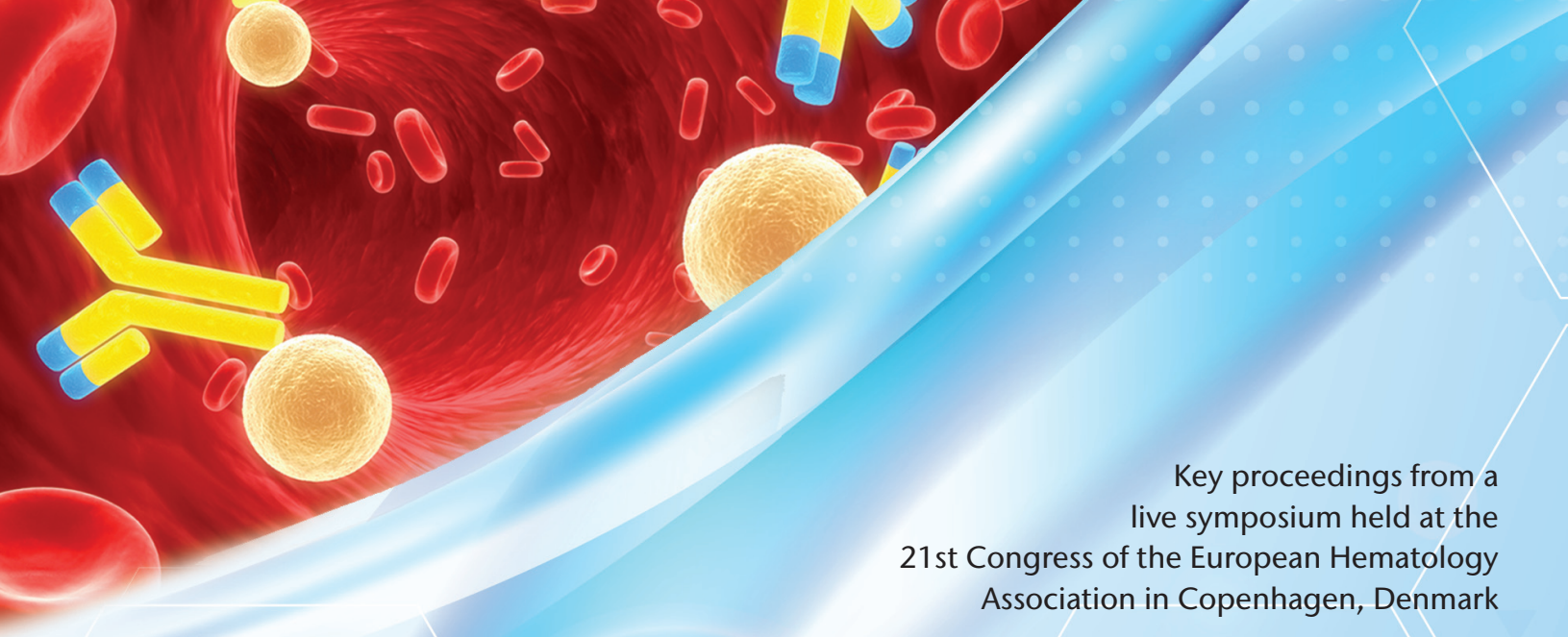

Key proceedings from a
live symposium held at the
21st Congress of the European Hematology
Association in Copenhagen, Denmark

The Role of CD30:
New Frontiers in Targeting Therapy for Malignant Lymphomas

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Activity Information

Release Date: October 21, 2016
Expiration Date: October 21, 2017
Expected time to complete this activity: 120 minutes

There are no fees for participating in or receiving credit for this activity.

PROGRAM OVERVIEW

The rapid pace of scientific advances in lymphoma research makes it challenging for clinicians to stay up-to-date on the latest treatment options and ongoing clinical trials. To meet this challenge, a panel of lymphoma experts has provided the latest information on current and future developments in the treatment of CD30+ lymphomas and on novel therapeutic options that target CD30 in HL. Summaries of recent clinical trials studying CD30-targeted therapy in other lymphoma subtypes will address safety and efficacy data in these diseases.

