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Safety, feasibility, and efficacy of anti-PD-1 therapy for the treatment of classical Hodgkin lymphoma

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Short Title: Anti-PD-1 Therapy in Hodgkin lymphoma

Abstract

The clinical paradigm for treatment of classical Hodgkin lymphoma has been transformed by the use of anti-PD-1 therapy, driven by foundational work revealing near-universal 9p24.1 alterations resulting in overexpression of PD-L1 and PD-L2 on Reed-Sternberg cells. Use of PD-1 inhibitors has demonstrated remarkable clinical activity for patients with Hodgkin lymphoma. Anti-PD-1 monotherapy has demonstrated durable remissions in the relapsed/refractory setting, including a 5-year overall survival of around 70% in clinical trials. Further efforts have evaluated these treatments in various combinations and demonstrated efficacy in both the salvage setting prior to stem cell transplantation (SCT) and the relapsed/refractory setting after SCT. After such promising results, these agents were moved into the frontline setting with landmark trials such as SWOG S1826, establishing Nivo-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine) as an emerging standard for advanced-stage classical Hodgkin lymphoma. Similarly, Nivo-AVD in the NIVAHL trial demonstrated remarkable efficacy in early stage, unfavorable disease. These agents have a unique mechanism of action that shows promise for patients who would otherwise be chemotherapy-ineligible. The use of these agents is also of interest in the adolescent and young adult populations who would be at risk from long-term side effects of chemotherapy or radiation. This review seeks to examine the safety, efficacy, and feasibility of anti-PD-1 therapy in classical Hodgkin lymphoma.

Keywords: Hodgkin lymphoma, PD-1 inhibitor, nivolumab, pembrolizumab, checkpoint inhibitor, immunotherapy

Introduction

Hodgkin lymphoma is an uncommon malignancy involving B lymphocytes and represents approximately 10% of all lymphomas. In 2025, an estimated 8720 people were diagnosed with Hodgkin lymphoma in the United States and 1150 people died from the disease.[1] Hodgkin lymphoma has a bimodal distribution and is most frequently observed in young adults (ages 15-30) as well as individuals 55 and older.[1] The global burden of Hodgkin lymphoma has been stable since the 1990s and mortality has been slowly decreasing. [2] Though there are multiple subtypes, the disease can be classified into two main groups: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. In Western countries, classical Hodgkin lymphoma accounts for ~95% and nodular lymphocyte-predominant B-cell lymphoma (NLPBL) accounts for ~5%.[3,4]

Classical Hodgkin lymphoma (cHL) has been recognized since 1832 when Thomas Hodgkin first described the condition occurring in young adults. Carl Sternberg in 1898 and Dorothy Reed Mendenhall in 1902 described the typical Reed-Sternberg cells on microscopic analysis of lymph nodes.[5-7] Though the Reed-Sternberg cells are essential for diagnosis of the disease, they account for only a small percentage of the cells seen on biopsy.[7] Because Reed-Sternberg cells are sparse and surrounded by a dense reactive infiltrate of lymphocytes, eosinophils, and histiocytes, an excisional biopsy is preferred for diagnosis; though core needle biopsies may be diagnostic in the majority of cases and are easier to obtain in the clinical setting, fine needle aspiration however is typically inadequate. On the molecular level, one of the defining features of cHL is genetic amplification of chromosome 9p24.1, leading to an overexpression of PD-L1 and PD-L2 leading to constitutive activation of JAK stat signaling pathways.[8,9]

While first-line treatment with multi-agent chemotherapy cures the majority of patients, up to 30%, will ultimately require additional therapy representing a substantial unmet need.[6] However, the introduction of anti-PD-1 antibodies into frontline treatment combinations has improved patient outcomes and may decrease the number of relapsing patients requiring treatment in the future. Similarly, the use of combination therapy in the relapsed setting that includes an anti-PD-1 antibody has substantially increased the response rate thereby allowing more patients to undergo consolidative transplantation resulting in better outcomes.[6] This review therefore examines the clinical evidence supporting the safety, feasibility, and efficacy of anti-PD-1 therapy in cHL, encompassing both monotherapy and combination approaches in all lines of treatment.

Biological Basis for use of Checkpoint inhibition in Hodgkin Lymphoma

The discovery of the near-universal alterations at the 9p24.1 chromosomal locus, which encodes PD-L1 (CD274), PD-L2 (PDCD1LG2), and Janus kinase 2 (JAK2), explains the unique susceptibility of this disease to checkpoint blockade. The seminal work by Green and colleagues utilized genomic analysis to demonstrate that selective 9p24.1 amplification drives increased PD-1 ligand expression in nodular sclerosing cHL and primary mediastinal large B-cell lymphoma, with further induction via JAK2 signaling.[8] Green and colleagues also demonstrated that there were populations with lower amplification of 9p24.1 and that there was an alternative mechanism for PD-L1 overexpression driven by Epstein-Barr Virus (EBV) though EBV latent membrane protein 1 increasing PD-L1 promotor activity.[10] (Figure 1) Subsequent work by Roemer and colleagues established that PD-L1/PD-L2 alterations are a defining molecular feature of cHL, and demonstrated a paradoxical biomarker relationship: 9p24.1 amplification and high PD-L1 expression were associated with inferior progression free survival (PFS) on conventional chemotherapy but predicted superior responses to PD-1 blockade.[9,11] This represents a relative dose response relationship in that the higher the PD-L1 expression the more robust the response to anti-PD-1 directed therapy. More recent efforts have evaluated peripheral blood mutational profiles to detect the signature of these near-universal alterations as a measure of treatment response and to assess minimal residual disease post therapy that may predict the need for additional treatment.[12,13]

PD-L1 expression alone does not tell the entire story. The microenvironment surrounding Reed-Sternberg cells also plays a key role. Steidl and colleagues identified a tumor associated macrophage (TAM)-associated gene expression signature that predicted primary treatment failure; high CD68-positive macrophage infiltration was associated with shortened PFS and increased relapse risk after autologous stem-cell transplant (ASCT), while the absence of CD68-positive cells correlated with 100% disease-specific survival.[14] Further work by Carey and colleagues used multiplex immunohistochemistry and topographical analysis to demonstrate that PD-L1 expressing TAMs co-localize with Reed-Sternberg cells forming a physical buffer that could be considered a protective zone around the malignant cells. In this zone, PD-L1 positive TAMs are enriched for contacts with T cells. PD-L1 positive Reed-Sternberg cells are also enriched for contacts with CD4+ T cells, a subset of which are PD-1 positive, and thereby implicate CD4+ T cells as a target of anti-PD-1 therapy.[15]

T cells make up the largest cellular component of the cHL microenvironment, and their roles continue to be elucidated. While CD8+ and Th1 CD4+ T cells contribute to antitumor activity, Th2-polarized CD4+ T cells form rosettes around Reed-Sternberg cells, suppressing CD8 and NK-cell function.[16,17] Further work by Cader and colleagues using mass cytometry at single-cell resolution, demonstrated that newly diagnosed cHL harbors an abundant population of Th1-polarized regulatory T cells and PD-1-high

exhausted T-effector cells, implicating both active immune suppression and T-cell exhaustion.[18] This exhausted state of T-cells is thought to develop from chronic antigen exposure and persistent T-cell receptor stimulation, manifesting as a progressive loss of effector function and the sustained co-expression of multiple inhibitory receptors.[19] In cHL this is reinforced by the near-universal high level expression of PD-1 ligands on Reed-Sternberg cells. Continuous signaling through PD-1 and other co-inhibitory receptors progressively impairs effector cytokine production, proliferative capacity, and cytotoxicity, driving differentiation toward a terminally exhausted phenotype.[20] Reinke et al. analyzed tumor samples from cHL patients with limited stage disease treated in the NIVAHL trial and found rapid reduction in Type 1 regulatory T cells and PD-L1+ TAMs within days of nivolumab exposure, without evidence of cytotoxic CD8+ T-cell activation or clonal expansion. This was striking because most cHL tumors lose MHC class I expression, which would otherwise predict dependence on cytotoxic CD8+ T-cell-mediated killing. The role of MHC class II in PD-1-mediated immunity in cHL was demonstrated in samples from patients treated with nivolumab from the CheckMate 205 trial, where patients with retained MHC class II expression or Reed-Sternberg cells was associated with longer progression free survival following anti-PD-1 therapy.[11] The finding suggests that PD-1 blockade acts primarily through microenvironmental remodeling rather than classical cytotoxic T-cell induction in cHL.[21]

