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New Developments in the Front-line Treatment of Advanced Stage Classic Hodgkin Lymphoma: A Canadian Perspective

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Introduction

Classic Hodgkin lymphoma (cHL) is highly curable, with excellent outcomes achieved through decades of treatment refinement. Recent years have witnessed a paradigm shift in the management of patients with advanced stage disease, driven by the integration of novel therapies into front-line treatment. Minimizing long-term complications remains an important objective, especially for patients in the adolescent/young adult (AYA) age group. Herein, we summarize the latest developments in the treatment of advanced stage cHL through a Canadian lens, focusing on recent clinical trials that have reshaped the therapeutic landscape.

Definition of Advanced Stage in cHL

The definition of advanced stage has varied widely across guidelines and clinical trials worldwide, with potential downstream funding implications. The National Comprehensive Cancer Network (NCCN) and European Organization for Research and Treatment of Cancer (EORTC) define advanced stage as stage 3–4, while the German Hodgkin Study Group (GHSG) also includes stage 2B with risk factors (large mediastinal mass >0.33 of the maximum transverse thoracic diameter on chest X-ray [CXR] and/or extranodal disease) (**Table 1**). In the RATHL study, advanced stage also included high-risk stage 2, defined as stage 2B or 2A with adverse features (bulky disease >0.33 of transthoracic diameter or >10 cm elsewhere; ≥3 involved nodal sites).[1] Similarly, the Children's Oncology Group (COG) AHOD1331 Phase 3 trial evaluated upfront brentuximab vedotin (BV-AVEPC) with ABVEPC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) in patients aged 2–21 years with advanced stage disease, and included stage 2B with large mediastinal mass (>0.33 of the maximum transverse thoracic diameter on CXR or continuous nodal aggregate >6 cm in other sites), but excluded stage 3A.[2] Finally, at BC Cancer, we define advanced stage as 2B, 3, 4, and stage 1 or 2 with bulky mass (≥10 cm in any dimension) or disease determined to be too extensive to encompass in a radiotherapy field.

Evolution of Treatment Strategies for Advanced Stage cHL: From ABVD to PET-adapted Approaches

For many years, the standard front-line therapy for advanced stage cHL was the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine). ABVD has demonstrated high efficacy, with cure rates approaching 80%, though failure can occur in 20–30% of patients, and bleomycin-associated pneumonitis remains a concern.[1,3-9] Dose intensive escBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has demonstrated improved progression-free survival (PFS) but not overall survival (OS) compared with ABVD, and is associated with long-term toxicity, including secondary malignancies and infertility.[3,4] Early studies with positron emission tomography (PET) scanning suggested that those with a PET2-positive scan have poor outcomes (PFS: 13–28%) if ABVD is continued.[8,10] Thus, several PET-adapted studies have investigated dose escalation (i.e., to escBEACOPP) if PET2-positive[1,11,12] and de-escalation (omission

	EORTC/LYSA	GHSG	COG	NCCN	RATHL	BC Cancer
Early/limited stage						
Risk factors	Large mediastinal mass[a], age ≥50 years, elevated ESR (>50 mm/h without B symptoms, >30 mm/h with B symptoms, involvement of ≥4 supradiaphragmatic nodal areas	Large mediastinal mass[b], extranodal disease, elevated ESR (>50 mm/h without B symptoms, >30 mm/h with B symptoms), involvement of ≥3 nodal areas on both sides of the diaphragm		Bulky disease[d], elevated ESR ≥50 mm/h, B symptoms, involvement of ≥4 nodal sites	Bulky disease[d], ≥3 nodal sites	
Early favourable	Stage 1–2 without risk factors	Stage 1-2 without risk factors	Stage 1A, 2A	Stage 1–2 without risk factors		
Early unfavourable	Stage 1–2 with ≥1 risk factor	Stage 1-2A with ≥1 risk factor, 2B with elevated ESR or ≥3 nodal areas or both	Stage 1A/ 2A with bulky disease[c] ± extranodal disease (E), 1B/2B±E,3A±bulky±E	Stage 1–2 with ≥1 risk factor		
Limited stage						Stage 1, 2A, non-bulky (<10cm)
Advanced stage						
Advanced	Stage 3–4	Stage 2B with large mediastinal mass and/or extranodal disease Stage 3–4	Stage 2B bulky[c] Stage 3B, 4	Stage 3–4	Stage 2A with risk factors Stage 2B Stage 3–4	Stage 2B Bulky mass[e] (≥10 cm) Stage 3–4

Table 1. Definitions of risk and stage groups in clinical trials and practice guidelines in cHL; *courtesy of Jowon L. Kim, MD and Kerry J. Savage, MD.*

B symptoms: fever, drenching night sweats, unexplained weight loss >10% of baseline body weight over 6 months.

