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Review Articles

Classical Hodgkin Lymphoma Today

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Abstract. Classical Hodgkin Lymphoma is one of the most curable neoplasms worldwide, particularly among young adults. Significant advances have been made to maximize treatment efficacy and minimize acute and long-term toxicities, including infertility, cardiovascular complications and secondary primary malignancies. Pretreatment prognostic stratification and *interim* PET response are the cornerstones of personalized treatment strategies. Circulating tumor cell-free DNA represents an investigational tool for genotyping Hodgkin Lymphoma at diagnosis and monitoring treatment response. An abbreviated course of polychemotherapy followed by involved-site/involved nodal radiotherapy continues to be the gold standard in early-stage diseases, while polychemotherapy remains the mainstay for the treatment of advanced-stage disease with or without the incorporation of novel agents, such as the anti-CD30 antibody-drug conjugate brentuximab-vedotin (BV) or the anti-PD1 checkpoint inhibitors (CPI) nivolumab and pembrolizumab. In elderly patients, treatment requires careful adaptation to minimize acute toxicities, often reducing the chemotherapy load or incorporating new targeted therapies. Although consolidation with autologous stem cell transplantation (ASCT) after salvage chemotherapy remains the standard approach in patients with chemosensitive relapsed/refractory cHL, significant improvements in response rate and duration have been achieved when BV and CPI are integrated into salvage regimens prior to ASCT or as post-transplant maintenance. Both classes of drugs are also approved as monotherapy in patients who are transplant-ineligible or have refractory/relapsed disease. Novel therapeutic approaches, including anti-CD30 CAR-T cells and the combination of the anti-CD30/CD16A bispecific antibody AFM13 with preactivated allogeneic cord blood-derived NK cells, are under investigation for patients who have failed the currently approved treatment options.

Keywords: Hodgkin lymphoma; Treatment.

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Introduction. Hodgkin lymphoma (HL) is a B-cell derived neoplasm that accounts for 0.4% of all cancers. According to the Surveillance, Epidemiology and End Results (SEER) Program the annual incidence is 2.5 new cases per 100.000 persons and is more common in young adults and among men than in women. The median age at diagnosis is 39 years and a bimodal incidence distribution has been described as a first peak in young

adults aged 15-35 years and a second peak after 60 years of age. Over the last decades, advances in treatment strategies, largely driven by PET-adapted therapeutic approaches and the introduction of novel agents such as the anti-CD30 antibody-drug conjugate brentuximab-vedotin (BV) and the anti-PD1 checkpoint inhibitors (CPI) nivolumab and pembrolizumab, have significantly improved outcomes. These developments have contributed to a reduction in the annual mortality rate from 0.6 deaths per 100,000 persons at the beginning of 1990s to 0.3 deaths per 100,000 persons during the 2019-2023 period. Today, the expected 5-year survival rate is 89% and HL accounts for only 0.2% of all cancer-related deaths. However, most HL-related deaths occur in elderly patients, with the highest mortality among people aged 75–84 years and a median age at death of 71 years.[1]

Epstein-Barr virus (EBV) infection is causally associated with 25–40% of classical HL cases, particularly among older individuals and those with a personal history of autoimmune disease or immunodeficiency.[2] A significantly increased standardized incidence ratio (SIR) for HL has been reported in several autoimmune diseases, including autoimmune hemolytic anemia, sarcoidosis, systemic lupus erythematosus, immune thrombocytopenic purpura, polyarteritis nodosa, polymyositis/dermatomyositis, Behcet's disease, Sjögren's syndrome, rheumatoid arthritis, polymyalgia rheumatica, and psoriasis.[3] The incidence of HL is 5- to 25-fold higher in people living with HIV (PLWH) and in other immunodeficient conditions, and HL in these populations is almost universally EBV-positive.[4] Although the incidence of HL is increased in PLWH, HL is not considered an acquired immunodeficiency syndrome (AIDS)-defining malignancy and is usually treated as in immunocompetent patients. Currently, evidence supporting a role for other specific environmental risk factors is limited.[2] Registry-based studies have shown that the risk of HL in first-degree relatives of affected individuals ranges from 1.2- to 5.8-fold, with a stronger association observed among siblings than between parents and offspring. Several genome-wide association studies (GWASs) have shown that the risk of HL is strongly influenced by variation in the human leukocyte antigen (HLA) genotype as well as by non-HLA genotype variation.[5,6] In rare cases, HL can arise from the transformation of an underlying low-grade B-cell lymphoma, mostly chronic lymphocytic leukemia, as "Hodgkin-like Richter transformation".[7,8]

Biology and histopathological subtypes. Classical HL (cHL) originates form the neoplastic transformation of germinal center B-cells and is characterized by a paucity of tumor cells within an abundant immunosuppressive microenvironment. The diagnostic Hodgkin/Reed-Sternberg (HRS) cells are large, atypical cells with a defective B-cell program. They lack expression of the B-cell receptor and characteristically express CD30 (100% of cells), CD15 (75–80%), and weakly PAX5 (95%).[7,8] The B cell antigen CD20 can be expressed in up to 20% of cases. HRS cells actively interact with the surrounding microenvironment and create a supportive network of reactive immune cells, which promote cellular proliferation and inhibit apoptosis. Constitutively expressed NF-κB transcription factor, along with clonal EBV infection in a subset of cases, contribute to HRS cell survival and proliferation. Moreover, HRS cells evade antitumor immune responses through multiple mechanisms including expression of PD-1 ligands PD-L1 and PD-L2, often driven by copy-number alterations of chromosome 9p24.1 (**Figure 1**). [9]

Although the relative paucity of malignant cells within cHL tumors has historically hampered its molecular profiling, liquid biopsies have helped to overcome this limitation by enabling noninvasive cHL genotyping.[10-12] Tumor-derived cHL mutations are often enriched in circulating cell-free DNA in blood plasma compared with corresponding bulk tumor specimens. Molecular profiling of liquid biopsies identified recurrent somatic mutations in at least 41 genes as well as recurrent amplifications and deletions. Moreover, two distinct molecular clusters have been described: cluster H1, accounting for approximately 68% of cases, is more common in in younger patients, and is characterized by a higher somatic single nucleotide variant (SNV) mutational burden with enrichment of mutations affecting key signaling pathways, including NF-kB, JAK/STAT, and PI3K. In contrast, cluster H2 tumors representing about 32% of cases, is characterized by a variety of somatic copy number alterations (SCNA) as well as mutations in TP53 and KMT2D (Figure 1). This subgroup shows the typical bimodal age distribution, is enriched for EBV-positive tumors and the mixed cellularity subtype and is associated with higher ctDNA levels and inferior clinical outcomes.[11]

The WHO-HAEM5 and the International Consensus Classification (ICC) retain the histological subtypes of cHL and their diagnostic criteria, which remain unchanged from the WHO-HAEM4: nodular sclerosis (NSCHL), mixed cellularity (MCCHL), lymphocyte-rich (LRCHL), and lymphocyte-depleted (LDCHL). Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) differs biologically and morphologically from cHL, as it lacks HRS cells and is instead characterized by a neoplastic population of larger CD20+, CD30- cells with folded lobulated nuclei known as lymphocytic and histiocytic (L&H) cells. The WHO-HAEM5 continues to list NLPHL under the family of HL, while the ICC changed the term NLPHL into "Nodular Lymphocyte Predominant B-Cell Lymphoma", since the neoplastic cells conserve a functional B-cell program and show a