An additional mechanism that may promote Reed Sternberg cell growth and survival beyond the immune suppressive effect on the microenvironment of PD-1/PD-L1 signaling is reverse signaling through PD-L1. Reverse signaling through PD-L1, in which engagement of PD-L1 by PD-1 conveys a signal back to the PD-L1 expressing cell is a two way exchange rather than one way signal to the T cell.[22,23] This signal is sent though a cytoplasmic signaling component and promotes chemokine signaling and cell migration.[22] Jalali and colleagues demonstrated that engagement of PD-L1 on Reed-Sternberg cells send a pro-survival/anti-apoptotic signal into the Reed-Sternberg cells via the MAPK pathway.[24] This signaling was induced by both membrane-bound and soluble PD-1. The study also showed that patients with cHL have high serum levels of soluble PD-1 and the reverse signaling was abrogated by nivolumab.[24]

Because the cHL microenvironment fosters an immunosuppressive and exhausted T-cell phenotype, efforts have focused on understanding what drives exhaustion and how these cells might be rescued. Sustained JAK/STAT signaling has been correlated with checkpoint inhibitor resistance; consequently, there is interest in combining JAK inhibitors such as ruxolitinib with anti-PD-1 therapy. Together, these biological features establish cHL as the prototypical disease for checkpoint blockade and provide the rationale for the clinical activity reviewed below. (Figure 1)

Anti-PD-1 therapy in Clinical Practice

Initial Studies in R/R cHL

Anti-PD-1 therapy in classical Hodgkin lymphoma was first validated in the relapsed/refractory setting, where the high tumor-cell expression of PD-1 ligands and the limited efficacy of conventional salvage treatment created both a strong biological rationale and a clear unmet medical need. Foundational single-agent studies in patients who had failed brentuximab vedotin and/or an autologous stem cell transplant established the durable activity of immune checkpoint blockade that subsequently supported moving anti-PD-1 therapy into the frontline setting.

Initial single agent studies in relapsed and refractory patients showed high response rates with durable remissions and a relatively low side effect profile. (Table 1) The CheckMate 205 trial administered nivolumab to relapsed and refractory cHL patients and demonstrated an overall response rate (ORR) of 71.2% and complete response (CR) rate of 21.4% across the three cohorts, with median PFS of 15.1 months and 5-year overall survival (OS) of 71.4% at extended follow-up.[25,26] Importantly, some patients who discontinued nivolumab after sustained CR and were re-treated upon progression achieved another objective response supporting the feasibility of retreatment. In KEYNOTE-087, single-agent pembrolizumab demonstrated an ORR of 71.4% and CR rate of 27.6%, with a median PFS of 13.7 months and 5-year OS of 82.8% at extended follow-up. [27,28] In the subsequent phase 3 KEYNOTE-204 trial, pembrolizumab was compared to brentuximab vedotin, and treatment with pembrolizumab was shown to result in superior outcomes compared to brentuximab vedotin (median PFS 13.2 vs 8.3 months).[29]

The similar outcomes between pembrolizumab and nivolumab reinforce that the efficacy and modest toxicity is a class effect rather than agent specific. These data showed that PD-1 blockade resulted in durable responses in heavily pretreated patients, with manageable toxicity, and provided a strong rationale to move anti-PD-1 therapy into the front line.

Advanced stage cHL

Building on the efficacy discussed above, frontline trials have shown high efficacy across multiple regimens. (Table 2) CheckMate 205 cohort D evaluated nivo-AVD in the phase II setting using frontline nivolumab followed by nivo-AVD. The combination achieved high complete response rates (65–70%) and encouraging early progression-free survival in advanced-stage classical Hodgkin lymphoma.[30] Nivolumab-AVD therapy avoids bleomycin-associated pulmonary injury and showed low rates of severe immune-related adverse events, with endocrine toxicity being the most notable long-term concern.[30]

Similar efficacy of PD-1 blockade with chemotherapy as initial therapy was seen in a single-arm phase II trial of concurrent pembrolizumab plus AVD. The regimen was well tolerated with no significant treatment delays and grade 3–4 immune-related adverse events (irAEs) were infrequent (≤10%). The regimen achieved a 100% overall response rate and 90% CR rate, with a 2-year PFS of 97% and OS of 100%.[31] This study also demonstrated that ctDNA clearance by PhasED-Seq strongly correlated with durable remission.[31] Notably, pembrolizumab-AVD was shown to be effective regardless of the level of PD-L1 expression in the biopsy specimen.[32]

The subsequent phase 3 SWOG S1826 trial was a paradigm-shifting study in the treatment of advanced stage cHL. The study evaluated 994 patients, ages 12+, and patients were randomized 1:1 to nivolumab plus AVD (Nivo-AVD – experimental arm) versus brentuximab vedotin plus AVD (BV-AVD – control arm) for six 28-day cycles, with study drugs on days 1 and 15 of each cycle. At the initial interim analysis (median follow up of 12 months), nivo-AVD had significantly superior PFS compared to BV-AVD (94% vs 86%; HR 0.48; 99%CI 0.27-0.87). Updated results at a median follow-up of 2.1 years confirmed these findings, with a 2-year PFS of 92% for Nivo-AVD versus 83% for BV-AVD (HR 0.45; 95% CI, 0.30–0.65). At a median follow-up of 3.1 years, the PFS benefit was sustained: 3-year PFS 91% vs 82% (HR 0.48; 95% CI 0.34–0.69; P<0.0001). The 3-year overall survival was 98% vs 97% (HR 0.48; 95% CI 0.20–1.15), with no significant OS difference given the high cure rate in both arms.[33,34]

Additionally, safety outcomes from S1826 showed that irAEs were infrequent and rates of febrile neutropenia, pneumonitis, and liver function test abnormalities were similar between groups. Patients receiving Nivo-AVD had higher rates of thyroid dysfunction (hypothyroidism 7% and hyperthyroidism 3% in nivo-AVD vs <1% and 0% in BV-AVD respectively), whereas those receiving BV-AVD experienced substantially more peripheral neuropathy (54.2% vs. 28.1%). Nivo-AVD had fewer patients discontinue treatment; 46 patients (9.4%) discontinued Nivo-AVD for any reason of which 19 (3.9%) discontinued nivolumab only but continued AVD, and 107 patients (22.2%) discontinued BV-AVD, of which 59 (12.2%) discontinued BV and continued AVD. Only 7 patients (less than 1%) in the study received consolidative radiation, demonstrating that radiation was largely not needed. Given the robust outcomes in advanced-stage disease, prognostic indices such as the international prognostic score (IPS) may need recalibration as the data used to create this prognostic score was based on treatments that did not have outcomes as good as those seen with anti-PD-1 therapy or movement to treatment agnostic scores like the advanced-stage Hodgkin lymphoma international prognostic index (A-HIPI) which appears to maintained the ability prognosticate in S1826.[35]

Furthermore, trial results are increasingly being confirmed in real-world practice. A multicenter cohort receiving front line Nivo-AVD, had ORR and CR rates of 96% and 90% respectively with 1-year PFS of 94%, closely mirroring the S1826 trial and showing

reproducibility outside of the trial setting. [36] Subgroup analyses have begun to identify at risk groups or those with less benefits. EBV positive patients who historically have inferior outcomes are one such group: in a subgroup analysis of S1826, patients with EBV positivity had inferior 2-year PFS when treated with BV-AVD (76% EBV+ vs 85% for EBV-, p=0.03), whereas in patients treated with Nivo-AVD this difference was abrogated (95% vs 92%, p=0.88), which one may hypothesize is due to the increased PD-L1 expression in EBV driven disease.[10,37] Notably, however, in the real word multicohort study by Bock and colleagues, EBV+ status was still associated with inferior PFS in a univariate analysis, suggesting that EBV may continue to warrant attention as a risk factor.[36]

Early Stage cHL

The use of nivolumab containing regimens in early-stage disease continues to be explored. (Table 2) The German Hodgkin Study Group conducted the NIVAHL phase II trial as a front-line treatment in early-stage unfavorable risk patients. In this study, 109 patients were randomized to either four cycles of concurrent Nivo-AVD or four doses of nivolumab followed by two cycles of Nivo-AVD and two cycles of AVD, each followed by 30 Gy involved-site radiotherapy.[38] After completion of treatment, the CR rate was 92% in both arms; notably, 51% of patients in the sequential arm achieved CR after the 4-dose nivolumab lead-in alone. The PFS was 98% in the concomitant arm and 100% in the sequential arm, with 100% OS in both.[38]

