

Immunotherapy in the Management of Hodgkin Lymphoma: Time for Immunotherapy for All?

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Abstract

Hodgkin lymphoma (HL) is a lymphoid malignancy of germinal center B cell origin. Conventional chemotherapy with or without radiation induces high cure rates but these treatments can have relevant long-term toxic side effects. As a result, there remains a lot of debate about the optimal management of these patients, especially for limited-stage disease. The last two decades have resulted in a greater understanding of the underlying biology of HL, including the presence of an aberrant phenotype on the tumor cells and the necessity of immune escape. Based on these insights, novel therapeutic approaches have been introduced, including the CD30-directed antibody drug conjugate brentuximab vedotin (BV) and the immune checkpoint inhibitors (ICI), nivolumab and pembrolizumab. After demonstrating to be effective and well tolerated in patients with relapsed/refractory (R/R) disease, these agents are currently being investigated as part of front-line regimens in clinical trials for both limited and advanced stage HL. Results are encouraging and the expectation is that these immunotherapies will be incorporated for the treatment of all stages of the disease. Not only is the hope these agents will further improve outcomes, but it will also reduce our dependence on chemotherapy and radiation in these settings, thereby mitigating the risk of long-term toxicity. This review will provide an overview of the molecular biology of HL, discuss the current standard of care for all stages of the disease, and highlight how immunotherapies are changing the current treatment landscape.

Keywords: Hodgkin Lymphoma, Brentuximab vedotin, Immune checkpoint inhibitor, Nivolumab, Frontline

Introduction

Hodgkin Lymphoma (HL) is an aggressive malignancy of B cell lymphocytes accounting for approximately 11% of lymphomas diagnosed world-wide [1]. Though HL had previously been subdivided into classical HL and nodular lymphocyte-predominant HL, this latter entity was renamed in 2022 as nodular lymphocyte-predominant B-cell lymphoma because of distinct pathological, biological and clinical differences [2,3]. Treatment advances over the last five decades, have significantly improved the outcome of patients diagnosed with HL, which is reflected by a 5-year survival rate of nearly 89% [4]. The goal of treatment for most patients is cure, including for patients with advanced and relapsed disease. With further improvements in multi-modal treatment approaches, the goal has been to maximize cure rates and

minimize long-term toxicity. The latter is crucial as a significant number of patients are diagnosed with HL in the third decade of their life. Novel therapeutic approaches have been introduced that specifically target abnormalities unique to the disease as a result of a greater understanding of the underlying biology. Among these novel therapeutic approaches are the CD30-directed antibody-drug conjugate brentuximab vedotin (BV), and the immune checkpoint inhibitors (ICI), nivolumab and pembrolizumab. Both BV as well as pembrolizumab and nivolumab have been shown to be highly efficacious in clinical trials of HL and have been approved for use in the advanced and relapsed and refractory (R/R) settings. Moreover, it is the expectation that these immunotherapy agents will be increasingly used in the frontline setting, not only because of their efficacy but also because of their favorable safety profile. Here, we will review the current knowledge about the

molecular biology of HL and summarize the important clinical advances in management of HL for both the frontline as well as the R/R settings.

Clinical Presentation and Staging

HL has a bimodal age distribution with a first peak seen among adults 20-30 years and a second peak in patients after 60 years of age [5,6]. However, incidence patterns vary among socio-economic status, gender and race. Most patients present with painless supradiaphragmatic nodal enlargement, often located cervical and supraclavicular [1,7,8]. Approximately 50-60% of patients have mediastinal lymphadenopathy at time of diagnosis, which can be bulky. Although the definition of “bulky” disease has changed over the last decades, this designation is generally given if a single nodal mass is over 10 cm in diameter, or if a mediastinal mass has a mass to mediastinal ratio (MMR) greater than 1/3 the maximum diameter of the thorax [9]. This distinction is important, because the presence of bulky disease has long been considered to be a poor prognostic factor. Symptoms can arise as a result of local compression by this growing mediastinal mass [10]. Other sites of nodal involvement include axillary, splenic, abdominal, and inguinal. Bone marrow involvement is rare at the time of diagnosis. About 30% of patients exhibit constitutional symptoms (“B” symptoms), which include (cyclical) fever, drenching night sweats and >10% unintended weight loss. Although less frequent, other symptoms could include pruritic, alcohol-related pain at nodal sites, as well as fatigue and decreased appetite. Excisional lymph node biopsy should be obtained to establish a diagnosis. Although a core needle biopsy is less ideal, this can be pursued in cases that have no easily accessible disease. Fluorodeoxyglucose

(FDG) positron emission tomography (PET) – computed tomography (CT) has high sensitivity and specificity in HL and is recommend for clinical staging. In the absence of FDG uptake on PET/CT in the bone marrow, a bone marrow biopsy does not have to be performed [11]. Radiographic staging is based on the Lugano classification, which is derived from the Ann Arbor staging system (**Table 1**) [12]. Treatment is based on classifying patients as having either limited stage (stage I or II) disease, also sometimes referred to as early-stage disease, or advanced disease (stage III or IV). Limited stage disease is further classified as either “favorable” of “unfavorable” disease based on the presence of baseline risk factors including age, number of nodal sites affected, extranodal status, presence of constitutional symptoms, erythrocyte sedimentation rate, and the presence of bulky disease [13]. The internal prognostic score (IPS) is the most widely used clinical prediction model to predict progression-free survival (PFS) and overall survival (OS) for advanced stage HL [14].

Molecular Biology of Hodgkin Lymphoma

For years, the cellular origins of HL remained unknown due to its unique morphology and immunophenotype [15]. The malignant cells are collectively termed Hodgkin and Reed-Sternberg (HRS) cells and consist of the mono-nuclear Hodgkin and the Patho gnomic multi-nucleated Reed-Sternberg (RS) cells [16]. Classical RS cells have a large-cell morphology with abundant basophilic cytoplasm and often a bilobed nucleus containing eosinophilic nucleoli. Most studies support that RS cells are continuously being generated as a result of incomplete cytokinesis and re-fusion of Hodgkin cells [17]. Despite being neoplastic, the presence of HRS cells in tumor tissue is rare, and their limited number is surrounded

Table 1. Lugano staging classification.		
Stage	Involvement	Extranodal (E) Status
Limited		
I	Involvement of one node or a group of adjacent nodes (one region) (I)	Single extra-lymphatic site in the absence of nodal involvement (I _E)
II	Involvement of two or more nodal groups on the same side of the diaphragm (II)	Stage I or stage II by nodal involvement with limited contiguous extranodal involvement (II _E)
Advanced		
III	Involvement of nodes on both sides of the diaphragm; nodes above the diaphragm with splenic involvement	Not applicable
IV	Involvement of non-contiguous extranodal sites (bone marrow, liver, lungs)	Not applicable
1. All cases to indicate the absence (A) or presence (B) of systemic symptoms at time of diagnosis (fever, night sweats, or unexplained weight loss).		
2. Designation of (E) refers to extranodal contiguous extension that can be encompassed within a radiation field appropriate for nodal disease of the same anatomic extent.		
3. Designation of bulky disease if a single nodal mass ≥ 10 cm or if a mediastinal mass is ≥ 1/3 of transthoracic diameter. Stage II bulky may be grouped in limited or advanced stage disease depending on presence of risk factors.		

by a complex inflammatory microenvironment composed of various elements, including reactive T cells, granulocytes, plasma cells, fibroblasts and endothelial cells [18]. Based on the composition of this tumor micro-environment (TME), HL is further divided into nodular sclerosing (80%), mixed cellularity (15%), lymphocyte-rich (5%) and lymphocyte depleted (<1%) subtypes. The presence of HRS cells surrounded by resetting CD4⁺ T cells is not an uncommon finding and highlights the dependance of HRS cells on the surrounding TME.

