Review

Advances in First-Line Treatment of Classical Hodgkin Lymphoma in the Era of Novel Agents

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Advances in First-Line Treatment of Classical Hodgkin Lymphoma in the Era of Novel Agents

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Abstract

Classical Hodgkin lymphoma (cHL) remains one of the most curable hematologic malignancies, with long-term survival exceeding 80–90% in most contemporary series. However, a subset of patients experience primary refractory disease, relapse, treatment related toxicity, or late complications associated with conventional chemotherapy and radiotherapy. Over the last decade, major advances in frontline treatment have transformed the therapeutic landscape of cHL through the incorporation of targeted therapy and immune checkpoint inhibition into first-line regimens. Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, and programmed death-1 (PD-1) inhibitors such as nivolumab and pembrolizumab have significantly improved outcomes in advanced-stage disease and are increasingly being explored in limited-stage settings. The ECHELON-1 trial established BV-AVD as superior to ABVD in advanced-stage disease with improved progression-free survival and overall survival, while the SWOG S1826 study demonstrated superior progression-free survival and reduced toxicity with nivolumab-AVD compared with BV-AVD. These advances have shifted frontline treatment paradigms toward chemotherapy de-escalation, PET-adapted strategies, and immune-based treatment approaches. In parallel, the role of radiotherapy continues to evolve with efforts aimed at minimizing long-term toxicity without compromising cure rates. This review summarizes the biological rationale, pivotal clinical trials, evolving treatment strategies, and future directions in first-line treatment of cHL, with emphasis on evidence-based incorporation of novel agents and practical implications for modern clinical practice.

Keywords: classical hodgkin lymphoma; brentuximab vedotin; nivolumab; pembrolizumab; frontline therapy; PET-adapted treatment

Introduction

Classical Hodgkin lymphoma (cHL) is a highly curable B-cell malignancy characterized by the presence of Reed–Sternberg cells within a rich inflammatory tumor microenvironment (Shanbhag & Ambinder, 2018). Contemporary treatment strategies have resulted in cure rates exceeding 90% in early-stage disease and approximately 80–90% in advanced-stage disease (Ansell, 2015). Nevertheless, treatment-related toxicities including pulmonary toxicity, infertility, secondary malignancies, cardiovascular disease, and neuropathy remain major concerns, particularly in younger patients with long anticipated survival (Ng & Mauch, 2009).

For decades, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) represented the standard frontline regimen for most patients with cHL owing to its favorable balancebetween efficacy and toxicity compared with more intensive regimens such as escalated BEACOPP (Canellos et al., 1992). While escalated BEACOPP improved disease control in selected high-risk patients, its use has been limited by substantial hematologic toxicity, infertility risk, infections, and secondary leukemia (Engert et al., 2012).

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The introduction of positron emission tomography (PET)-adapted treatment represented a major milestone in risk-adapted therapy, enabling treatment escalation or de-escalation based on early metabolic response (Johnson et al., 2016). More recently, targeted therapy and immunotherapy have revolutionized the treatment landscape of cHL. Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, and PD-1 inhibitors including nivolumab and pembrolizumab demonstrated remarkable activity in relapsed/refractory disease and subsequently moved into frontline settings (Younes et al., 2012; Ansell et al., 2015).

The ECHELON-1 study established BV-AVD as a frontline standard in advanced-stage cHL with improvement in progression-free survival and overall survival compared with ABVD (Connors et al., 2018; Ansell et al., 2022). Subsequently, the SWOG S1826 trial demonstrated that nivolumab-AVD achieved superior progression-free survival with a more favorable toxicity profile than BV-AVD, positioning PD-1-based therapy as a potentially new frontline standard (Herrera et al., 2024).

These advances have fundamentally changed the treatment paradigm of cHL and raised important questions regarding optimal sequencing, radiotherapy integration, toxicity management, survivorship, and biomarker-driven treatment selection. This review summarizes current evidence regarding frontline treatment advances in cHL with emphasis on novel-agent integration and evolving therapeutic strategies.

Biological Rationale for Novel Agents in cHL

The biology of cHL uniquely supports susceptibility to both CD30-targeted therapy and immune checkpoint blockade. Reed–Sternberg cells universally express CD30, making it an attractive therapeutic target (Stein et al., 1985). Brentuximab vedotin combines an anti-CD30 monoclonal antibody with the antimicrotubule agent monomethyl auristatin E, allowing selective intracellular delivery of cytotoxic therapy (Younes et al., 2010). In addition, cHL demonstrates marked dependence on immune evasion pathways. Genetic amplification of chromosome 9p24.1 leads to overexpression of PD-L1 and PDL2 on Reed–Sternberg cells, resulting in profound susceptibility to PD-1 inhibition (Green et al., 2010). This biological feature explains the remarkable efficacy of nivolumab and pembrolizumab observed across multiple clinical trials (Ansell et al., 2015). The integration of these agents into frontline therapy has allowed improvement in diseasecontrol while potentially reducing reliance on highly toxic chemotherapy regimens and radiotherapy.