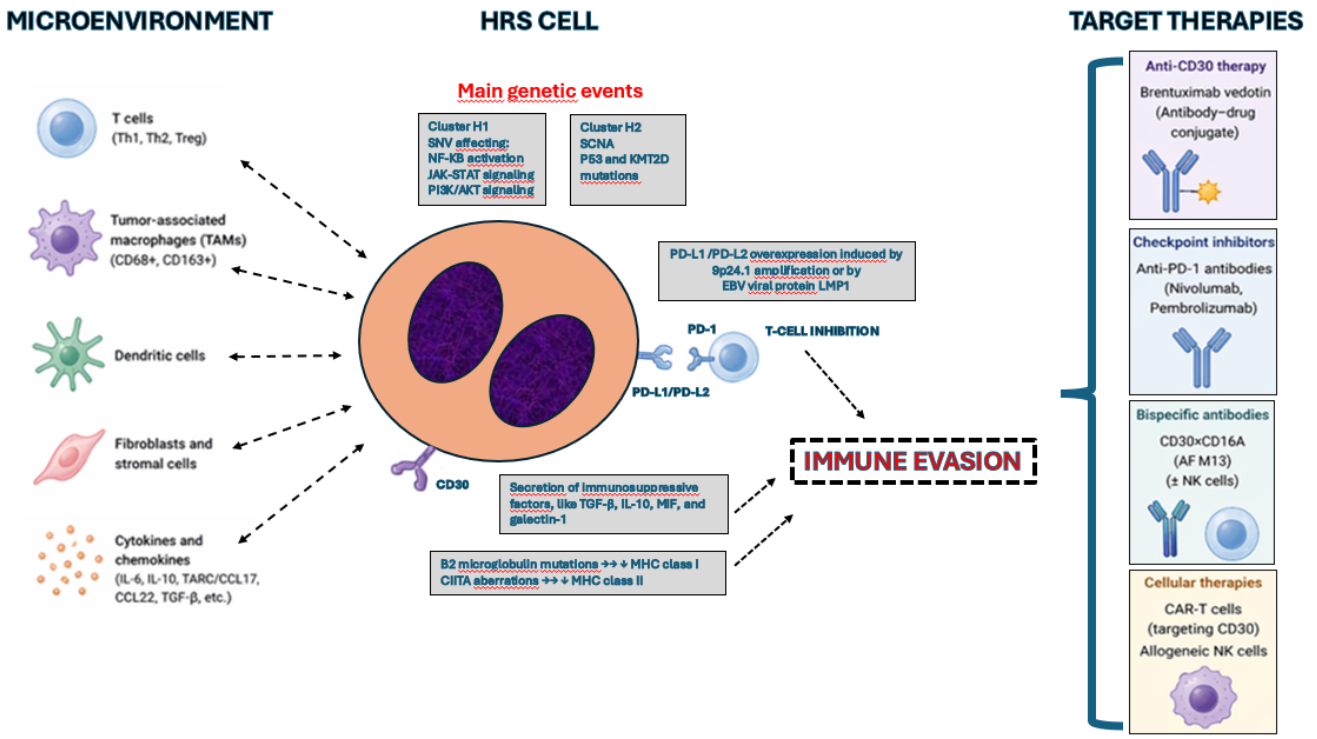

Figure 1. Biology of classical Hodgkin Lymphoma and targeted therapies. HRS cells are characterized by constitutive activation of NF-KB and JAK/STAT pathways and by an immunosuppressive microenvironment. Overexpression of PD-L1/PD-L2, frequently due to 9p24.1 amplification or to viral protein LMP1 in EBV-associated cases, leads to T-cell inhibition. CD30 is expressed on HRS cells, and the PD-L1/PD-L2–PD-1 axis between HRS cells and T lymphocytes is a main target of currently available or emerging investigational therapies.
Abbreviations. HRS: Hodgkin Reed Stemberg; SCNA: somatic copy number aberrations; SNV: single nucleotide variant; PD-1: programmed death 1; PD-L1/PD-L2: programmed death ligand 1 / 2; MHC: major histocompatibility complex; MIF: macrophage migration inhibitory factor; EBV: Epstein Bar Virus; LMP1: latent membrane protein 1.

closer relationship to T-cell/histiocyte-rich large B-cell lymphoma than to cHL.[7,8]

Clinical presentation, staging, and prognosis. HL patients usually present with painless superficial lymphadenopathy, most commonly involving the cervical and supraclavicular sites. Mediastinal involvement occurs in 60% of patients, with 20-25% having mediastinal bulk disease associated with symptoms such as cough, shortness of breath, or even superior vena cava syndrome. Advanced stages occur in 40 % cases with extranodal site involvement, including lung (21%), bone (15%), liver (10%), and bone marrow (9%). Other types of extranodal involvement are uncommon. B-symptoms, such as fevers, drenching night sweats, or unintentional weight loss, occur in 40 % of patients, approximately in 20% of patients with localized disease and 70% with advanced-stage disease. *Pruritus sine materia* can be a presenting symptom in classical HL.

According to the Lugano recommendations, fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) is the preferred staging modality, given its higher accuracy than CT scanning for both nodal and extranodal disease, upstaging the disease in up to 41% of patients and downstaging in up to 10% of patients. However, contrast-enhanced computed tomography (CE-CT) is still useful in the setting of compression or thrombosis of mediastinal vessels and for radiation planning. PET-CT has high sensitivity in detecting bone involvement in patients with HL, therefore eliminating the need for bone marrow biopsy in most cases.[13]

Routine prognostic scores at the diagnosis, including both clinical, imaging and laboratory parameters, differ between early stages (the European Organization for Research and Treatment of Cancer (EORTC) and the German Hodgkin Study Group (GHSG) prognostic systems), and advanced stages (International Prognostic Score (IPS)). The major difference between the EORTC and GHSG classification systems concerns the advanced stage, for which the GHSG system includes stage IIB disease with either bulky mediastinal or extranodal disease alongside stage III/IV diseases (Table 1-2).[14,15]

Using the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines, the Holistic Consortium developed novel prognostic scoring systems for both early (E-HIPI) and advanced (A-HIPI) stages of cHL. These models include continuous variables and provide improved prognostic accuracy compared with traditional prognostication systems (**Table 1-2**).[16,17]

Table 1. Prognostic classification of early-stage Hodgkin Lymphoma.

EORTC	GHSG	E-HIPI	
Variable	**Variable**	**Variable**	**HR**
Age ≥50 years, Bulky disease (MMR > 0.35) >3 involved sites, ESR >50 or >30 with B-symptoms **Risk Group**	>2 involved sites bulky disease (MMR > 0.33) extranodal extension ESR> 50 or >30 with B-symptoms **Risk Group**	Female sex Maximum Tumor Diameter per 1 SD Hemoglobin per 1 SD Albumin per 1 SD	0.59 1.09 0.83 0.83
Early Stage Favorable: stage I and II and no risk factors Early Stage Unfavorable: stage I and II with any risk factor	Early Stage Favorable: stage I and II and no risk factors Early Stage Unfavorable: stage I and II with any risk factor *Stage IIB with bulky disease or extranodal extension is classified as an advanced stage*	online calculator https://rtools.mayo.edu/holistic_ehipi/	

Abbreviations. EORTC: European Organization for Research and Treatment of Cancer; GHSG: German Hodgkin Study Group; E-HIPI: Early-Stage cHL International Prognostication Index; MMR: mediastinal mass ratio (maximum width of mass/maximum intrathoracic diameter) at T5-T6; ESR: Erythrocyte Sedimentation Rate. HR: hazard ratio; SD: standard deviation.

Table 2. Prognostic classification of advanced stage Hodgkin Lymphoma.

IPS			A-HIPI[1] online calculator https://rtools.mayo.edu/holistic_ahipi/		
Variable			**Variable**	**5-y PFS HR**	**5-y OS HR**
Age ≥ 45 y Gender Male Albumin < 40 g/l Hemoglobin < 10.5 g/dl Stage IV White Blood Cells ≥15000/mm³ Lymphocytes <600/mm³ OR <8% of WBC count			Age (years) - Linear effect in 18–30 - Linear effect in 31–65 Female Stage - IIB - III - IV Any bulk Lymphocyte count, x 10^3/mmc - Linear effect in 0.1–2 - Linear effect in 2–5 Hemoglobin, g/dl Albumin, g/dl	 0.97 1.02 1.23 1.53 0.75 1.21 0.74	 0.98 1.05 0.78 1.33 1.37 0.61 1.49 0.88 0.67
IPS score	5-y FFP (%)	5-y OS (%)			
0	84	89			
1	77	90			
2	67	81			
3	60	78			
4	51	61			
5-7	41	56			

Abbreviations. IPS: International Prognostic Score. A-HIPI; Advanced-Stage cHL International Prognostication Index; PFS: progression-free survival; OS: overall survival; HR: hazard ratio.

Early PET evaluation after the first cycles of chemotherapy, assessed according to the Deauville criteria, has been established as a robust prognostic factor. It is now widely used to guide subsequent treatment de-escalation or intensification, and, over the past decade, most pivotal clinical trials in cHL have incorporated *interim* PET assessment.[18-20]

Baseline metabolic tumor volume (MTV) has also been shown to influence the risk of relapses in cHL, with the risk increasing by approximately 19 to 21% for each additional cm increase in baseline tumor size. Importantly, MTV provides prognostic information independent of PET-2 results.[21-23] However, several methods are currently used to measure MTV, and standardization is required before its routine integration into clinical practice.[24]

Pretreatment plasma ctDNA has emerged as an important prognostic biomarker showing a strong correlation with total MTV, with higher levels associated with inferior PFS.[11] Dynamic assessment of ctDNA during therapy represents a promising, radiation-free tool for tracking residual disease and identifying clonal evolution in cHL. It may complement PET imaging for the early identification of chemorefractory patients, to distinguish ambiguous PET-positive lesions after treatment, and to detect radiographically occult minimal residual disease.[11-13]

Finally, several tumor microenvironment-related parameters have been associated with poorer outcomes, including the proportion of tumor-infiltrating CD68+ macrophages greater than 5%, and elevated plasma levels of thymus and activation-regulated chemokine (TARC) and Interleukin-10 (IL10).[25-27]

Treatment. Treatment modalities for patients with Hodgkin lymphoma vary according to disease stage (early versus advanced), prognostic factors (favorable versus unfavorable), age (children versus young-adult and elderly), patient comorbidities and, importantly, national guidelines and healthcare reimbursement policy.[14,28,29]

Over the past decade, the treatment landscape of cHL has evolved significantly with the adoption of PET-guided strategies and the integration of novel targeted agents modifying conventional chemotherapy regimens, such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). These newer agents have, in part, replaced more toxic components of traditional therapies. The key agents of this change include the antibody-drug conjugate BV, which consists of a chimeric anti-CD30 monoclonal antibody carrying the microtubule-disrupting agent monomethyl auristatin E (MMAE) as a payload, and the anti-PD1 checkpoint inhibitors nivolumab and pembrolizumab, which enhance the antitumor immune response. Initially approved as monotherapy for relapsed/refractory disease, these agents are increasingly being incorporated into earlier lines of treatment.[30-32] These novel frontline chemo/immunotherapy combinations resulted in higher response rates and longer durations compared to historical regimens. In this evolving therapeutic landscape, the role of consolidative radiotherapy remains an area of ongoing investigation.

For the purposes of this review, we will discuss the treatment of young adult and elderly patients with cHL separately.