Additional analysis have been undertaken in both early stage favorable and unfavorable disease as part of a phase II study which evaluated 154 patients with early-stage cHL who received nivolumab, brentuximab vedotin, doxorubicin, and dacarbazine for 4 cycles.[39] There were 56 patients with favorable disease and 97 patients with unfavorable disease, CR rates were 95% (95% CI, 85.1-98.9) and 91% (95% CI, 83.1-95.7), respectively. With a median follow-up of 27.9 months (95% CI, 27.2-28.6), the estimated PFS rate at 2 years was 97% (95% CI, 92.0-98.8). All 5 patients who had progressive disease had unfavorable disease at enrollment. Twenty-two percent of patients experienced an immune-mediated adverse event, most commonly hypo- or hyperthyroidism; all other immune-mediated AEs occurred in less than 5% of patients. The most common grade 3 treatment related adverse event was neutropenia in 9% of patients, followed by liver function test (LFT) abnormalities (AST and ALT) in 6 and 5% of patients respectively. Together, these trials demonstrate that anti-PD-1-based regimens achieve high response rates in early-stage cHL, supporting their continued investigation as alternatives to traditional ABVD-based and BV-AVD approaches. However, with PD-1 inhibitors and brentuximab vedotin both moving into frontline therapy, the implications for salvage strategies need to be reconsidered. Patients relapsing after Nivo-AVD frontline will be PD-1-exposed at first salvage, with limited rechallenge data to guide management. (Figure 2)

Anti-PD-1 combination therapy for Relapsed/Refractory cHL

PD-1 inhibitors have also demonstrated great utility in relapsed/refractory patients when combined with chemotherapy as part of salvage therapy. (Table 1) Pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) as second-line treatment demonstrated a CR rate of 95% (92% after only 2 cycles) and an ORR of 100%.[40] Most patients in this study (95%) proceeded to autologous stem cell transplant (ASCT). Pembrolizumab plus ifosfamide, carboplatin, and etoposide (ICE) demonstrated a CR rate of 86.5% with strong post-ASCT outcomes (2-year PFS 87.2%; 2-year OS 95.1%).[41] Similarly, nivolumab plus ICE has shown high efficacy in transplant-eligible patients (ORR 95%, CR 86%), with 2-year post-ASCT PFS of 94% and OS of 100%.[42,43] Across these combination regimens, CR rates of 85–95% have replaced the historical 50% CR rate seen with conventional second-line chemotherapy, fundamentally raising the bar for salvage outcomes in transplant-eligible patients.[5,40]

Other PD-1 agents

Other PD-1 targeted agents have been approved in countries outside of the US and further support the efficacy of PD-1 blockade in cHL. (Table 1) Sintilimab, a fully human IgG4 monoclonal antibody with markedly higher PD-1 binding affinity than first generation agents (approximately 40-fold higher than nivolumab and about 25 fold higher than pembrolizumab), demonstrated an ORR of 80.4% and CR rate of 34% in the ORIENT-1 trial; ctDNA dynamics were also shown to be predictive of treatment response.[44-46] Camrelizumab, a humanized IgG4 monoclonal antibody that binds to a distinct PD-1 epitope on the N-glycosylated ASN58 residue (different from the N-terminal C′D-Loop epitope targeted by pembrolizumab and nivolumab), showed similar efficacy but with a distinctive toxicity profile, including reactive cutaneous capillary endothelial proliferation (RCCEP) in 97.3% of patients and pyrexia in 42.7%.[47,48]

Tislelizumab, a fully humanized IgG4 antibody, with a Fcγ receptor-engineered design (intended to minimize macrophage-mediated T-cell depletion),is notable for an unusually high CR rate of 62.9% in its Chinese registration study, which for a single agent is substantially higher than the 21–28% CR rates seen with nivolumab and pembrolizumab and had a 3-year median PFS of 31.5 months. However, this high CR rate has not been reproduced in Western populations: in the prospective LYSA TIRHOL study, tislelizumab produced an ORR of 66.7%, and a CR rate of only 31%, more in line with nivolumab and pembrolizumab.[49] Whether this reflects differences in patient selection (more heavily pretreated patients in the Western cohort), response assessment methodology, or the agent's specific Fcγ receptor-engineered design is unknown.[49-51]Penpulimab differs from the other agents listed as it is a humanized IgG1 monoclonal antibody rather than IgG4, is engineered with Fc mutations that eliminate Fc gamma receptor and C1q binding, and binds with a slower off rate than pembrolizumab

or nivolumab. In a phase II trial with a median follow-up of 15.8 months, penpulimab demonstrated an ORR of 89.4%, and a CR rate of 47.1%. The 12-month PFS was 72.1%. Penpulimab was associated with a high rate of treatment-related adverse events of any grade (>90%), with 26.6% experiencing grade 3 or higher. Immune related adverse events occurred in 54.3% of patients, with 4.3% experiencing grade 3 or higher irAEs.[52] While these agents remain primarily available outside the United States, their consistent activity supports anti-PD-1 efficacy in cHL as a class effect and the unusually high CR rate seen with tislelizumab raises mechanistic questions worthy of further evaluation.

Special Populations

Elderly and/or Chemotherapy ineligible patients

Older patients (over age 60 years) with cHL have inferior outcomes due to comorbidities and treatment related complications and the use of novel agents such as PD-1 blocking antibodies are very appealing in this patient population.[53,54] (Table 2)To avoid the complications seen with chemotherapy, Cheson and colleagues evaluated nivolumab plus the antibody drug conjugate brentuximab vedotin in a phase II ACCRU study.[53] The trial closed early for failing to meet prespecified efficacy criteria; however, 48% of patients still achieved a CR. Peripheral neuropathy was common and seen in 48% of patients and unfortunately grade 4 liver enzyme elevations and pancreatitis were also observed.[53] Longer term follow up (median follow up 58.5 months) showed a median PFS of 18.3 months. At the time of analysis, 41.3% of patients had not had a progression event, the median OS was not reached and 84.8% of patients were still alive.[55] Similarly, Friedberg and colleagues presented data from a phase II trial of brentuximab vedotin plus dacarbazine or brentuximab vedotin plus nivolumab as frontline therapy for cHL in older patients ineligible for chemotherapy. Though the trial was relatively small (n=43, with 21 in the BV-nivolumab arm), response rates were high in the BV-nivolumab group: ORR was 86% and CR 67%. A key question raised by comparing the two studies is the optimal treatment duration. Patients in the Friedberg study were treated for up to 16 cycles (15 of 21 beyond 24 weeks), with median PFS was not reached at a median follow-up of 51.6 months.[54] In contrast, patients in the ACCRU study were treated for a maximum of 8 cycles of nivolumab plus brentuximab vedotin, raising the possibility that abbreviated treatment exposure contributed to the lower CR rate (48%) and the trial's early closure for failing prespecified efficacy criteria. Together, these comparisons suggest that longer treatment duration may be required to achieve durable disease control with anti-PD-1 plus brentuximab vedotin in older patients. However, adverse events remained common in this older population, with 76% experiencing grade ≥3 events; most frequent were peripheral neuropathy (27%) and neutropenia (9%). Despite this, the regimen was tolerable enough to deliver extended

treatment in most patients (15 of 21 beyond 24 weeks), supporting the feasibility of this treatment with durations beyond 8 cycles when patient tolerance permits.[54]

Elderly patients able to tolerate chemotherapy benefit substantially from the addition of a PD-1 blocking antibody. Phase II data from Torka et al. supports good outcomes for older patients receiving nivolumab plus AVD, with an ORR of 92%, CR rate of 71%, 3-year PFS of 79%, and 3-year OS of 97%.[56] Although 50% experienced grade ≥3 adverse events, the regimen was tolerable in this older population and produced excellent efficacy. Notably, baseline geriatric assessment did not correlate with survival outcomes or toxicity, suggesting that standard fitness measures alone may not reliably identify which older patients can safely receive nivolumab plus AVD and perhaps new tools are needed to assess fitness for these regimens.[56] Interim PET was not predictive of PFS or OS in this study, suggesting fewer scans may be needed with this regimen.[56] Outcomes for older patients (≥60 years) were also evaluated in SWOG S1826: surprisingly 69% did not require dose reductions, with 2-year PFS of 89% and 2-year OS of 96% in patients receiving nivo-AVD. Notably, these outcomes were significantly better than those achieved with BV-AVD (2-year PFS 64% and 2-year OS 85%); together with substantially lower rates of peripheral neuropathy and treatment discontinuation. This supports nivo-AVD as the preferred regimen for the fit older population able to tolerate combination chemotherapy.[57]

In summary, older patients tolerate PD-1-based regimens reasonably well, and PD-1 plus chemotherapy is the preferred frontline approach for this population. Combinations with brentuximab vedotin or single-agent nivolumab remain reasonable for chemotherapy-ineligible patients, though optimal treatment duration remains undefined.