Evolution of Frontline Therapy in Classical Hodgkin Lymphoma

ABVD Era

ABVD became the standard frontline regimen following randomized studies demonstrating superior efficacy and lower toxicity compared with MOPP-containing regimens (Canellos et al., 1992). Long-term outcomes with ABVD showed durable remission rates with relatively acceptable toxicity profiles. However, bleomycin pulmonary toxicity remained a significant limitation, particularly among older patients and those receiving growth factor support (Martin et al., 2005). Furthermore, approximately 20–30% of advanced-stage patients experienced relapse or refractory disease following ABVD (Engert et al., 2010).

Escalated BEACOPP

Escalated BEACOPP improved progression-free survival compared with ABVD in advanced-stage disease, particularly among high-risk patients (Diehl et al., 2003). Longterm follow-up from the German Hodgkin Study Group confirmed superior disease control but at the expense of increased infertility, infections, myelodysplasia, and secondary acute leukemia (Engert et al., 2012). Consequently, many centers adopted PET-adapted strategies aimed at limiting BEACOPP exposurewhile preserving efficacy.

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PET-Adapted Therapy

Interim PET imaging became central to frontline treatment decisions after studies demonstrated strong prognostic significance of early metabolic response (Gallamini et al., 2007). The RATHL trial demonstrated that bleomycin could safely be omitted after negative interim PET following two cycles of ABVD, significantly reducing pulmonary toxicity without compromising outcomes (Johnson et al., 2016). PET-adapted escalation strategies similarly improved outcomes in PET-positive patients through treatment intensification. PET-guided treatment has therefore become standard in modern cHL management and remains essential even in the era of novel agents.

Brentuximab Vedotin in Frontline Therapy

ECHELON-1 Trial

The phase III ECHELON-1 trial represented a major advance in frontline treatment. This study randomized patients with stage III–IV cHL to BV-AVD versus standard ABVD (Connors et al., 2018). BV-AVD demonstrated improved modified progression-free survival compared withABVD. Updated long-term analysis further demonstrated overall survival benefit favoring BV-AVD, with 6-year overall survival rates of 93.9% versus 89.4% for ABVD (Ansell et al., 2022).

Peripheral neuropathy and neutropenia were more common with BV-AVD, although pulmonary toxicity was significantly lower due to bleomycin omission (Connors et al., 2018). The ECHELON-1 trial established BV-AVD as a frontline standard for advanced-stage cHL and marked the first significant survival improvement over ABVD in decades.

BRECADD Study

More recently, the German Hodgkin Study Group HD21 trial evaluated the novel BrECADD regimen (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) compared with escalated BEACOPP in patients with advanced stage cHL (Fuchs et al., 2024).

The study demonstrated that BrECADD achieved superior tolerability with reduced treatment-related morbidity and fewer serious adverse events while maintaining excellent disease control. Importantly, BrECADD was associated with lower hematologic toxicity, reduced infertility risk markers, and fewer treatment discontinuations compared with escalated BEACOPP.

At interim analysis, BrECADD showed non-inferior efficacy with excellent progression free survival outcomes and significantly lower treatment-related toxicity, supporting its role as a potential new intensive-treatment standard for younger fit patients with advanced-stage disease.

Additionally, BrECADD offers the potential advantage of shorter effective treatment duration and reduced cumulative anthracycline exposure compared with traditional escalated BEACOPP approaches, which may translate into lower long-term cardiotoxicity and improved tolerability, particularly in younger patients expected to achieve long-term survivorship (Fuchs et al., 2024).

PD-1 Inhibitors in Frontline Therapy

Nivolumab-AVD and SWOG S1826

The SWOG S1826 trial represented a landmark study in frontline classical Hodgkin lymphoma (cHL) treatment by comparing nivolumab-AVD with BV-AVD in adolescents and adults with advanced-stage disease (Herrera et al., 2024). This large multicenter phase III trial enrolled more than 900 patients with stage III–IV cHL and demonstrated that nivolumab-AVD significantly improved progression-free survival compared with BV-AVD. The 2-year progression-free survival was 92% in the nivolumab-AVD arm versus 83% in the BV-AVD arm (hazard ratio 0.45), representing one of the most favorable frontline outcomes ever reported in advanced stage cHL (Herrera et al., 2024).