Treatment of Favorable Early-Stage HL. Current guidelines recommend two cycles of ABVD followed by involved nodal/involved site radiotherapy (INRT/ISRT) as the preferred treatment approach for patients with early-stage cHL without risk factors, according to the GHSG risk stratification system.[29] This approach was validated by the GHSG HD10 clinical trial, which randomized 1190 patients with newly diagnosed favorable early-stage cHL to two or four cycles of ABVD, followed by 20 Gy or 30 Gy involved-field radiotherapy (IFRT).[33] Ten-year PFS and OS were 87% and 94%, respectively, both in those treated with two cycles of ABVD followed by 20 Gy IFRT and those treated with four cycles of ABVD followed both by 30 Gy IFRT, confirming the non-inferiority of reduced intensity combined modality treatment (CMT) in this patient population.[34]

Several studies have subsequently explored the omission of radiotherapy in patients with favorable early-stage HL achieving a negative early PET (**Table 3**).

In the RAPID trial, 392 patients with favorable early-stage HL and a negative PET after three cycles of ABVD were randomized to receive either 30 Gy IFRT or no further treatment. The 3-year PFS was 94.6% in the radiotherapy group and 90.8% in the group that received no further therapy, therefore the study failed to demonstrate the non-inferiority of the strategy of no further treatment after chemotherapy.[35] However, no differences in long term OS were observed.[36]

Similarly, the EORTC/LYSA/FIL H10F trial randomized 747 patients with favorable early-stage HL to either a standard arm consisting of three ABVD followed by INRT or a PET-guided experimental arm. In the experimental arm, PET2-negative patients after two ABVD cycles continued with two additional cycles for a total of four ABVD, whereas PET2-positive patients switched to escalated BEACOPP (eBEACOPP), receiving a total of two ABVD cycles, two eBEACOPP cycles, and INRT.[37] At 10 years of follow-up, among PET2-negative patients, the PFS rate was significantly higher with the combined treatment modality (98.8%) than with chemotherapy alone (85.4%). In the PET2-positive group, the difference in PFS between standard ABVD and intensified eBEACOPP was no longer statistically significant.[38]

Similarly, the GHSG HD16 trial reported a 5-year PFS of 93.4% in PET2 negative patients with favorable early-stage HL receiving IFRT after two cycles ABVD versus 86.1% in PET2 negative patients who did not receive further treatment after chemotherapy.[39,40]

Collectively, the RAPID, EORTC H10, and GHSG HD16 trials failed to demonstrate non-inferiority of PET-adapted omission of radiotherapy with respect to PFS compared with CMT in patients with favorable early-stage cHL. However, no significant differences in OS were observed in early PET negative patients not receiving radiotherapy. Omission of radiotherapy may reduce long-term toxicities including the risk of secondary primary neoplasms. Consequently, in real-world clinical practice, many clinicians favor a chemotherapy-only approach for selected patients with early-stage cHL, accepting a modest reduction in PFS in the light of the availability of effective savage treatments capable of achieving durable remissions in most relapsed patients.

Treatment of Early-Stage Unfavorable HL. Current guidelines recommend four cycles of ABVD followed by 30 Gy INRT/ISRT as the preferred treatment approach for patients with unfavorable early-stage cHL.[29] Key randomized clinical trials evaluating frontline treatment in this setting are summarized in **Table 3**.

In the GHSG HD11 trial, four cycles of ABVD, followed by 30 Gy IFRT, were not inferior to four cycles of baseline BEACOPP, followed by 20 or 30 Gy IFRT. In contrast, treatment consisting of four cycles of ABVD followed by 20 Gy IFRT was associated with inferior PFS in this not-PET-guided approach.[41]

In the PET-guided EORTC/LYSA/FIL H10U trial, four cycles of ABVD followed by INRT resulted in a higher PFS than the experimental arm, which received 6 cycles of ABVD, in early PET-negative patients; however, this difference was modest and not statistically

Table 3. Pivotal randomized clinical trials for frontline treatment of early-stage favorable (F) and unfavorable (U) Hodgkin Lymphoma.

TRIAL	n	Treatment	PFS	OS
GHSG HD10 [33,34]	F ITT 1190	4 ABVD + 30 Gy IFRT 2 ABVD + 20 Gy IFRT 4 ABVD + 20 Gy IFRT 2 ABVD + 30 Gy IFRT	8-y 88.4% 8-y 86.5% HR 1.07 (95% CI 0.65 -1.77) 8-y 90.0% 8-y 85.4%	8-y 94.4% 8-y 95.1% HR 0.85 (95% CI 0.41 -1.79) 8-y 94.7% 8-y 93.6%
UK RAPID [35,36]	F ITT 420 PP 392	3 ABVD > PET neg > 30 Gy IFRT 3 ABVD > PET neg > no further treatment	3-y 97% 3-y 90.8% HR 2.36 (95% CI 1.13-4.95)	15-y 94.2% 15-y 92.3 HR 0.71 (95% CI 0.33-1.55)
EORTC/LYSA/ FIL H10 [37,38]	F ITT 747 U ITT 1178	Favorable 2 ABVD > PET2 neg > 1 ABVD + RT 2 ABVD > PET2 neg > 2 ABVD Unfavorable 2 ABVD > PET neg > 2 ABVD + 30 Gy INRT 2 ABVD > PET neg > 4 ABVD Favorable and Unfavorable 2 ABVD > PET2 pos > 1 (F) or 2 (U) ABVD + RT 2 ABVD > PET2 pos > 2 eBEACOPP + INRT	 10-y 98.8% 10-y 85.4% HR 13.2 (95% CI 3.1-55.8) 10-y 91.4% 10-y 86.5% HR 1.52 (95% CI 0.84-2.75) 10-y 79.2% 10-y 85.1% HR 0.67 (95% CI 0.37-1.20)	 10-y 100% 10-y 98% HR 2.80 (95% CI 0.26-26.9) 10-y 94.3% 10-y 94.8% HR 0.84 (95% CI 0.36-1.98) 10-y 90.4% 10-y 92.0% HR 0.92 (95% CI 0.43- 1.97)
GHSG HD16 [39,40]	F ITT 1150 PP 968	2 ABVD > PET neg > 20 Gy IFRT 2 ABVD > PET neg > no further treatment 2 ABVD > PET pos > 20 Gy IFRT	5-y PFS 93.4% 5-y PFS 86.1% HR 2.05 (95% CI 1.20-3.51) 5-y PFS 90.3%	5-y PFS 98.3% 5-y PFS 98.8% HR 2.05 (95% CI 1.20-3.41) /
GHSG HD11 [41]	U ITT 1395	4 ABVD + 30 Gy IFRT 4 ABVD + 20 Gy IFRT 4 BEACOPP baseline + 30 Gy IFRT 4 BEACOPP baseline + 20 Gy IFRT	5-y 87.2% 5-y 82.1% HR 1.49 (95% CI 1.04 - 2.15) 5-y 87.9% 5-y 87.0%	5-y 94.3 5-y 93.8 5-y 94.6 5-y 95.1
HD17 [42]	U ITT 979 PP 905	Standard: 2 eBEACOPP + 2 ABVD + 30 Gy INRT PET-guided strategy: 2 eBEACOPP + 2 ABVD > PET pos > 30 Gy INRT 2 eBEACOPP + 2 ABVD > PET neg	5-y 97.3% 5-y 95.1% HR 0.523 (95% CI 0.226-1.211)	5-y 98.8% in all study population

Abbreviations. ITT: intent to treat population set; PP: per protocol population set; PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; PET: positron emission tomography; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; eBEACOPP: escalated BEACOPP; IFRT: involved field radiotherapy; INRT: involved nodal radiotherapy.

significant. At 10-year follow-up analysis, there was no statistically significant difference in PFS between PET2-positive patients after two ABVD cycles who continued standard therapy (two cycles of ABVD followed by 30 Gy INRT) and those who received an intensified approach consisting of two cycles of eBEACOPP followed by 30 Gy INRT.[37,38]

In GHSG HD17 trial, the omission of INRT in patients with unfavorable early-stage cHL who achieved a negative PET after two cycles of eBEACOPP and continued with two cycles of ABVD was not inferior to standard CMT consisting of the same chemotherapy induction followed by 30 Gy INRT.[42]

Overall, these studies suggest that when more intensive upfront chemotherapy is administered such as six cycles of ABVD or intensified therapy with eBEACOPP, the additional benefit of consolidative radiotherapy in terms of PFS may be limited or absent.

New agent combinations in early stage cHL. Several phase II clinical trials have investigated the incorporation of novel monoclonal antibodies into frontline regimens for early stage cHL (**Table 4**)

The addition of BV to doxorubicin, vinblastine and dacarbazine (AVD) for 4-6 cycles, guided by PET2 evaluation, while omitting both bleomycin and consolidative radiotherapy, resulted in a high response rate and a 3-year PFS of 94%. However, this approach was associated with a higher incidence of grade $\geq$ 3 febrile neutropenia (35%) and peripheral sensory neuropathy (24%).[43] To reduce the overlapping toxicity of BV and vinblastine, BV was combined with doxorubicin and dacarbazine alone (BV-AD) in 34 patients with non-bulky limited-stage cHL. Treatment duration (4 or 6 cycles) was guided by interim PET. ORR and CR were 100% and 97%, respectively, and 5-year PFS was 91%. No cases of febrile neutropenia, grade >3, or peripheral sensory neuropathy were reported.[44]

The multicenter, randomized, open-label, phase II BREACH trial enrolled 170 patients with early-unfavorable cHL and compared 4 cycles of BV-AVD or standard ABVD, both followed by 30 Gy INRT. PET2-

Table 4. Phase 2 trials incorporating new agents in frontline treatment of early stage classical Hodgkin Lymphoma.

