



## Review Article

# Refractory and Relapsed Hodgkin Lymphoma: A Comprehensive Review of Biology and Recent Advances in Therapy

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## Abstract

HL accounts for nearly 3% of pediatric cancers. Compared to NLPHL, cHL primarily affects older children and adolescents. The risk-adapted, response-based management approach, which uses combined modality therapy, advances in modern imaging techniques, and careful use of consolidation RT, has led to steady improvements in EFS and OS, with current rates surpassing 90%. However, nearly 10–30% of patients may still experience resistant disease or relapse at different times. Achieving a second CR is generally difficult. Conventional CTR, HD CTR, and ABMT have been the main treatments for several decades. Advanced-stage (stage III and IV) R&R HL generally requires intensive treatment. Meanwhile, treatment for low-stage relapses (stage I and II) require a less intensive approach. The popularity of purely conventional CTR agents is decreasing. Combining one or more of the newer targeted medications, such as brentuximab vedotin, with conventional CTR, or utilizing pure targeted medications to induce second remission, has become standard practice. The treatment outcomes for R&R HL decline with each subsequent relapse. Second and third relapses usually result in much worse outcomes. Depending on the pattern and timing of relapse, the EFS after second-line treatment ranges from 10% to 50%. Many newly identified genetic mutations and molecular pathways are linked to the disease development and progression. Targeting these pathways may help cure patients who do not respond to current therapies. Allogeneic BMT may offer some assistance. The recently developed anti-CD30, CAR T-cell therapy shows promise, especially for patients with refractory disease and those experiencing frequent relapses. In this review, we discuss the mechanisms behind the disease's resistance to treatment and modern approaches to overcoming it.

## Keywords

CAR – T Cell Therapy, Chemotherapy, Autologous Blood and Marrow Transplantation, Relapsed and Refractory Hodgkin Lymphoma, Radiotherapy, Targeted Therapy

## 1. Introduction

HL is a slowly progressive B-cell neoplasm. It commonly involves the central and peripheral LNs and less commonly the lungs, liver, CNS, bone, and bone marrow [1-6].

HL constitutes 10% of all lymphomas and 3% of pediatric

neoplasms. The annual incidence is 11-12 cases/million in the 5 -14-year age group. Nearly 5% of younger patients develop the less aggressive NLPHL. The only difference between adult

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and pediatric *HL* is in the incidence of the histological subtypes. *Classical (cHL)* and the *NLPHL* variants are systemic diseases that require systemic therapy. Both are derived from the B-cell lineage but have distinct immunohistochemical profiles (CD15+ve, CD30+ve, CD20-ve, and CD45-ve for *cHL*; CD45+, CD30-ve for *NLPHL*) [7-11].

Before 1960, *HL* was largely considered a fatal disease. Treatment outcomes have gradually improved. Currently, *HL* is one of the most curable malignancies. *EFS* and *OS* are currently well above 90%. However, 5 - 10% still have refractory disease, and 20 - 30% develop relapses [7, 12-16].

Patients with *R & R HL* generally have poor outcomes. Depending on the pattern and timing of relapse, 3-year *EFS* and *OS* rates range from 10–50% [10, 13, 14, 16, 17]. Generally, patients with primary refractory *HL* have lower survival rates, with an *EFS* of 10-15% at 3 years [16, 18, 19].

Currently available treatments for *R&R cHL* have a low likelihood of inducing a second persistent remission. Therefore, efforts have primarily focused on improving frontline therapy to reduce relapse risk [18-21].

For several decades, conventional *CTR* regimens have been the primary treatment for *R & R HL*. Second- and later-line conventional *CTR* agents have slightly improved survival. *HD CTR* and *ABMT*, along with novel targeted medications and *Allogeneic BMT (allo BMT)*, have slightly increased the cure rates. However, long-term toxicities are significant. New targeted molecules, such as *anti-CD30 antibody-drug conjugates* and *PD-1* checkpoint inhibitors, have shown promising results, especially when incorporated into frontline therapy, which has become a standard practice. [18-21].

Most studies on new targeted agents have been conducted in adult patients. However, pediatric and adult *HL* have similar biology and pathology. Therefore, study results can be safely applied to both adult and pediatric patients. Nonetheless, only pediatric-designed protocols should be used for younger children [19, 22-24].

*HD CTR & ABMT* remain the primary consolidation therapy for *R&R HL*. Relapse after *ABMT* carries a poor prognosis. The use of targeted medications to induce further remission may be effective; however, such remission is often short-lived. A second *ABMT* may be performed, but the outcomes are often disappointing. *Allogeneic BMT* offers some hope. *CAR T-cell immunotherapy* is a newly emerging treatment that has shown efficacy in early clinical trials but is not yet widely used [21, 25-29].

Currently, there is no consensus on the best treatment for *R&R NLPHL*. Treatment is highly individualized. Generally, except for patients with high-risk relapse, most patients need less intensive *CTR* to achieve long-term second remissions. The use of *rituximab* and *ofatumumab* in patients with relapsed *NLPHL* has been very successful. Conventional *CTR* and/or *RT* have also been generally effective, but data on these approaches remain limited. *ABMT* is typically reserved for high-risk relapse patients [20, 30, 31].

In this review article, we will examine a wide range of basic

clinical data on *cHL* and *NLPHL*. (The term *HL* is used when the data apply to both subtypes.) In addition to recent advances in the disease's biology, we provide evidence-based information on the recent developments in *HL* treatment approaches.

## 2. Frontline Management of Hodgkin Lymphoma

Modern treatment protocols have separated *NLPHL* from *cHL*. However, both types are mostly included when it comes to the treatment of relapse. Standard *CTR* protocols such as *OPPA {VCR, PSN, PZN, DOX}*, *OEPA {VCR, PSN, ETOP, DOX}*, *MOPP {MCL, VCR, PZN, PSN}*, *ChlVPP {ChL, VBL, PZN, PSN}*, *ABVD {DOX, BCN, VBL, DZN}* and *BEACOPP {BCNU, ETOP, DOX, CPA, VCR, PZN, PSN}*, *ABVD {DOX, BCN, VBL, DZN}* were used to treat the different stages of pediatric and adolescent *HL*. The later-introduced *ABVD* has proved a superior outcome and less toxicity. Therefore, until recently, the *ABVD* regimen was the treatment of choice for patients with newly diagnosed advanced-stage *HL*. Early-stage *HL* (stage I and II) patients were treated with fewer cycles of *ABVD* or one of its modifications. *RT* was nearly always added to the treatment. The *EFS* and *OS* at 5 years were approximately 79% and 88%, respectively. The treatment, however, was associated with significant toxicities [21, 32-34].