Abbreviations: cHL: classic Hodgkin lymphoma; **COG:** Children's Oncology Group; **ESR:** erythrocyte sedimentation rate; **EORTC:** European Organization for Research and Treatment of Cancer; **GHSG:** German Hodgkin Study Group; **LYSA:** Lymphoma Study Association; **NCCN:** National Comprehensive Cancer Network; **RATHL:** Risk-adapted therapy in Hodgkin lymphoma.[1]

a: mediastinum to thoracic ratio >0.35;
b: mediastinum to thoracic ratio >0.33;
c: mediastinal mass >0.33 thoracic diameter, extramediastinal nodal aggregate >6 cm in longest transverse diameter;
d: mediastinum to thoracic ratio >0.33 or >10 cm elsewhere;
e: also includes rare stage 1 with bulky mass.

of bleomycin from ABVD[1] and omission of consolidative radiotherapy (RT) in those with bulky disease[13-16]) if PET2-negative. An alternate approach is to start with escBEACOPP and de-escalate to ABVD if PET2-negative (AHL2011 study; **Table 2**).[17] Since the RATHL study demonstrated comparable PFS with PET2-guided omission of bleomycin[1], this practice has been widely adopted globally. Although subsequent studies (mostly real-world analyses) have demonstrated a higher 2–5 year PFS of 38–64% in PET2-positive patients who continued on ABVD[18-21], PET2-guided dose escalation to escBEACOPP appears to result in a higher PFS of 60-66% (with limitations of cross-trial comparison), but with similar OS.[11,12,22] Thus, with uncertainty of benefit and toxicity concerns with escBEACOPP, practices vary. With the brentuximab vedotin containing alternate BrECADD demonstrating improved efficacy and safety (**Table 3**), use of escBEACOPP will likely diminish.

Integration of Novel Agents in the Front-line Treatment of Advanced Stage cHL

Brentuximab Vedotin (BV)-AVD and Other BV-containing Front-line Regimens

Brentuximab vedotin (BV), an antibody-drug conjugate targeting CD30, initially demonstrated efficacy in a pivotal Phase 2 trial in patients with relapsed/refractory cHL after autologous stem cell transplant, with an overall response rate (ORR) of 75% and a complete response (CR) rate of 34%.[27] The ECHELON-1 trial compared BV-AVD (BV, doxorubicin, vinblastine, and dacarbazine) to ABVD in patients ≥18 years with stage 3–4 cHL.[7] The modified PFS, which included use of subsequent therapy for incomplete response (defined as Deauville [D] score 3–5) by blinded review, was superior for BV-AVD (2-year modified PFS: 82.1% vs. 77.2%; hazard ratio [HR]: 0.77, 95% confidence interval [CI]: 0.6–0.98).[24] However, in subgroup analysis, benefit was confined to those with stage 4 disease only, which led to initial approval restricted to stage 4 by Health Canada and the European Medicines Agency (EMA). However, with longer follow-up, 5-year PFS benefit was observed in stage 3 and 4 (82.2% vs. 75.3%; HR: 0.68, 95% CI: 0.53–0.87)[18], and subsequent 6-year OS benefit was demonstrated in the intention-to-treat population (93.9% vs. 89.4%; HR: 0.59, 95% CI: 0.40-0.88).[7] This resulted in expanded approval to stage 3 by the EMA in October 2023 and endorsement by Canada's Drug Agency (CDA) in September 2024. Simultaneously, the pediatric regimen BV-AVEPC was CDA endorsed in those aged 2–21 years.[2]

Other upfront BV-containing regimens have demonstrated significant benefit in patients with high-risk stage 2 disease (**Table 2**). The landmark GHSG Phase 3 HD21 trial compared BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) and escBEACOPP in patients with advanced stage cHL aged 18–60 years, with two co-primary endpoints (superiority in safety/treatment-related morbidity, and non-inferiority in efficacy/PFS).[26] The omission of vincristine allowed for a higher dose of BV (1.8 mg/kg) in this regimen compared to BV-AVD (1.2 mg/kg). Following results from HD18, a trial amendment introduced PET2-guided treatment, with patients receiving 4 cycles if PET2-negative (D1-3) vs. 6 cycles if PET2-positive (D4-5). PET2-negative status was lower than in other trials (64%), which may highlight a greater frequency of false positives with this regimen. Consolidative RT was recommended in those with end-of-treatment (EOT) PET-positive residual disease and administered in 15% of the escBEACOPP group and 14% of the BrECADD group. BrECADD demonstrated significantly lower treatment-related morbidity (42% vs. 59%; p<0.0001), driven mostly by reduced hematologic toxicity. Although the study was designed to demonstrate non-inferiority for PFS, a superior 4-year PFS was demonstrated (94.3% vs. 90.9%; p=0.035), with similar OS (98.6% vs. 98.2%). Notably, patients <40 years of age derived the greatest benefit (HR: 0.53) from BrECADD, as did those with stage 2 disease (HR: 0.35), which was likely the predominant stage in this younger age group. Study follow-up remains short to evaluate for long-term complications; however, gonadal function recovery by follicle-stimulating hormone levels was observed in 95% of patients with BrECADD vs. 72.5% with escBEACOPP in women and 86% vs. 39% in men, respectively. Successful childbirths were observed, with 62 births among 59 couples with BrECADD, and 46 births among 40 couples with escBEACOPP. BRECADD is currently under CDA review.