Study population	n	Treatment	ORR	CR	PFS	OS	Ref.
Early non-bulky	34	1 BV + 4-6 BV-AVD according to PET2	91.2%	91.2%	3-y 94%	3-y 97%	[43]
Early non-bulky	34	4-6 BV-AD according to PET2	100%	97%	5-y 91%	5-y 96%	[44]
Early unfavorable	170	4 BV-AVD + 30 Gy INRT 4 ABVD + 30 GY INRT (BREACH trial)	89% 77%	88 % 77%%	2-y 97.3% 2-y 92.6%	/	[45]
Early unfavorable	109	Concomitant 4 N-AVD + 30 Gy ISRT Sequential 4 N + 2 N-AVD + 2 AVD + 30 Gy ISRT (NIVHAL trial)	100% 98%	90% 94%	3-y 100% 3-y 98%	3-y 100% 3-y 100%	[46]
Early non-bulky	154	AN-AD x 4 cycles (SGN35-027 Part C)	96%,	92%	2-y 97%	/	[47]

Abbreviations. ORR: overall response rate; CR: complete remission rate; PFS: progression-free survival; OS: overall survival; PET2: positron emission tomography performed after 2 cycles; BV: brentuximab-vedotin; BV-AVD: brentuximab-vedotin, doxorubicin, vinblastine, dacarbazine; BV-AD: brentuximab-vedotin, doxorubicin, dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; N-AVD: nivolumab, doxorubicin, vinblastine, dacarbazine; N: nivolumab; AN-AD: brentuximab-vedotin, nivolumab, doxorubicin, dacarbazine; ISRT: involved site radiotherapy; INRT: involved nodal radiotherapy.

negativity was achieved in 82.3% of patients in the BV-AVD arm and in 75.4% in the ABVD arm. Two-year PFS was higher in the BV-AVD arm compared to the ABVD arm (97.3% versus 92.6%, respectively).[45]

The NIVAHL Trial incorporated the checkpoint inhibitor nivolumab into the AVD regimen in adult patients with early-stage unfavorable cHL. One hundred nine patients were randomly assigned to either concomitant treatment with four cycles of N-AVD or sequential treatment with four cycles of nivolumab, two cycles of N-AVD, and two cycles of AVD. Both strategies were followed by 30 Gy ISRT. CR rates reached 100% with 3-year PFS rates of 100% and 98% in the concomitant and sequential groups, respectively.[46]

In another phase II study, BV and nivolumab were combined with doxorubicin and dacarbazine (AN+AD) in 154 patients with non-bulky early stage cHL. This regimen achieved an ORR of 96%, a CR rate of 92%, and a 2-year PFS of 97%, with a favorable safety profile, including a low incidence of grade ≥3 peripheral sensory neuropathy (3%) and no reported cases of febrile neutropenia.[47]

Overall, these strategies aim to reduce chemotherapy intensity by replacing more toxic agents with targeted monoclonal antibodies, potentially diminishing the need for radiotherapy and reducing both acute and long-term toxicities. However, compared with the large phase III randomized trials that established current standards of care, larger patient cohorts and longer follow-up are required to confirm their superiority in terms of efficacy and safety over the current standard CMT.

Advanced stage. For more than two decades, the optimal treatment of advanced-stage cHL has been debated, balancing the greater efficacy but higher toxicity of intensified regimens such as eBEACOPP against the more favorable safety profile but slightly lower efficacy of ABVD.[48] This dilemma has been largely addressed through PET-guided clinical trials, in which treatment is escalated or de-escalated based on early *interim* PET assessment, typically performed after two cycles of treatment (**Table 5**).

The RATHL trial explored a de-escalation strategy in PET2-negative patients after two cycles of ABVD by omitting bleomycin and continuing four cycles of AVD. The study included patients with cHL in stage IIB, III, IV, as well as selected high-risk stage IIA. The non-inferiority analysis showed comparable efficacy between the two approaches, with a lower incidence of pulmonary toxicity in patients receiving AVD compared with those continuing ABVD. In contrast, PET2 positive patients underwent treatment escalation to four cycles of eBEACOPP or six cycles of BEACOPP14, achieving favorable efficacy outcomes without any increase in secondary malignancies.[49,50]

Similarly, in the AHL2011 trial, de-escalation to four cycles of ABVD after two initial cycles of eBEACOPP in PET2-negative patients with advanced stage cHL resulted in PFS and OS similar to that of patients continuing four more cycles of eBEACOPP. In contrast, patients with PET2 positive disease – whether PET4-negative or PET4-positive - had inferior outcomes.[51]

In GHSG HD18 trial, PET2-negative patients with advanced stage cHL after two initial cycles of eBEACOPP were randomized to further 4-6 cycles (total of 6-8) or only 2 further cycles (total of 4) of eBEACOPP. Both approaches resulted in similar PFS and OS, while the abbreviated regimen was associated with reduced hematological toxicity and lower transfusion requirements. The addition of rituximab to eBEACOPP in PET2-positive patients did not improve outcomes.[52]

More recently, randomized clinical trials have integrated novel agents such as antibody drug conjugated BV and the checkpoint inhibitors nivolumab and pembrolizumab, into the chemotherapy backbone for first line treatment of advanced stage cHL.

The randomized ECHELON-1 trial demonstrated a significant improvement in long-term PFS and OS for patients with stage III and IV cHL treated with 6 cycles of BV-AVD versus ABVD. At a median follow-up of

Table 5. Pivotal randomized trials in advanced stage classical Hodgkin Lymphoma.

TRIAL	*n*	Treatment	PFS	OS
RATHL [49,50]	ITT 1201 PP 1105	2 ABVD > PET2 neg > 4 ABVD (standard) 2 ABVD > PET2 neg > 4 AVD 2 ABVD > PET2 pos > 4 eBEACOPP or 6 BEACOPP14	7-y 81.2% 7-y 79.2% HR 1.10 (95% CI 0.82-1.47) 7-y 65.9%	7-y 93.2 7-y 93.5 HR 0.84 (95% CI 0.51-1.37) 7-y 83.2%
AHL2011 [51]	ITT 823 PP 739	Standard arm: 6 eBEACOPP PET driven arm: 2 eBEACOPP >PET2 neg > 4 ABVD 2 eBEACOPP >PET2 pos > 4 eBEACOPP	5-y 88.1% 5-y 86.5% HR 1.01 (95% CI 0.75-1.66) 5-y 90.5% 5-y 68.2%	5-y 97.1% 5-y 96.3% HR 1.2 (95% CI 0.55-2.60) 5-y 97.8% 5-y 92.0%
GHSG HD18 [52]	ITT 1945	2 eBEACOPP > PET2 pos: - 4-6 eBEACOPP (total 6-8 cycles) - 4-6 R-eBEACOPP (total 6-8 cycles) 2 eBEACOPP > PET2 neg: - 4-6 eBEACOPP (total 6-8 cycles) - 2 eBEACOPP (total 4 cycles)	5-y 89.7% 5-y 88.1% HR 1.25 (95% CI 0.69-2.26) 5-y 90.8% 5-y 92.2% HR 0.79 (95% CI 0.5-1.24)	5-y 96.4% 5-y 93.9% HR 1.62 (95% CI 0.70-3.75) 5-y 95.4% 5-y 97.7% HR 0.32 (95% CI 0.2-4.9)
ECHELON-1 [53-55]	ITT 1334	6 BV-AVD 6 ABVD	7-y 82.3% 7-y 74.5% HR 0.68 (95% CI 0.53-0.86)	7-y 93.5% 7-y 88.8% HR 0.62 (95% CI 0.42-0.9)
GHSG HD21 [56]	ITT 1482	4-6 BrECADD (according to PET2) 4-6 eBEACOPP (according to PET2)	4-y 94.3% 4-y 90.1% HR 0.66 (95% CI 0.45-0.97)	4-y 98.6% 4-y 98.2%
S1826 [57]	ITT 970	6 N-AVD 6 BV-AVD	2-y 92% 2-y 83% HR 0.45 (95% CI 0.3–0.65)	2-y 99% 2-y 98% HR 0.39 (95% CI 0.15-1.03)

Abbreviations. ITT: intent to treat population set; PP: per protocol population set; PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; PET2: positron emission tomography performed after 2 cycles; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AVD: doxorubicin, bleomycin, dacarbazine; eBEACOPP: escalated, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; R-eBEACOPP: rituximab-eBEACOPP; BV-AVD: brentuximab-vedotin, doxorubicin, vinblastine, dacarbazine; N-AVD: nivolumab, doxorubicin, vinblastine, dacarbazine.