Adolescents and Young Adults (AYA)

Nivolumab and pembrolizumab have both been shown to be safe and effective in children and young adults with cHL.[58,59] (Table 3) In the relapsed/refractory setting, CheckMate 744 was a phase II study in patients aged 5–30 years with R/R cHL, in which patients received four cycles of BV plus nivolumab induction, intensification if not in CR, and a consolidative ASCT.[60] Complete metabolic response after induction was 59% and increased to 94% with BV plus bendamustine intensification in those patients who did not achieve CR and the 1-year PFS was 91%.[60] A separate transplant-free cohort of CheckMate 744, reported by Daw and colleagues, challenged current paradigms regarding the need for autologous transplant. In this nonrandomized single-arm study enrolling children and adolescents aged 5–30 with low-risk relapsed cHL, patients received four cycles of BV plus nivolumab; those with suboptimal response received an additional two cycles of BV plus bendamustine, followed by maintenance nivolumab. Upon completion of therapy, 93% achieved a complete metabolic response, and 82% required only the initial four cycles of BV plus nivolumab.[61] Not only have

checkpoint inhibitor containing regimens showed great efficacy in clinical trials but also in real world data. Pouthier and colleagues reported real-world outcomes in relapsed/refractory AYA patients, with an ORR of 93% and 63% achieving complete metabolic response and 3-year PFS was 48% and OS was 95% in a relapsed/refractory AYA population. Together these data demonstrate that anti-PD-1-containing salvage treatment achieves response rates approaching clinical-trial efficacy and preserves overall survival. However, the gap between PFS and OS highlights the ongoing challenge of durable disease control, supporting strategies such as response-adapted intensification or MRD-guided treatment to continue to improve outcomes.[62] Given the favorable safety profile, anti-PD-1 therapy has also been moved to the frontline setting in adolescent patients, supported by the S1826 study, in which approximately one-quarter of patients were under age 18. The 3-year PFS in adolescents (<18 years) was 93% compared to 82% with BV-AVD.[33,63]

Beyond efficacy, the favorable safety profile of anti-PD-1 based regimens supports continued adoption in the AYA population. Reduced radiation exposure is a particular advantage, in S1826 fewer than 1% of patients received consolidation, sharply contrasting with the HD21 trial of escalated BEACOPP vs BrECADD in patients with advanced stage cHL where 14% of patients receiving BrECADD underwent radiation.[33,64] Decreasing exposure to toxicities associated with bleomycin and reduction in peripheral neuropathy are also advantages gained by anti-PD-1 based regimens.[33] Limited fertility data from NIVAHL suggest that fertility is preserved in both men and women receiving PD-1-based frontline therapy, however longer term data still needed to make more definitive conclusions.[65]

Autologous Transplant

PD-1 blockade has produced impressive outcomes as both salvage therapy and as a bridge to a stem cell transplant.(Table 3) Treatment with pembrolizumab-GVD resulted in 95% of patients achieved a CR with subsequently 95% proceeding to ASCT and all transplanted patients still in remission by the median follow up of 13.5 months.[40] A recent analysis by Desai and colleagues showed that patients who received PD-1 inhibitors at any point before ASCT had significantly higher 2-year PFS than those receiving BV-based or chemotherapy-only salvage (88.2% vs 70.2% vs 67.4%, respectively), supporting PD-1-containing salvage in PD-1-naive patients.[66] The biological basis for this benefit remains incompletely understood but appears to extend beyond simple disease debulking. Anti-PD-1 therapy has been observed to sensitize cHL to subsequent chemotherapy. Rossi and colleagues first reported an ORR of 67% (CR 41%) with chemotherapy after anti-PD-1 failure in 30 R/R cHL patients regardless of prior chemotherapy resistance and Carreau and colleagues subsequently confirmed in a multicenter analysis of 81 patients that the ORR to post-checkpoint blockade therapy was 62% with median OS of 21 months.[67,68] Mariotti and colleagues

documented an even higher rechallenge response rate (82% CR), with exploratory clonal-evolution analyses suggesting that anti-PD-1 treatment may select for subclones with altered chemotherapy sensitivity.[69] These observations are consistent with the rapid microenvironmental remodeling Reinke and colleagues described with a reduction in Treg and PD-L1+ TAM populations within days of nivolumab, together with reinvigoration of exhausted T-effector cells producing a more immune-permissive tumor state that may persist through subsequent therapy.[18,21] Whether the pre-ASCT benefit is driven primarily by improved disease control before transplant or by durable post-transplant immunologic effects remains an open question. Maintenance therapy post-ASCT has also shown promise. In a phase II trial, 59 patients received brentuximab vedotin plus nivolumab maintenance after ASCT for a median of 8 cycles; 18-month PFS was 94%, with peripheral neuropathy (53%) the most common adverse event.[70] Pembrolizumab maintenance has also been explored, with an 18-month PFS of 82% post-ASCT.[71]

Allogeneic Transplant

While well tolerated in patients undergoing an autologous transplant, PD-1 blockade has historically been associated with increased graft-versus-host disease (GVHD) risk after allogeneic hematopoietic cell transplantation (allo-HCT). An initial study reported a 180-day cumulative incidence of grade 3–4 acute GVHD of 15%, with a 2-year cumulative incidence of chronic GVHD of 34%.[72] Post-transplant cyclophosphamide (PTCy) significantly reduces this risk (grade 3–4 GVHD 5.9% with PTCy vs 19.6% with ATG) and is recommended for these patients.[72] Similarly, GVHD rates of approximately 30% have been observed when nivolumab is administered after allo-HCT without PTCy.[73]

Recommendations to reduce GVHD risk include cessation of anti-PD-1 therapy 8 weeks or more prior to transplantation, PTCy prophylaxis and, if PD-1 blockade is considered post-allo-HCT, starting at a low dose (e.g., nivolumab 0.5 mg/kg) with close monitoring and aggressive early treatment of GVHD.[74]

Safety Considerations

The safety profile of PD-1 directed therapy significantly differs from classical chemotherapy and is generally viewed more favorably. Interestingly, irAEs in cHL patients tend to be lower than in solid tumor patients, possibly reflecting the different mechanism of PD-1 activity in cHL described previously. (Figure 1) Recent evaluation by Argnani and colleagues evaluated patients with relapsed refractory cHL to identify adverse events. In their study 22.9 % of patients developed at least 1 irAE.[75] Whether irAEs predict efficacy remains uncertain, with conflicting data: some studies suggest improved outcomes in patients who experience irAEs, while others find no difference.[75,76] (Table 4-5)

Endocrinopathies are the most common irAEs. Hypothyroidism occurs in up to 16% of patients in major trials and is generally grade 1–2, but is often irreversible and requires lifelong thyroid hormone replacement.[26,27,38] Hyperthyroidism is less common (<5%) and may precede hypothyroidism in a Graves disease-like presentation. Women have been noted as being at particularly higher risk of thyroid related adverse events.[77] Other endocrine toxicities such as adrenal insufficiency and hypophysitis are rare but clinicians should be aware of these as they monitor patients given the high risk of complications. Checkpoint inhibitor-induced type 1 diabetes merits, although rare (~1%), merits specific attention as it is typically irreversible, frequently presents acutely with diabetic ketoacidosis, and commits the patient to lifelong insulin therapy. Glucose should be monitored during treatment and patients counseled to report polyuria, polydipsia, or unexplained weight loss without delay.[78-80] For these rarer adverse events such as adrenal insufficiency or persistent endocrinopathies, endocrinology consultation is recommended.