The pediatric trial AHOD1331 included patients aged 2–21 years with "high-risk" cHL (**Table 2**), who were randomized to 5 cycles of BV-AVEPC (BV replacing bleomycin) or

Trial	Advanced stage definition	Treatment arms	Median follow-up	PFS	OS	Comment
PET2-adapted studies						
RATHL[1,22] n=1,201	Stage 2B-4, 2A with risk factors Age 18–79y	After 2ABVD: PET2-neg (D1–3): 4ABVD vs. 4AVD PET2-pos (D4–5): BEACOPP#	3.4y, 7.3y	**All:** 7y PFS 78.2% **PET2-neg:** • 3y PFS 85.7% with ABVD vs. 84.4% with AVD • 7y PFS 81% with ABVD vs. 79.2% with AVD **PET2-pos:** • 3y PFS 67.5% • 7y PFS 65.9%	**All:** 7y OS 91.6% **PET2-neg:** • 3y OS 97.2% with ABVD vs. 97.6% with AVD • 7y OS 93.2% with ABVD vs. 93.5% with AVD **PET2-pos:** • 3y OS 87.8% • 7y OS 83.2%	Led to widespread practice of dropping bleomycin if PET2-neg post ABVD. The practice of PET2-guided dose escalation to BEACOPP varies.
GITIL/FIL HD0607[11,14] n=782	Stage 2B–4 Age 18–60y	After 2ABVD: PET2-neg (D1-3): 4ABVD PET2-pos (D4-5): 4escBEACOPP (+/- R)	3.6y, 5.9y	**All:** 3y PFS 82% **PET2-neg:** • 3y PFS 87% • Bulky (>5 cm) with PET2/EOT PET-neg scan randomized to RT vs. no RT: 6y PFS 92% with RT vs. 90% without RT (p=0.48) **PET2-pos:** • 3y PFS 60% (vs. PET2-neg, p<0.001) • By D score, 3y PFS 73% with D4 vs. 35% with D5 (p<0.001)	**All:** 3y OS 82% **PET2-neg:** • 3y OS 99% • Bulky (>5cm) with PET2/EOT PET-neg scan randomized to RT vs. no RT: 6y OS 99% with RT vs. 98% without RT (p=0.61) **PET2-pos:** • 3y OS 89%	Established that consolidative RT can be omitted in patients with bulky disease (>5 cm) treated with ABVD if PET2 and EOT PET-neg. Subset with 'classic' bulky >10 cm also showed no impact of omission of RT (6y PFS: 89% vs. 86%, p=0.53).
AHL 2011[17,23] n=823	Stage 2B with large mediastinal mass (>33% maximal thoracic diameter), 2BE, 3, 4 Age 16-60y	After 2escBEACOPP: PET2-neg (D1-3): 4escBEACOPP vs. 4ABVD PET2-pos (D4-5): 4escBEACOPP	4.2y, 5.6y	**PET2-neg:** • 5y PFS 87.5% with 6escBEACOPP vs. 86.7% with 2escBEACOPP + 4ABVD (p=0.67) **PET2-pos:** • 5y PFS: 68.2%	**PET2-neg:** • 5y OS 97.7% in both arms, p=0.53 **PET2-pos:** • 5y OS: 92%	Led to practice of starting therapy with escBEACOPP for 2 cycles and de-escalation to ABVD if PET2-neg in some centres.
Trials incorporating frontline brentuximab vedotin or nivolumab						
ECHELON-1[7,24] n=1,334	Stage 3–4 cHL Age ≥18y	6 cycles of BV-AVD vs. ABVD	2.1y, 6.1y	**All:** • 2y modified PFS 82.1% with BV-AVD vs. 77.2% with ABVD (HR: 0.77, 95% CI: 0.6-0.98) • 6y PFS 82.3% with BV-AVD vs. 74.5% with ABVD (HR: 0.68, 95% CI: 0.53-0.86)	**All:** • 2y OS 96.6% with BV-AVD vs. 94.2% with ABVD (HR: 0.73, 95% CI: 0.45-1.18) • 6y OS 93.9% with BV-AVD vs. 89.4% with ABVD (HR: 0.59, 95% CI: 0.4-0.88)	BV-AVD Health Canada approved in 2017 for stage 4 (CDA endorsed 2020). CDA endorsed for stage 3 in 2024.