89.3 months, the 7-year PFS rates were 82.3% versus 74.5% (HR 0.68; p=0.001), and the 7-year OS rates were 93.5% versus 88.8% (HR 0.62; p=0.011) for BV-AVD and ABVD, respectively. A higher incidence of febrile neutropenia and peripheral sensory neuropathy was observed in the BV-AVD arm.[53-55]

In the phase III GHSG HD21 trial, the novel regimen brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) was compared with eBEACOPP in a PET-guided strategy in adult patients aged ≤60 years with advanced-stage, cHL. PET2-negative patients received two further cycles of the assigned regimen while PET2-positive patients received four further cycles. In both arms, 30 Gy IFRT or INRT was permitted on residual PET-positive disease at the end of treatment. BrECADD was associated with lower treatment-related morbidity and improved PFS compared with eBEACOPP, with no difference in OS. With a 4-year PFS of 94.3%, BrECADD achieved an unprecedented primary cure rate in large, randomized trials for advanced-stage cHL. Together with its more favorable toxicity profile compared with eBEACOPP and, in some respects, also with ABVD, these results strongly support BrECADD as a new standard treatment option for adult patients aged ≤60 years with newly diagnosed adult advanced stage cHL.[56]

The phase III SWOG S1826 trial compared nivolumab plus AVD (N-AVD) for 6 cycles with BV-AVD in adolescent and adult patients with advanced-stage cHL. At a median follow-up of 2.1 years, both PFS and EFS were superior in the N-AVD arm, and this advantage was confirmed across subgroups defined by age, stage, and IPS score. BV-AVD was associated with a higher rate of peripheral neuropathy and treatment discontinuation, whereas neutropenia was more frequent in the N-AVD arm where G-CSF prophylaxis was not mandatory. Compared with BV-AVD, N-AVD was well tolerated in older patients and showed outcomes similar to those in younger patients, without significantly increased morbidity or mortality.[57]

Pembrolizumab has also been evaluated in combination with AVD in either sequential or concomitant schedules in two single-arm phase 2 trials, both enrolling approximately 30 patients. Overall response rates were 100% in both studies, with CR rates of 100% and 90% in the sequential and concomitant cohorts, respectively, and approximately 100% 2-year PFS in both studies.[58,59] However, larger studies with longer follow-up are needed to confirm these promising results.

In the phase II SGN35-027 clinical trial, treatment-naïve patients with bulky stage I-II and stage III-IV cHL received up to 6 cycles of brentuximab-vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD). The aim of the study was to reduce the high rate of peripheral neuropathy of BV-AVD caused by concurrent use of two microtubule-disrupting agents by substituting vinblastine with nivolumab. Among 57 patients (aged 19-78 years), the ORR was 93%, CR 88%, and 2-year PFS 88%. Peripheral neuropathy occurred in 44% of patients, with only 4% grade 3.[60]

Elderly patients with Hodgkin lymphoma. Older patients account for approximately 20% of newly diagnosed cases of cHL, and this proportion is expected to increase in the coming years. Advanced age at diagnosis is often associated with a more aggressive disease biology, including a higher prevalence of mixed cellularity and lymphocyte-depleted subtypes, as well as EBV-associated HL. In addition, older patients show reduced tolerance to chemotherapy with a higher rate of treatment-related toxicities such as neurotoxicity, cytopenias, infections, bleomycin-induced pulmonary toxicity, and anthracycline-related cardiotoxicity. Consequently, long-term outcomes in older adults remain significantly inferior, with 5-year OS rates ranging from 49 to 65%, compared with approximately 90% in younger patients. Comorbidities, functional decline and organ dysfunction further limit tolerance to chemotherapy, and frailty itself represents an independent adverse prognostic factor even with intensive therapy.[61]

Several geriatric assessment tools and scoring systems, including the Charlson Comorbidity Index (CCI), Cumulative Illness Rating Scale for Geriatrics (CIRS-G), and activities of daily living (ADL) and instrumental ADL (IADL) scales, have been used in lymphoma clinical trials, including those in HL. The Fondazione Italiana Linfomi (FIL) has conducted a prospective study to improve prognostic stratification of older patients with cHL aged ≥65 years, incorporating a simplified Geriatric Assessment (sGA) previously validated in DLBCL (clinicaltrials.gov ID: NCT03552003).[62,63] Fit older patients with cHL are often treated with the same regimens used in younger patients, and ABVD remains the cornerstone of treatment in both early and advanced stages. Several strategies have been adopted to mitigate toxicity. These include omitting bleomycin from the outset (AVD) or after two cycles of ABVD in PET2-negative patients, as in the RATHL trial, to reduce the risk of pulmonary toxicity. Substituting conventional doxorubicin with non-pegylated liposomal doxorubicin (MBVD) has also been shown to be safe and effective in elderly patients (> 70 years) or those with underlying cardiac disease.[64] Alternative lower-intensity regimens, such as PVAG (prednisone, vinblastine, doxorubicin, and gemcitabine), AVG (doxorubicin, vinblastine, gemcitabine), and PVAB (prednisone, vinblastine, doxorubicin, bendamustine), may offer durable remissions with improved tolerability in this population.[65-67]

BV monotherapy has demonstrated activity in elderly patients unfit for chemotherapy, although responses are often not durable.[68,69] To increase the response rate, combination strategies with single cytotoxic drugs have been explored in elderly, unfit patients. BV plus bendamustine was associated with a high incidence of serious adverse events (65%), leading to early trial termination. In contrast, a combination of BV with dacarbazine achieved a 100% ORR and 62% CR rate with a median PFS of 17.9 months, representing a reasonable frontline option for frail patients.[70]

In the ECHELON-1 trial, concomitant BV-AVD was not superior to ABVD in the subgroup of 187 patients over age 60 and was associated with increased toxicity, including higher rates of febrile neutropenia, peripheral neuropathy, and treatment-related mortality.[53] The 5-year PFS rates for BV-AVD (67.1%) and ABVD (61.8%) were not significantly different.[71] Conversely, a sequential approach incorporating BV followed by AVD (2 cycles of BV + 6 cycles of AVD + 4 cycles of BV) was better tolerated in elderly patients, with 2-year PFS and OS rates of 84% and 93%, respectively, and manageable toxicity.[72]

In the HD21 older cohort, PET-guided BrECADD was shown to be feasible and effective in patients aged 61-75 years with advanced stage cHL, although it required more frequent dose adjustments compared with younger patients. Among 85 patients, the estimated 2-year PFS and OS were 91.5% and 90.7%, respectively, after a median follow-up of 23 months. Neutropenic fever and sensory neuropathy occurred in 54% and 38% of patients, respectively, and no treatment-related deaths were reported.[73]

The non-overlapping toxicity profiles of checkpoint inhibitors and conventional chemotherapy have prompted investigation of anti-PD1 agents as frontline treatment in elderly patients with cHL. In a French trial of older frail patients with cHL and significant comorbidities (CIRS-G ≥ 6), frontline nivolumab monotherapy resulted in 28.6% complete metabolic responses (CMR) and a median PFS of 9.8 months, providing temporary disease control without curative potential.[61] The N-AVD regimen has shown favorable tolerability in fit older patients, with outcomes comparable to those observed in younger patients and without a significant increase of morbidity or mortality. In a subgroup analysis of patients aged more than 60 years from the SWOG S1826 trial, 2-year PFS and OS were 89% and 96%, respectively, with N-AVD, compared with 64% and 85% with BV-AVD. Notably, treatment discontinuation rates for the targeted agent

were lower with nivolumab (14%) than with BV (55%)..[74]

The multicenter phase II ACCRU trial evaluated the combination of BV plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with cHL. Although the prespecified efficacy endpoint was not met, the regimen achieved an ORR of 61% and a CMR of 48%, with a favorable safety profile and a low incidence of grade >3 adverse events.[75]

More recently, a non-comparative phase II study assessed BV combined with dacarbazine or nivolumab in elderly patients aged (≥60 years), unfit for conventional chemotherapy. Among 22 patients (median age 74 years) treated with BV and dacarbazine, ORR was 95%, CR 64%, median PFS 46.2 months and median OS not reached. In 21 patients treated with BV plus nivolumab (median age 72.1 years), ORR was 86%, CR 67%, median PFS, and median OS were not reached.[76] These results demonstrate safety and promising durable efficacy of BV-dacarbazine and BV-nivolumab combinations as potential alternatives for frontline treatment of older patients with cHL unfit for conventional chemotherapy.

Relapsed/refractory disease. Although cHL is a highly curable disease with frontline therapy, 10-25% of patients develop refractory disease or experience relapse. Established adverse prognostic factors at relapse include primary refractory disease (failure to achieve complete remission), relapse within 12 months from the end of first-line therapy, extranodal involvement at relapse, B symptoms, and stage IV disease.[77] Historically, salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) has represented the standard treatment for eligible fit patients aged ≤ 65-70 years without significant comorbidities. PET imaging performed after salvage chemotherapy and before ASCT has emerged as the strongest prognostic factor for ASCT outcome. Achieving PET negativity (Deauville score 1-3) is now considered a key prerequisite before proceeding to ASCT.[78-79] Several salvage regimes are currently used in patients with relapsed/refractory cHL and can be broadly grouped into platinum-based or gemcitabine-based combinations.[80,81] No randomized trials demonstrated superiority of one regimen over another. Traditional salvage chemotherapies include DHAP (dexamethasone, high-dose cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GVD (gemcitabine, vinorelbine, and liposomal doxorubicin), IGEV (ifosfamide, gemcitabine, and vinorelbine), ICE (ifosfamide, carboplatin, and etoposide), and BEGEV (bendamustine, gemcitabine, and vinorelbine). Complete responses with these regimens occur in a range from approximately 50% of patients reported for platinum-based regimens to 70% reported for the BEGEV regimen, resulting in PFS rates of 52–77% at 3-5 years for patients who successfully undergo ASCT (**Table 6**).[82-90]

Until the early 2010s, patients with refractory or relapsed cHL after ASCT had a poor prognosis, with limited therapeutic options aside from allogeneic stem cell transplantation (SCT) in selected cases achieving a second remission. This scenario has changed drastically with the advent of novel targeted therapies, which have reshaped the therapeutic landscape of cHL across all treatment lines.

In 2012, Younes and colleagues published the results of a pivotal phase II study evaluating treatment with the anti-CD30 antibody-drug conjugate BV in 102 patients with relapsed or refractory cHL after ASCT. Results

Table 6. Salvage chemotherapy regimens used before ASCT in relapsed/refractory Hodgkin Lymphoma.