Pneumonitis is rare (1–6%) but is among the most serious irAEs and is one of the most common causes of treatment discontinuation in anti-PD-1 studies.[33,38,54,56] Pneumonitis occurs regardless of stage as trials in early stage cHL showed an incidence of around 2%.[39] It is imperative that this condition be recognized by looking for new onset shortness of breath, cough, activity intolerance, or decrease in pulse oximetry, with a low threshold for CT imaging of the chest, and prompt treatment with corticosteroids .[78,79]

Other immune reactions such as hepatitis, colitis, dermatologic reactions, and myocarditis are rare, but clinicians should have a high index of suspicion for immune adverse events.[78,79] Furthermore patients with pre-existing autoimmune disorders warrant particular caution as checkpoint blockade can precipitate flares of the underlying condition. For this reason, patients were largely excluded from the pivotal trials discussed. The decision to treat patients with anti-PD-1 therapy in the setting of pre-existing autoimmune conditions should be carefully considered based on the severity and activity of the condition and any concurrent immunosuppression. Decisions such as these should ideally be made in discussion with the other relevant medical specialties.

Long-term follow-up beyond 5 years will be needed to define the risk of late complications, particularly as anti-PD-1 therapy moves into the frontline setting and is administered to younger patients.

Feasibility and practical considerations

Several practical considerations should be noted with anti-PD-1 containing regimens. Some pivotal studies, including S1826, did not include an interim PET after cycle 2, in contrast to most other cHL regimens.[33] In clinical trials that may use PET scans to

determine therapy choices, response assessment by PET scan in anti-PD-1 treated patients may be difficult. Although most patients respond early, pseudoprogression can occur. Chen and colleagues reported pseudoprogression in 12.5% of apparent early progressions, corresponding to 4.4% of treated patients overall.[81] Caution is also warranted when interpreting end-of-treatment PET scans, as some patients develop sarcoid-like reactions with persistent mediastinal lymphadenopathy that may occur at sites distinct from the original lymphoma involvement.[82] To help address the unique patters seen after anti-PD-1 regimens, the Lugano criteria were refined into the LYRIC criteria, which introduce an indeterminate response (IR) category that allow for continued treatment and reassessment rather than premature classification as progressive disease.[83] With some indeterminate results at the end of treatment PET scan, a biopsy and/or continued PET surveillance is recommended. If a sarcoid-like reaction is confirmed and the patient is symptomatic, corticosteroid treatment can be considered, though most cases resolve with discontinuation of anti-PD-1 treatment.[82]

Optimal dosing of checkpoint inhibitors remains uncertain. Most trials have used fixed doses (nivolumab 240 mg or 3 mg/kg; pembrolizumab 200 mg or 2 mg/kg), but efforts have been made to evaluate lower doses, particularly given the cost of these agents and limited deployment in resource-constrained settings. Several retrospective cohorts evaluating lower doses have suggested similar outcomes.[84-88] Prospective trials are needed to confirm the safety and efficacy of reduced-dose strategies.

Optimal treatment duration is also unresolved. While CheckMate 205 cohort C showed feasibility of discontinuation after sustained CR, and successful retreatment after progression, the results of the ACCRU trial suggest that abbreviated treatment in patients not yet achieving a CR may compromise outcomes. In this study, the median PFS of patients who received a fixed duration therapy of 8 cycles was 18.3 months, in contrast to a median PFS that was not reached in the Friedberg trial in which patients were treated with up to 16 cycles.[54,55] Further study is needed to define the minimum effective duration of anti-PD-1 therapy in cHL.[26]

Future Directions

Checkpoint inhibitor therapy has transformed the treatment of cHL, but many questions remain. Can we continue to refine frontline therapy to target the biology of the disease and minimize toxicity? The phase II GHSG INDIE study (NCT04837859) is evaluating tislelizumab monotherapy versus tislelizumab plus AVD, followed by ISRT for residual disease at end of treatment, to address the necessity of chemotherapy in this setting. In a complementary effort to reduce the chemotherapy burden in older patients, the UK RATiFY study (NCT05627115) is evaluating a response-adapted strategy in which patients aged 60 and older receive an initial course of single agent tislelizumab with

subsequent treatment, including the amount of chemotherapy, tailored to the interim PET response.

An additional question is how to identify patients at risk for primary refractoriness or acquired resistance to anti-PD-1 therapy? Efforts to evaluate resistance by Paczkowska and colleagues identified a population of IL1β+ inflammatory monocytes and macrophages in the blood of patients with cHL that were not present in healthy donors.[89] These cells co-expressed PD-L1 and SIRPα and localized in the vicinity of Reed-Sternberg cells. The cells also contained a proinflammatory signature that was associated with resistance to anti-PD-1 therapy that could potentially be detected in the peripheral blood.[89] This could be utilized for to determine which patients would benefit from intensification of checkpoint blockade or need alternative strategies.

Efforts to further capitalize on the vulnerability to immunotherapy have led to studies of multi-checkpoint blockade in both immunotherapy-naive and checkpoint-refractory populations. The RELATIVITY-022 trial, evaluating nivolumab plus relatlimab (anti-LAG-3 antibody) in cHL, showed an ORR of 62% and CR rate of 19% (median PFS 19 months) in checkpoint-naive patients. In patients previously exposed to checkpoint inhibitors, the response was limited with an ORR of 15% and CR rate of 0%, and median PFS of 6 months. [90] Favezelimab (anti-LAG-3) plus pembrolizumab was evaluated in patients who had progressed on prior checkpoint inhibitor therapy, with an ORR of 37%, suggesting modest efficacy in this difficult-to-treat population.[91] Tifcemalimab (anti-BTLA antibody) plus toripalimab (anti-PD-1) is also being evaluated in checkpoint-refractory cHL. In a phase 1 trial (NCT04477772) of the combination, the ORR was 37% with one CR.[92]

Other efforts have attempted to utilize different mechanisms of action to restore efficacy to anti-PD-1 treatments. Hypomethylating agents were evaluated to reverse epigenetic silencing of immune related genes. In a study of 51 patients refractory to prior PD-1 therapy, decitabine plus camrelizumab achieved an ORR of 52%, with a CR rate of 36%, and a median PFS of 20 months.[93] Pembrolizumab was combined with the HDAC inhibitor vorinostat with a goal of promoting T-cell recruitment and function, and achieved an ORR of 56% with a CR rate of 11% in a phase 1 study in checkpoint-refractory cHL.[94] Efforts to rescue exhausted T-cells by targeting the JAK/STAT pathway to restore sensitivity to anti-PD-1 agents have shown initial promise. A phase 1 trial of a JAK inhibitor added to PD-1 blockade yielded an overall response rate of 53% (n=10/19).[95]

Other approaches have looked at the potential of bispecific antibodies and CAR-T cells to target the high CD30 expression on Reed-Sternberg cells.[96] AFM13 is a CD30/CD16A bispecific tetravalent chimeric antibody designed to activate native NK cells. This agent showed promising results in a phase 1b study in combination with

pembrolizumab with an OR rate of 88% at the highest dose and 83% OR rate in the study overall.[97] However, a phase II trial of AFM13 as a single agent produced a far more modest response rate of 16.6% (4/24 patients) and the trial was terminated due to low accrual.[98] Alternative approaches have combined AFM13 with cord-blood-derived cytokine preactivated NK cells in a phase 1 trial and demonstrated an OR rate of 92.9% and a CR-rate of 66.7% with no cytokine release syndrome. Eleven of the forty-two patients remained in CR at 14-40 months (6 with consolidation and 5 without consolidation) and the 2-year EFS was 26.2%.[99]

Autologous CD30-directed CAR T cells demonstrated an ORR of 72% and a 59% CR rate in patients with relapsed refractory disease (median prior lines =7) in a phase I/II trial of 32 patients. Despite some promising initial responses, the one-year PFS was 36%.[100] The CHARIOT trial of another autologous CD30 CAR-T therapy showed an OR rate of 75% and a CR rate of 50% but development was complicated by dissolution of the sponsor. Twelve of 15 patients were evaluated for longer term outcomes, and with a median follow up of 45 months, 9 patients had relapse/progression and 1 patient had died without progression. The median PFS was 7.1 months and the 3 year PFS was 17%. Four patients had consolidative allogeneic transplants and one of those patients had continued response without relapse. [101] Grover and colleagues have also tried to improve CD30 CAR-T outcomes by leveraging CCR4 expression to improve tumor homing. A phase 1 study in relapsed/refractory cHL showed an OR rate of 91.7% and CR rate of 67%.[102]

Together, these strategies attempt to address two interconnected challenges: how to design safer, less toxic regimens, and how to overcome resistance through complementary biological mechanisms. Validating predictive biomarkers, including the IL1β+ inflammatory monocyte signature, ctDNA dynamics, or microenvironmental composition, and incorporating them into biomarker-stratified trials will be essential next steps. Equally important is rational sequencing of treatment. As anti-PD-1 therapy moves into frontline use, the choice of cHL salvage therapy, use of stem cell transplantation, and selection of post-checkpoint therapy must evolve to minimize both clinical toxicity and the financial toxicity that accompanies extended immunotherapy and cellular therapy programs.