The insight that HRS cells represent transformed B cells, came from studies that showed that HRS cells carried clonal Ig V gene rearrangements [19]. Subsequent sequence analysis of rearranged V genes in HRS cells revealed presence of somatic hypermutation suggesting that the cells were descendants of germinal center (GC) B cells [20]. Importantly, 25% of HRS cells carried non-sense mutations rendering originally functioning gene rearrangements non-functional [21]. Because this usually results in GC B cells undergoing apoptosis, the thought is that HRS are derived from pre-apoptotic GC B cells. Although the exact mechanism through which these GC B cells are able to escape apoptosis remains unclear, Epstein-Barr Virus (EBV), appears to have a lymphoma-initiating role [22]. Latent EBV is identified in HRS cells in up to 20-40% of cases of HL, preferentially in mixed cellularity and lymphocyte depleted subtypes, and in most cases of patients infected with HIV. In EBV positive cases, viral proteins LMP1 and LMP2 are expressed [23]. Studies have shown that these two membrane proteins can mimic CD40 and BCR signaling, respectively, and thereby prevent apoptosis of transformed GC B cells with non-functional BCR signaling. Although most tumor cells retain phenotypic features of the cells from which they originate, HRS cells, strikingly, have lost the expression of most B-cell associated antigens [24]. While prominent expression for CD30 is almost universally observed, HRS cells are also often positive for CD15, MUM1 and the B cell transcription factor PAX5 (dim/weak) [25]. HRS cells are usually negative for CD3, CD20, CD45, and CD79a. The exact mechanism that underlies this reprogramming is not well understood, but studies have revealed several contributing factors including downregulation of B cell transcription factors (OCT2, BOB1, PU.1), epigenetic silencing of B cell genes (CD19, IgH) and deregulated expression of inhibitors of B cell molecules (ID2, ABF1, and NOTCH1). Increased expression of the latter results in inhibition of early B cell factor 1 (EBF1) as well as E2A, which are necessary transcription factors for B cell development [24,26-28].

The observation that HRS cells are able to escape apoptosis resulted in the recognition that these cells must rely on alternative signaling pathways for their survival and growth. Moreover, considering the extensive TME, HRS cells must be able to evade anti-tumor mechanisms from the cells residing in it. Constitutive activation of both the canonical and non-canonical NF- κ B pathways is a contributor to the anti-apoptotic phenotype of HRS cells [29,30]. Similarly, gains

and amplifications in positive regulators of NF- κ B (*REL*, *NIK*, and *BCL3*), as well as deletions and inactivating mutations in negative regulators (*TNFAIP3*, *NFKBIA*, *NFKBIE*, *CYLD* and *TRAF3*) have been identified over the last two decades with often presence of multiple abnormalities in HRS cells at the same time. In addition to constitutive activation of NF- κ B, overactivation of the JAK/STAT pathway is an almost universal finding in HL and crucial for promoting tumor inflammation and suppressing antitumor immunity [31,32]. While copy number gain of 9p24.1, where the *JAK2* gene is located, is a recurrent abnormality and observed in over 95% of HRS cells, activating mutations in *STAT3* and *STAT6*, as well as inactivating mutations in negative regulators, *PTPN1* and *SOCS1*, are commonly seen as well [33]. In addition to *JAK2*, the 9p24.1 locus carries the PD-1 ligand genes, *PD-L1* and *PD-L2*, and co-amplification is commonly observed [34]. Furthermore, both *JAK2* expression as well as EBV infection are able to further induce PD-L1 expression [35]. Overexpression of *PD-L1* and *PD-L2* is able to induce immune evasion by directly engaging with PD-1 immune effector cells in the TME and suppressing their anti-tumor immune response [36]. Interestingly, despite PD-L1 expression, there only appears to be a limited role for true immune cell exhaustion in HL, and instead PD-L1 appears to have several roles in HRS survival, which all result in shaping the TME as a biological niche. While other genes and pathways have been implicated in Hodgkin lymphomagenesis, including PI3K/Akt (*GNA13*, *ITPKB*), MAPK/ERK (*DUSP2*), export signaling (*XPO1*), immune evasion (*B2M*, *MHC2TA*), and epigenetic regulation (*ARID1A*, *JMJD2C*), all ultimately support the growth and survival of HRS cells in the TME [37,38].

Limited-Stage Hodgkin Lymphoma

For decades, controversies have existed about the optimal treatment of patients with limited-stage HL (stage I-II). Although the majority of patients can be cured with combination chemotherapy alone, the role of radiation remains an issue of debate. HL is uniquely sensitive to radiation and the use of it results in improved disease control and increased PFS. However, delayed toxicities manifesting as increased cardiovascular complications and therapy-related malignancies have been observed even many decades after treatment completion. Due to high cure rates of this malignancy in this relatively young population of patients, attempts have been made to minimize radiation therapy (RT) as part of curative therapy. However, even by limiting radiation fields, the risk remains. The introduction of MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) back in the 1970's was a major advancement in advanced HL yielding a 10-year overall survival (10-OS) of 66% without the need for radiation [39]. Further improvement came with the development of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), which showed a survival benefit over MOPP [40]. Importantly, ABVD was also found to significantly lower the risk of secondary malignancies, as a result of omitting alkylating agents. The

phase III HD10 trial further evaluated the number of cycles of ABVD and the dose of involved-field radiation therapy (IFRT) for patients with limited-stage HL with a favorable prognosis [41,42]. Favorable prognosis was defined as having absence of unfavorable risk factors, including the presence of a large mediastinal mass (mediastinal mass ratio MMR > 1/3), extra-nodal disease, involvement of ≥ 3 nodal areas, or elevated ESR (≥ 50 mm/hr for stage IA, IIA; ≥ 30 mm/hr for stage IB, IIB). This trial showed that two cycles of ABVD followed by 20 Gy is as effective, and less toxic, than four cycles of ABVD with 30 Gy for patients with limited-stage disease and no risk factors. 10-year PFS (10-PFS) was 87% each (HR 1.0; 95% CI 0.6-1.5) and 10-OS 94% each (HR 0.9; 95% CI 0.5-1.6), respectively. Based on the results of this trial, a new standard of care was established. However, no chemotherapy-only arm was included, and the rate of cardiovascular events and secondary malignancies had almost doubled at a median follow-up of 7.5 years. The HD.6 and RAPID trials further evaluated ABVD with or without radiotherapy for non-bulky, limited-stage HL [43,44]. Both studies highlighted that patients with non-bulky, limited-stage HL have excellent outcomes if they are treated with chemotherapy alone. Subsequent trials further improved our understanding by assessing the value of an interim PET/CT to guide early treatment adaptation and to identify patients who would benefit from additional cycles of chemotherapy and/or IFRT. In addition, trials tried to improve outcomes for patients with unfavorable disease characteristics, despite world-wide differences in classification of prognostic risk factors [13]. HD11 attempted to improve outcomes for patients with limited-stage, unfavorable HL. Four cycles of ABVD with either 20 or 30 Gy IFRT was compared to four cycles of the more intensified BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen with 20 or 30 Gy IFRT [45]. At 5-year follow-up, four cycles of ABVD + 20 Gy IFRT were found to be non-inferior to the other three arms with similar 5-OS (BEACOPP + 20Gy vs ABVD + 20Gy; 95.1 vs 93.8%).