Trial	Advanced stage definition	Treatment arms	Median follow-up	PFS	OS	Comment
GHSG HD21[26] n=1,500	Stage 3–4, 2B with risk factors (large mediastinal mass ≥1/3 maximal thoracic diameter, 2BE) Age 18–60y	4–6 cycles of BrECADD vs. escBEACOPP PET2-adapted, 4 cycles if PET2-neg and 6 cycles with PET2-pos (D4-5)	4y	**All:** 4y PFS 94.3% with BrECADD vs. 90.9% with escBEACOPP; p=0.035	**All:** 4y OS 98.6% with BrECADD vs. 98.2% with escBEACOPP	BrECADD improved treatment-related morbidity. Greatest PFS benefit in patients <40y (HR: 0.53) and high-risk stage 2B (HR: 0.35). BrECADD currently under CDA review.
AHOD1331[2] n=587	Stage 2B with risk factors (bulky mediastinal mass >1/3 thoracic diameter on x-ray, or extramediastinal mass >6 cm), 3B, 4 Age 2-21y	5 cycles of BV-AVEPC vs. standard ABVEPC Not interim PET-adapted	3.5y	**All:** 3y EFS 92.1% with BV-AVEPC vs. 82.5% with ABVEPC (p<0.001)	**All:** 3y OS 99.3% with BV-AVEPC vs. 98.5% with ABVEPC	BV-AVEPC CDA endorsed in 2024 in ages 2–21y, 2B bulky, 3B, 4. Greatest benefit in 2B bulky (HR: 0.09).
SWOG S1826[25] n=994	Stage 3–4 Age ≥12y	6 cycles of N-AVD vs. BV-AVD Not interim PET-adapted	2.1y	**All:** 2y PFS 92% with N-AVD vs. 83% with BV-AVD (HR: 0.45, 95% CI: 0.30–0.65)	**All:** 2y OS 99% with N-AVD vs. 98% with BV-AVD (HR: 0.39, 95% CI: 0.15–1.03)	N-AVD a new standard in stage 3–4. Striking results in older adults ≥60y. Extrapolated to early unfavourable disease (with RT) in NCCN guidelines. CDA endorsed June 2025, funding approved.

Table 2. Select clinical trials in advanced stage cHL leading to practice changes in Canada; *courtesy of Jowon L. Kim, MD and Kerry J. Savage, MD.*

#: Either 6 cycles BEACOPP14 (if PET-negative after 4 cycles) or 4 cycles of escBEACOPP (if PET-negative after 3 cycles). Salvage if interim PET-positive after switching to BEACOPP.

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; **ABVEPC:** doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; **BrECADD:** brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; **BV-AVD:** brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; **BV-AVEPC:** brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; **CDA:** Canada's Drug Agency; **CI:** confidence interval; **D:** Deauville; **EOT:** end of treatment; **escBEACOPP:** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; **HR:** hazard ratio; **N-AVD:** nivolumab, doxorubicin, vinblastine, and dacarbazine; **NCCN:** National Comprehensive Cancer Network; **Neg:** negative; **OS:** overall survival; **PET:** positron emission therapy; **PET2:** interim PET scan after 2 cycles; **PFS:** progression-free survival; **Pos:** positive; **Pts:** patients; **R:** rituximab; **RT:** radiation therapy; **Y:** years.

Trial	Longest median follow-up	Peripheral neuropathy	Febrile neutropenia	Grade ≥3 toxicity	Treatment-related mortality	Treatment discontinuation due to toxicity	Secondary malignancy	Pregnancy/fertility outcomes
RATHL[1,22]	7.3y	Not reported	5% in ABVD, 2% in AVD, 17% in BEACOPP (G-CSF mandated)	69% with ABVD, 65% with AVD, 81% with BEACOPP	0.9% in ABVD, 0% in AVD, 2% in escBEACOPP	Not reported	**Secondary malignancies at 7y:** 5.1% in ABVD, 5.8% in AVD, 2.5% in escBEACOPP **Secondary AML/MDS:** not observed	Not reported
GITIL/FIL HD0607[11,14]	5.9y	Not reported	Not reported	**Hematologic:** 76% with BEACOPP vs. 30% with ABVD **Infections:** 10% with BEACOPP vs. 1% with ABVD **Pulmonary toxicity:** 1% with BEACOPP vs. 2% with ABVD	<1%	Not reported	**Secondary malignancies:** none with 3.6y follow-up, 2% in 5.9y follow up of pts with LNM (all received RT) **Secondary AML/MDS:** not observed	Not reported
AHL 2011[17,23]	5.6y	23% in standard arm vs. 22% in PET-adapted arm	35% in standard arm vs. 23% in PET-adapted arm (G-CSF mandated with escBEACOPP)	**Neutropenia:** 87% with standard arm vs. 90% with PET-adapted arm **Anemia:** 69% with standard arm vs. 28% with PET-adapted arm **Thrombocytopenia:** 66% with standard arm vs. 40% with PET-adapted arm **Infections:** 22% with standard arm vs. 11% with PET-adapted arm	1% in standard arm vs. <1% in PET-adapted arm	7% in standard arm vs. <1% in PET-adapted arm	**Second malignancies:** 3.2% in standard arm, 2.2% in PET-adapted arm **Secondary AML:** 1% in standard arm, 0.5% in PET-adapted arm	**Pregnancies:** 8.5% in 6escBEACOPP, 12.5% in 2escBEACOPP + 4ABVD **Assisted reproductive technology use:** 20.5% in 6escBEACOPP vs. 10.8% in 2escBEACOPP + 4ABVD
ECHELON-1[7,24]	6.1y	29% with BV-AVD vs. 17% with ABVD	**Serious AE of febrile neutropenia, sepsis, or infections:** 24% with BV-AVD (G-CSF mandated) vs. 9% with ABVD	83% with BV-AVD vs. 66% with ABVD	1% in both arms	13% with BV-AVD vs. 16% with ABVD	**Secondary cancer:** 3.5% with BV-AVD vs. 4.9% with ABVD **Secondary AML/MDS:** 2 in each arm	**Pregnancies:** 114/82 couples with BV-AVD and 81/61 couples with ABVD
GHSG HD21[26]	4y	43% with BrECADD vs. 53% with escBEACOPP	28% with BrECADD vs. 21% with escBEACOPP	**Febrile neutropenia:** 28% with BrECADD vs. 21% with escBEACOPP **Infections:** 20% with BrECADD vs. 19% with escBEACOPP **Organ toxicity grade ≥3:** 19% with BrECADD vs. 17% with escBEACOPP **Grade 4 hematologic AE or infection:** 31% with BrECADD vs. 52% with escBEACOPP	**Treatment-related mortality:** <1% with both arms **Treatment-related morbidity:** 42% with BrECADD vs. 59% with escBEACOPP; p<0.0001	2% with BV vs. 18% with vincristine	**Secondary cancer:** 3% with BrECADD vs. 2% with escBEACOPP **Secondary AML/MDS:** <1% with BrECADD, 1% with escBEACOPP	**Gonadal function recovery (FSH level):** 95% with BrECADD vs. 72.5% with escBEACOPP in women; 86% with BrECADD vs. 39% with escBEACOPP in men **Successful childbirths:** 62/59 with BrECADD, 46/40 with escBEACOPP