Conclusions

PD-1 inhibitor therapy has transformed the treatment landscape of cHL across all treatment settings. These treatments are highly efficacious, supported by the strong biological rationale of near-universal 9p24.1 alterations and a suppressive tumor microenvironment. In the frontline setting, Nivo-AVD is an emerging standard for advanced stage cHL as well as in early-stage unfavorable disease. In the

relapsed/refractory setting, for patients who are checkpoint inhibitor-naive, combination strategies such as pembrolizumab plus GVD achieve high CR rates. In older patients or those unfit for standard chemotherapy, single-agent approaches are reasonable and provide durable remissions. As utilization of checkpoint inhibitors moves into the frontline, novel regimens will be needed for refractory disease. Long-term follow-up will also be needed to detect late complications and inform optimal treatment duration. Trials focused on sequencing therapies to promote the most benefit with the least toxicity will be needed to define the next era of cHL treatment.

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Tables:

Table 1. Efficacy of anti-PD-1 therapy in relapsed/refractory classical Hodgkin lymphoma.

Trial / Reference	Ph	Regimen	N	ORR (%)	CR (%)	PFS	OS	Ref.
RELAPSED/REFRACTORY — Monotherapy								
CheckMate 205 (Armand 2018; Ansell 2023, 5-yr)	II	Nivolumab monotherapy	243	71	21	Median PFS 15.1 mo; 5-yr PFS 18%	5-yr OS 71%	25, 26
KEYNOTE-087 (Chen 2019; Armand 2023, 5-yr)	II	Pembrolizumab monotherapy	210	71.4	27.6	Median PFS 13.7 mo; 5-yr PFS ~14%	5-yr OS 82.8%	27, 28
KEYNOTE-204 (Kuruvilla 2021)	III	Pembrolizumab vs BV	304 (151 vs 153)	65.6 vs 54.2	24.5 vs 24.2	Median PFS 13.2 vs 8.3 mo	Not mature at interim	29
RELAPSED/REFRACTORY — Combination therapy								
Pembro-GVD (Moskowitz 2021)	II	Pembrolizumab + GVD ×2–4	39	100	95	Not reached (med F/U 13.5 mo)	—	40
Pembro-ICE (Bryan 2023)	II	Pembrolizumab + ICE ×2	37	97	86.5	2-yr PFS 87.2%	2-yr OS 95.1%	41
Nivo + ICE (Mei 2022; Mei 2025)	II	Nivo ± ICE (response-adapted)	43	95	86	2-yr post-ASCT PFS 94%	2-yr post-ASCT OS 100%	42, 43
OTHER ANTI-PD-1 AGENTS								
ORIENT-1 (Shi 2019; Shi 2020)	II	Sintilimab monotherapy	96	80.4	34	Not reported as median	—	44, 45
Camrelizumab (Song 2019)	II	Camrelizumab monotherapy	75	76	28	—	—	47
Tislelizumab (Song 2020; Song 2022, 3-yr)	II	Tislelizumab monotherapy	70	87.1	62.9	3-yr median PFS 31.5 mo	3-yr OS ~85%	50, 51
Penpulimab AK105-201 (Song 2022)	I/II	Penpulimab monotherapy	94	89.4	47.1	12-mo PFS 72.1%	—	52

*Abbreviations: Ph, phase; AVD, doxorubicin/vinblastine/dacarbazine; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; benda, bendamustine; CMR, complete metabolic response; CR, complete response; DTIC, dacarbazine; F/U, follow-up; fav., favorable; HR, hazard ratio; ICE, ifosfamide/carboplatin/etoposide; IFRT, involved-field radiotherapy; mPFS, median progression-free survival; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-1, programmed death-1; pembro, pembrolizumab; PFS, progression-free survival; R/R, relapsed/refractory; unfav., unfavorable; yr, year(s). PFS and OS reflect the median and/or longest-reported follow-up; the timepoint is indicated in each cell. *Estimated from reported data.*

Table 2. Efficacy of frontline anti-PD-1–based regimens in classical Hodgkin lymphoma.

Trial / Reference	Ph	Regimen	N	ORR (%)	CR (%)	PFS	OS	Ref.
FRONTLINE — Advanced stage								
CheckMate 205 cohort D (Ramchandren 2019)	II	Nivo lead-in → Nivo-AVD ×6	51	84	67	9-mo PFS 92%	9-mo OS 98%	30
SWOG S1826 (Herrera NEJM 2024; Herrera ASH 2025; Casulo ASH 2025)	III	Nivo-AVD vs BV-AVD ×6	994	—	—	3-yr PFS 91% vs 82% (HR 0.48)	3-yr OS 98% vs 97%	33, 34, 35
Pembro-AVD (Lynch 2023)	II	Concurrent pembrolizumab + AVD ×6	30	100	90	2-yr PFS 97%	2-yr OS 100%	31
Sequential pembro→AVD (Allen 2023)	II	3 cycles pembrolizumab → AVD	30	100	100*	Not yet mature	—	32
FRONTLINE — Early stage								
NIVAHL (Bröckelmann 2020)	II	4×Nivo-AVD vs 4×Nivo lead-in → 2×Nivo-AVD → 2×AVD (each + 30 Gy IFRT)	109	—	92 (both arms); 51 after Nivo lead-in alone	3-yr PFS 98–100%	3-yr OS 100%	38
SGN35-027 (Abramson 2026)	II	Nivo + BV + doxorubicin + dacarbazine ×4	154	—	95 (fav.) / 91 (unfav.)	2-yr PFS 97%	—	39
FRONTLINE — Older adults / chemotherapy-ineligible								
ACCRU (Cheson 2020; Cheson 2025, long-term)	II	BV + Nivolumab (early closure)	46	61	48	mPFS 18.3 mo; ~41% PFS at 5-yr F/U	5-yr OS ~85%; mOS not reached	53, 55
Friedberg 2024	II	BV + Nivolumab (vs BV + DTIC)	21 (Nivo arm)	86	67	Not reached at 51.6 mo	—	54
Torka 2025 (Nivo-AVD older)	II	Nivo + AVD ×6	39	92	71	3-yr PFS 79%	3-yr OS 97%	56
S1826 older subset (Rutherford 2025)	III subset	Nivo-AVD vs BV-AVD	97	—	—	2-yr PFS 89% (Nivo arm)	2-yr OS 96% (Nivo arm)	57

*Abbreviations: Ph, phase; AVD, doxorubicin/vinblastine/dacarbazine; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; benda, bendamustine; CMR, complete metabolic response; CR, complete response; DTIC, dacarbazine; F/U, follow-up; fav., favorable; HR, hazard ratio; ICE, ifosfamide/carboplatin/etoposide; IFRT, involved-field radiotherapy; mPFS, median progression-free survival; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-1, programmed death-1; pembro, pembrolizumab; PFS, progression-free survival; R/R, relapsed/refractory; unfav., unfavorable; yr, year(s). PFS and OS reflect the median and/or longest-reported follow-up; the timepoint is indicated in each cell. *Estimated from reported data.*

Table 3. Efficacy of anti-PD-1 therapy in adolescent and young adult and peri-transplant settings.

Trial / Reference	Ph	Regimen	N	ORR (%)	CR (%)	PFS	OS	Ref.
AYA AND PERI-TRANSPLANT								
CheckMate 744 (Harker-Murray 2023)	II	BV + Nivo ± BV + bendamustine intensification → ASCT	44	—	59 post-induction; 94 post-intensification	1-yr PFS 91%	—	60
S1826 adolescents (Castellino 2026, 3-yr)	III subset	Nivo-AVD vs BV-AVD	~one-quarter of 970 (subset)	—	—	3-yr PFS 93% vs 82%	—	33, 63
CheckMate 744 transplant-free (Daw 2025)	II (cohort)	BV + Nivo ×4 → optional BV + benda → Nivo maintenance	29	—	93 (CMR)	Not yet reported	—	61
Pouthier 2026 (real-world AYA)	Real-world	PD-1 ± combinations	—	93	63 (CMR)	3-yr PFS 48%	3-yr OS 95%	62
Herrera 2023 (BV + Nivo post-ASCT)	II	BV + Nivo ×8 maintenance	59	—	—	18-mo PFS 94%	—	70
Pembro maintenance post-ASCT (Armand 2019)	II	Pembrolizumab maintenance	30	—	—	18-mo PFS 82%	—	71

*Abbreviations: Ph, phase; AVD, doxorubicin/vinblastine/dacarbazine; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; benda, bendamustine; CMR, complete metabolic response; CR, complete response; DTIC, dacarbazine; F/U, follow-up; fav., favorable; HR, hazard ratio; ICE, ifosfamide/carboplatin/etoposide; IFRT, involved-field radiotherapy; mPFS, median progression-free survival; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-1, programmed death-1; pembro, pembrolizumab; PFS, progression-free survival; R/R, relapsed/refractory; unfav., unfavorable; yr, year(s). PFS and OS reflect the median and/or longest-reported follow-up; the timepoint is indicated in each cell. *Estimated from reported data.*

Table 4. Safety of frontline anti-PD-1–based regimens in classical Hodgkin lymphoma, including older adults.

