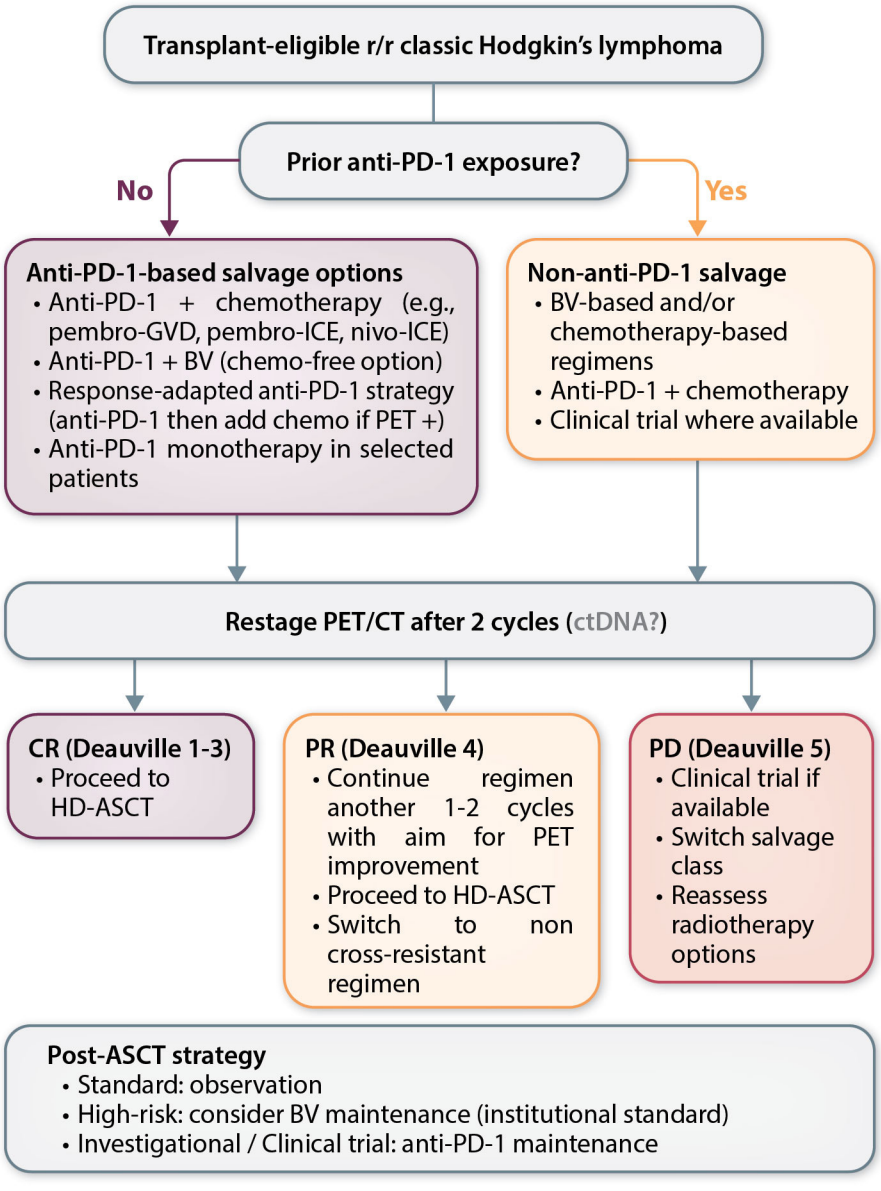
Evidence / setting [Ref]	Regimen (example)	n	ORR (%)	CR (%)	Key PFS signal	Consolidation intent	Practical "take-home" message
European multicenter real-world [1]	**Any anti-PD-1–based salvage** (mono, +chemo, +BV)	47	90.9	47.7	**1y-PFS 83.9%; 1y-OS 95.6%**	91.5% consolidated; 78.7% HD-ASCT	**Key message:** response deepens after consolidation (**97% CR post-consolidation** among evaluable)
European multicenter real-world [1]	**Anti-PD-1 + chemotherapy** (mostly P-GVD; also P-ICE/N-ICE)	34	93.6	61.3	**1y-PFS 90.2%**	HD-ASCT/allo-SCT in most	Real-world CR lower than US phase II, but **excellent early PFS** and **high post-consolidation CR**, demonstrates **feasibility outside trials**, **off-label** in the second line setting in the EU
Phase II (US) [2]	**P-GVD**	39	100	95	**30 month PFS 96%**	HD-ASCT intent	**Benchmark for "high CR",** anti-PD-1/chemo bridge with efficient cytoreduction, antrhacycline exposure (liposomal doxorubicin), **engraftment syndrome 68%,** pembrolizumab maintenance w/o ASCT being evaluated
Phase II (US) [3]	**P-ICE**	42	97	87	**2y-PFS 87.2%**	HD-ASCT intent	**high CR, familiar backbone**, myelosuppression
Phase II (US) [4]	**N-ICE** (response-adapted; nivo alone or +ICE)	43	93	91	**2y-PFS 72% overall / 94% when receiving aSCT**	HD-ASCT intent	**Reduce chemo exposure while preserving depth,** 58% achieved CR with Nivo alone beforte ASCT, requires tight PET adaptation, **suggests benefit of achieving aSCT after anti-PD-1–based salvage**
Phase II (China) [6]	**Tislelizumab + GemOx**	30	100	97	**1y-PFS 96%**	No mandatory HD-ASCT	**Low toxicity**, highly active anti-PD-1/chemo **without conoslidative ASCT**, strategy depends on setting, longer follow-up required
Phase II (US) [8]	**BV + nivolumab** (chemo-free)	91	85	67	**3y-PFS 77%**	Mixed; many proceed to HD-ASCT	**Attractive when chemo avoidance** (platinum/alkylators) is a priority; outpatient administration; **neuropathy**, CR may be lower than anti-PD-1+chemo; increased use of BV in frontline
Phase III (China, abstract) [9]	**Sintilimab + ICE** vs. Placebo + ICE **(ORIENT-21)**	34	-	61.8	**Median PFS not reached**	Second-line study, no HD-ASCT intent	Still incomplete reporting (**CR/PFS details pending,** no full publication)
European multicenter real-world [1]	**Anti-PD-1 monotherapy**	10	80	10	(trend to Inferior PFS vs combos; selection bias likely)	HD-ASCT/allo-SCT intent	**Consider mainly when chemo cannot be delivered**; less reliable for PET-CR