To improve efficacy and reduce toxicity, modern treatment strategies use risk stratification and tailor therapy based on response. The patient's initial risk group is assigned based on strict clinical and radiological criteria using *MRI*, *CT*, and *FDG-PET* scans. Response assessment is determined using preset radiological criteria. *CTR* regimens are assigned based on the patient's initial risk group. Treatment is then tailored according to response to induction *CTR*. *RT* is given only to patients who show poor response and achieve no *CR* after completing induction *CTR* [16, 35-38].

Treatment strategies for pediatric *cHL* and *NLPHL* vary significantly across cooperative groups. Therefore, no single standard therapy exists. However, certain principles are agreed upon. Patients with low risk (stage I and stage II without bulky disease or B symptoms) have a low relapse probability. They would receive 2-3 cycles of *CTR*. Those who achieve *CR* after induction *CTR* do not receive *RT*. The *EFS* and *OS* were 85% and 95%, respectively. Patients with intermediate risk (stage I and II with B symptoms and/or bulky disease, and stage III with no B symptoms or bulky disease) would receive 4–5 cycles of *CTR*. Those who do not achieve *CR* after 2 cycles of *CTR* receive 2 additional cycles of *CTR* followed by *RT*. *RT*, however, is omitted in patients who achieve early *CR*. The treatment results were good, with a 4-year *EFS* of 86.9% for *RERs* and 77.4% for *SERs* ( $P < 0.001$ ). At 4 years, the *OS* was 97.8% for *RERs* and 95.3% for *SERs* ( $P < 0.001$ ) [34, 36, 39].

Patients with high-risk disease (stage III and IV, with or

without B symptoms and/or bulky disease) have increased relapse probability. Those patients receive 5 cycles of intensive CTR, followed by consolidation RT. Some cooperative groups omit RT for patients who achieve CR after 3 cycles of induction CTR. The EFS at 5 years was 86% for RERs and 83% for SERs ( $P = 0.85$ ), and the OS was 95% [12, 40-42].

BV is an anti-CD30 antibody-drug conjugate approved by the USA FDA for pediatric and adult patients with R&R HL [43, 44]. The significant benefits achieved with BV and the low toxicity profile in treating patients with R&R HL encouraged investigators to move BV and some other targeted agents into frontline therapy. Many newly diagnosed HL treatment protocols, therefore, add BV, PLZ, and NLM to conventional CTR regimens. The COG phase III randomized AHOD1331 trial incorporated BV into AVD-PC {DOX, VCR, DZN, PSN, CPA} regimens to treat stage III and IV cHL. A total of 664 patients received 6 cycles of BV+AVD-PC, and 670 received ABVD. The 6-year EFS was 93.9% (95% CI, 91.6 to 95.5) in the BV+AVD-PC group and 89.4% (95% CI, 86.6 to 91.7) in the ABVD group. Toxicity was minimal in the BV – AVD – PC group. The study showed a clearly higher BV – AVD – PC group FDG – PET scan metabolic response rate at the end of 6 cycles of therapy, resulting in fewer patients receiving RT [45, 46].

### 3. Predictors of Relapse

The CHIPS for children with newly diagnosed HL was created by the COG based on risk factors derived from the COG AHOD0331 study. Predictors of EFS included advanced-stage HL (stage III and IV), bulky mediastinal disease, fever, and serum albumin <3.5 mg/dL at diagnosis. Each factor was assigned a score of 1. Patients with a CHIPS of 0 have an EFS of 93.1% at 4 years. Those with CHIPS of 1 have an EFS of 88.5%; CHIPS of 2, 77.6%; and CHIPS of 3, 69.2%. A subset of patients with a CHIPS score of 2 or 3 has an EFS of less than 80% at 4 years. This group was considered eligible for early treatment intensification. The CHIPS has proven to be a highly reliable predictor of EFS in HL [36, 39].

FDG-PET is considered the gold-standard radiologic test for HL. Non-avid FDG-PET at the end of therapy indicates CR and has a good prognosis regardless of residual tumor mass. Any significant residual FDG-PET avidity at the end of therapy may suggest treatment failure and predict higher relapse risk. Negative FDG-PET at the end of treatment has a higher negative predictive value for relapse [47-49].

Jan S et al. retrospectively studied the prognostic significance of the NLR, inflammatory marker levels, and their correlation with B symptoms and disease burden in 64 patients with HL {16 (25%) had B symptoms}. Patients with B symptoms had higher ferritin, monocyte, neutrophil, and NLR levels, and lower lymphocyte counts at presentation ( $P < 0.0003$ ). Patients with  $NLR > 3.5$  and ferritin > 173 (cutoff < 173 ng/ml) had advanced stage, bulky disease, and B symptoms ( $P <$

0.0001). However, higher ferritin levels and NLR did not predict worse outcomes [50].

The NLR at diagnosis is recognized as a significant independent prognostic factor in many cancers. A retrospective study of 83 HL patients was reported by Hajder J et al. After a median follow-up of 92 months (range, 9-180), 63 patients (80%) achieved CR. An ROC curve was created, with an AUC of  $0.655 \pm 0.064$  (95% CI 0.53-0.724) and a cut-off value of  $\geq 4.3$ . The median OS was 61 months in patients with an  $NLR > 4.3$ , compared with 50 months in those with a lower NLR ( $p < 0.018$ ) [51].

Yan Y et al. retrospectively studied the predictive value of BLNK, measured by immunohistochemistry. The OS and EFS in HL patients with BLNK-positive B lymphocytes (10-49% BLNK expression) were significantly higher [52].

### 4. Transformation Mechanisms Causing Resistance and Relapse

HL is characterized by a few malignant RS cells surrounded by a mixture of T helper cells, cytotoxic T lymphocytes, and macrophages attracted by cytokines secreted by the tumor cells. These background immune cells secrete anti-apoptotic signals and tumor growth-stimulating factors. Other cells, such as natural killer T lymphocytes, exert antitumor immune responses. However, it is clearly insufficient to halt tumor growth. Specific stromal cells appear to regulate the activity of background immune cells. Therefore, tumor behavior and treatment responses cannot be precisely predicted. Researchers at Martin Luther University in Halle, Germany, proposed a multisystem model that may help simulate HL tumor features and predict behavior. In this model, tumor growth depends on the presence of CSCs, with surrounding stromal cells promoting growth. Immune-regulatory cells mediate this process by suppressing natural killer and cytotoxic T cells. Paradoxically, tumor growth can occur even after therapy, resulting in disease progression or relapse. Therefore, this model may help design new treatment strategies for tumors with strong interactions with the surrounding stroma, such as HL [53].

### 5. Genetic Profile of Hodgkin Lymphoma

Treatment outcomes for patients with relapsed HL decline with each subsequent relapse, resulting in much poorer outcomes. Novel genetic abnormalities are increasingly identified and are believed to confer resistance. The impact of newly developed targeted medications on these abnormalities remains to be seen. [21].