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Importantly, the benefit of nivolumab-AVD was consistent across multiple predefined subgroups including older patients, adolescents, and patients with high-risk International Prognostic Score (IPS) features. In addition, the regimen demonstrated lower rates of peripheral neuropathy, febrile neutropenia, and treatment discontinuation compared with BV-AVD.

Another important observation from the study was the reduced reliance on consolidative radiotherapy, with only a very small proportion of patients requiring radiation at the end of therapy, supporting the concept that highly active immunochemotherapy combinations may reduce long-term radiation-associated toxicity.

Furthermore, nivolumab-AVD demonstrated favorable tolerability despite omission of routine growth factor support in many patients, and immune-related adverse events were generally manageable and infrequently led to treatment discontinuation. These findings established PD-1 blockade as a highly effective frontline strategy and suggested that immune-based approaches may outperform antibody-drug conjugate–based therapy in advanced stage cHL. The SWOG S1826 study is now considered practice-changing and has positioned nivolumab-AVD among the preferred frontline regimens in contemporary NCCN and ESMO recommendations for advanced stage cHL.

Pembrolizumab-Based Frontline Strategies

Pembrolizumab has similarly shown promising frontline activity. Early-phase studies evaluating pembrolizumab sequentially or concurrently with AVD demonstrated high complete response rates and durable remissions (Allen et al., 2021). The favorable toxicity profile and impressive efficacy of PD-1 blockade have generated interest in chemotherapy minimization and potentiallychemotherapy-free approaches in selected patients.

Novel Agents in Limited-Stage Disease

The incorporation of novel agents into limited-stage disease remains an active area of investigation. Efforts primarily focus on reducing radiotherapy exposure, improving early PET negativity, and minimizing long-term toxicity.

Several studies evaluating BV or PD-1 inhibitors combined with abbreviated chemotherapy have demonstrated excellent response rates and encouraging progression free survival (Moskowitz et al., 2021).

The phase II BREACH trial evaluated BV-AVD versus ABVD in patients with early stage unfavorable classical Hodgkin lymphoma (cHL), followed by involved node radiotherapy. BV-AVD demonstrated improved PET negativity after two cycles compared with ABVD (82.3% vs 75.4%) and showed excellent 2-year progression-free survival of 97.3%, supporting the activity of BV-based therapy in limited-stage disease (Casadei et al., 2023).

The phase II German Hodgkin Study Group NIVAHL trial evaluated nivolumab combined with AVD using either sequential or concomitant schedules in patients with early-stage unfavorable cHL followed by involved-site radiotherapy. The study demonstrated very high complete remission rates, high PET-negativity rates, and excellent survival outcomes, supporting PD-1 blockade as a promising frontline strategy in limited-stage disease (Brockelman et al., 2020).

Additional early-phase pembrolizumab-based frontline studies have explored sequential pembrolizumab followed by AVD or concurrent pembrolizumab-containing approaches, demonstrating encouraging metabolic response rates and durable short-term disease control. However, these studies remain less mature and continue to be considered investigational in limited-stage disease (Allen et al., 2021).

Together, these studies suggest that BV- and PD-1–based frontline approaches may improve early metabolic response and potentially allow reduction or omission of radiotherapy in carefully selected PET-negative patients. Nevertheless, longer follow-up and randomized phase III studies are needed before radiotherapy omission can be considered standard practice.

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A summary of the pivotal frontline trials evaluating brentuximab vedotin- and PD-1 inhibitor–based strategies in advanced-stage and limited-stage classical Hodgkin lymphoma is presented in Table 1 and Table 2, respectively.

Table 1. Frontline Trials Incorporating Novel Agents in Advanced-Stage.