After successful introduction of BV and ICI for the treatment of HL in the advanced-stage as well as R/R setting, several studies have started to evaluate the efficacy of these agents for the frontline treatment of limited-stage HL (**Table 2**). A single-arm, pilot phase II trial evaluated efficacy of four cycles of BV-AVD followed by 30 Gy involved-site radiotherapy (ISRT) in 30 patients with untreated, limited-stage HL with unfavorable risk features as defined by German Hodgkin Study Group (GHSG) criterion [46]. 47% of patients had bulky disease and 57% had an MMR >1/3. After two and four cycles of BV-AVD, 90% and 93% of patients achieved PET/CT negativity, respectively. Two patients had primary refractory disease, and one patient discontinued treatment due to intolerable toxicity. All patients who completed BV-AVD + ISRT obtained a CR. 1-PFS was 93.9% (95% CI 84-102). Overall, the treatment was well tolerated with no evidence of significant pulmonary toxicity. A subsequent multicenter pilot study further evaluated the BV-AVD regimen with and without consolidative radiotherapy for

limited-stage, unfavorable HL [47]. Patients received 4 cycles of BV-AVD, and divided in one of four cohorts, if PET/CT was negative after four cycles or PET/CT positive, but subsequent biopsy was negative, to receive either 30Gy ISRT, 20 Gy ISRT, 30Gy consolidation volume radiation therapy (CVRT) or no consolidation radiotherapy. Patient with a positive biopsy for HL went off study. 117 patients were enrolled with 30 patients in cohort 1 and 29 patients each in cohorts 2-4. There was a greater proportion of patients with bulky disease in cohorts 3 and 4. Complete response rates in cohorts 1-4 were 93%, 100%, 93%, and 97%, respectively. With a median follow-up of 3.8 years, 2-PFS was 93% (95% CI 83.9-1.0), 97% (95% CI 89.9-1.0), 90% (95% CI 78.5-1.0), and 97% (95% CI 89.9-1.0), respectively. These findings supported the safe reduction and even elimination of consolidative radiation among patients that are PET/CT negative after four cycles of BV-AVD. The larger BREACH trial was a multi-center, randomized, phase II trial evaluating the efficacy of BV-AVD also for patients with limited-stage, unfavorable HL [48]. Patients were eligible if they had limited-stage HL with ≥ 1 unfavorable EORTC/LYSA criterion. 170 patients were enrolled and randomized in a 2:1 ratio to either four cycles BV-AVD with IFRT or four cycles ABVD with IFRT. Primary endpoint was PET/CT response rate after two cycles based on 2007 Cheson criteria. After two cycles, PET/CT negativity (Deaville score 1-3) was observed in 82.3% of patients who received BV-AVD (90% CI 75.3-88) compared to 75.4% (90% CI 64.3-84.5) of patients who received ABVD. 2-PFS was 97.3% (95% CI 91.9-99.1) and 92.6% (95% CI 81.4-97.2), respectively. Strikingly, in patients that were PET/CT positive (Deaville score 4-5) after two cycles, 2-PFS was 90.9% (95% CI 74.4-97) for patients who received BV-AVD versus 70.7% (95% CI 39.4-87.9) for patients that received ABVD. Similarly, a non-randomized phase II trial was performed in 34 patients with non-bulky, limited stage HL [49]. All patients received a lead-in of two doses of BV followed by 4-6 cycles of BV-AVD based on PET/CT imaging obtained after the second cycle. No consolidative radiation was used. 38% of patients had unfavorable risk factors. An ORR was observed in 100% of patients after the initial two doses of BV, with a CR rate of 52.9% (95% CI 35.1-70.2). After two additional cycles of BV-AVD, CR rate was 97.1% (95% CI 84.7-99.9) with one fatality from sepsis. Although BV-AVD was well tolerated, peripheral neuropathy was observed in 79% of patients with 24% having grade 3-4 adverse events. The same group subsequently evaluated 4-6 cycles of BV-AD for the treatment of limited-stage HL in the hope that the omission of vinblastine would reduce the incidence of peripheral neuropathy as a result of overlapping toxicity between BV and vinblastine [50]. Again, no consolidative radiation was used. 34 non-bulky patients with stage I-II HL were enrolled. 47% of patients had unfavorable disease factors. ORR and CR rates were 100% (95% CI 76.3-98.1) and 97% (95% CI 87-100), respectively, with a 5-PFS of 91% (95% CI 75-99). Peripheral neuropathy was observed in 59% of patients, with most cases being grade 1 and no patients were observed of grade 3 or higher.

Only limited data is currently available about the use of ICI in limited-stage HL. A phase II non-randomized trial evaluated single-agent pembrolizumab for three cycles followed by 4-6 cycles of AVD in patients with both limited and advanced-stage HL [51]. 30 patients were enrolled, including 12 patients with limited-stage, unfavorable disease. CMR rate after single-agent pembrolizumab was 42% in patients with limited-stage, unfavorable disease, and increased to 100% after two additional cycles of AVD. At a median follow-up of 33.1 months (range, 26.0-43.0), PFS and OS remained at 100%. An international phase II trial to confirm the findings is currently ongoing. The NIVAH study also evaluated efficacy of ICI for the treatment of limited-stage HL [52]. In this larger phase II trial, 109 patients with limited-stage, unfavorable HL were enrolled based on GHSG criteria and randomized to either four cycles of nivolumab-AVD (N-AVD) or sequential treatment of four cycles nivolumab, followed by two cycles of N-AVD, followed by two cycles of AVD. Both arms received ISRT for consolidation. At final analysis, 3-PFS and 3-OS estimates for the total cohort were 99% (95% CI 97-100) and 100%, respectively. One case of histologically-proven primary progression was observed in a patient while on nivolumab monotherapy. Several studies are currently underway evaluating novel agents for the treatment of limited-stage HL. Clinical trials are currently underway evaluating the efficacy of BV with nivolumab for the frontline treatment of patients with limited-stage HL, including for elderly patients (NCT03712202, NCT02758717). Another phase II trial (INDIE) is evaluating the efficacy of a different PD-1 inhibitor, Tislelizumab, for patients with limited stage, unfavorable HL (NCT04837859).

In summary, these smaller studies have evaluated both BV and ICI in limited-stage HL, and the data that we have is encouraging. Large randomized trials are needed to evaluate BV-AVD or ICI with AVD versus the standard of care of ABVD with or without consolidative radiation therapy. Further, these trials should omit mandatory consolidative radiation therapy in the experimental arms. BV-AVD should be considered for patients with limited-stage disease with unfavorable disease characteristics, especially in patients with bulky disease or MMR > 1/3, and this is our standard practice at our institution. In our opinion, combined modality treatment for limited-stage HL is likely a thing of the past rapidly approaching extinction as current approaches utilizing chemo-immunotherapy are showing high cure rates without the need for consolidative radiation therapy.