Regimen	*n*	Response before ASCT	PFS/EFS after ASCT	OS after ASCT	Ref.
ICE/aug-ICE x 2 +/- GVD x 2 (if not in CMR after ICE/aug-ICE)	97	CR 60% after ICE + further 17% after GVD by PET	5-y 79%	5-y 88%	[79]
DHAP x 2 cycles	102	CR 21%, PR 67% by CT	-	-	[82]
ESHAP x 3-6 cycles	82	CR 50%, PR 17% by CT	Median 56 m	5-y 74.4%	[83]
GDP x 2-3 cycles	22	CR 17.3%, PR 52.2% by CT	-	-	[84]
GDP x 2 cycles	45	CR 53.3%, PR 26.7% by PET or CT	4-y 72%	4-y 92%	[85]
GVD x 2-6 cycles	91	CR 19%, PR 70% by CT	4-y 52%	4-y 70%	[86]
ICE x 2 cycles	65	CR 26.2%, PR 58.5% by CT	43-m 68%	43-m 83%	[87]
IGEV x 4 cycles	91	CR 53.8%, PR 27.5% by CT	3-y 53%	3-y 70%	[88]
BEGEV	59	CR 73%, PR 10% by PET/TC	5-y 77%	5-y 91%	[89,90]

Abbreviations. PFS: progression-free survival; EFS: event-free survival; OS: overall survival; ASCT: autologous stem cell transplantation; CR: complete response; PR: partial response; CMR: complete metabolic response; CT: computed tomography; PET: positron emission tomography; ICE: ifosfamide, carboplatin, etoposide; aug-ICE: augmented-ICE; DHAP: dexamethasone, high dose cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; GDP: gemcitabine, dexamethasone, and cisplatin; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; IGEV: ifosfamide, gemcitabine, vinorelbine; BEGEV: bendamustine, gemcitabine, and vinorelbine.

Table 7. Pivotal clinical trial with BV or checkpoint inhibitors in monotherapy in relapsed/refractory cHL.

Trial	Study population	n	Schedule	ORR %	CR %	Median PFS months	Median OS months
SG035-0003 (phase 2) [30,91]	R/R cHL after ASCT	102	BV 1.8 mg/kg every 3 weeks up to 16 cycles	75	34	5.6	22.4
AETHERA (randomized, double-blind, placebo-controlled, phase 3) [92,93]	Maintenance after ASCT in high risk R/R cHL	165 164	BV 1.8 mg/kg every 3 weeks Placebo every 3 weeks	/	/	Not reached 15.8 HR, 0.52 95% CI 0.38-0.72	NR
CheckMate205 (phase 2) [31]	R/R cHL after ASCT	243	Nivo 3 mg/kg every 2 weeks up to PD or unacceptable toxiciy	71.2	21.4	15.1	not reached
Keynote-087 (phase 2) [32]	R/R cHL after ASCT and/or BV	210	Pembro 200 mg every 3 weeks up to 24 months, or PD, or unacceptable toxiciy	69	22.4	13.7	not reached
Keynote-204 (randomized, open-label, phase 3) [112]	R/R cHL ineligible or relapsed after ASCT	151 153	Pembro 200 mg every 3 weeks BV 1.8 mg/kg every 3 week (all up to 35 cycles or PD)	65.6 54.2	25 24	13.2 8.3 HR 0.65 95% CI 0.48-0.88	NR

Abbreviations. ORR: overall response rate; CR: complete remission rate; PFS: progression-free survival; OS: overall survival; R/R cHL: relapsed/refractory classical Hodgkin Lymphoma; ASCT: autologous stem cell transplantation; BV: brentuximab-vedotin; HR: hazard ratio; CI: confidence interval; Nivo: nivolumab; Pembro: pembrolizumab; PD: progressive disease.

Table 8. BV-based and CPI-based salvage regimen before ASCT in relapsed/refractory Hodgkin Lymphoma.

Regimen	N	Pre-ASCT CMR	PFS after ASCT	OS after ASCT	Ref.
BV+DHAP x 3 cycles	52	81%	2-y 74%	2-y 95%	[96]
BV+Bendamustine x 4-6 cycles	38	78.9%	3-y 67.3%	3-y 88.1%	[97]
BV+ESHAP x 3 cycles	66	70%	30-m 71%	30-m 91%	[98]
BV+Nivo x 4 cycles	91	67%	3-y 91%	3-y 93%	[99]
Weekly BV (1-8-15) x 2 cycles + aug-ICE x 2 (only for patients not in CMR after BV)	46	76%	2-y 80%	2-y 95%	[100]
BV+Gemcitabine x 2-16 cycles	42	67%	NR	NR	[101]
BV+ICE	42	61.9%	3-y 64.3%	3-y 100%	[102]
BV+Bendamustine x 2-6 cycles	55	73.6%	2-y 69.8%	2-y 94.9%	[103]
Nivo x 6 +/- Nivo-ICE x 2 (only for patients not in CMR after Nivo)	42	91%	2-y 72%	2-y 95%	[106]
Nivo x 1+ Nivo-ICE x 2-3	35	88%	2-y 88%	2-y 100%	[107]
Pembro-GVD x 2-4 cycles	39	95%	13-m 100%	13-m 100%	[108]
Pembro-ICE x 2 + Pembro x 1	37	86.5%	2-y 87.2%	2-y 95.1%	[109]

Abbreviations. BV: brentuximab-vedorin; CPI: checkpoint inhibitors; ASCT: autologous stem cell transplantation; CMR: complete metabolic response; PFS: progression-free survival; OS: overall survival; NR: not reported; ICE ifosfamide, carboplatin, etoposide; aug-ICE: augmented-ICE; DHAP: dexamethasone, high dose cytarabine, cisplatin; BV-ESHAP: brentuximab-vedotin, etoposide, methylprednisolone, high-dose cytarabine, cisplatin; Nivo: nivolumab; Nivo-ICE: nivolumab-ICE; Pembro: pembrolizumab; Pembro-GVD: pembrolizumab, gemcitabine, vinorelbine, liposomal doxorubicin; Pembro-ICE: Pembolizumab-ICE;

were encouraging, with an ORR of 75%, a CR rate of 34%, a median PFS of 5.6 months, and a median duration of response (DOR) of 20.5 months among patients achieving CR. During the 5 years of follow-up, patients who achieved a CR had estimated OS and PFS rates of 64% and 52%, respectively. The most common treatment-emergent adverse event was peripheral sensory neuropathy, which occurred in 43% of patients (grade 3 events occurred in 8%) and resolved or improved after drug discontinuation in 88% of cases (**Table 7**).[30,91]

Thereafter, BV was evaluated in multiple settings in relapsed/refractory cHL. In the randomized, double-blind, placebo-controlled, phase III AETHERA trial, 329 patients with high-risk relapsed or primary refractory cHL who had undergone ASCT were randomly assigned 16 cycles of BV or placebo every 3 weeks, starting 30-45 days after transplantation. 5-year PFS was significantly improved with BV maintenance (59% vs 41% with placebo).[92,93] As the AETHERA trial did not include patients previously exposed to BV, the EBMT Lymphoma Working Party performed a retrospective real-world analysis of 353 refractory/relapsed cHL

patients who received BV maintenance after ASCT. Of these, 52.6% received BV prior to ASCT. The 5-year OS and PFS from the start of BV maintenance were 85.1% and 69.9%, respectively, and a trend toward improved PFS and lower relapse risk was observed in patients exposed to BV before ASCT.[94]

The combination of BV with the CPI Nivolumab as post-ASCT consolidation has also been explored. In a study of 59 high-risk patients, 8 cycles of BV plus nivolumab, administered every 3 weeks, resulted in an 18-month PFS of 94%.[95]

BV was incorporated into several salvage regimens before ASCT, both sequentially and concomitantly with chemotherapy, yielding high CMR rates of 66% to 83%. However, no randomized studies have directly compared these approaches with conventional chemotherapy-based salvage regimens (**Table 8**).[96-103] A propensity score-matched analysis of 10 single-arm salvage studies found that BV-based salvage regimens did not increase pre-ASCT CMR but improved 3-year PFS in patients with relapsed HL. Notably, this benefit was not observed in patients with primary refractory disease, suggesting that BV may not overcome chemoresistance in this subgroup.[104]

A second class of drugs that has revolutionized the treatment of relapsed/refractory cHL consists of the anti-PD1 CPI. By blocking the interaction between PD-L1 on HRS cells and tumor-associated macrophages, and between PD1 on tumor-infiltrating T-lymphocytes, these drugs restore host immune responses, leading to meaningful clinical responses even in heavily pretreated and chemo refractory patients. Two pivotal clinical studies led to the approval of nivolumab and pembrolizumab by FDA and EMA for the treatment of refractory/relapsed patients after or ineligible for ASCT (**Table 7**). [31,32] In the multicenter, single-arm, phase II CheckMate-205 study, which enrolled 243 patients, nivolumab monotherapy until disease progression or unacceptable toxicity achieved an ORR of 71.2%, with CR rate of 21.4%, a median PFS of 15.1 months, a median DOR of 18.2 months, a median duration of CR of 30.3 months, and a 5-year OS of 71.4%.[31] Similarly, in the KEYNOTE-087 trial, pembrolizumab administered as monotherapy for up to 2 years in 210 cHL patients resulted in an ORR of 71.4%, with CR rate of 27.6%, a median PFS of 13.7 months, a median DOR of 16.6 months; median duration of CR and median OS were not reached. Retreatment upon relapse after discontinuation achieved a secondary ORR of 73.7% and a median secondary DOR of 15.2 months.[32] The widespread use of CPI has led to a revision of PET response criteria, as immune-mediated inflammatory changes may mimic disease progression (pseudo-progression). This has prompted the development of Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC), which better captures these atypical response patterns.[105]