Evidence / setting [Ref]	Regimen (example)	n	ORR (%)	CR (%)	Key PFS signal	Consolidation intent	Practical “take-home” message
European multicenter real-world [1]	**Anti-PD-1 + BV**	3	100	33.3	**1y-PFS 100%** (very small n)	HD-ASCT	Promising but underpowered; interpret cautiously

Table 1. ORR/CR and PFS values are reported as published in the cited trials. Real-world European data are from Tharmaseelan et al. where response assessment was collected locally; comparisons across studies are confounded by patient selection and PET assessment heterogeneity as well as limited follow-up. ORR: overall response rate; CR: complete response; PFS: progression-free survival; HD-ASCT: high-dose therapy with autologous stem cell transplantation; allo-SCT: allogeneic stem cell transplantation; w/o: without; P: pembolizumab; N: nivolumab; GVD: gemcitabine, vinorelbin, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; BV: brentuximab vedotine; GemOx: gemcitabine, oxaliplatin.

Figure 1. Pragmatic pathway for anti-PD-1–based salvage therapy with transplant intent in relapsed/refractory classical Hodgkin lymphoma. The algorithm highlights regimen selection (anti-PD-1 plus chemotherapy vs. anti-PD-1 plus brentuximab vedotin vs anti-PD-1 monotherapy when chemotherapy is not feasible), response-adapted consolidation, and post-ASCT strategies. Side annotations summarize and key efficacy signals, regulatory and safety considerations. r/r: relapsed/refractory; GVD: gemcitabine, vinorelbin, liposomal doxorubicin; ICE: ifosfamide, carboplatin, etoposide; BV: brentuximab vedotine; ctDNA: circulating tumor DNA; CR: complete response; PR: partial remission; PD: progressive disease; HD-ASCT: high-dose therapy with autologous stem cell transplantation.

Anti-PD-1-based Salvage in Relapsed or Refractory Classic Hodgkin's Lymphoma



Efficacy

Anti-PD-1 plus chemotherapy regimens have produced high PET-negative CR rates in phase II trials and retrospective series with efficient bridging to HD-ASCT.

Regulatory gap

Checkpoint inhibitors are increasingly used as second-line bridge strategies, yet formal approval in transplant-eligible second-line settings remains inconsistent across regions.

Transplant-related inflammation

Alongside immune-related adverse events (irAE), anti-PD-1 exposure prior to transplant can increase the risk of engraftment syndrome, requiring careful timing and monitoring.