Advanced-Stage Hodgkin Lymphoma

Frontline therapy for advanced-stage HL (stage III-IV) remains curative intent due to its high susceptibility to chemotherapy. As a result, over 80% of patients with advanced-stage HL can be cured with multi-drug combination chemotherapy approaches. After the initial introduction of MOPP, and subsequent development of ABVD, both regimens were compared, not only against each other, but also as an

alternating hybrid regimen (MOPP vs ABVD vs MOPP/ABVD) in newly diagnosed patients with advanced-stage HL [53]. This study demonstrated superiority of ABVD and MOPP/ABVD over MOPP alone, but also significant less toxicity of ABVD when compared to MOPP-containing regimens. This study established ABVD as a standard of care for patients with advanced-stage HL. Subsequent trials comparing ABVD with more complex multi-drug regimens failed to show similar outcomes, except for maybe therapy with escalated BEACOPP [54]. However, while treatment with escalated BEACOPP has been shown to result in higher PFS rates when compared to ABVD (5-PFS 93% vs 75%; HR 0.3, $p=0.007$), no significant difference have been observed in OS (5-OS 99% vs 92%; HR 0.18; $p=0.06$). Studies then tried to determine whether PET/CT could be used for risk adapted management. As part of the RATHL trial, 1214 patients with a new diagnosis of advanced-stage HL received two cycles of ABVD and subsequently underwent interim PET/CT after two cycles [55,56]. Patients with a negative PET/CT (Deaville 1-3) were randomly assigned to either continue ABVD or omit bleomycin (AVD) for the next 3-6 cycles. Patients with a positive PET/CT (Deaville 4-5) had treatment intensified with BEACOPP. For all patients, 7-year PFS and 7-year OS were 78.2% (95% CI 75.6-80.5) and 91.6% (95% CI 89.7-93.2), respectively. 3-PFS was 85.5% (95% CI 81.9-88.4) for the ABVD arm and 84.3% (95% CI 80.6-87.3) for the AVD arm, which fell within the predefined margin of non-inferiority. Patients who failed to obtain a negative PET/CT after two cycles, and proceeded with BEACOPP, had significantly inferior outcomes with observed 7-year PFS of 65.9% (95% CI 58.1-72.6) and 7-year OS of 83.2% (95% CI 76.2-88.3). Similar inferior outcomes were observed for patients with positive interim PET/CTs in the SWOG S0816 and GITIL/FIL HD 0607 trials, highlighting the need to escalate treatment in these patients [57,58].

After showing efficacy in R/R HL, BV was further evaluated in advanced-stage HL by incorporating it into established backbone regimens to not only improve efficacy but also with the hope to reduce toxicity. ECHELON-1 was a multi-center, randomized phase III clinical trial that involved patients with previously untreated stage III and IV HL (**Table 2**) [59,60]. A total of 1334 patients were enrolled and randomly assigned to receive either six cycles of BV-AVD ($n=664$) or ABVD ($n=670$). Interim PET/CT was performed after the second cycle. Long-term follow-up revealed a 6-OS benefit favoring BV-AVD over ABVD in both interim PET/CT negative patients (94.9% vs 90.6%; HR 0.53, 95% CI 0.34-0.86) as well as in interim PET/CT positive patients (95% vs 77%; HR 0.16, 95% CI 0.04-0.72). 6-PFS also favored BV-AVD over ABVD (82.3% vs 74.5%; HR 0.68, 95% CI 0.53-0.86) in all patient subgroups independent of stage, age, and IPS. A significantly higher incidence of peripheral neuropathy was observed in the BV-AVD arm, as well as incidence of neutropenic sepsis mandating addition of growth factor support. Based on ECHELON-1, BV in combination with chemotherapy was approved by the FDA

Table 2. Summary of immunotherapies for the frontline treatment of HL and crucial trials.						
Setting	Trial	Treatment	Dose	Patients (age)	Disease	Outcome
Limited Stage – Favorable	Abramson [49] Phase 2	BV + AVD	1.2 mg/kg days 1 & 15 followed by 1.2 mg/kg + AVD x 4-6 cycles	34 (20-75 yrs)	21 Stage I/II favorable HL 13 Stage I/II unfavorable HL	CR 52.9% BV only (95% CI 35.1-70.2); 97.1% BV-AVD x2 (95% CI 84.7-99.9); 3-PFS 94% (95% CI 78-98); 3-OS 97% (95% CI 81-100)
	Abramson [50] Phase 2	BV + AD	1.2 mg/kg days 1 & 15 + AVD x 4-6 cycles	34 (18-63 yrs)	18 Stage I/II favorable HL 16 Stage I/II unfavorable HL	ORR 100% (95% CI 76.3-100); CR 97% (95% CI 87-100); 5-PFS 91% (95% CI 75-99)
Limited Stage – Unfavorable	Kumar [46] Phase 2	BV + AVD	1.2 mg/kg q3w + AVD x4 cycles + RT	30 (18-59 yrs)	Stage I/II unfavorable HL (GHSG criteria)	PET2 negativity 90% PET4 negativity 93% 1-PFS 93.5% (95% CI 84-102)
	Kumar [47] Phase 2	BV-AVD	1.2 mg/kg q3w + AVD x4 cycles + RT (30 Gy ISRT, 20 Gy ISRT, 30 Gy CVRT, no RT)	117 (18-59 yrs)	Stage I/II unfavorable HL (GHSG criteria)	2-PFS 30Gy 93.1% (95%CI 83.9-1.0), 20Gy 96.6% (95%CI 89.9-1.0), 30Gy CVRT 89.7% (95%CI 78.5-1.0), 96.6% (95%CI 89.9-1.0).
	For Necker [48] Phase 2 BREACH	BV+AVD vs ABVD	1.2mg/kg q3w + AVD x4 cycles + RT vs ABVD x4 cycles + RT	170 (18-60 yrs)	Stage I/II unfavorable HL (EORTC/LYSA)	PET2 negativity 82.3% BV-AVD (90% CI 75.3-88) vs 75.4% ABVD (90% CI 64.3-84.5); 2-PFS 97.3% BV-AVD (95% CI 91.9-99.1) vs 92.6% ABVD (95% CI 81.4-97.2).
	Brockelman [52] Phase 2 NIVAHL	A: Nivolumab + AVD B: Nivolumab, N-AVD, AVD	A: 240 mg q3w + AVD + RT B: 240 mg q3w, 240 mg q3w + AVD x2, AVD x2 + RT	109 (18-60 yrs)	Stage I/II unfavorable HL (GHSG criteria)	3-PFS 99% N-AVD (95 CI 97-100) and 100% in sequential cohort. 3-OS 100% and 100%.
	Allen [51] Phase 2 KeyNote-667	Pembrolizumab + AVD	2 mg/kg q3w x3 cycles followed by AVD x 4-6 cycles	30 (21-77 yrs)	12 Stage I/II unfavorable HL 18 Stage III/IV HL	CMR 37% (monotherapy pembro); 100% (pembro + 2x AVD); 3-PFS and 3-OS 100%
Advanced Stage	Connors [59] Phase 3 ECHELON-1	BV + AVD vs ABVD	1.2 mg/kg q3w + AVD x6 cycles vs ABVD x6 cycles	1334 (26-53 yrs)	Stage III/IV HL	6-PFS 82.3% BV-AVD vs 74.5% ABVD (HR 0.68, 95% CI 0.53-0.68); 6-OS 93.9% BV-AVD (95% CI 91.6-95.5) vs 89.4% ABVD (95% CI 86.6-91.7)
	Herrera [62] Phase 3 SWOG-S1826	Nivolumab + AVD vs BV + AVD	240 mg q3w + AVD x 6 cycles vs 1.2 mg/kg q3w + AVD x 6 cycles	970 (12-83 yrs)	Stage III/IV HL	2-PFS 92% N-AVD vs 83% BV-AVD (HR 0.45; 95%CI 0.3-0.65)
	Borchmann Phase 3 GHSG-HD21	BV+ECADD vs escBEACOPP	1.2mg/kg + ECADD q3w x 4-6 cycles vs escBEACOPP x 4-6 cycles	1500 (18-61 yrs)	Stage III/IV HL	3-PFS 94.9% BV-ECADD vs 92.3% (HR 0.63, 95% CI 0.42-0.94)
BV: Brentuximab Vedotin; yrs: years; HL: Hodgkin Lymphoma; CR: Complete Remission; CI: Confidence Interval; 3-PFS: 3-year Progression-Free-Survival; 3-OS: 3-year Overall Survival; PET2: PET/CT after 2 cycles; Nivo: Nivolumab; q3w: each 3 weeks; CMR: Complete Metabolic Remission.						