As observed with BV, once their efficacy as monotherapy was established in relapsed/refractory patients, anti-PD1 CPI were combined with several agents in pretransplant salvage regimens, including ICE, GVD or BV, with high pretransplant CMR rates (**Table 8**).[99,106-109] In a large retrospective study, including 1280 patients with relapsed/refractory cHL who underwent ASCT from 2010 to 2022 in 6 transplant centers, patients who received PD-1 inhibitors at any point before ASCT had a significantly higher 2-year PFS than those who received BV without PD-1 inhibitors or patients receiving chemotherapy alone (88.2%, 70.2%, and 67.4%, respectively; $P < 0.0001$). This benefit was observed both in patients achieving CMR and those in partial metabolic response (PMR) prior to ASCT, although no differences in OS were noted. These findings support the use of PD-1–based salvage regimens in patients proceeding to ASCT.[110]

The introduction of novel agents has significantly improved outcomes in cHL patients relapsed after ASCT with PFS increasing from 43 % to 71 %.[111] Anti-PD1 CPI have shown superior efficacy and are considered the preferred treatment option in this setting. In the phase III KEYNOTE-204 trial, pembrolizumab treatment resulted in superior PFS compared with BV among 304 patients with cHL who relapsed after ASCT or were ineligible for ASCT (**Table 7**). [112]

For younger and fit patients who relapse after ASCT, either responding to CPI or with disease refractory to CPI, allogeneic SCT still represents a potentially curative option owing to the graft-versus-lymphoma effect. However, concerns persist regarding the increased risk of acute graft-versus-host disease (GVHD) following prior CPI exposure. A large analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT) including 2186 adult patients transplanted between 2008 to 2023, demonstrated that prior CPI exposure was associated with improved PFS and reduced relapse risk, but also with increased incidence of grade 2-4 acute GVHD, without impacting OS, non-relapse mortality and chronic GVHD. Importantly, the use of post-transplant cyclophosphamide (PTCy) was associated with improved OS and reduced rates of grade 2-4 acute GVHD and chronic GVHD in this setting.[113] These findings are supported by additional retrospective studies showing improved PFS and lower relapse rates in patients treated with CPI prior to allogeneic SCT compared with those treated with chemotherapy alone or BV-containing regimens without CPI before allogeneic SCT.[114,115] The increased risk of acute GVHD associated with pretransplant exposure to CPI appears to be

mitigated in those receiving longer immunosuppression (day 180) compared with a shorter duration (60 days).[115]

Based on current evidence, the American Society of Transplantation and Cellular Therapy Committee on Practice Guidelines recommends a washout period of at least 30-60 days between exposure to CPI and allogeneic SCT, the use of reduced intensity conditioning, and post-transplant cyclophosphamide for GVHD prophylaxis.[116]

Novel agents. Despite the substantial advances achieved by the introduction of the antibody drug conjugate BV and the anti-PD1 CPI nivolumab and pembrolizumab, therapeutic options remain limited for patients who progress after these agents. Novel immunotherapies are under development for patients with relapsed/refractory cHL, including chimeric antigen receptor-T cell (CAR-T) products, EBV-specific T cells, bispecific antibodies, and new checkpoint inhibitor combinations.[117] Among these, anti-CD30 CAR-T cells and the anti-CD30/CD16A bispecific antibody AFM13 represent particularly promising approaches.

A meta-analysis of 151 patients from eight studies investigating anti-CD30 CAR-T cell therapy in relapsed/refractory cHL reported an ORR of 57% with 34% CR, 1-year PFS of 39%, and 1-year OS of 89%. The most common hematologic adverse event was leukopenia (71.4%), while among non-hematologic adverse events, cytokine release syndrome (CRS) and immune effector cells associated neurologic syndrome (ICANS) occurred in 30.4% and 13.2% of patients, respectively.[118]

AFM13 (Acimtamig) is a first-in-class, tetravalent anti-CD30/CD16A bispecific antibody, designed to engage and activate NK cells to the selective killing of CD30+ tumor cells. In a phase I-II trial, AFM13 showed modest activity, with ORR ranging from 16.7-23%.[119,120] However, when combined with pembrolizumab in a phase Ib study enrolling 30 heavily pretreated patients with CD30+ HL, the ORR increased to 83% with a CR rate of 37%.[121] More recently, AFM13 was combined with preactivated allogeneic cord blood-derived NK cells and administered to heavily pretreated patients with CD30+ lymphomas (37 of the 42 patients had HL), resulting in ORR and CR rates of 92.8% and 66.7%, respectively. No cases of CRS, neurotoxicity, or GVHD were reported, and 2-year EFS and OS were 26.2% and 76.2%, respectively. Overall, these emerging immunotherapeutic strategies represent promising options for relapsed patients with cHL and warrant further investigations.[122]

Follow-up and Survivorship. Follow-up for patients with cHL aims to detect disease relapses and to monitor treatment-related late toxicities. Given the high curability of cHL, long-term survivorship care is a crucial component of post-treatment management. Current recommendations, largely based on international guidelines, distinguish between follow-up during the first five years after therapy and long-term monitoring beyond this period.[14,28,29]

At the completion of treatment, response assessment should include FDG-PET/CT within three months to document complete remission.

During the first five years after therapy, clinical follow-up is primarily based on periodic history and physical examination, performed every 3–6 months during the first two years, every 6–12 months until the third year, and annually thereafter. Laboratory testing generally includes complete blood count and metabolic profile as clinically indicated, with annual thyroid function testing in patients who received cervical irradiation. Preventive care is also recommended during this phase, including annual influenza vaccination, reduction of cardiovascular risk factors, and patient education on the risk of secondary malignancies.

Routine surveillance imaging is no longer recommended in asymptomatic patients. Imaging studies should be performed only when clinically indicated, as surveillance PET/CT is associated with a high rate of false-positive findings and does not improve survival outcomes.[13] This approach is supported by population-based data showing no survival benefit from routine surveillance imaging in patients with cHL in first complete remission.[123]

Beyond 5 years, follow-up focuses primarily on detecting and preventing late treatment-related complications, particularly cardiovascular disease and second primary malignancies. Long-term observational studies have demonstrated that survivors of cHL have a two- to four-fold increased risk of these conditions, which represent the leading causes of late mortality.[124] Although contemporary treatment strategies, such as PET-adapted approaches and reduced use of radiotherapy, may mitigate some of these risks, long-term monitoring remains essential.

In this context, the use of advanced echocardiographic assessment tools may provide additional clinical value. Beyond conventional parameters, such as left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), myocardial work (MW) analysis enables a more comprehensive and less load-dependent evaluation of cardiac function, by integrating blood pressure into the assessment. In a cohort of Hodgkin lymphoma survivors, global work index (WI) and global constructive work (GCW) has been shown to be reduced compared with healthy controls, suggesting the presence of subclinical myocardial impairment, whereas global wasted work (GWW) and global wasted efficiency (GWE) remain unchanged. MW indices have been found to correlate strongly with LVEF and systolic blood pressure, consistent with prior evidence. Importantly, MW may

facilitate the diagnosis of cancer therapy-related cardiac dysfunction (CTRCD), particularly in patients with preserved LVEF and borderline GLS. As such, it represents a sensitive tool for the early detection of cardiac dysfunction in this high-risk population, reinforcing the importance of incorporating advanced echocardiographic parameters into long-term survivorship surveillance strategies.[125]

Critical Perspectives and Future Directions. In recent years, significant progress has been made in the treatment of Hodgkin lymphoma, with improved efficacy and reduced toxicity. These advances have been driven by pivotal clinical trials based on PET-adapted approaches and the integration of novel targeted agents into modified multi-agent chemotherapy regimens.

In early-stage cHL, two ABVD followed by 20 Gy ISRT/INRT and four ABVD followed by 30 Gy ISRT/INRT represent the standard of treatment in favorable and unfavorable risk groups, respectively. For now, radiotherapy is far from being abandoned. Omission of radiotherapy is associated with inferior PFS but can reduce the risk of late toxicities, especially secondary primary malignancies, although this may be debated given modern approaches such as INRT and ISRT, which significantly limit the irradiation fields. The advantage of CMT is not significant when a more intensive chemotherapy regimen, like eBEACOPP, or a longer chemotherapy course, like six cycles of ABVD, is used as induction treatment, but in these cases, patients should deal with other kinds of toxicities. Moreover, both NIVHAL and BREACH trials, which combine Nivolumab or BV with AVD, respectively, still consider radiotherapy as consolidation after chemotherapy. Until randomized clinical trials with new drug combinations are available, eventual omission of radiotherapy should be personalized according to the patient's preference and comorbidities, disease extension, fields of irradiation, and PET-related radiomic parameters.