Trial	Population	Regimen/Comparator	Phase/Status	Key Results/Outcomes
SWOG S1826/CA209-8UT	Stage III–IV cHL, age ≥12 years	Nivolumab + AVD (N-AVD) vs BV + AVD (BV-AVD) ×6 cycles	Phase III; practice-changing	N-AVD significantly improved PFS versus BV-AVD; HR 0.42. Lower treatment discontinuation and fewer serious toxicities. Established N-AVD as a new frontline standard for advanced cHL.
GHSG HD21	Advanced-stage cHL	BrECADD vs escalated BEACOPP	Phase III	BrECADD improved tolerability while maintaining or improving disease control versus eBEACOPP. 4-year PFS reported around 94% in updated analyses.
ECHELON-1	Previously untreated stage III–IV cHL	BV-AVD vs ABVD	Phase III	First frontline novel-agent trial showing durable benefit over ABVD. 6-year OS: 93.9% vs 89.4%; HR 0.59. Sustained PFS advantage with reduced relapse risk.
SGN35-027 (AN+AD cohort)	Untreated advanced-stage cHL	BV + nivolumab + doxorubicin + dacarbazine (vinblastine omitted)	Phase II	ORR approximately 93–95%, CR approximately 88–89%; 2-year PFS around 88%. Demonstrated feasibility of a vinblastine-free regimen.
AHOD1331	Pediatric/AYA high-risk advanced cHL	BV-AVE-PC vs ABVE-PC	Phase III	Addition of BV significantly reduced relapse/event risk; HR approximately 0.41. Important pediatric frontline BV study.

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Trial	Population	Regimen/Comparator	Phase/Status	Key Results/Outcomes
HLHR13	Pediatric advanced/high-risk cHL	BV-containing frontline chemotherapy	Phase II	3-year EFS approximately 97% in advanced pediatric disease.
Older-patient BV studies	Older/unfit untreated advanced cHL	Sequential BV → AVD or BV + dacarbazine	Phase II	High response rates with improved tolerability for elderly patients; not considered standard for fit younger patients.

Table 2. Frontline Trials Incorporating Novel Agents in Limited-Stage cHL.

Trial	Population	Regimen/Comparator	Phase/Status	Key Results/Outcomes
NIVAHL	Early-stage unfavorable cHL	Sequential or concomitant nivolumab + AVD followed by radiotherapy	Randomized Phase II	CR rates approximately 90–94%; 12-month PFS 98–100%. Long-term follow-up demonstrated excellent durability with minimal progression events.
BREACH	Early-stage unfavorable cHL	BV-AVD vs ABVD followed by involved-node RT	Randomized Phase II	PET-negative rate after 2 cycles significantly higher with BV-AVD (~82%). Demonstrated improved early metabolic response and excellent 2-year PFS.
RADAR	Early-stage favorable cHL	PET-adapted BV-based strategy with omission of radiotherapy in selected patients	Phase II	Demonstrated high PET-negativity rates and feasibility of response-adapted radiotherapy reduction strategies with encouraging progression-free survival outcomes.
SGN35-027 (early-stage cohort)	Early-stage cHL	BV + nivolumab + doxorubicin + dacarbazine	Phase II	ORR approximately 95%, CR approximately 92%. Suggested highly active chemotherapy de-escalated approach.

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Trial	Population	Regimen/Comparator	Phase/Status	Key Results/Outcomes
Pilot BV-AVD limited-stage studies	Favorable/unfavorable early-stage cHL	BV-AVD ± radiotherapy	Early phase studies	Demonstrated high PET-negativity and encouraging short-term PFS, supporting ongoing de-escalation strategies.

Toxicity and Survivorship Considerations

As cure rates improve in classical Hodgkin lymphoma (cHL), survivorship considerations have become increasingly important, particularly because many patients are adolescents and young adults expected to live for decades after treatment completion. Consequently, modern frontline treatment strategies aim not only to maximize cure rates but also to minimize long-term treatment-related morbidity and preserve quality of life (Ng & Mauch, 2009).

Historically, conventional chemotherapy and radiotherapy were associated with substantial late toxicities including pulmonary injury, infertility, secondary malignancies, cardiovascular disease, and endocrine dysfunction. Bleomycin-induced pulmonary toxicity remains one of the most clinically significant acute and chronic toxicities associated with ABVD, particularly in older patients and those receiving granulocyte colony-stimulating factor support (Martin et al., 2005). The omission of bleomycin in BV-AVD and PD-1–based regimens therefore represents an important advancement in reducing pulmonary complications.

However, BV-containing regimens introduce different toxicity considerations, most notably peripheral neuropathy. In ECHELON-1, peripheral neuropathy occurred significantly more frequently with BV-AVD compared with ABVD, although many cases improved or resolved with time and dose modification (Connors et al., 2018; Ansell et al., 2022). The cumulative neurotoxicity associated with repeated BV exposure is particularly relevant when BV is incorporated into both frontline and salvage settings.