Trial	Longest median follow-up	Peripheral neuropathy	Febrile neutropenia	Grade ≥3 toxicity	Treatment-related mortality	Treatment discontinuation due to toxicity	Secondary malignancy	Pregnancy/fertility outcomes
AHOD1331[2]	3.5y	**Grade ≥2:** 19% in both arms	31% with with BV-AVEPC vs. 33% with ABVEPC	74% with BV-AVEPC vs. 68% with ABVEPC	None	Not reported **Dose modifications:** 13% with BV-AVEPC vs. 23% with ABVEPC	**Secondary cancers:** 1 in both arms (<1%) **Secondary AML:** 1 in BV-AVEPC arm	Not reported
SWOG S1826[25]	2.1y	29% with N-AVD vs. 56% with BV-AVD	**Febrile neutropenia:** 6% with N-AVD vs. 7% BV-AVD (GCSF mandated) **Neutropenia:** 56% with N-AVD vs. 34% BV-AVD **G-CSF use:** 56% with N-AVD (not mandated) vs. 97% with BV-AVD (mandated) **Sepsis:** 2% with N-AVD vs. 3% BV-AVD	**Febrile neutropenia:** 6% with N-AVD vs. 7% with BV-AVD **Infections:** 2% with N-AVD vs. 3% with BV-AVD **Neuropathy:** 1% with N-AVD vs. 8% with BV-AVD **LFT elevation:** 7% with N-AVD vs. 8% with BV-AVD **Possible immune-related AE (all grades):** **Thyroid abnormalities:** 10% with N-AVD vs. <1% with BV-AVD **Rash:** 15% in both arms LFT elevation: 38% with N-AVD vs. 76% with BV-AVD	<1% with N-AVD vs. 1% with BV-AVD	9% with nivolumab vs. 22% with BV	Not reported	Not reported

Table 3. Safety outcomes in advanced stage cHL trials; *courtesy of Jowon L. Kim, MD and Kerry J. Savage, MD.*

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; **AE:** adverse event; **ABVEPC:** doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; **AML:** acute myeloid leukemia; **BrECADD:** brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; **BV:** brentuximab vedotin; **BV-AVD:** brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; **BV-AVEPC:** brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; **escBEACOPP:** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; **G-CSF:** granulocyte colony-stimulating factor; **LFT:** liver enzyme; **LNM:** large nodal mass; **MDS:** myelodysplastic syndrome; **N-AVD:** nivolumab, doxorubicin, vinblastine, and dacarbazine; **Neg:** negative; **OS:** overall survival; **PET:** positron emission therapy; **PFS:** progression-free survival; **Pos:** positive; **RT:** radiation therapy; **Y:** years.

standard ABVEPC.[2] Consolidative involved site RT was administered to those with a large mediastinal mass at diagnosis, PET2-positive "slow-responding lesions" (D4-5), and EOT PET-positive (D3-5) lesions, resulting in 53% and 57% receiving RT in the BV and standard arms, respectively. An improved event-free survival (EFS), an endpoint that includes the development of secondary neoplasm, was observed with a 3-year EFS of 92.1% vs. 82.5% (HR: 0.41, 95% CI: 0.25–0.67) in favour of the BV arm, with greater benefit seen in stage 2B bulky disease (HR: 0.09, 95% CI: 0.01–0.69).

Nivolumab (N)-AVD

Reed-Sternberg cells frequently overexpress programmed cell death ligand 1 (PD-L1) and 2 (PD-L2), contributing to immune evasion and making them particularly susceptible to programmed cell death protein 1 (PD-1) blockade. Anti-PD-1 antibodies demonstrated striking efficacy in the relapsed/refractory setting (ORR 64–74%, CR: 12–29%), leading to approval of both pembrolizumab and nivolumab, including in Canada.[27,28,30] The Phase 3 KEYNOTE-204 study confirmed improved PFS (median 13.2 vs 8.3 months, p=0.003) of pembrolizumab over BV in relapsed/refractory cHL (including "transplant ineligible", a definition that includes insufficient response to salvage therapy for those planned for autologous stem cell transplant).[30]