TARGET AUDIENCE

This activity is designed for physicians, pharmacists, physician assistants, nurses, and other health care professionals who have an interest in enhancing their knowledge of current and emerging treatments for CD30-positive lymphomas.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Recognize the clinical significance of CD30 as a biomarker in Hodgkin lymphoma and other malignant lymphomas
- Summarize the safety and efficacy data of novel agents and treatment strategies in Hodgkin lymphoma
- Outline the clinical trial data for emerging therapies in CD30-expressing lymphomas

AGENDA

CD30 Expression in Lymphoma
Anton Hagenbeek, MD, PhD – Activity Chair

The Promising Role for Anti-CD30 Treatment in a Wider Subset of CD30+ Lymphomas
Tim Illidge, PhD, MRCP, FRCR, FRCPath

The Evolving Role of Targeted Therapy for Patients with CD30+ Hodgkin Lymphoma
Anas Younes, MD

INSTRUCTIONS FOR PARTICIPATION AND CREDIT

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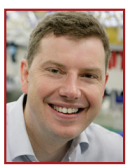

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Introduction: CD30 Expression in Lymphoma

Anton Hagenbeek, MD, PhD

Assessing CD30 Expression

The cluster of differentiation 30 (CD30) antigen is a tumor necrosis factor expressed by activated T and B lymphocytes. Although the function of CD30 in normal human physiology is not completely understood, elevated expression has been linked to hematologic malignancies.[1] However, not all hematologic malignancies express CD30; CD30-positivity may be defined as CD30-expression in 10% to 20% of malignant cells. The cutoff values for CD30-positivity vary due to differences in the methods of quantitation between studies; CD30-expression may range from unspecified values to more than 80% of malignant cells.[2-8] CD30 is typically assessed by use of immunohistochemistry (IHC), flow cytometry (FC), or enzyme-linked immunosorbent assay (ELISA). IHC is the most common method of assessing CD30 expression. FC can be substituted for IHC or combined with it based on sample state, resources, and experience with use of the methods. ELISA is more typically used to score levels of CD30 in the serum.[2,8,9] In addition to these testing methods, CD30 staining increases the reproducibility of diagnosis. For example, the addition of CD30 immunostaining to morphologic analysis has been found to increase the reproducibility of lymphoma diagnosis by 39% for patients with anaplastic large cell lymphoma (ALCL), which is highly CD30-positive.[10,11] However, staining must be performed optimally to obtain adequate results. Data have demonstrated that nearly 1 in 4 laboratories participating in quality control (QC) testing returned inadequate results from CD30 staining. One independent scientific organization promoting the quality of IHC (NordiQC), assessed CD30 staining amongst 172 laboratories in 2011, which was the third quality study performed in the series dating back to 2004 and 2007. Results demonstrated that only 133/172 (77%) of the sites assessed actually achieved adequate staining; this was an absolute decrease of 15% from 2004. Technical challenges in staining may affect accurate interpretation and diagnosis. In 90% of inadequate results in the NordiQC study, staining was found to be either too weak or false negative, and in the remaining 10%, both weak and false-positive staining were identified. Poor staining was seen in nearly all cases, and the primary causes of insufficient staining were too-low concentrations of the primary antibody and/or a too-short time of heat-induced epitope retrieval (HIER). These factors must be taken into consideration in interpreting study data.[2,12]

CD30 Expression in Hodgkin Lymphoma

CD30 is a differential marker in Hodgkin lymphoma (HL), distinguishing between classical HL and CD30-negative nodular lymphocyte predominant HL (NLPHL) according to World Health Organization (WHO) classifiction.[3,9,13] More than 98% of cases of HL express CD30 compared to fewer than 8% of cases of NHPHL.[3,13] Per WHO classification data, a variety of frequently occurring B-cell non-Hodgkin lymphomas (NHLs) show at least some degree of CD30 expression:

- Diffuse large B-cell lymphoma: 4% to 26%[14,15]
- Follicular lymphoma: 14% to 50%[16,17]
- Primary mediastinal B-cell lymphoma (PMBL): 69% to 86%[18,19]

CD30 is variably expressed in approximately 30% of T-cell lymphomas. Even more subtypes of T-cell lymphoma show CD30 expression, including[20]:

- Peripheral T-cell lymphoma (not otherwise specified/NOS): 5% to 32%[4,5]
- Angioimmunoblastic T-cell lymphoma (AITL): 0% to 33%[7,21]
- Extranodal NK/T-cell lymphoma 13% to 75%[22,23]
- Adult T-cell leukemia/lymphoma: 0% to 23%[24,25]
- Anaplastic large cell lymphoma, anaplastic lymphoma kinase (ALK)-positive: 100%[26]
- Anaplastic large cell lymphoma, ALK-negative: 100%[27]
- Enteropathy-associated T-cell lymphoma (EATL): 13% to 87%[28,29]
- Primary cutaneous ALCL: 100%[30]
- Other disorders:
  - Mycosis fungoides (MF): 11%[31]
  - Transformed MF: 24% to 100%[32,33]
  - Lymphomatoid papulosis: 60% to 100%[34]

These data demonstrate the potential eligibility of several B-cell and T-cell lymphomas, in addition to HL, for treatment with anti-CD30 antibodies or anti-CD30 drug conjugates.

Relationship Between CD30 Expression and Response to Brentuximab Vedotin

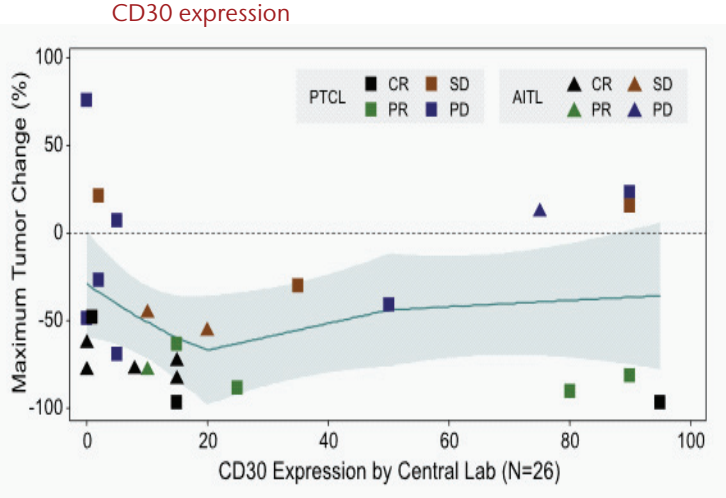
Brentuximab vedotin (BV) is an antibody drug conjugate (ADC) comprised of a chimeric IgG1 antibody and the microtubule disrupting agent, monomethyl

auristatin E (MMAE), directed against CD30. When BV binds CD30-expressing cancer cells, the complex undergoes clathrin-mediated endocytosis, and the endosome fuses with lysosomes. The proteases then cleave the dipeptide linker in the drug, releasing free MMAE into the cellular cytoplasm, where it binds microtubules and inhibits polymerization to induce cell cycle arrest and subsequent apoptosis. BV is FDA-approved for both classical Hodgkin lymphoma (cHL) and systemic anaplastic large cell lymphoma (sALCL).[35]

For patients with cHL, BV is used after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, or in patients at high risk of relapse or progression as post-auto-HSCT consolidation. For patients with sALCL, BV is used after failure of at least one prior multi-agent chemotherapy regimen.[35]

Inadequate response to treatment, whether it manifests as disease relapse or inability to achieve remission, remains a critical problem in the management of patients with T-cell lymphoma. Because of this, there remains a strong need for new agents to treat these malignancies in both the frontline and relapsed settings. A study by Horwitz, et al., was designed to evaluate the safety and efficacy of BV in patients with relapsed/refractory CD30-positive NHLs. Results demonstrated objective responses observed with brentuximab vedotin in 41% of patients with relapsed T-cell lymphomas, including 54% of patients diagnosed with AITL. Responses were seen in patients with all CD30 expression levels in tumor samples. (*Figure 1*) Objective responses were observed across a wide range of CD30 expression, including undetectable CD30 expression per central review. Based on the eligibility criteria, all patients had lymphoma that expressed CD30 by institutional pathology assessment; however, 6 patients (17%) had undetectable CD30 expression by this measure. CD30 expression per central laboratory assessment ranged from 0% to 95%. There was no apparent correlation between response and CD30 expression as evidenced by complete response (CR) or partial response (PR) in 9 of 14 patients (64%) with little to no detectable CD30 expression (≤15% CD30 expression) by central review. The response rates in this trial and the lack of correlation with CD30 expression suggested that the potential activity of BV among various T-cell lymphoma subtypes may be fairly broad. However,

Figure 1. Maximum tumor size decrease by quantitative CD30 expression



Adapted from Horwitz SM, et al. *Blood*. 2014;123(20):3095-3100.