Immune checkpoint inhibitors are associated with a distinct spectrum of immune-related adverse events (irAEs). In the SWOG S1826 trial, nivolumab-AVD demonstrated favorable overall tolerability compared with BV-AVD, with lower rates of febrile neutropenia and neuropathy (Herrera et al., 2024). Nevertheless, PD-1 blockade may cause immune-mediated toxicities including thyroid dysfunction, hepatitis, pneumonitis, colitis, adrenal insufficiency, hypophysitis, and dermatologic reactions. Although most irAEs are manageable with corticosteroids and treatment interruption, long-term endocrine dysfunction may persist permanently in some patients.

Fertility preservation remains another major survivorship consideration, particularly in younger patients. Escalated BEACOPP has historically been associated with substantial gonadal toxicity and infertility risk due to high cumulative alkylator exposure (Engert et al., 2012). Novel-agent–based approaches such as BV-AVD, nivolumab-AVD, and BrECADD may potentially reduce infertility risk through chemotherapy de-escalation and lower cumulative exposure to gonadotoxic agents, although long-term fertility data remain limited.

Cardiovascular toxicity also remains an important issue due to anthracycline exposure and historical mediastinal radiotherapy. Long-term survivors of cHL have increased risks of coronary artery disease, valvular heart disease, heart failure, and stroke decades after treatment (Ng & Mauch, 2009). Emerging strategies aimed at reducing cumulative anthracycline exposure, such as PET-adapted therapy and BrECADD-based approaches, may help reduce long-term cardiotoxicity.

Secondary malignancies remain a significant concern among long-term survivors, especially following combined modality therapy involving radiotherapy and alkylator intensive chemotherapy. Breast cancer, lung cancer, thyroid cancer, and therapy-related myeloid neoplasms are among the

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most recognized late complications. Efforts to reduce radiation exposure in limited-stage disease and minimize chemotherapy intensity represent major priorities in contemporary treatment design.

Another increasingly important aspect of survivorship is patient-reported quality of life. Fatigue, neuropathy, cognitive dysfunction, sexual health concerns, psychosocial stress, and financial toxicity may persist long after treatment completion. Incorporation of survivorship-focused care pathways, rehabilitation, fertility counseling, vaccination strategies, cardiovascular screening, and psychosocial support is becoming an essential component of comprehensive cHL management.

Ultimately, future frontline treatment strategies in cHL will likely focus on achieving the optimal balance between maximizing cure rates and minimizing long-term toxicity. Biomarker-driven therapy selection, PET-adapted treatment, chemotherapy reduction strategies, and incorporation of highly effective immunotherapy-based approaches may collectively improve survivorship outcomes while preserving the excellent disease control achieved in modern cHL therapy.

Future Directions

The therapeutic landscape of classical Hodgkin lymphoma (cHL) continues to evolve rapidly, with ongoing research increasingly focused on improving precision medicine approaches while minimizing long-term treatment-related toxicity. Emerging strategies include biomarker-driven therapy selection using molecular and immunologic profiling to better identify patients most likely to benefit from specific frontline regimens. Circulating tumor DNA (ctDNA) monitoring is also gaining significant interest as a potential tool for early response assessment, minimal residual disease detection, and prediction of relapse before radiographic progression becomes clinically evident. In parallel, chemotherapy minimization strategies are being explored through incorporation of highly active immunotherapy-based regimens aimed at reducing cumulative exposure to anthracyclines, alkylating agents, and bleomycin. Response-adapted immunotherapy approaches using interim PET imaging and biologic markers may further personalize treatment intensity according to individual disease biology and treatment response.

Additionally, multiple studies are evaluating radiotherapy omission strategies in selected PET-negative patients in an effort to decrease long-term cardiovascular toxicity and secondary malignancies. Beyond PD-1 blockade, novel immunotherapeutic approaches including bispecific antibodies and cellular therapies are also under active investigation and may eventually expand treatment options across different stages of disease. Collectively, these advances reflect a broader shift toward individualized treatment strategies in cHL that aim to maximize cure while optimizing long-term survivorship and quality of life.

Conclusion

Frontline treatment of classical Hodgkin lymphoma has undergone major transformation with the integration of brentuximab vedotin and PD-1 inhibitors into first-line therapy. BV-AVD established the first survival advantage over ABVD in advanced-stage disease, while nivolumab-AVD demonstrated superior progression-free survival with improved tolerability compared with BV-AVD. PET-adapted therapy remains central to treatment optimization, while novel-agent incorporation continues to evolve in both advanced-stage and limited-stage disease. Future therapeutic strategies will likely focus on chemotherapy reduction, biomarker driven approaches, and survivorship optimization while preserving the exceptional cure rates achieved in cHL.

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