The limited number of malignant RS cells in cHL tissue makes it challenging to conduct proper genomic studies. However, this issue was recently partially overcome by using advanced laboratory techniques, such as fluorescence-activated

cell sorting, to isolate *RS* cells. Researchers could perform *WGS* of *RS* cells and map the sequence of pathological events leading to *HL* development. Genetic studies using *WGS* identified driver gene mutations, such as *B2M*, *BCL7A*, *GNA13*, and *PTPN1*, at early stages of disease progression. Larger chromosomal gains appeared much later. Recent research links *HL* resistance and relapse to ongoing activation of genomic *NF- $\kappa$ B*, *PI3K/AKT*, *NOTCH*, *JAK/STAT*, and *STAT6* signaling pathways. These somatic mutations and pathways exhibit anti-apoptotic and pro-inflammatory features and are crucial for *HL* development. These mutations occur more frequently in patients with *cHL*.

*STAT6* is a gain-of-function mutation and is the most common genetic mutation in *cHL* patients. The mutated *STAT6* gene is believed to support *RS* cell survival and growth. The *JAK2/STAT6* signaling pathway regulates gene expression and is activated by lymphotoxin produced by *RS* cells. The *JAK/STAT* pathway has been linked to immune evasion by malignant *HL* cells through the expression of *PD-L1* and *PD-L2* receptors. Mutations at chromosome *9p24.1* have been shown to upregulate *PD-1* and *PD-L1* ligands on the *HL* cell membrane via activation of the *JAK/STAT* signaling pathway [11, 21, 54, 55].

The genetic pattern in *NLPHL* is less complex. Typically, malignant tumor cells in *NLPHL* are found within a lymphocyte-rich microenvironment. In contrast, more aggressive mature *B-cell* and peripheral *T-cell* lymphomas show nuclear *PLK1* expression. This protein stabilizes *MYC* (also known as *c-myc*) and promotes cell proliferation. *PLK1* expression correlates with poorer treatment outcomes. Weiss *J et al.* studied 146 histopathological samples (76 *NLPHL* and 70 *cHL*). The analysis revealed 100% *PLK1* protein expression in *cHL* but only 5% in *NLPHL* tumors. Increased *PLK1* expression in *cHL* patients was linked to advanced stages and higher tumor cell proliferation. The *PLK1* pathway presents a potential target for inhibiting tumor growth with *PLK1* inhibitors [56].

## 6. Refractory & Relapsed Hodgkin Lymphoma

Despite the progressive improvement in the initial management of *HL*, nearly 5-10% of patients still show refractoriness, and 20-30% relapse after initial response to *CTR*. Relapse is diagnosed in about a quarter of patients with stage III–IV and 10% of those with stage I–II disease. Patients with bulky nodal and extranodal involvement are more likely to relapse. However, this relationship has not been proven in patients with B symptoms.

Unlike *lymphoblastic lymphoma* and *Burkitt's lymphoma*, *HL* is a relatively slow-growing tumor with limited potential for rapid progression, which is common even in relapse situations. However, the rate of progression increases with each subsequent relapse. The outlook for patients with R&R *HL* is generally poor. Depending on the pattern and timing of relapse, the

3-year OS ranges from 10% to 50%. The prognosis is particularly bleak for those who experience second and later relapses or show poor response to second-line *CTR* [13, 18, 20, 40, 57].

### 6.1. Diagnosis of Relapse

Detecting relapse is usually straightforward, as it can be identified when the patient exhibits symptoms or signs of relapse, or through routine follow-up imaging studies. *FDG-PET* avidity, however, may persist for up to 1 year after treatment, but in most cases, it is minor and resolves on its own, with the patient remaining in remission. Therefore, careful interpretation of *FDG-PET* scan avidity is essential. Only scores higher than the normal liver uptake (*Deauville score*  $\geq 4$ ) should be considered positive. Whenever feasible, a tissue biopsy should be performed to confirm residual disease [18, 20, 47-49].

Despite the good yield in detecting disease relapse, the value of routine radiological imaging is questioned. Most treatment protocols recommend routine *CT*, *MRI*, and/or *FDG-PET* scans at regular intervals for 3–5 years. A review of patients treated according to multiple *COG* trials between 1990 and 2006 has shown that routine radiological monitoring is probably unnecessary. At a median follow-up of 1.7 years, out of 402 *HL* patients, relapse was diagnosed in 64 (15.9%). Most relapses (47%) were identified after a patient's complaint. Another 17% were found following abnormal clinical examination. The remaining 36% were diagnosed due to abnormal routine imaging scans. Nevertheless, the data confirmed that the timing and method of detecting relapse did not affect survival.

The *POG 9425* clinical trial enrolled 212 patients with *HL*. At a median follow-up of 17.6 months, relapse was diagnosed in 25 (11.6%) patients. In 19 patients (76%), relapse was identified through symptoms, abnormal physical exams, or abnormal lab tests. Two patients (8%) were diagnosed with relapse following routine radiological imaging within the first year, and 4 patients (16%) after the first year of completing therapy. Relapse timing did not significantly affect overall survival [18, 20, 34, 40, 58].

*FDG-PET* and *CT* scans have improved diagnostic accuracy, disease staging, and response assessment. However, these tests still have limitations. Genomic characterization of the *RS* cell is complex. Nonetheless, newer techniques such as single-cell molecular analysis and *NGS* have identified several tissue mutations. Circulating tumor *DNA* particles, extracellular vesicles, and cytokines act as liquid biopsies that may help assess treatment response and predict early relapse. Although some liquid biopsy genetic materials have been identified in the laboratory, they have not been widely used clinically [59].

### 6.2. Patterns of Relapse

According to the *AETHERA* trial, published in 2018, patients diagnosed with refractory *HL*, relapse within 12 months,

or relapse more than 12 months but with extranodal tissue involvement are classified as high-risk relapse. Patients with relapse more than 12 months after initial treatment and those with limited-stage relapse are classified as low-risk relapse [57, 60].

Dharmarajan KV *et al.* reported HL relapse patterns in the COG AHOD0031 study. All patients received CTR, but RT was administered only to those with positive FDG-PET. A total of 198 out of 1712 patients (12%) relapsed, while only 14 (0.01%) experienced disease progression. The median time to relapse was 12.8 months. The most common relapse sites were the mediastinum (63%), the supraclavicular fossa (39%), and the neck (32%). The lungs were the most frequent site of extranodal relapse (23%). Patients relapsed at both initial bulky (45%) and non-bulky (55%) sites. However, relapses were more common among patients with initial bulky disease who showed RER without receiving RT. The first relapse occurred either at the same anatomical site of disease (40%) or at that site along with a new site (52%). Only 7% of patients developed relapse at a new location. Patients with SER and those with RER to CTR who were randomized to no RT had higher risk of relapse. Relapse at the previous RT field was uncommon but more frequent within the SER group. Relapse rates were similar across all cHL histological subtypes; however, they were significantly lower in NPLHL patients. Relapses involving extralymphatic sites, such as the liver, were associated with poorer outcomes [12, 60].