in 2018 for previously untreated patients with stage III or IV HL. A follow-up phase II trial looked at sequential treatment of BV and AVD to minimize toxicity and improve curability for older patients with HL [61]. 48 patients with a median age of 69 years (range, 60-88) were enrolled and received two lead-in doses of single-agent BV, followed by six cycles of AVD, followed by four consolidative doses of BV. 81% of patients had advanced-stage HL, and 19% limited-stage, unfavorable disease. 52% of patients completed all 12 cycles of therapy. 2-EFS, 2-PFS and 2-OS were 80%, 84%, and 93%, respectively. Geriatric-based measures were strongly associated with survival. The currently ongoing GHSH HD21 trial attempts to further improve outcomes in this setting, by combining BV with ECADD (etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone). This phase III trial included 1500 patients with advanced HL who are randomized in a 1:1 ratio to either receive two cycles of BV-ECADD or two cycles of escalated BEACOPP before undergoing interim PET/CT. Patients that are PET/CT negative, will receive two additional cycles of the prescribed regimen, whereas patients that are PET/CT positive, will receive an additional four cycles. Data presented at the 2024 annual meeting of the American Society of Clinical Oncology revealed that at a median follow-up of 48 months, estimated 4-year PFS for patients receiving BV-ECADD was superior compared to patients who received escalated BEACOPP (94.3% vs 90.9%; HR 0.66, 95% CI 0.45-0.97), with similar 4-year OS.

Studies have also incorporated ICI with chemotherapy regimens for the frontline setting of patients with advanced HL. A pilot phase II trial evaluated concurrent administration of pembrolizumab with AVD in 30 patients with HL [51]. Patients of all stages were enrolled in the study, with the majority having advanced disease (60%). 2-PFS and 2-OS were 97% (95% CI 90-100) and 100%, respectively. None of the four patients that were found to have end-of-treatment positive PET/CT, yet negative ctDNA, have relapsed to date. More recently, the long-awaited results of the SWOG-S1826 trial were published after the second interim analysis had already shown promising results with achievement of the efficacy threshold [62]. This multicenter phase III study was a collaboration between the North American adult and pediatric cooperative groups. 994 patients with newly diagnosed, advanced-stage HL were enrolled and randomized between six cycles of either Nivolumab+AVD (n=496) or BV+AVD (n=498). 970 patients were eligible for evaluation and stratified based on age, IPS and intended use of RT for residual disease. The median age was 27 years (range, 12-84 years). With a median follow-up of 2.1 years (range, 0-4.2 years), 2-PFS was 92% (95% CI 89-94) after N+AVD compared to 83% (95% CI 79-86) after BV+AVD (HR 0.45; 95%CI 0.3-0.65). 2-OS was 99% in the N+AVD group and 98% in the BV+AVD group (HR 0.39; 95%CI 0.15-1.0). Only seven patients received end of treatment RT across arms. Overall, N+AVD was also better tolerated than BV+AVD. Fewer patients stopped treatment early on the N+AVD arm (7.6% versus 12.0% of patients treated with BV+AVD) and

fewer deaths occurred during treatment with N+AVD (0.6% versus 1.7% for patients treated with BV+AVD). Grade ≥ 3 side effects occurred more frequently with BV+AVD, especially the occurrence of peripheral neuropathy (32% versus 2.9% for patients treated with N+AVD). Grade ≥ 3 neutropenia was more frequently seen with N+AVD (48% versus 26% for patients treated with BV+AVD). Immune-related adverse events were infrequent with nivolumab, and rates of pneumonitis, dermatitis and colitis were similar between arms. Hypothyroidism (7%) and hyperthyroidism occurred more frequently with N+AVD (7% and 3%, respectively) than with BV+AVD (0.01% and 0%, respectively). The differences in toxicity were particularly pronounced in patients older than 60 years of age. Rutherford *et al.* performed a subset analysis of the SWOG-S1826 trial data of patients aged 60 years and over and presented the data at the 2023 annual meeting of the American Society of Hematology. At the time of analysis, 97 patients ≥ 60 years had been enrolled with 48 patients being randomized to N+AVD and 49 patients to BV+AVD. The median age was 66 years (range, 60-83 years). 61% of patients had stage IV disease and 47% had IPS 4-7. After a median follow-up of 12.1 months, a superior PFS was observed in the N+AVD arm (HR 0.35; 95% CI 0.12-1.02). 1-PFS was 93% (95% CI 79-98) for N+AVD and 64% (95% CI 45-77) for BV+AVD. 1-OS was 95% (95% CI 83-99) for N+AVD and 83% (95% CI 67-92) for BV+AVD. In the N+AVD group there were 2 deaths observed (sepsis) and 3 patients with progression/relapse, whereas in the BV+AVD group 7 deaths were observed (sepsis, pneumonitis, unknown) and 8 patients with progression/relapse. Treatment was discontinued early in 5 patients (10%) on N+AVD and 16 patients (33%) on BV+AVD. This analysis highlighted that not only does N+AVD have an improved PFS when compared with BV+AVD in patients ≥ 60 years with advanced stage HL, it also is better tolerated in this patient population. Currently several trials are ongoing that are incorporating both BV and ICI with chemotherapy for the treatment of advanced stage HL (NCT06045195, NCT03907488). The phase II Pembo-FLASH trial is evaluating the efficacy of a combination of Pembrolizumab + EACOPP using a response-adapted approach in advanced stage HL (NCT06045195).

Based on the recent results of the SWOG-S1826 trial, N+AVD will become a new standard of care for the frontline treatment of patients with advanced HL. Although we are still awaiting long-term follow-up data, current results support that N+AVD is the preferred treatment over BV+AVD not only for patients ≥ 60 years of age, but also for younger patients with advanced stage HL. These recommendations also reflect the practice at our institution.