The landmark SWOG S1826 trial compared nivolumab-AVD (N-AVD) to BV-AVD in patients aged ≥12 years with stage 3–4 cHL.[25] At a median follow-up of 2.1 years, N-AVD demonstrated superior PFS compared to BV-AVD (2-year PFS: 92% vs. 83%; HR: 0.45, 95% CI: 0.30-0.65) and similar OS (99% vs. 98%). Importantly, N-AVD showed remarkable efficacy in patients >60 years, with superior 2-year PFS (89% vs. 64%, p=0.001) and OS (96% vs. 85%, p=0.005).[31] N-AVD was better tolerated, and although there was more grade ≥3 neutropenia (48% vs. 26%), febrile neutropenia rates were similar, even though granulocyte colony-stimulating factor (G-CSF) was not mandated in the N-AVD arm (although we would endorse use in this age group regardless).[25] Overall, immune-related adverse events (irAE) were low, with expected hypo/hyperthyroidism more frequent in the N-AVD arm. Consolidative RT to residual metabolically active lesions was allowed if the intent was pre-specified, but not mandated. Excellent outcomes were observed with near elimination of consolidative RT use (0.7% regardless of arm). Minimizing RT use is of particular significance in AYA patients, in whom future secondary cancers and cardiac disease remain a concern. N-AVD is now listed in the NCCN guidelines for stage 3–4 disease. The NCCN guidelines also include both N-AVD (adapted from the Phase 2 study NIVAHL[32]) and BV-AVD (adapted from the Phase 2 study BREACH[33]) for 4 cycles in combination with RT, as treatment options in stage 1/2 unfavourable cHL.[33] Longer follow-up is needed to confirm response durability, long-term side effects, and impact on fertility. N-AVD recently received a positive CDA endorsement in Canada (June 2025) for use in patients ≥12 years of age with stage 3–4 cHL. As of this writing, the CDA endorsed inclusion of high-risk stage 2 patients along with stage 3 and 4 indication and has been funding approved by the pan-Canadian Pharmaceutical Alliance (pCPA) with provinces rolling out their programs over the next few months.

Older Patients with cHL

Older patients with advanced stage cHL have shown inferior outcomes with conventional therapies, due to higher toxicity and more treatment-resistant tumour biology.[35] In a subgroup of older patients (≥60 years) from the ECHELON-1 trial, although not powered for this comparison, there was no improvement in PFS with BV-AVD (5-year PFS 67.1% with BV-AVD vs. 61.6% with ABVD, p=0.44), and it was associated with increased grade ≥3 neuropathy (18% vs 3%), febrile neutropenia (37% vs. 17%), and more dose modifications (80% vs. 71%).[36] Studies have suggested that HL patients ≥70 years have particularly worse outcomes.[35] A Phase 2 study of sequential administration of BV and AVD (i.e., BV x 4, AVD x 6, BV x 2) in patients >60 years demonstrated improved outcomes (2-year PFS: 84%, OS: 93%) and tolerance compared to historical expectations; however, treatment duration is long and neuropathy still a concern.[35,37,38] Preliminary results from a Phase 2 study assessing BrECADD in patients aged 61–75 years with a median follow-up of almost 2 years demonstrated very encouraging results (2-year PFS: 91.5%) and no treatment-related deaths, although febrile neutropenia occurred in 54% of patients.[39] However, this regimen is unlikely to supplant N-AVD given the excellent tolerance and OS advantage over BV-AVD demonstrated in older patients observed in the SWOG1826 study.[31] Treatment

was much better tolerated in the N-AVD arm, with less discontinuation (14% vs. 55%), febrile neutropenia (12% vs. 19%; despite mandated G-CSF with BV-AVD), infections (18% vs. 34%), and neuropathy (33% vs. 68%), also allowing delivery in those aged >80 years.[31,40] With even longer follow-up, similar results were observed in a separate phase 2 study of N-AVD in this age group (3-year PFS 79%, OS 97%).[41]

Canadian Landscape

N-AVD now has CDA endorsement and funding negotiations are complete. Some provinces can already access this regimen for advanced stage patients and fortunately, high-risk stage 2 patients were also included. A recent study from BC Cancer suggests this is highly relevant in the AYA group, as these patients frequently present with high-risk stage 2 disease, and when treated with ABVD, have outcomes similar to stage 3 and 4, and more frequent RT use due to incomplete response.[42] BrECADD is still under CDA review but given the level of evidence, it will also be an available regimen for patients. One remaining question is whether there is a very low-risk group with excellent outcomes with ABVD alone (RATHL approach) given the potential for chronic irAE with PD1 inhibitors observed in melanoma.[43]

New challenges will include personalizing therapy choice, managing novel toxicities, sequencing of therapies in patients with relapsed disease post novel front-line therapies, and ensuring equitable access. As PD-1 inhibitors have been shown to synergize with other therapies, there can be re-induction of response at relapse.[44] BV-based regimens may also be appealing in this setting. In Canada, GDP is the only approved combination in the transplant-eligible population with an ongoing Canadian Cancer Trials Group (CCTG) randomized Phase 2 study comparing GDP to BV-pembrolizumab (NCT05180097). Refinement of conventional PET-based interim response assessment with circulating tumour DNA assessment may aid in selecting patients who may benefit from a more intensive approach or who can have shorter therapy duration.[45] Canadian oncologists and policymakers face complex yet exciting decisions to further refine treatment in advanced stage cHL.