### 6.3. Early Versus Late Relapse

Patients with evidence of active disease at the end of front-line therapy are considered refractory to treatment. Some groups, however, extend this period by 3 months. Patients who relapse between 3 and 12 months are classified as having early relapse, while those who relapse after 12 months of treatment completion are classified as having late relapse. Some patients may present with recurrence of previous symptoms and signs, such as fever, weight loss, and enlarged lymph nodes. As expected, the outcomes of patients with refractory disease are generally worse than those who experience later relapse. The prognosis for patients with late relapse is significantly better than for those with early relapse [17, 18].

### 6.4. Treatment of Refractory and Relapsed Hodgkin Lymphoma

No single standard CTR regimen exists for treating R&R HL. Several conventional CTR regimens have been used with varying results. Consolidation RT was commonly added, especially to previously non-irradiated sites. Patients with late relapse (> 12 months after treatment completion) may only receive RT for consolidation. Patients with refractory HL and those experiencing early relapse (< 12 months after treatment completion) receive consolidation with ABMT. ABMT should be strongly considered for patients with advanced-stage (stage

III and IV) relapse, regardless of the time of relapse.

Over the past two decades, clinical trials have demonstrated the effectiveness of the anti-CD30 antibody-drug conjugate BV and the PD-1/PD-L1 checkpoint inhibitors (PLZ and NLM) as salvage therapies for HL. Researchers are studying newly identified aberrant epigenetic mechanisms in tumors as potential targets for both older and newer anticancer drugs, such as histone deacetylase inhibitors (*vorinostat*, *romidepsin*, *belinostat*, *panobinostat*) and hypomethylating agents (*azacytidine* and *decitabine*). These drugs recently received FDA approval to treat hematological malignancies in children. Targeting the JAK2 gene mutation shows promise. In vitro studies indicate that ruxolitinib is highly effective at inhibiting the JAK2/STAT pathway in HL cells. However, clinical trials have not yet started. Targeting the NF- $\kappa$ B pathway, a transcription factor that controls apoptosis and tumor cell proliferation, with proteasome inhibitors such as *bortezomib* (BZM) and *carfilzomib* has shown promise in preclinical trials for multiple myeloma cell lines, but preclinical studies in HL are yet to begin [62, 63].

#### 6.4.1. Conventional Chemotherapy

Dose-intensified, conventional CTR regimens such as DZN, ETOP, CRB, DOX {DECA}, ETOP, CPL, IFO, and Ara C {EPIC}, IFO, CRB, and ETOP {ICE}, BCNU, ETOP, Ara C and MEL {mini-BEAM}, have been used to treat R&R HL for several decades. Although these regimens successfully induced a second remission, toxicity was high, and the results showed no improvement in OS [41, 44, 64, 65].

More biologically based targeted therapies are being studied. Most studies on targeted agents are conducted in adult patients. Pediatric, adolescent, and adult HL have similar biology and pathology. Therefore, clinical study results could be applied to both adult and pediatric patients. However, care is needed, especially for younger patients [25].

Only a few new targeted medications have been developed in the last three decades. Some conventional CTR agents were modified to reduce toxicity. Liposomal and pegylated DOX formulations are in clinical use and have been shown to be less cardiotoxic. The cardioprotective agent *dexrazoxane* has been shown to reduce cardiomyopathy [66, 67]. *Amifostine* is used as an adjuvant to CBP and has been proven to reduce kidney injury [67-69].

GC is a pyrimidine nucleoside analog, a prodrug that requires activation within tumor cells. Studies have proven GC efficacy in treating HL. A COG phase II study recruited 30 pediatric patients with R&R HL. Patients had at least received 2 prior salvage CTR regimens, and 17 patients (57%) received consolidation ABMT. Patients received three-weekly cycles of VRN (25 mg/m<sup>2</sup>/dose) and GC (1000 mg/m<sup>2</sup>/dose). Toxicities were minimal. Nineteen patients had measurable responses (95% CI, 55% to 91%). Six patients (20%) achieved CR, 11 (37%) had VGPR, and 2 patients (7%) had a PR [70-73].

### 6.4.2. Targeted Medications

There has been a significant shift toward incorporating newer targeted medications into *R&R HL* treatment regimens, or using them as sole agents. The remission rate after salvage conventional *CTR* was approximately 60%. The 10-year *PFS* remains around 50% [25, 74].

*BZM* is a 26S proteasome inhibitor that stabilizes proteins and small molecules, including *NF-κB*, which promotes cancer cell survival. The *COG-AHOD0521* multicenter, open-label, phase II clinical trial enrolled 26 patients aged < 30 years with *R&R HL*. Patients received *IFO*, *VRN*, and *BZM*. Patients who achieved *CR* directly proceeded to *ABMT*, and those who did not received 2 additional cycles of *IFO*, *VRN*, and *BZM*. Twelve (52%) of the 23 evaluable patients achieved *CR*. An additional 9 (39%) patients achieved *PR* after 4 cycles of *CTR*. All received consolidation *ABMT*. The 4-year *EFS* and *OS* were 68% (95% CI: 45–82%) and 79% (95% CI: 57–91%), respectively [75].

*BV* is an *anti-CD30* antibody-drug conjugate approved by the *FDA* for patients with *R&R cHL*, particularly those who have received *ABMT* [43, 44].

A *COG* phase I – II, single-arm study recruited 46 patients with *R&R HL*. All patients received 3 weekly cycles of *GC* (1000 mg/m<sup>2</sup>/dose) on days 1 and 8 and *BV* (1.4–1.8 mg/kg/dose) on day 1. Twenty-four (57%) of the 42 evaluable patients achieved *CR* after 4 cycles of treatment (95% CI 41–72%). Four patients (10%) showed *PR* [34, 72, 73].

*BM* is a nitrogen mustard alkylating agent primarily used as salvage therapy in adult patients with *R&R HL*, most often in combination with a targeted agent. *Pinczés LI et al.* studied 41 patients with *R&R cHL* treated with a median of 3 cycles (1–6 cycles) of *BM* (90 mg/m<sup>2</sup> on days 1 and 2) and *BV* (1.8 mg/m<sup>2</sup> on day 1). The overall response rate was 78%, with 29 patients (70.7%) achieving *CR*. All 41 patients received *ABMT*, but unfortunately, 12 (29%) patients developed a second relapse. The 2-year *OS* and *PFS* were 93% and 62%, respectively [76].