Relapsed and Refractory Hodgkin Lymphoma

Although the majority of patients with HL will obtain cure after frontline treatment, 10-15% of patients with limited-stage disease and 15-30% of patients with advanced-stage disease will eventually relapse. Moreover, in approximately

10-15% of patients, the disease will be refractory to initial treatment. The management of these patients has long been salvage treatment followed by, if eligible, high-dose-therapy with autologous stem cell rescue (HDT/ASCR). This recommendation is based off results from two phase III trials that revealed significant improvements in EFS, PFS and time-from-treatment-failure (TTF) for patients with R/R HL treated with HDT/ASCR when compared to patients treated with conventional salvage chemotherapy alone [63,64]. Although a significant proportion of patients can be cured with HDT/ASCR, approximately 40-50% of patients still relapse [65]. Prognostic models have been developed to predict the outcome of patients with R/R HL undergoing HDT/ASCR. Although over the years, several prognostic factors for TTF and OS have been identified, all studies highlight that response to salvage treatment is one of the most important predictors of outcome, and that the presence of metabolically active residual disease before undergoing HDT/ASCR confers an inferior prognosis [66-69].

Although optimal cytoreduction is crucial before HDT/ASCR, no randomized phase III trials exist in this setting to give evidence-based recommendations. Commonly used regimens include ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, high-dose cytarabine, cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin), GCD (gemcitabine, cisplatin, dexamethasone), and GVD (gemcitabine, vinorelbine, liposomal doxorubicin) [68,70-74]. ORR and CR rates are about similar between regimens and vary between 59-89% and 19-50%, respectively. Bendamustine in combination with gemcitabine and vinorelbine (*BeGEV*) was evaluated as well in a phase II trial as salvage regimen before HDT/ASCR in patients with R/R HL [75]. ORR was found to be 83%, with 73% of patients obtaining a CR.

High level CD30 expression is an almost universal finding on HRS cells in HL. However, initial efforts in phase I and II studies to target CD30 in patients with R/R HL using unconjugated monoclonal antibodies did not show significant anti-tumor activity [76-78]. These findings prompted further development of CD30 antibody-drug conjugates, which would have to rely less on the host immune response for clinical efficacy in patients that likely already have an impaired antibody-dependent cell-mediated immunity as a result of their tumor microenvironment. Initial phase I trials evaluating BV for R/R HL in heavily pre-treated patients revealed ORR of 50-59% and CR rates in the 25-35% [79,80] (**Table 3**). This prompted further evaluation of the efficacy of BV for the treatment of R/R HL in a pivotal phase II trial that looked at the efficacy and safety of single-agent BV in 102 patients with R/R HL who had progressed after HDT/ASCR [80]. 75% of patients had an ORR, and 34% of patients obtained a CR. Median PFS was 5.6 months (95% CI 5.0-9.0) and median duration of response for those in CR was 20.5 months (95% CI 10.8-NE). 5-year end-of-study results revealed a PFS rate of 22% (95% CI, 13-31%) and OS rate of 41% (95% CI, 31-51%) [81]. 13 patients remained in CR at 5 years. Based on these results, the FDA approved single-agent BV in 2011 for treatment of patients with HL who had progressed after HDT/ASCR, or who had at least two prior lines of therapy and were deemed not a candidate for HDT/ASCR.

After this initial approval, BV was further evaluated for treatment in the second-line, before HDT/ASCR, in combination with chemotherapy. Using a PET-adapted strategy, a trial conducted at Memorial Sloan Kettering Cancer Center evaluated the combination of BV with ICE as part of a non-randomized, single-Centre phase II clinical trial for patients with R/R HL [82]. 46 patients were enrolled, but only 45 patients received treatment with two cycles of BV. After completion

Table 3: Summary of immunotherapies for the treatment of R/R HL and crucial trials.						
Setting	Trial	Treatment	Dose	Patients (age)	Disease	Outcome
Salvage Treatment Post-HDT/ASCR	Forero-Torres [77] Phase 2	SGN-30 (CD30 mAB)	6 mg/kg or 12 mg/kg weekly	79 (20-82 yrs)	38 R/R HL 41 ALCL	ORR R/R HL 0/38 (0%) Stable disease R/R HL 11/38 (28.9%)
	Ansell [78] Phase 1/2	MDX-060 (CD30 mAB)	0.1, 1, 5, 10 mg/kg weekly	48 (19-78 yrs)	40 R/R HL 6 ALCL 2 CD30+ TCL	CR R/R HL 1/40 (2.5%) PR R/R HL 2/40 (5%)
	Younes [80] Phase 1	BV (SGN-35)	0.1-3.6 mg/kg q3w	45 (20-87 yrs)	42 R/R HL 2 ALCL 1 AITL	CR R/R HL 9/26 (35%) PR R/R HL 4/26 (15%)
	Fanale [79] Phase 1	BV	0.4-1.4 mg/kg weekly	44 (12-82 yrs)	38 R/R HL 5 ALCL 1 PTCL-NOS	ORR R/R HL 54% CR R/R HL 25% PR R/R HL 22%
	Younes [80] Phase 2	BV	1.8 mg/kg q3w up to 16 cycles	102 (15-77 yrs)	R/R HL	ORR 75%; CR 34% mPFS 5.6mo (95% CI 5.0-9.0); mOS 22.4mo (95% CI 21.7-NE)

Salvage Treatment Pre-HDT/ASCR	Moskowitz [82] <i>Phase 2</i>	BV ± augmICE	1.2 mg/kg q3w x2 ± augmICE x2 cycles	45 (13-65 yrs)	R/R HL	CMR after BV x2 27% (95% CI 13-40); CMR after BV x2 + ICE x2 76% (95% CI 62-89)
	Lacasse [85] <i>Phase 1/2</i>	BV + bendamustine	1.8 mg/kg q3w + bendamustine 90 mg/m ² x2-6 cycles	55 (19-79 yrs)	R/R HL	ORR 92.5% (95% CI 81.8-97.9%); CR 73.6% (95% CI 59.7-84.7); 2-PFS 69.8%
	Garcia [84] <i>Phase 1/2</i>	BV + ESHAP	1.2 mg/kg q3w + ESHAP x 3x cycles	66 (18-66 yrs)	R/R HL	ORR 91% (95% CI 84-98); CR 70% (95% CI 59-81); mPFS 71% (95% CI 65-77) mOS 91% (95% CI 84-98)
Maintenance Post-HDT/ASCR	Moskowitz [86] <i>Phase 3</i> <i>ETHERA</i>	BV vs placebo	1.8 mg/kg q3w up to 16 cycles vs placebo	329 (18-71 yrs)	R/R HL	5-PFS 59% vs 41% (HR 0.52; 95% CI 0.38-0.72)
Salvage Treatment Post-HDT/ASCR	Armand [88] <i>Phase 2</i> <i>CheckMate-205</i>	Nivolumab	3 mg/kg q3w until progression or toxicity	243 (26-46 yrs)	A: 63 R/R HL, BV naïve B: 80 R/R HL, BV after HDT/ASCR C: 100 R/R HL, BV before HDT/ASCR	A: ORR 65% (95% CI 52-77); CR 29%, PR 37% B: ORR 68% (95% CI 56-78); CR 13%, PR 55% C: ORR 73% (95% CI 63-81); CR 12%, PR 61%
	Kuruville [90] <i>Phase 3</i> <i>KeyNote-204</i>	Pembrolizumab vs BV	Pembrolizumab 200 mg q3w vs BV 1.8 mg/kg q3w	304 (28-53 yrs)	R/R HL	mPFS pembro 13.2mo vs 8.3mo BV (HR 0.65; 95% CI 0.48-0.88)
Salvage Treatment Pre-HDT/ASCR	Mei [92] <i>Phase 1/2</i>	Nivolumab ± Nivolumab-ICE	240 mg q3w x3-6 cycles ± Nivolumab-ICE x2 cycles	43 (19-79yrs)	R/R HL	ORR 93% (95% CI 81.8-97.9) CR 91%; 2-PFS 72% (95% CI 56-83); 2-OS 95% (95% CI 82-99%)
	Moskowitz [93] <i>Phase 2</i>	Pembrolizumab + GVD	200 mg + GVD q3w x2-4	39 (21-72 yrs)	R/R HL	ORR 100% (95% CI 91-100) CR 95% (95% CI 82-99); PR 5% (95%CI 1-18)
	Advani [91] <i>Phase 1/2</i>	Nivolumab + BV	Nivolumab 3 mg/kg + BV 1.8 mg/kg q3w x4 cycles	91 (18-69 yrs)	R/R HL	ORR 85% (95% CI 75.5-91.3); 3-PFS 77% (95% CI 65-86); 3-OS 93% (95% CI 85-97)
HDT/ASCR: High-Dose Therapy with Autologous Stem Cell Rescue; MAB: Monoclonal Antibody; R/R: Relapsed / Refractory; HL: Hodgkin Lymphoma; yrs: years; ALCS: Anaplastic Large-Cell Lymphoma; CR: Complete Remission; ORR: Overall Response Rate; PR: Partial Remission; q3w: each 3 weeks; TCL: T-cell Lymphoma; BV: Brentuximab Vedotin; PTCL: Peripheral T-Cell Lymphoma; NOS: Not Otherwise Specified; CI: Confidence Interval; CMR: Complete Metabolic Remission; MPFS: Median Progression-Free-Survival; MOS: Median Overall Survival; AICE: Augmented ICE; 2-PFS: 2-year Progression-Free-Survival.						