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References

1. Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, Carella A, et al. adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016;374(25):2419–29.
2. Castellino SM, Pei Q, Parsons SK, Hodgson D, McCarten K, Horton T, et al. Brentuximab vedotin with chemotherapy in pediatric high-risk Hodgkin's lymphoma. N Engl J Med. 2022;387(18):1649–60.
3. Federico M, Luminari S, Iannitto E, Polimeno G, Marcheselli L, Montanini A, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi trial. J Clin Oncol. 2009;27(5):805–11.
4. Viviani S, Zinzani PL, Rambaldi A, Brusamolino E, Levis A, Bonfante V, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med. 2011;365(3):203–12.
5. Merli F, Luminari S, Gobbi PG, Cascavilla N, Mammi C, Ilariucci F, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. J Clin Oncol. 2016;34(11):1175–81.
6. Gordon LI, Hong F, Fisher RI, Bartlett NL, Connors JM, Gascoyne RD, et al. Randomized Phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013;31(6):684–91.
7. Ansell SM, Radford J, Connors JM, Długosz-Danecka M, Kim WS, Gallamini A, et al. Overall survival with brentuximab vedotin in Stage III or IV Hodgkin's lymphoma. N Engl J Med. 2022;387(4):310–20.
8. Gallamini A, Barrington SF, Biggi A, Chauvie S, Kostakoglu L, Gregianin M, et al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. Haematologica. 2014;99(6):1107–13.
9. Biggi A, Gallamini A, Chauvie S, Hutchings M, Kostakoglu L, Gregianin M, et al. International validation study for interim PET in ABVD-treated, advanced-stage Hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. J Nucl Med. 2013;54(5):683–90.

10. Gallamini A, Hutchings M, Rigacci L, Specht L, Merli F, Hansen M, et al. Early interim 2-[18F]Fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;25(24):3746–52.
11. Gallamini A, Tarella C, Viviani S, Rossi A, Patti C, Mulé A, et al. early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 Trial. J Clin Oncol. 2018;36(5):454–62.
12. Stephens DM, Li H, Schöder H, Straus DJ, Moskowitz CH, LeBlanc M, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. Blood. 2019;134(15):1238–46.
13. Ricardi U, Levis M, Evangelista A, Gioia DM, Sacchetti GM, Gotti M, et al. Role of radiotherapy to bulky sites of advanced Hodgkin lymphoma treated with ABVD: final results of FIL HD0801 trial. Blood Adv. 2021;5(21):4504–14.
14. Gallamini A, Rossi A, Patti C, Picardi M, Romano A, Cantonetti M, et al. Consolidation radiotherapy could be safely omitted in advanced Hodgkin lymphoma with large nodal mass in complete metabolic response after ABVD: final analysis of the randomized GITIL/FIL HD0607 trial. J Clin Oncol. 2020;38(33):3905–13.
15. LaCasce AS, Dockter T, Ruppert AS, Kostakoglu L, Schöder H, Hsi E, et al. positron emission tomography–adapted therapy in bulky stage I/II classic Hodgkinlymphoma: CALGB 50801 (Alliance). J Clin Oncol. 2022;41(5):1023-34.
16. Kim JL, Villa D, Tonseth RP, Gerrie AS, Wilson D, Benard F, et al. Long-term follow-up of bulky classic Hodgkin lymphoma managed with ABVD and PET-guided RT demonstrates excellent outcomes in PET-negative cases. Br J Haematol. 2025;206(1):167–71.
17. Casasnovas RO, Bouabdallah R, Brice P, Lazarovici J, Ghesquieres H, Stamatoullas A, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2019;20(2):202–15.
18. Straus DJ, Długosz-Danecka M, Connors JM, Alekseev S, Illés Á, Picardi M, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021;8(6):e410–21.
19. Zheng S, Gupta K, Goyal P, Nakajima R, Michaud L, Batlevi CL, et al. outcomes of patients with positive interim positron emission tomography (PET) continuing ABVD in the clinical setting. Cancers. 2023;15(6):1760.
20. Hamid MS, Rutherford SC, Jang H, Kim S, Patel K, Bartlett NL, et al. outcomes among classical Hodgkin lymphoma patients after an interim PET scan: a real-world experience. Clin Lymphoma Myeloma Leuk. 2022;22(7):e435–42.
21. Kim JL, Villa D, Tonseth RP, Gerrie AS, Wilson D, Benard F, et al. Evaluation of long-term outcomes in advanced stage classic Hodgkin lymphoma treated with ABVD using a PET-guided strategy. HemaSphere. 2025;9(S1):1135–6.
22. Luminari S, Fossa A, Trotman J, Molin D, d'Amore F, Enblad G, et al. long-term follow-up of the response-adjusted therapy for advanced Hodgkin lymphoma trial. J Clin Oncol. 2024;42(1):13–8.
23. Casasnovas RO, Bouabdallah R, Brice P, Lazarovici J, Ghesquieres H, Stamatoullas A, et al. Positron emission tomography–driven strategy in advanced Hodgkin lymphoma: prolonged follow-up of the AHL2011 Phase III Lymphoma Study Associationstudy. J Clin Oncol. 2022;40(10):1091–101.
24. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018;378(4):331–44.
25. Herrera AF, LeBlanc M, Castellino SM, Li H, Rutherford SC, Evens AM, et al. Nivolumab+AVD in advanced-stage classic Hodgkin's lymphoma. N Engl J Med. 2024;391(15):1379–89.
26. Borchmann P, Ferdinandus J, Schneider G, Moccia A, Greil R, Hertzberg M, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024;404(10450):341–52.
27. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol. 2017;35(19):2125–32.
28. Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, et al. Nivolumab for relapsed/refractory classic Hodgkin Lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm Phase II CheckMate 205 trial. J Clin Oncol. 2018;36(14):1428–39.
29. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30(18):2183–9.
30. Kuruvilla J, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, Johnson NA, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. Lancet Oncol. 2021;22(4):512–24.
31. Rutherford SC, Li H, Herrera AF, LeBlanc M, Ahmed S, Davison K, et al. Nivolumab-AVD Versus brentuximab vedotin–AVD in older patients with advanced-stage classic Hodgkin lymphoma enrolled on S1826. J Clin Oncol. 2025;0(0):JCO-25-00204.