*Forlenza CJ et al.* reported the results of a multicenter, retrospective study of 29 pediatric patients with *R&R cHL* (17 with refractory and 12 with relapsed *HL*). Patients received 2 – 7 cycles of *BV-BM* (median 3 cycles). An objective response was achieved in 23 patients (95% CI 60–92%), and 19 patients (66%) achieved *CR*. Seventeen (17) patients received consolidation *ABMT*. *EFS* and *OS* at 3 years were 65% (95% CI, 46–85%) and 89% (95% CI, 74–100%), respectively [26].

Because targeted medications have improved the remission rates (60–70%) and *PFS* (60%), some centers have eliminated conventional *CTR* agents and now use only targeted medications to induce remission. Results from these studies show continued improvements in *EFS* and *OS* [25, 74].

*PD* ligands 1 and 2 (*PD-1* and *PD-2*) immune checkpoint inhibitors (*PLM* and *NLM*) are *FDA*-approved and have become a first-line therapy for *R&R HL*. *RS* cells are derived from the B-cell germinal center. They exhibit genomic instability and overexpression of *PD-1* and *PD-2*, which enhances

their immune-surveillance evasion. *PLM* and *NLM* have been shown to improve *OS* in *R&R HL* and have a tolerable toxicity profile. They are very beneficial in patients who experience disease progression or poor tolerance to *BV* [77].

*Moskowitz AJ et al.* reported the results of a phase II study evaluating *PLM*, *GC*, *VRN*, and *liposomal DOX* as second-line therapy for 39 patients with *R&R cHL*. Patients received 2–4 3-weekly cycles of *PLM* (200 mg/m<sup>2</sup>) on day 1, plus day 1 and day 8 *GC* (1,000 mg/m<sup>2</sup>), *VRN* (20 mg/m<sup>2</sup>), and *liposomal DOX* (15 mg/m<sup>2</sup>). Thirty-one patients received two cycles, and 8 received 4 cycles. Side effects were minimal. Of the 38 evaluable patients, the *CR* rate was 95%. Thirty-six patients (95%) received *ABMT*; all were alive and well 13.5 months (range 2.66–27.06) after therapy [57].

*Greve P et al.* reported results from adding *NLM* to *BV* and *BM* to treat children with *R&R HL*. Patients were given 4 to 6 cycles of *NLM* (3 mg/kg) and *BV* (1.8 mg/kg) on day 1. Those who were not in *CR* received 2 additional cycles of *BM* to achieve *CR*. Seven patients received *ABMT*, and 3 received *RT*. All 10 patients were well and in *CR*, 25 months after completing therapy [22].

The significant benefits and safety of targeted medications in treating *R&R HL* have encouraged investigators to move the *anti-CD30* drug conjugate *BV* to frontline therapy. The *COG* phase III randomized study *AHOD1331* incorporated *BV* into the *AVD-PC* (*DOX*, *VLB*, *DZN*, *PSN*, *CPA*) regimen for de novo stage III and IV *cHL*. A total of 664 patients received 6 cycles of *BV+AVD-PC*, and 670 received 6 cycles of *ABVD*. The 6-year *EFS* was 93.9% in the *BV+AVD-PC* group and 89.4% (*P* < 0.055; 95% CI, 86.6 to 91.7) in the *ABVD* group. Short- and long-term toxicities were tolerable. The study showed a clearly higher *FDG-PET* scan response after 6 cycles of *BV-AVD-PC* therapy, resulting in fewer patients receiving *RT* [46].

Based on the results of *COG AHOD1331*, the *NCTN S1826* randomized, phase 3 clinical trial evaluated *NLM* in stage III and IV *cHL*. They recruited 997 adult and adolescent patients (496 received *NLM + AVD* and 498 received *BV + AVD*). At a median follow-up of 2.1 years, the *PFS* after *NLM + AVD* was 92% (95% CI, 89–94%) compared with 83% (95% CI, 79–86%) after *BV + AVD* [45].

The *COG*, in collaboration with the *EuroNet-PHL* group, is currently running a trial evaluating response to *PLM*, another *PD-1* inhibitor, in newly diagnosed children and adolescents with *HL* and *SER* compared with *ABVD* and *OEPA* (*VCR*, *ETOP*, *PSN*, *DOX*) [78].

*Chen R et al.* reported results from the *KEYNOTE-087* study, which recruited 210 adults and adolescents with *R&R cHL* who relapsed or progressed after second-line *CTR*, *ABMT*, and maintenance *BV*. Patients received single-agent *PLM* (200 mg) every 3 weeks for 2 years or until disease progression. For a median follow-up of 27.6 months, the *ORR* was 71.9%. The *PR* rate was 44.3%. The median duration of response was 16.5 months (range: 0.0–27.0) [79].

### 6.4.3. Autologous BMT

Since the approval of *anti-CD30* monoclonal antibodies and *PD-1* checkpoint inhibitors for treating *R&R HL*, there has been a noticeable decline in the use of consolidation *ABMT* and *allo BMT*. *ABMT* are often employed to consolidate patients with progressive *HL* and those with early relapse. Unfortunately, nearly half of these patients still experience further relapses. Currently, *ABMT* are considered standard of care for patients who do not achieve *CR* after frontline *CTR* and those unable to tolerate *targeted* medications [24].

A randomized clinical trial confirmed *ABMT* superiority over conventional *CTR*. Schmitz *N et al.* reported the results for 161 patients with *R&R HL* who received 2 cycles of *Dex-BEAM CTR*. Patients who responded well to *Dex-BEAM* (*CR* or *VGPR*) was randomized to receive either an additional 2 cycles of *Dex-BEAM* (56 patients) or *HD BEAM* plus *ABMT* (61 patients) for consolidation. The 3-year *PFS* was 55% in patients who received *ABMT*, compared with 34% in those who received conventional *CTR* (95% *CI*, 39.87; *P* = 0.019) [23].

*ABMT* is currently the standard consolidation treatment for patients with *R&R HL*. Recent studies have shown significantly improved survival rates after consolidation with *ABMT*. Depending on specific predictive risk factors—such as early relapse, advanced disease stage at relapse, or relapse in a previously irradiated field—the 5-year *EFS* ranges from 43% to 95%. *OS*, at 10 years, however, is approximately 60%. Patients with a non-avid *FDG-PET* scan before consolidation *ABMT* tend to have better *EFS* and *OS*. Tandem cycles of *ABMT* showed no clinical benefit [80].

Most treatment centers use *BCNU*, *ETOP*, *AraC*, *MEL* {*BEAM*}, or, less frequently, *CPA*, *BCNU*, *ETOP* (*CBV*) for conditioning before *HSC* infusion. Additional consolidation with *RT* is often needed after *ABMT*, especially in areas not previously irradiated [23, 24, 48, 60, 81].