of two cycles of BV, patients received a PET/CT. Patient who achieved a PET/CT negative status (Deauville score of 1 or 2) underwent directly HDT/ASCR. Patients who had persistent abnormalities on PET/CT (Deaville 3-5) received two cycles of augmented ICE before consideration of HDT/ASCR. After BV treatment, 12 patients (27%, 95% CI 13-40%) were found to be PET/CT negative and 33 patients (73%, 95% CI 60-86) were PET/CT positive. One patient withdrew consent, 32 patients received augmented ICE. 22 patients (69%, 95% CI 53-85) were found to be PET/CT negative after two cycles augmented ICE. Overall, 34 patients (76%, 95% CI 60-86) achieved PET/CT negativity. The combination of BV with ICE was overall well tolerated with few grade 3-4 adverse events. Similarly, BV has been evaluated in combination with other regimens to further improve CR rates before HDT/ASCR, including platinum-containing regimens such as ESHAP and DHAP, as well as, bendamustine [83-85]. In addition to improving CR rates before HDT/ASCR, BV has been evaluated as consolidation therapy after HDT/ASCR in the phase III AETHERA trial [86,87]. 329 BV-naïve patients with high-risk of relapse after HDT/ASCR, defined as either having relapsed or progressive HL within 12 months after frontline therapy, a history of refractory disease, or extranodal involvement before HDT/ASCR, where randomly assigned to either BV or placebo for up to 16 cycles starting 30-45 days after HDT/ASCR. At 5-year follow-up, a sustained PFS benefit was observed for patients treated with BV versus placebo (59% vs 41%; HR 0.521, 95% CI 0.379-0.717). Although neuropathy was observed with BV consolidation, it resolved in 90% of patients. Based on this trial, BV was approved by the FDA for consolidation post HDT/ASCR in 2015.

Overtime, immune checkpoint inhibitors (ICI) were found to have efficacy in HL. Initial studies, evaluated both PD-1 inhibitors, nivolumab (CheckMate-205) and pembrolizumab (KEYNOTE-087), as single-agents for the treatment of patients with R/R HL who progressed after HDT/ASCR [88,89]. Studies revealed strong efficacy, durable responses with a known toxicity profile. Pembrolizumab was subsequently compared head-to-head to BV in a multicenter, randomized, phase III trial (KEYNOTE-204) [90]. 304 patients with R/R HL who were ineligible or who had relapsed after HDT/ASCR were enrolled and randomly assigned to either pembrolizumab (151 patients) or BV (153 patients). After a median time to cutoff of 25.7 months, median PFS was 13.2 months in the pembrolizumab arm versus 8.3 months in the BV arm (HR 0.65; 95% CI 0.48-0.88). Based on the above results, the FDA approved single-agent nivolumab for patients with R/R HL whose disease had progressed after HDT/ASCR in 2016, and single-agent pembrolizumab for the treatment of patients with R/R HL whose disease has relapsed after three lines of therapy in 2017.

ICI were further evaluated as first salvage treatment in combination with either BV or chemotherapy. The combination of nivolumab with BV was evaluated as a chemotherapy-sparing option as part of a phase 1/2 trial in 91 patients with

R/R HL [91]. After four cycles, ORR was found to be 87% (95% CI 75.5-91.3) with 67% (95% CI 56.4-76.5) of patients achieving a CR. Estimated 3-PFS was 77% (95% CI 65-86) with median PFS not reached. The estimated 3-OS was 93% (95% CI 85-97). No new toxicities were observed, and the adverse event profile of the combination was similar to each agent administered individually. Using a response-adapted approach, nivolumab alone or nivolumab with ICE was further evaluated in a phase II trial in 43 patients with R/R HL [92]. Patient would receive up to six cycles of nivolumab and upon achieving CR proceed to HDT/ASCR. Patients with progressive disease at any point, or patients not in CR after six cycles, would receive two cycles of nivolumab plus ICE (N-ICE). ORR and CR rates in patients with monotherapy nivolumab was 81% and 71%, respectively. Patients who received N-ICE had an ORR and CR of 93% and 91%, respectively. 2-PFS was found to be 72% (95% CI 56-83%) and 2-OS 95% (95% CI 82-99). Impressive results were seen in a phase II trial combining the other ICI, pembrolizumab, with GVD for second-line treatment of R/R HL [93]. Patients received 2-4 cycles of pembrolizumab with GVD. 39 patients were enrolled of which 41% of patients had primary refractory disease and 38% had relapsed within one year after frontline treatment. 31 patients received two cycles, and the other eight patients received four cycles. ORR and CR rates were 100% (95% CI 91-100) and 95% (95% CI 82-99), respectively. Thirty-six patients (95%) proceeded with HDR/ASCR. With a median follow-up of 13.5 months (range 2.66-27.06) after HDT/ASCR, all transplanted patients remained in remission.

Although allogeneic stem cell transplant (alloSCT) has been used for decades as salvage strategy for R/R HL and is able to provide durable disease control for some patients, the reality is that as a result of a lack of potential donors and the significant treatment-associated toxicity in patients that have already been heavily pre-treated, this is not an option for most patients that have progressed after HDT/ASCR [94]. In addition to the novel agents discussed, chimeric antigen receptor T (CAR-T) cell therapy has been explored in this setting. The currently ongoing CHARIOT trial is a multi-center, phase II trial enrolling patients between 12-75 years of age with R/R HL and progression after at least three lines of therapy, including BV and ICI. Patients were treated with anti-CD30 CAR-T cells after lymphodepletion using bendamustine and fludarabine. The study allowed for second CAR-T injection in patients who progressed after initial response. Interim results were published at the 2022 annual conference of the American Society of Hematology. At that time, 15 patients had been enrolled. The median number of prior therapies was six (range: 3-18). Seven patients received a second infusion. ORR after the first infusion was 73.3%, with a CR rate of 60%. Of the five patients that received a second infusion and had data available, ORR was 100% with a CR rate of 60%. Overall, treatment was well tolerated. One case of grade 1 cytokine release syndrome was observed and no neurotoxicity. Several trials are underway to evaluate novel immunotherapy agents and combinations for the treatment of patient with R/R HL.