Trial / Regimen	N	Thyroid (hypo / hyper)	Pneumonitis	Transaminitis (ALT)	Peripheral neuropathy	Discontinuation	Treatment-related death	Ref.
FRONTLINE								
SWOG S1826 (Nivo arm)	489	Hypo 7%; Hyper 3%	2.0%	33%	29% (sensory; gr ≥2 2.9%)	8% all-cause	<1% (n=2)	33
SWOG S1826 (BV arm)	481	Hypo <1%; Hyper <1%	3.2%	39.8% (42%)	56% (sensory; gr ≥2 32%)	12% all-cause	<1% (n=8)	33
NIVAHL (concomitant or sequential + 30 Gy)	109	Hypo ~6% (grade 2 or lower)	~5% (1 case G2 intermittent)	Liver/GI/pancreas org tox most common; G≥3 in 16-18%	< 1%	~5%; mostly grade 1–2 irAE	0	38
SGN35-027	154	Hypo 6%; Hyper 5%	2% any Gr (1% G3)	3%	—	3% all cause	0	39
Pembro-AVD (Lynch 2023)	30	Hypo 7% (gr 2; 2/30)	0% (no pneumonitis observed)	Gr 3 transaminitis ≤10%	Low	Low	0	31
OLDER ADULTS								
S1826 older subset (Rutherford 2025)	48 (Nivo)	Hypo 14.3%	6% (2% G3)	8.2% >G3	32.7% (10.2% ≥G2)	6% nivolumab discontinuation	NRM 6% (vs 16% BV-AVD)	57
Friedberg 2024 (BV-Nivo)	21	—	4.7%	14%	48%	24%	—	54
Torka 2025 (Nivo-AVD older)	39	Hypo 8%; Hyper 3%	3%	5%	18% sensory; 3% motor	—	0	56

The thyroid column combines hypothyroidism and hyperthyroidism (any grade); the regimen is shown beneath each trial name. Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVD, doxorubicin/vinblastine/dacarbazine; BV, brentuximab vedotin; Dox, doxorubicin; DTIC, dacarbazine; G/gr, grade; ICE, ifosfamide/carboplatin/etoposide; irAE, immune-related adverse event; NRM, non-relapse mortality; PN, peripheral neuropathy; RCCEP, reactive cutaneous capillary endothelial proliferation; TRAE, treatment-related adverse event.

Table 5. Selected safety outcomes of anti-PD-1 therapy in relapsed/refractory classical Hodgkin lymphoma.

Trial / Regimen	N	Thyroid (hypo / hyper)	Pneumonitis	Transaminitis (ALT)	Peripheral neuropathy	Discontinuation	Treatment-related death	Ref.
RELAPSED/REFRACTORY — Combination								
Pembro-GVD (Moskowitz 2021)	39	Hypo 8% (developed after hyperthyroidism); Hyper 13% (5/39; G3 in 1)	0% (none reported)	41% any gr; G3 10% (4/39)	—	0% discontinuation; 5% GVD dose reduction	0	40
Pembro-ICE (Bryan 2023)	37	Hypo 0% (none reported); Hyper 0% (none reported)	0% (none reported)	0% hepatitis (none reported)	—	12% serious TRAE related to pembrolizumab	0	41
Nivo + ICE (Mei 2022)	43 enrolled (28 received NICE)	Hypo 3% (G1); Hyper 6% (G1)	— (not separately reported)	26% (mostly G1)	—	0% (no toxicity-related discontinuations)	0	42, 43
RELAPSED/REFRACTORY — Monotherapy								
CheckMate 205 (5-yr)	243	Hypo 14.4%; Hyper 2.5% (No G3)	Total 6.2%; Serious 2.1%; led to discont. 2.9%	—	— (not reported)	9.1% (TRAE)	0	26
KEYNOTE-087 (5-yr)	210	Hypo 14.3%	—	—	—	6.7% (TRAE)	0	27, 28
KEYNOTE-204 (Pembro arm)	148	Hypo 19% (any gr); 0% gr ≥3	11% (any); 4% gr ≥3	G3-4 TRAEs 19.6% overall	1% gr ≥3	13% (TRAE; pneumonitis 6%)	1 (pneumonia)	29
KEYNOTE-204 (BV arm)	152	Hypo 3%; Hyper <1% (none/rare)	3% (any); 1% gr ≥3	G3-4 TRAEs 25% overall	Any-grade neuropathy higher in BV; 3% gr ≥3	16% (TRAE; PN 5%)	0	29
OTHER ANTI-PD-1 AGENTS								
ORIENT-1 (Sintilimab)	96	Hypo 22%; Hyper 1%	13% (3% serious)	10%	1%	3%	0	44
Camrelizumab (Song 2019)	75	Hypo 26.7%	4%	25.3%	—	RCCEP 97.3%; pyrexia 42.7%; gr ≥3 TRAEs 26.7%	0	47
Tislelizumab (3-yr)	70	Hypo 37%	7.1%	20%	—	8.6% AE-related	0 (none reported)	50, 51
Penpulimab	94	Hypo 31.9%; Hyper 11.7%	4.3%	23.4%	—	irAE 54.3%; gr ≥3 irAE 4.3%; gr ≥3 TRAE 26.6%	0	52

The thyroid column combines hypothyroidism and hyperthyroidism (any grade); the regimen is shown beneath each trial name. Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVD, doxorubicin/vinblastine/dacarbazine; BV, brentuximab vedotin; Dox, doxorubicin; DTIC, dacarbazine; G/gr, grade; ICE, ifosfamide/carboplatin/etoposide; irAE, immune-related adverse event; NRM, non-relapse mortality; PN, peripheral neuropathy; RCCEP, reactive cutaneous capillary endothelial proliferation; TRAE, treatment-related adverse event.

Figure 1. Biological Rationale for Anti-PD-1 Therapy in classical Hodgkin Lymphoma.

A. 9p24.1 genomic alterations a foundational genetic event in cHL: Reed-Sternberg cells have copy gains at chromosome 9p24.1 that drives overexpression of PD-L1, PD-L2, JAK2. **B. Reed-Sternberg Cells in Suppressive Microenvironment:** Reed-Sternberg cells surrounded by an abundant but dysfunctional immune infiltrate PD-L1 and PD-L2 engage PD-1 on surrounding T-cells to suppress anti-tumor activity. **1)** MHC Class I loss in ~70–80% of cHL, precludes CD8+ cytotoxicity. 2) EBV positivity in which is present in ~30–40% of cHL provides an additional mechanism for PD-L1 overexpression by which EBV-encoded latent membrane protein 1 (LMP1) drives AP-1 transcription factor activation, which directly increases PD-L1 promoter activity and subsequent overexpression. **C. Effect of anti-PD-1 blockade:** Blockade of PD-1 frees CD4+ T cells to mount a cytokine-driven response leading to indirect tumor killing. This differs from anti-PD-1 activity in solid tumors. ***Figure created in BioRender***.

Figure 2. Treatment considerations with anti-PD-1 therapy.

ASCT, autologous stem cell transplantation; allo-HCT, allogeneic hematopoietic cell transplantation; AVD, doxorubicin/vinblastine/dacarbazine; AYA, adolescent and young adult; BV, brentuximab vedotin; CMR, complete metabolic response; CR, complete response; DTIC, dacarbazine; GVD, gemcitabine/vinorelbine/liposomal doxorubicin; GVHD, graft-versus-host disease; HMA, hypomethylating agent; ICE, ifosfamide/carboplatin/etoposide; IFRT, involved-field radiotherapy; LAG-3, lymphocyte activation gene 3; Nivo, nivolumab; ORR, overall response rate; PD-1, programmed death-1; Pembro, pembrolizumab; PFS, progression-free survival; PN, peripheral neuropathy; PTCy, post-transplant cyclophosphamide; R/R, relapsed/refractory; RT, radiotherapy.