Recent data suggest that in the new *targeted* therapy era, *ABMT* might be omitted for patients with late (>12 months), limited disease relapse and those with advanced-stage relapse who achieve a rapid *CR*. However, if these patients have not been previously irradiated, they should receive *RT* [23, 57, 60, 61, 74, 82, 83].

### 6.4.4. Radiotherapy

Until the end of the 1960s, high-dose, wide-field *RT* (36–44 Gy) was part of the standard treatment for *HL*, resulting in significant early and late toxicities. Over the next two decades, multi-agent *CTR* was gradually added, the *RT* dose and field were significantly reduced. Today, *RT* remains an essential part of *HL* therapy, but its use has been refined. The modern approach of combining *IFRT* with *CTR* and using precise response assessment tools has substantially reduced *RT* dose, field, and volume without compromising the *EFS* and *OS* [12, 70, 84, 85].

Generally, any relapse site that was not previously irradiated requires consolidation *RT*. However, this has recently

been refined, and *RT* is now limited to previously non-irradiated fields that still show *FDG-PET* activity after consolidation *ABMT*, or *CTR* alone. Re-irradiating a previously treated field is not recommended. However, it may be considered particularly after a long interval (> 12 months) since the initial *RT* or when a palliative approach is taken. New *RT* modalities, such as *IMRT* and *Proton Beam* therapy, may help deliver *RT* in such situations [12, 84, 85].

### 6.4.5. Maintenance Therapy

The 5-year *EFS* after consolidation with *ABMT* for *R&R HL* is nearly 50%. A significant number of patients still progress or develop further relapse. Maintenance *BV* therapy following *ABMT* is highly recommended. The multicenter, randomized, double-blind, controlled (*ATHERA*) phase 3 study recruited 329 *R&R HL* patients who received salvage *CTR* followed by *ABMT*. One hundred and sixty-five patients were randomly assigned to receive 16 cycles of *BV* (1.8 mg/kg/dose) every 3 weeks, and 164 received placebo. The *PFS* was significantly better in the *BV* arm (*P* = 0.0013, 95% *CI* 0.40-0.81). More recent clinical trials have shown that *NLM* and *PLM* were effective and well tolerated. A phase II clinical trial reported by Armand *B et al.* recruited 30 patients with *R&R HL* who received 8 *PLM* maintenance cycles at 3-week intervals, starting 60 days after *ABMT*. The *PFS* and *OS* at 18 months were 82% and 100%, respectively [45, 57, 87-89].

## 7. Relapse After ABMT

Relapse after *ABMT* occurs in nearly 50% of cases and is associated with a poor prognosis. These patients have typically received substantial conventional and possibly *targeted* therapies. Some patients, however, may be ineligible for *ABMT* due to prior toxicity. *PD1* checkpoint inhibitors, *PLM* and *NLM*, and *CD30-antibody* conjugates—used alone or with conventional *CTR*—have become first-line therapies for *R&R HL*, even in patients previously exposed to them. The primary goal of treatment in these cases is often palliative disease control. As a result, some patients respond well, achieving *CR* or maintaining low-grade active disease as a chronic condition. Complete cure is unrealistic in these situations, though some exceptional cases may be cured. Other options for disease control include *allo BMT* or *CAR T-cell* therapy. A second *ABMT* may be considered, but this is a less favorable option [29, 77].

### 7.1. Allogeneic Blood and Marrow Transplantation (BMT)

As with *ABMT*, increased use of *BV*, *PLM*, and *NLM* has led to a decline in consolidation *allogeneic BMT* in *R&R HL*. *Allogeneic BMT* is generally recommended for patients who relapse after *HD CTR* and *ABMT*. These patients now typically receive *PD-1* inhibitors to induce remission. Emerging data support using consolidation *allogeneic BMT* as a curative

option for patients who do not tolerate or progress after *CD30-antibody* conjugates and *PD-1* inhibitor therapy. The allogeneic *BMT* procedure should be performed promptly once the patient achieves a meaningful remission. Stem cell sources such as matched related, matched unrelated, and haploidentical donors can be utilized. Conditioning regimens vary between myeloablative and *RIC*. However, most experts prefer using *RIC* to minimize toxicity. Maintenance therapy with *CD30-antibody* conjugates following allogeneic *BMT* is highly recommended [60].

The survival rates after allogeneic

*BMT* are modest. The *EFS* ranges from 20% to 30%, and the *OS* ranges from 30% to 50%. Martinez C *et al.* retrospectively reviewed 511 patients with *HL* who relapsed following *ABMT*. Treatments included conventional *CTR* and/or *RT* in 294 patients (64%), second *ABMT* in 35 patients (8%), and allogeneic *BMT* in 133 patients (29%). Patients who relapsed early (< 6 months), had stage IV relapse, bulky tumors, poor performance status, or were over 50 years old had lower *OS* at 32%. The 5-year *OS* for patients with no risk factors was 62% [89].

Patients who develop relapse after allogeneic *BMT* have a very poor prognosis. The treatment options are limited. Therapy is nearly always palliative. Options include palliative targeted medications, such as *PLM*, *NLM*, and *TKIs*, but achieving further remission is often challenging [60, 90].

## 7.2. Chimeric Antigen Receptor (CAR) T - Cell Therapy

The treatment outcomes for *R&R HL* remain disappointing. Recent advances in cancer biology have driven progress in cancer immunotherapy and led to new strategies. *CAR-T cell* therapy targeting the *CD19* protein on B-cell lymphocytes has been highly successful in treating B-cell neoplasms, despite safety concerns. Nevertheless, the *FDA* has approved *CAR-T cell* immunotherapy for treating adult and pediatric patients with B-cell neoplasms. The same approach has been applied to *CD30*-positive malignant cells in *R&R cHL*. *BV's* success in treating *CD30*-positive *R&R HL* has increased interest in pursuing *anti-CD30 CAR-T cell* therapy as a potential cure. *CD30* is part of the tumor necrosis factor family and is expressed on the surface of *RS* cells in over 97% of *cHL* cases, with minimal expression on nonmalignant cells. When stimulated, *CD30* induces hypoactivation of the *MAPK* antiapoptotic pathway. Overall, because of the complexity of the tumor microenvironment, *CAR-T cell* immunotherapy for solid tumors has been less successful [96].

Lymphodepletion before *CAR-T cell* infusion offers the best chance for *CAR-T cell* proliferation. *CAR-T cell* therapy without lymphodepletion was associated with poor outcomes. *FLD*-containing lymphodepleting regimens produced the best treatment results.