32. Bröckelmann PJ, Bühnen I, Meissner J, Trautmann-Grill K, Herhaus P, Halbsguth TV, et al. Nivolumab and doxorubicin, vinblastine, and dacarbazine in early-stage unfavorable Hodgkin lymphoma: final analysis of the randomized German Hodgkin Study Group Phase II NIVAHL trial. J Clin Oncol. 2023;41(6):1193–9.
33. Fornecker LM, Lazarovici J, Aurer I, Casasnovas RO, Gac AC, Bonnet C, et al. Brentuximab vedotin plus AVD for first-line treatment of early-stage unfavorable Hodgkin lymphoma (BREACH): a multicenter, open-label, randomized, phase II trial. J Clin Oncol. 2023;41(2):327–35.
34. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin lymphoma. [Internet]. National Comprehensive Cancer Network; 2025 [cited 2025 Jun 19]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1439
35. Cheng PTM, Villa D, Gerrie AS, Freeman CL, Slack GW, Gascoyne RD, et al. The outcome of older adults with classic Hodgkin lymphoma in British Columbia. Blood Adv. 2022;6(22):5924–32.
36. Evens AM, Connors JM, Younes A, Ansell SM, Kim WS, Radford J, et al. Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study. Haematologica. 2021;107(5):1086–94.
37. Evens AM, Hong F, Gordon LI, Fisher RI, Bartlett NL, Connors JM, et al. The efficacy and tolerability of ABVD and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American Intergroup Trial E2496. Br J Haematol. 2013;161(1):76–86.
38. Evens AM, Advani RH, Helenowski IB, Fanale M, Smith SM, Jovanovic BD, et al. Multicenter phase II Study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. J Clin Oncol. 2018;36(30):3015–22.
39. Ferdinandus J, Kaul H, Fosså A, Hüttmann A, Keil F, Ko YD, et al. PET-guided brecadd in older patients with advanced-stage classic Hodgkin lymphoma: results of the phase 2 part of the GHSG HD21 trial. Blood. 2024;144(Supplement 1):568.
40. Rutherford SC, Li H, Herrera AF, Leblanc M, Ahmed S, Davison KL, et al. Nivolumab-AVD Is better tolerated and improves progression-free survival compared to Bv-AVD in older patients (aged ≥60 years) with advanced stage Hodgkin lymphoma enrolled on SWOG S1826. Blood. 2023;142:181.
41. Torka P, Feldman T, Savage KJ, Ganesan N, Drill E, Hancock H, et al. Phase II Trial of Nivolumab Plus Doxorubicin, Vinblastine, Dacarbazine as Frontline Therapy in Older Adults With Hodgkin Lymphoma. J Clin Oncol. 2025 Mar 10;43(8):985–93.
42. Kim JL, Villa D, Gerrie AS, Tonseth RP, Wilson D, Benard F, et al. Adolescent/ young adult (aya) patients with high-risk stage 2 classic Hodgkin lymphoma have similar outcomes to stage 3 or 4 with 6 cycles of ABVD chemotherapy. Hematol Oncol. 2025;43(S3):e128_70093.
43. Patrinely JR Jr, Johnson R, Lawless AR, Bhave P, Sawyers A, Dimitrova M, et al. Chronic Immune-Related Adverse Events Following Adjuvant Anti–PD-1 Therapy for High-risk Resected Melanoma. JAMA Oncol. 2021 May 1;7(5):744–8.
44. Armand P, Zinzani PL, Lee HJ, Johnson NA, Brice P, Radford J, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. Blood. 2023 Sep 7;142(10):878–86.
45. Paczkowska J, Kaszkowiak M, LeBlanc M, Stewart C, Herrera AF, Fernando del Castillo JC, et al. Prognostic value of circulating tumor DNA in patients with advanced stage classic Hodgkin lymphoma treated on Swog S1826. Hematol Oncol. 2025;43(S3):e21_70093.