Figure 1. Biological Rationale for Anti-PD-1 therapy in classical Hodgkin Lymphoma

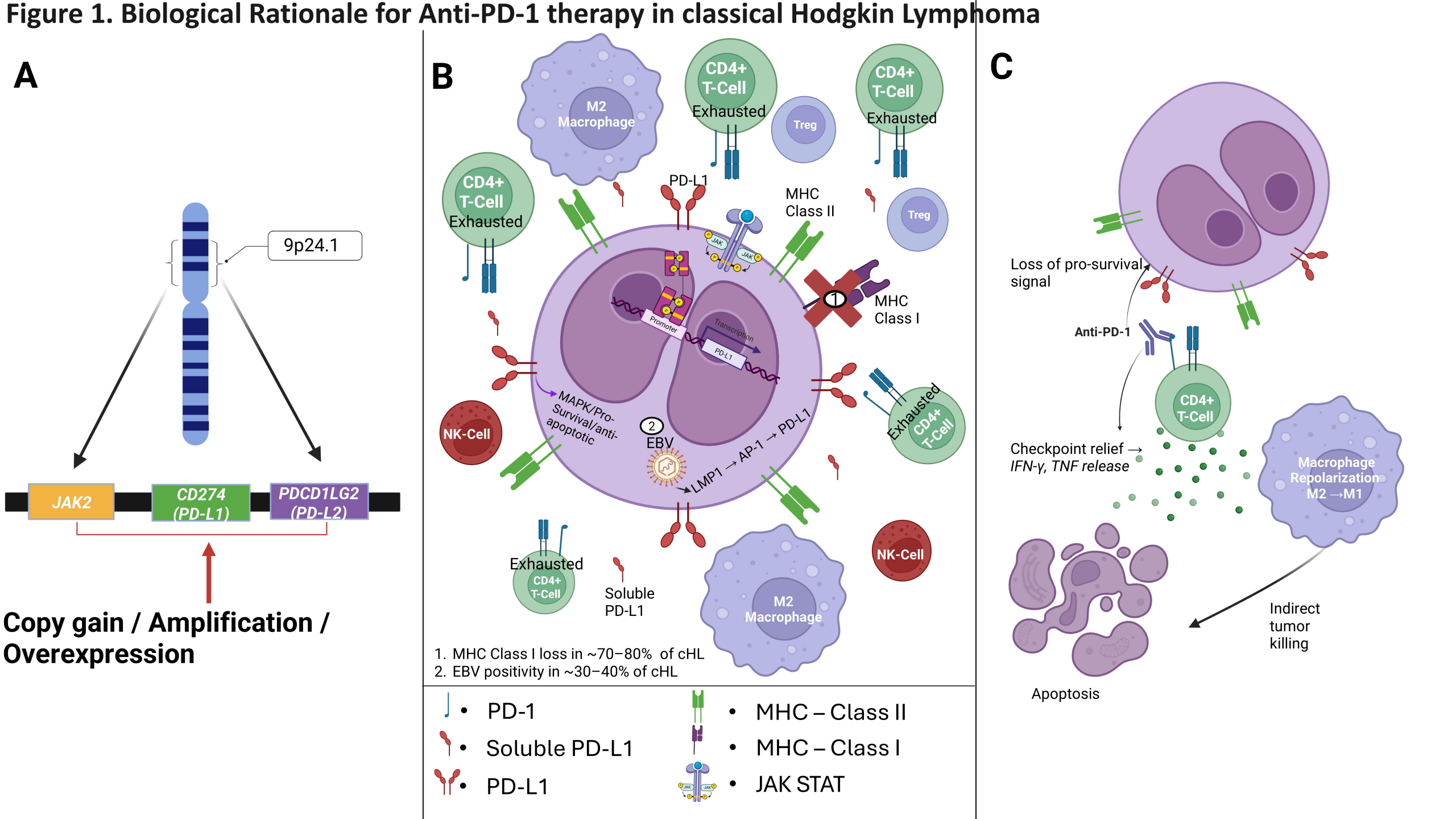

Figure 2. Treatment considerations with anti-PD-1 therapy

FRONTLINE

Advanced stage (III–IV)

- **Preferred: Nivo-AVD ×6 cycles**
  - PFS benefit over BV-AVD; less PN; <1% need RT
  - Avoid bleomycin; monitor thyroid function
  - No interim PET required
- **Alternative: Pembro-AVD ×6 (single-arm phase 2)**
  - ORR 100%, CR 90%; effective at all PD-L1 levels

S1826 (Herrera NEJM 2024; Herrera ASH 2025); Lynch Blood 2023; Allen Blood Adv 2023

Early-stage unfavorable (I–II)

- **Option A: Nivo-AVD ×4 + 30 Gy IFRT**
- **Option B: Nivo lead-in → 2× Nivo-AVD → 2× AVD + 30 Gy IFRT**
  - Both arms: CR ~92%; 3-yr PFS 98–100%
- **Alternative: N-BV-Dox-DTIC ×4 (SGN35-027) — RT-free**

NIVAHL (Bröckelmann 2020); SGN35-027 (Abramson 2026)

Older adults / chemo-ineligible

- **Fit older adults: Nivo-AVD preferred over BV-AVD**
  - Less PN, less early discontinuation in S1826 ≥60-yr subset
- **Chemo-ineligible: BV + Nivolumab**
  - Friedberg 2024: ORR 86%, CR 67%; mPFS not reached
- **Single-agent Nivo or Pembro for very frail patients**

Rutherford JCO 2025; Friedberg 2024; Torka 2025

RELAPSED / REFRACTORY

PD-1–naive, transplant-eligible (preferred)

- **Pembro + GVD ×2–4 cycles → ASCT**
  - CR 95%, ORR 100%; 95% proceed to ASCT
- **Alternative: Pembro + ICE or Nivo ± ICE**
  - CR 86–87%; 2-yr post-ASCT PFS 87–94%
- Consider post-ASCT maintenance: BV+Nivo or Pembro

PD-1–Exposed

- **If brief PD-1 exposure: consider Pembro-GVD or BV-based salvage**
- BV monotherapy or BV + bendamustine
- Conventional salvage chemo (ICE, GVD) → ASCT
- **Enroll on clinical trial when available**

Later lines / checkpoint-refractory

- **Single-agent Nivo or Pembro (durable in selected patients)**
- **Enroll on clinical trial when available**
- LAG-3 combinations: favezelimab+pembro; nivo+relatlimab
- HMA + PD-1 (e.g., decitabine + camrelizumab) for refractory
- Consider allo-HCT in eligible patients (see right column)

Ansell 2023; Armand 2023; Gopal 2025; Armand 2025; Wang 2021

SPECIAL POPULATIONS

Pediatric / AYA

- **Frontline (≥12 yr): Nivo-AVD per S1826; 2-yr PFS 95% in <18 yr**
- R/R: BV+Nivo induction → bendamustine intensification → ASCT
- **Consider transplant-free approach in low-risk relapse:**
  - 4× BV+Nivo ± BV+benda → Nivo maintenance; 93% CMR
- Goal: minimize late effects (RT, anthracyclines, infertility)

Castellino 2023; Harker-Murray 2023; Daw JAMA Oncol 2025

Peri-allogeneic HCT

- **PD-1 before allo-HCT: ↑ GVHD risk**
- Use post-transplant cyclophosphamide (PTCy) for prophylaxis
  - PTCy: gr 3–4 GVHD 5.9% vs ATG 19.6%
- **PD-1 after allo-HCT (relapse): start low-dose**
  - e.g., nivolumab 0.5 mg/kg; close GVHD monitoring
- Multidisciplinary input recommended

Merryman 2021; Herbaux 2017, 2018

Practical considerations across settings

- **Pseudoprogression in ~4–13% — biopsy if uncertain**
- Sarcoid-like reaction at end-of-treatment PET — consider biopsy
- Hypothyroidism in ~14–19% — typically irreversible, monitor TSH
- Pneumonitis 1–6% — most common cause of discontinuation
- Fertility: largely preserved with Nivo-AVD frontline
- Lower-dose strategies under investigation

Chen 2020; Argnani 2026; Bröckelmann 2023; Schneider 2021