*CAR-T cell* immunotherapy has become an established therapy for B-cell neoplasms; however, the treatment is associated

with potentially serious complications. The most common complications are *CRS* and *ICANS*. These complications can be severe and sometimes fatal, but fortunately, severe forms occur in a minority of patients [96, 97].

*Tocilizumab* is a humanized anti-human *IL-6* receptor antibody that binds to both the soluble and membrane-bound *IL-6* receptors, hence reducing the inflammatory response caused by excessive cytokine release. *Tocilizumab* has been approved by the *FDA* for the treatment of moderate-to-severe, life-threatening *CRS*. However, the neurologic complication *ICANS* is mainly treated with corticosteroids [97, 98].

*Anakinra* is a recombinant, competitive *IL-1* receptor antagonist. It competitively binds to *IL-1 alpha* and *beta* receptors on the cell surface, thereby reducing the tissue inflammatory response. *Anakinra* has been approved by the *FDA* to treat rheumatoid arthritis. However, it has been used off-label as a second-line treatment for *CRS* and *ICANS* [86].

Wang *et al.* reported a phase I clinical trial that enrolled 18 patients with progressive *R&R cHL* despite prior multiple lines of therapy, including *BV* and *PLM*. All patients received salvage anti-*CD30 CAR-T cell* therapy. Lymphodepletion with *FLD* and *CPA* or *paclitaxel* and *CPA*. Two patients (11%) developed grade 3 and 4 cardiac and liver toxicities. Seven (39%) patients achieved *PR*, 6 (33%) had *SD*, and 5 (25%) had *PD* [29].

Ramos CA *et al.* reported the results of a phase I dose-escalation study. No lymphodepletion was used. Nine (9) patients with *CD30+ve* lymphoma were enrolled (8 with *cHL* and 1 with anaplastic large B-cell lymphoma). All patients received *CAR-T cell* products and tolerated the treatment well. The *ORR* was 33%, with 3 patients achieving *CR*, 3 achieving *SD*, and 3 developing *PD* [28].

Ramos CA *et al.* reported the results of a phase I/II clinical trial involving 41 patients (age 17 - 69 years) with *R&R HL* who had experienced multiple relapses. Patients received *BM* alone, *BM* and *FLD*, or *CPA* with *FLD* for lymphodepletion. The *ORR* was 62%. Of the 32 (78%) patients with active disease at the time of *CAR T-cell* therapy, 19 (59%) achieved *CR*. Treatment-associated toxicities were minimal. At 1 year, *PFS* and *OS* were 36% and 94%, respectively.

The *NLPHL* malignant cells, however, predominantly express *CD45* cell-surface markers but show little to no *CD30* expression. To date, researchers have not identified T-cell target molecules for *NLPHL* [27, 98].

## 8. Treatment of Relapsed Limited Stage Classical Hodgkin Lymphoma

Patients who develop low-stage (stage I & II) relapse (early & late) may benefit from less intensive or more localized therapy. Local surgical resection or *RT* alone is often followed by relapse. The logical approach is to use conventional *CTR* or targeted therapy to induce remission. Consolidation with involved field *RT* is often sufficient to achieve long-lasting re-

mission. However, given the likelihood of further relapses, especially in patients with localized, low-stage disease, some authorities choose to offer consolidation *ABMT*, especially in patients with early relapse and those who failed to achieve *CR* following induction *CTR* or targeted therapy [60, 91].

## 9. Relapsed Nodular Lymphocytic Predominant Hodgkin Lymphoma

*NLPHL* accounts for nearly 5% of *HL* cases. Most patients are young children (aged 3–9 years) who present with early-stage (stages I & II) disease without B symptoms. Few patients develop advanced-stage (stage III & IV) disease and extralymphatic tissue involvement. Depending on the risk factors, treatment options include *RT* alone, conventional *CTR*, and targeted medications. Surgical resection as the sole treatment for limited disease has been successful, but with a higher risk of relapse [20, 30–32].

*NLPHL* usually follows an indolent clinical course. However, because of the minimal therapy approaches applied, relapse is relatively more common than *cHL* [20, 30, 91].

The overall prognosis of *R&R NLPHL* is generally better than that for *cHL*, but disease stage and timing of relapse significantly impact the ultimate outcome.

The optimal treatment for *R&R NLPHL* is not yet well established. Generally, these patients require less intensive *CTR*. Aggressive therapy may only be required in a small percentage of patients with advanced (stage III–IV) disease. However, the best therapy depends on several factors, such as relapse timing and prior treatment. *CD20* positivity in B-lineage *NLPHL* cells makes *anti-CD20* monoclonal antibodies (*rituximab*) highly effective. Multiple prospective trials evaluated single-agent *rituximab* and *ofatumumab* in patients with *R&R NLPHL* and showed nearly 100% response rates. However, a significant proportion of patients developed late relapse, especially those with advanced-stage disease. Conventional *CTR* and/or *RT* was generally successful [20, 30, 31, 32, 92, 93]. *Schulz H et al.* reported results from the multicenter *GHSB* study on 4-weekly *rituximab* (375 mg/m<sup>2</sup>) in 15 patients with *R&R NLPHL*. Of the 9 patients with stage I/II disease, 94% responded (5 *CR* and 4 *PR*). The 6 patients with stage III/IV disease had an 83% response rate (3 *CR* and 3 *PR*). *PFS* and *OS* were 55% and 93%, respectively [94]. *Akhtar S et al.* reported 17 patients with *R&R NLPHL* (12 refractory and 5 relapse) who received *ABMT*. Five patients had transformed into *DLBCL*. Salvage *CTR* consisted of *ETOP*, *PSN*, *CPL*, and *Ara-C* {*ESHAP*}. Eight patients received *rituximab* in addition. The conditioning therapy consisted of *BCNU*, *ETOP*, *Ara-C*, and *MEL* {*BEAM*}. The 5-year *EFS* and *OS* were 76% and 94%, respectively. Patients who received salvage *CTR* plus *rituximab* had a better 5-year *EFS* than those who did not, [100% versus 56%] (*P*=0.041) [31]. *Eichenauer DA et al.* reported outcomes for 99 patients with *NLPHL* who relapsed or progressed after frontline treatment in 12 *GHSB* studies. With

a median follow-up of 11.2 years, relapse occurred at 3.7 years. In front-line therapy, 20% of patients received *RT* alone. *CTR* with or without *RT* in 74%, and *CTR* with *rituximab* in 6% of patients. In *R&R NLPHL*, 37% of patients received single-agent *rituximab* or *RT* alone. *CTR* with or without *RT* in 74%, *CTR* with or without *rituximab* and with or without *RT* in 27%, and *ABMT* in 31%. No salvage *CTR* was given in 4% of patients. The 5-year *PFS* and *OS* were 75.6% and 89.5%, respectively. For patients who received single-agent *rituximab* and *RT*, *PFS* and *OS* were 74.1% and 97.2%, respectively. For patients who received *CTR* with or without *rituximab* and/or *RT*, *PFS* and *OS* were 68%, 77.8%, and 84.6% and 89.8% after *ABMT*, respectively [93, 94].