testing with IHC for CD30 or the presence of elevated serum CD30 (sCD30) may provide a valuable biomarker for patient selection for therapy.[36]

Similar results were seen in a study of patients with MF performed by Krathen, et al. In this trial, patients with MF/Sézary syndrome (SS) stage IB to IV who had received at least one prior therapy were treated with BV, regardless of pre-treatment CD30 staining status. The overall response rate was 68%. After 25 weeks, 74% or responses were found to be continuing with 73% of patient progression-free at 36-week follow-up (range 6-55 weeks). Clinical responses were observed in patients with all levels of CD30 expression; however, CD30 expression did not correlate with clinical response as assessed by routine IHC or by multispectral image analysis.[37]

Potential explanations for why some CD30-negative lymphomas respond to BV have been suggested. It is possible that assays (eg, IHC, flow cytometry) may provide false-negative results. It is also possible that CD30 antigen density on tumor cells may be below conventional detection levels. Another possible explanation for death of non-CD30-expressing lymphomas is the leakage of MMAE out of CD30-positive cells into the microenvironment; the diffusion of MMAE out of the cytoplasm, into the extracellular space, and into CD30-negative cells is called the "bystander" effect.[38] (*Figure 2*)

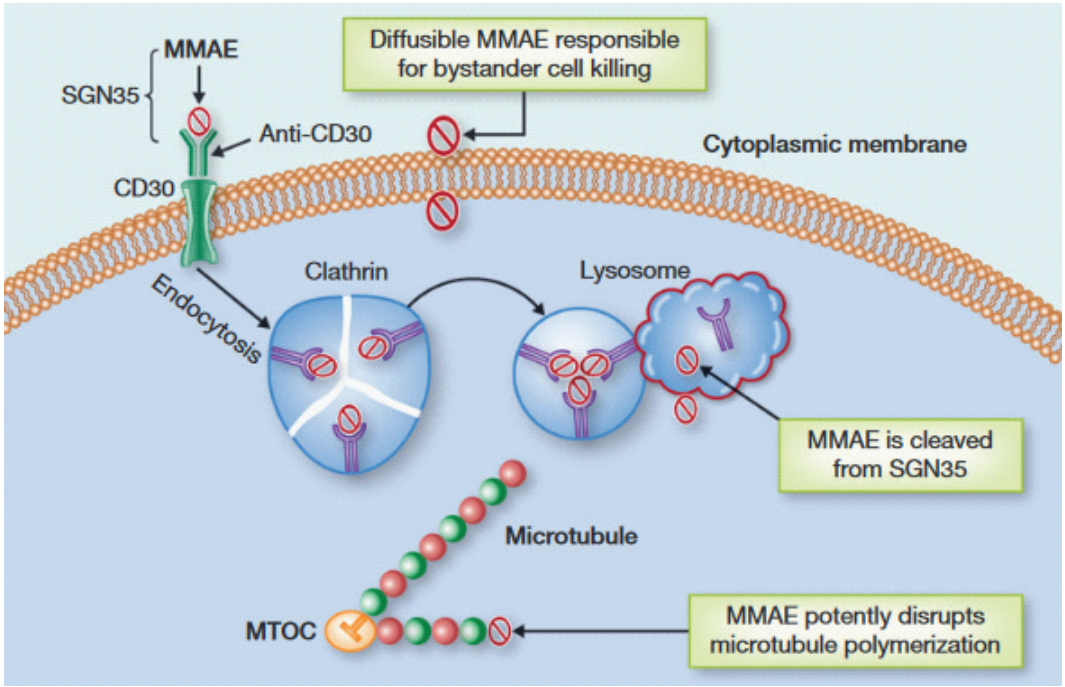


Figure 2. MMAE "Bystander Effect"

Adapted from Deng C, et al. *Clin Cancer Res*. 2013;19(1):22-27.