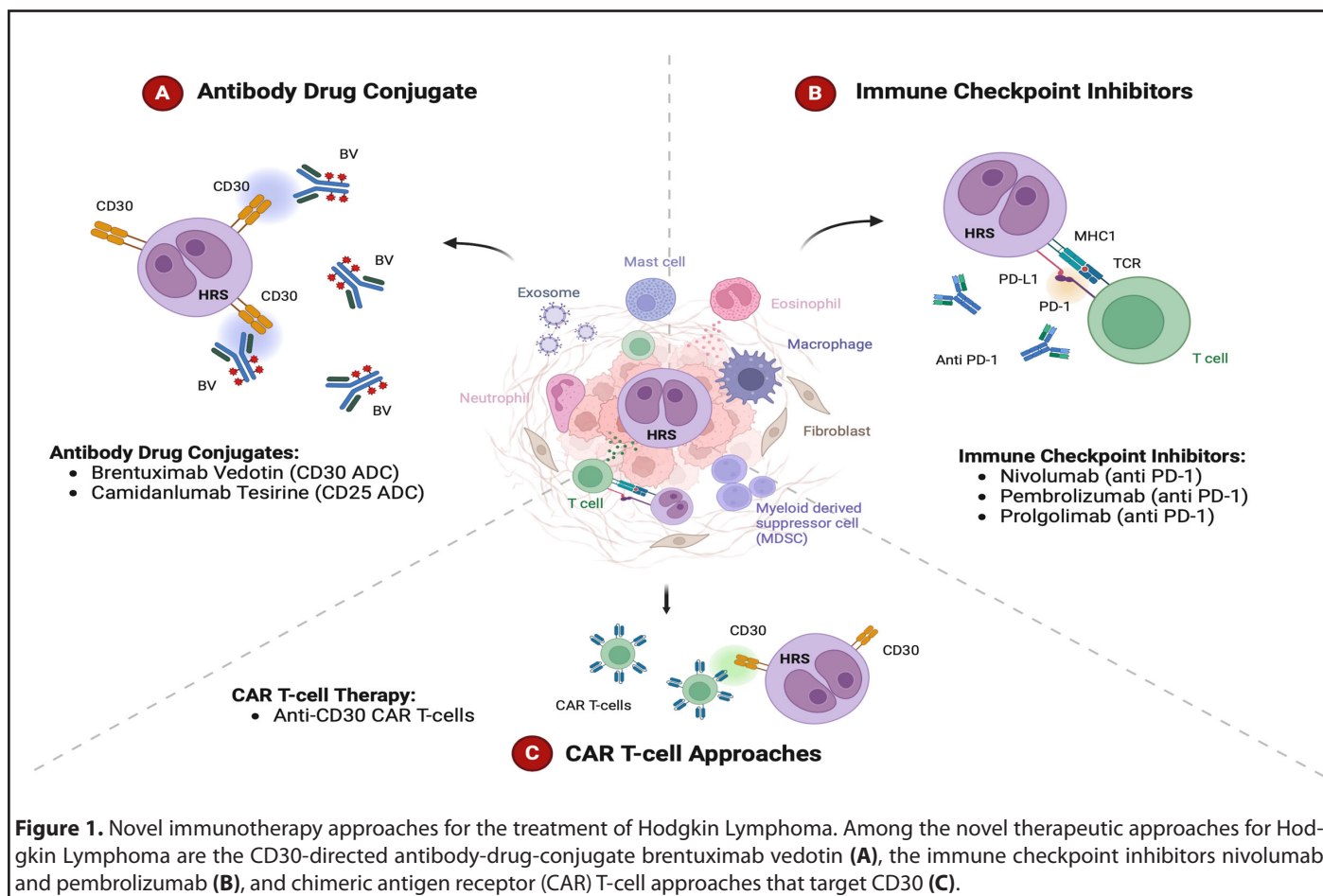
One trial is currently evaluating combination treatment with BV and the BTK inhibitor ibrutinib for patients with R/R HL after at least one prior line of therapy (NCT02744612). However, preliminary results have shown significant toxicity likely limiting future development. Several trials are combining nivolumab with other agents, including ipilimumab (anti-CTLA4), axatilimab (anti-CSF-1R), and azacytidine for treatment of R/R HL upon progression after HDT/ASCR (NCT05723055, NCT01896999, and NCT0516297). Another trial is evaluating the combination of nivolumab with gemcitabine and bendamustine for patients with R/R HL also upon progression after HDR/ASCR (NCT03739619). A novel PD-1 inhibitor, prolgolimab, is currently being evaluated as single-agent and in combination with bendamustine for patients with R/R HL with progression after first line treatment (NCT05757466). Finally, the combination of BV with nivolumab is currently being evaluated for patients with R/R HL as post HDT/ASCR consolidation treatment (NCT03057795).

Based on the currently available data in the R/R setting, we favor an individualized approach that takes into consideration prior front-line treatment, presence of primary refractory or early relapsed (< one year) disease and the presence of comorbidities such as auto-immune disorders. Especially in patients with primary refractory or early relapsed disease,

we would favor a regimen consisting of an ICI with either chemotherapy, or BV, if not received before as part of salvage treatment. All patients who obtain a CMR should undergo HDT/ASCR, if eligible. Consolidative radiation therapy should be used as appropriate in patients at high risk of treatment failure.

Future Directions

The treatment landscape of HL is evolving. BV and ICI have become integrated in salvage therapies and the combination of ICI with chemotherapy is challenging the paradigm of chemotherapy as a bridge to HDT/ASCR (**Figure 1**). However, the optimal sequencing of these new agents remains unclear as they are increasingly used in the upfront setting as well. In limited-stage HL, large frontline trials are needed to evaluate the combination of BV with AVD or ICI with AVD versus the standard of care of ABVD with or without consolidative radiotherapy. After four decades, these new approaches will hopefully further improve initial cure rates without the need for consolidative radiation. Trials are currently underway exploring the combination of BV with Nivolumab for the frontline treatment of limited-stage HL, and if found effective, this could be a chemo- and radiotherapy-free option (NCT03712202, NCT02758717). For advanced stage



HL, the results of the phase III SWOG S1826 trial support that the combination of nivolumab with AVD establishes a new standard of care for the frontline treatment of both younger and older patients in this setting. Despite these improvements, new treatment strategies are needed, because there is still a group of patients that will progress even after treatment with HDT/ASCR, BV and ICI. Trials evaluating new approaches are currently underway and include newer generation of immune checkpoint inhibitors (tislelizumab, prolgolimab, and retifanlimab-dlwr), JAK-STAT inhibitors, anti-CD25 ADC (camidanlumab tesirine), anti-LAG3 antibodies (favezelimab), and CAR-T cell approaches [95]. Future strategies will likely incorporate the use of ctDNA to identify patients at high risk for treatment failure [96]. Immunotherapy has changed the treatment landscape of HL over the last decade, and primes the future for immunotherapy for all, reducing our dependence on chemotherapy and radiation for this disease.

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