Transformations between chronic leukemia and lymphoma are not uncommon. In 3–14% of patients, *NLPHL* may transform into rapidly growing, aggressive lymphomas during relapse. The median time to transformation is 3–8 years. Transformation involves the popcorn-like malignant cells and often results in *DLBCL* or *TCRBCL*. Transformation is less common in *cHL*, which may evolve into a common non-Hodgkin lymphoma, such as mixed unclassifiable B- and T-cell lymphoma, or, rarely, *DLBCL*. Unlike patients with *cHL*, transformation in *NLPHL* can occur many years after therapy, requiring a longer period of follow-up. Treatment generally involves aggressive therapy. Induction *CTR* using *ABVD*, *BV+AVD* (*BV*, *DOX*, *VBL*, *DZN*), or *R-CHOP* (*rituximab*, *CPA*, *DOX*, *VCR*, *PSN*) may be employed. At least 2 cycles of *CTR* are administered before consolidation *ABMT* (for eligible patients) is given. *RT* is not typically indicated. Patients with *CD30* positivity may be considered for *CAR-T cell* therapy (when available). *Allogeneic BMT* could be an additional option [30, 31, 92].

The cumulative incidence of *NLPHL* transformation at 10 years is nearly 6% (95% *CI*, 4.2–9.6), and the treatment outcomes for patients who transform into *DLBCL* are generally significantly worse. [95].

## 10. Conclusion

The standard treatment for patients with *R&R HL* involves second-line salvage *CTR* followed by consolidation *ABMT*. However, despite this toxic regimen, nearly half of patients experience further relapses. Researchers are exploring newly discovered genetic and metabolic pathways as therapeutic targets. *CD30* and *PD1* checkpoint inhibitors have shown the best results. *CAR-T cell* therapy targeting *CD30* in *cHL* is a promising emerging treatment. *Allogeneic BMT* is reserved as a last resort. No *CAR-T cell* therapy has yet been developed to treat *R&R NLPHL*. Maintenance *BV* after consolidation with *ABMT* and *allogeneic BMT* offers significant benefits, but it is not yet considered standard.

## Abbreviations

HL

Hodgkin Lymphoma

|                |                                                |         |                                                       |
|----------------|------------------------------------------------|---------|-------------------------------------------------------|
| NLPHL          | Nodular Lymphocytic<br>Predominant HL          | Dex     | Dexamethasone                                         |
| cHL            | Classical HL                                   | TKIs    | Tyrosine Kinase Inhibitors                            |
| DLBCL          | Diffuse Large B-cell Lymphoma                  | MRI     | Magnetic Resonance Images                             |
| TCRBCL         | T-cell-rich B-Cell Lymphoma                    | CT      | Computerized Tomography                               |
| RT             | Radiotherapy                                   | FDG–PET | 18–Fluorodeoxyglucose Positron<br>Emission Tomography |
| CTR            | Chemotherapy                                   | COG     | Children’s Oncology Group                             |
| R&R            | Refractory and Relapsed                        | POG     | Pediatric Oncology Group                              |
| IMRT           | Intensity-Modulated Radiation<br>Therapy       | GHSG    | German Hodgkin Study Group                            |
| RIC            | Reduced-intensity Chemotherapy                 | CHIPS   | Childhood Hodgkin’s<br>International Prognostic Score |
| HD             | High-Dose                                      | FDA     | Food and Drug Administration                          |
| EFS            | Event-free Survival                            | RS      | Reed—Sternberg                                        |
| OS             | Overall Survival                               | CSC     | Cancer Stem Cells                                     |
| RER            | Rapid Early Response                           | NLR     | Neutrophil-to-lymphocyte Ratio                        |
| SER            | Slow Early Response                            | ROC     | Receiver Operating Characteristic                     |
| VGPR           | Very Good Partial Response                     | BLNK    | B-cell Linked Protein                                 |
| PR             | Partial Response                               | WGS     | Whole Genome Sequencing                               |
| CR             | Complete Remission                             | NGS     | Next-generation Sequencing                            |
| PR             | Partial Remission                              | PLK1    | Polo-like Kinase 1                                    |
| SD             | Stable Disease                                 | PD      | Programmed Cell Death                                 |
| PD             | Progressive Disease                            |         |                                                       |
| ORR            | Overall Response Rate                          |         |                                                       |
| PFS            | Progression-Free Survival                      |         |                                                       |
| AUC            | Area Under the Curve                           |         |                                                       |
| CAR            | Chimeric Antigen Receptor                      |         |                                                       |
| LN             | Lymph Nodes                                    |         |                                                       |
| CNS            | Central Nervous System                         |         |                                                       |
| ABMT           | Autologous Blood and Marrow<br>Transplantation |         |                                                       |
| ALLOGENEIC BMT | Allogeneic Bone Marrow<br>Transplantation      |         |                                                       |
| VCR            | Vincristine                                    |         |                                                       |
| PSN            | Prednisone                                     |         |                                                       |
| PZN            | Procarbazine                                   |         |                                                       |
| DOX            | Doxorubicin                                    |         |                                                       |
| ETOP           | Etoposide                                      |         |                                                       |
| MCL            | Mechlorethamine                                |         |                                                       |
| ChL            | Chlorambucil                                   |         |                                                       |
| GC             | Gemcitabine                                    |         |                                                       |
| VRN            | Vinorelbine                                    |         |                                                       |
| CPL            | Cisplatin                                      |         |                                                       |
| VBL            | Vinblastine                                    |         |                                                       |
| DZN            | Dacarbazine                                    |         |                                                       |
| BCNU           | Carmustine                                     |         |                                                       |
| CPA            | Cyclophosphamide                               |         |                                                       |
| CPL            | Cisplatin                                      |         |                                                       |
| IFO            | Ifosfamide                                     |         |                                                       |
| Ara C          | Cytosine Arabinoside                           |         |                                                       |
| MEL            | Melphalan                                      |         |                                                       |
| BV             | Brentuximab Vedotin                            |         |                                                       |
| BZM            | Bortezomib                                     |         |                                                       |
| PLZ            | Pembrolizumab                                  |         |                                                       |
| NLM            | Nivolumab                                      |         |                                                       |
| BM             | Bendamustine                                   |         |                                                       |

## Author Contributions

**Adil Abdelhamed Abbas:** Conceptualization, Data curation, Methodology, Resources, writing, review and editing.

## Conflicts of Interest

The author declares no conflicts of interest.

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