For advanced-stage cHL, large randomized clinical trials have shown that BrECADD and N-AVD are superior to eBEACOPP and BV-AVD, respectively, in terms of PFS but not OS. In the absence of a direct comparison through randomized controlled trials or propensity score matching studies, both BrECADD and N-AVD are considered the preferred first-line treatments for advanced-stage cHL by current major published guidelines, in place of previously favored BV-AVD, eBEACOPP, and ABVD.[14,28,29] The strength of BrECADD lies in longer follow-up, the highest PFS rate ever achieved in this patient population, and a PET-adapted approach that may reduce the number of cycles in PET2-negative patients, making BrECADD the preferred treatment option for fit patients aged < 60 with advanced-stage cHL, according to European Society of Medical Oncology (ESMO) guidelines.[29] The strength of N-AVD consists of reduced hematologic toxicity without mandatory G-CSF use and optimal results in older populations comparable to those seen in younger patients, making N-AVD the preferred treatment option for older patients aged 60-80 years, as well as an alternative to BrECADD in younger patients.[29] Other valid first-line treatments, such as PET-guided regimens like ABVD and eBEACOPP, or concomitant or sequential BV-AVD, can be considered where BrECADD and N-AVD are not available.

In the relapsed/refractory patients, the role of BV and CPI should be reconsidered according to their use in first line. While the benefit of BV incorporation in salvage regimens seems more evident in relapsed than in primary refractory patients, its role as maintenance after ASCT in high-risk patients is supported by the AETHERA randomized trial and has become a common clinical practice.[92,104] Previous BV use before ASCT does not negatively affect maintenance efficacy and should not be considered a contraindication.[94] On the contrary, the use of CPI at any point before ASCT significantly increases the post-transplant PFS, supporting the use of PD-1–based salvage regimens in patients proceeding to ASCT.[110] For patients who relapse after ASCT or are not candidates for it, pembrolizumab is, at present, the best available treatment, followed by allogeneic SCT with PTCy, depending on donor availability and the patient's age, comorbidities, and preferences.

Table 9 summarizes novel treatments in cHL compared with historical standard approaches.

The translation of the most recent advances of cHL treatment into routine clinical practice is often delayed due to the lengthy process of regulatory approval and reimbursement negotiations within of national health care systems. As a result, patient management may vary considerably across countries.

In Italy, current clinical practice is guided by the "Guidelines for the management of adult patients with classical Hodgkin Lymphoma" (version 3.2025), developed by the Società Italiana di Ematologia (SIE) and Associazione Italiana di Oncologia Medica (AIOM), and published within the National Guideline System of the Istituto Superiore di Sanità. These guidelines define the treatment strategies that are currently approved and reimbursed within the Italian HealthCare System.[126] (**Table 10**). Compared to the most recent ESMO, Lymphoma Study Association (LYSA) and National Comprehensive Cancer Network (NCCN) guidelines,[14,28,29] the Italian recommendations do not yet incorporate recently developed therapeutic approaches, such as BrECADD and Nivo-AVD in the frontline settings, as well as BV or CPI-based combinations in salvage regimens for refractory/relapsed patients. These treatments are therefore generally limited to off-label use. Future regulatory approvals are expected to help bridge

Table 9. Summary of recent treatment advances in cHL compared to historical standard approaches.

	Historical standard approaches	**Novel approaches**
Early-stage favorable	2 ABVD + 20 Gy ISRT (HD10)	BV-AVD x 4-6 according to PET
Early-stage unfavorable	4 ABVD + 30 Gy ISRT (EORTC/LYSA/ FIL H10)	BV-AVD x 4 + 30 Gy INRT (BREACH) N-AVD x 4 + 30 Gy ISRT (NIVHAL) AN-AD x 4 cycles (SGN35-027 Part C)
Advanced stage	PET-guided ABVD (de-escalation or escalation according to RATHL trial) PET-guided eBEACOPP (de-escalation according to AHL2011 and HD18)	BV-AVD x 6 (ECHELON-1) BrECADD x 4-6 (HD21) N-AVD x 6 (S1826)
Elderly	ABVD x 2 + AVD x 4 M(B)VD Other regimens as ABG, PVAG, PVAB	Sequential BV-AVD N-AVD + x 6 (S1826) BV-Dacarbazine BV-Nivolumab
Primary refractory/ relapsed disease	Platinum-based or gemcitabine-based salvage regimens + ASCT	BV or CPI combination with salvage chemotherapy followed by ASCT BV maintenance in high-risk patients (AETHERA)
Post-ASCT relapse	Chemotherapy and Allo-SCT	BV (SG035-0003) Nivolumab (CheckMate205) Pembrolizumab (Keynote-087 and 204) (preferred) Consolidation with Allogenic SCT + PTCy
Novel agents	-	Anti-CD30 CAR-T cells AFM13 + preactivated cord blood NK cells

Abbreviations. ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AVD: doxorubicin, vinblastine, dacarbazine; ISRT: involved site radiotherapy; INRT: involved nodal radiotherapy; BV-AVD: brentuximab-vedotin, AVD; N-AVD: nivolumab, AVD; AN-AD: brentuximab-vedotin, nivolumab, doxorubicin, dacarbazine; PET: positron emission tomography; eBEACOPP: escalated, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MBVD; Liposomal doxorubicin, bleomycin, vinblastine, dacarbazine; AVG: doxorubicin, vinblastine, gemcitabine; PVAG: prednisone, vinblastine, doxorubicin, and gemcitabine; PVAB: prednisone, vinblastine, doxorubucin, bendamustine; ASCT: autologous stem cell transplantation; BV: brentuximab-vedotin; CPI: checkpoint inhibitors; SCT: stem cell transplantation; CAR-T: chimeric antigen receptor – T cells

Table 10. Summary of the guidelines for the management of adult patients with classical Hodgkin Lymphoma elaborated by Società Italiana di Ematologia (SIE) and Associazione Italiana Oncologia Medica (AIOM), version 3.2025.[125]

Setting	**Recommendations for frontline treatment**
Early-stage favorable cHL (according to GHSG)	ABVD x 2 > PET2 negative > 20 Gy ISRT ABVD x 2 > PET2 positive > ABVD x 1 + 30 Gy ISRT or eBEACOPP x 2 + 30 Gy ISRT
Early-stage unfavorable cHL (according to GHSG)	ABVD x 2 > PET2 negative > ABVD x 2 + 30 Gy ISRT ABVD x 2 > PET2 positive > ABVD x 2 + 30 Gy ISRT or eBEACOPP x 2 + 30 Gy ISRT
Advanced stage	ABVD x 2 > PET2 negative > AVD x 4 ABVD x 2 > PET2 positive > eBEACOPP x 4 BV-AVD x 6 for patients aged < 60 years, stage IV and contraindication to bleomycin
Elderly patients	Elderly patients who are fit and aged ≤ 70 years can be treated as younger patients. MBVD can be used in place of ABVD in patients aged ≥ 60 years, cardiopathic or previously exposed to anthracyclines Sequential BV x 2 + AVD x 6 + BV x 4 in patients ≥ 60 years of age, stage IV and contraindication to Bleomycin Patients aged ≥ 70 years and with comorbidities can be treated with lower-intensive regimens. Elderly frail patients > monotherapy (gemcitabine or vinorelbine) +/- radiotherapy
cHL in PLWH	Treatment as in immunocompetent patients, in association with cART.
cHL in pregnancy	If it is possible, treatment should be deferred up to the beginning of second trimester. If treatment cannot be delayed, steroids or vinblastine monotherapy could be used in the first trimester. If treatment cannot be delayed up to after delivery, ABVD can be given in second and third trimesters and interrupted three weeks before delivery.
Setting	**Recommendation for second and further line of treatment**
First relapse cHL < 60 and ≥ 60 fit and without comorbidities	Salvage chemotherapy (preferred BEGEV) > - PET negative > HDT (BEAM) + ASCT - PET positive > BV or Pembrolizumab or Nivolumab > PET negative > ASCT - Radiotherapy can be used on localized PET positive residue before or after ASCT
Relapsed/refractory after 2 lines of treatment	Pembrolizumab (preferred treatment) > patients in response can be consolidated with - 2° ASCT if in CR and relapsed after at least 3 years - Non-myeloablative allogeneic SCT with familiar or non-familiar HLA-matched donor or haploidentical donor (cord blood stem cells are not recommended), if chemorefractory and at least in PR. Post-transplant cyclophosphamide is recommended after CPI for GVHD prevention.

Abbreviations. cHL: classical Hodgkin Lymphoma; GHSG: German Hodgkin Study Group; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; PET: positron emission tomography; PET2: PET performed after 2 cycles; ISRT: involved site radiotherapy; eBEACOPP: escalated, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; AVD: doxorubicin, vinblastine, dacarbazine; BV-AVD: brentuximab-vedotin, doxorubicin, vinblastine, dacarbazine; MBVD; Liposomal doxorubicin, bleomycin, vinblastine, dacarbazine; PLWH: people living with HIV; cART: combination antiretroviral therapy; BEGEV: bendamustine, gemcitabine, vinorelbine; HDT: high dose therapy; BEAM: carmustine, etoposide, cytarabine, melphalan; ASCT: autologous stem cell transplantation; SCT: stem cell transplantation; CPI: checkpoint inhibitors; GVHD: graft versus host disease; PR: partial remission; CR: complete remission.

the gap between emerging clinical evidence and its implementation in routine clinical practice.

For the next future, huge expectations are put on the anti-CD30 CAR-T cells and mostly on the combination of the anti-CD30/CD16A bispecific antibody AFM13 with preactivated allogeneic cord blood derived NK cells, which configure as interesting solution for multiple relapsed/refractory heavily pretreated patients, who have failed CPI.

Finally, ct-DNA and MTV are established as innovative and effective prognostic tools in clinical trials but need standardization to become integrated in current clinical practice and overcome limits of historical prognostic classification systems and ambiguous PET interpretations. This will further contribute to personalizing treatment, increasing cure rate and sparing needless toxicities in patients with cHL.

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