There is ongoing research and development to discover new generations of ADCs focusing on less toxic molecules per antibody in order to effectively kill the target cell, while simultaneously reducing the toxic side effects that may harm normal tissue. In addition, these efforts strive to develop even stronger cytostatic agent-antibody binding so that the drug is not released before the whole complex reaches the molecular target cell. That said, many challenges remain along every step of the drug development and assessment process.[39]

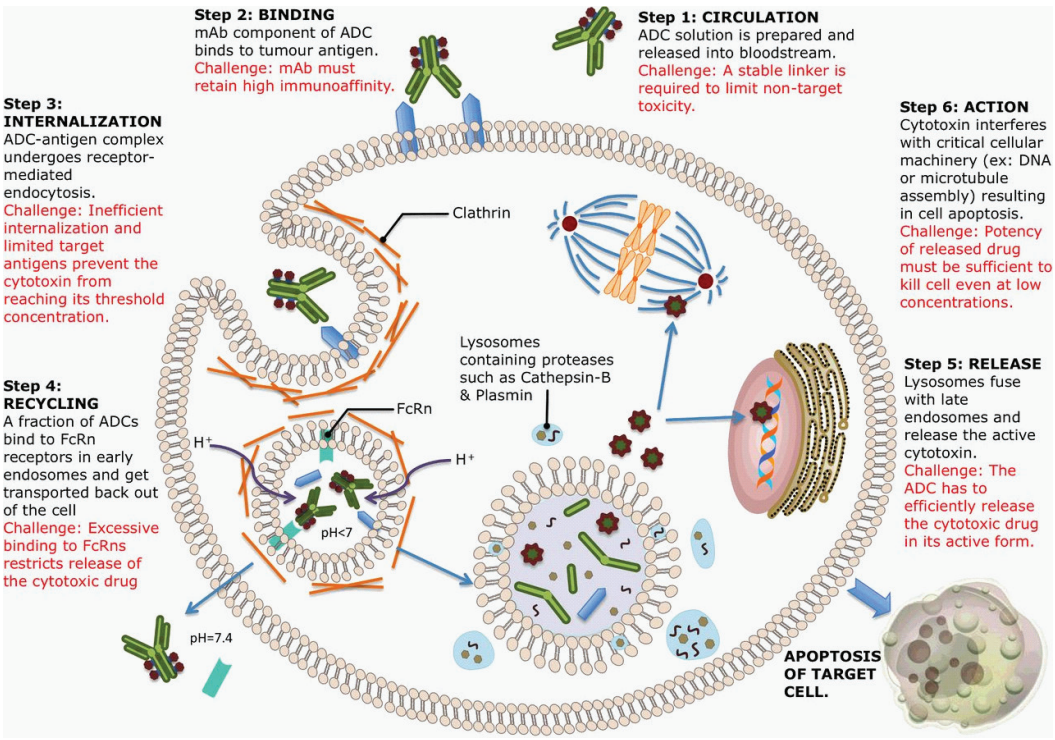


Figure 3. Mechanistic Pathway of ADCs Resulting in Tumor Cell Death

Adapted from Peters C, et al. *Biosci Rep*. 2015;35(4).

The Promising Role for Anti-CD30 Treatment in a Wider Subset of CD30+ Lymphomas

Tim Illidge, PhD, MRCP, FRCR, FRCPath

This is currently an exciting time for the development of anti-CD30-based therapies; a notable paradigm shift that began with the ability to target CD30 through the development of brentuximab vedotin.

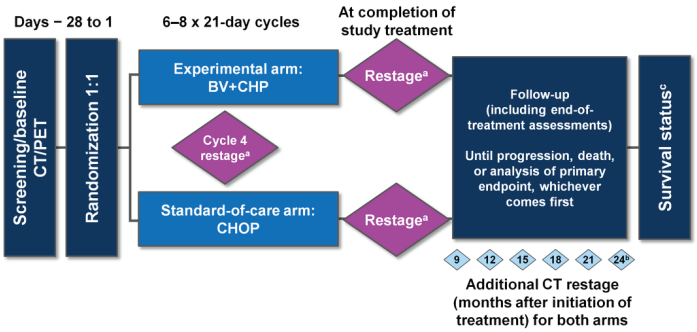
Brentuximab Vedotin: Initial Lymphoma Trials

Brentuximab vedotin was studied in a phase 2 trial of patients with systemic ALCL between 2009 and 2010 in 22 clinical sites across the United States, Canada, and Europe. This was the largest study ever performed in this patient population at the time. A total of 58 patients were enrolled, having been heavily pretreated and determined to have poor prognosis. Of these patients, 72% had ALK-negative disease, 62% had primary refractory disease following chemotherapy, and 26% of patients failed prior allogeneic stem cell transplant. Patients received a median of two cycles of prior chemotherapy, with a range between one and six cycles. BV at a dose of 1.8 mg/kg was given every 3 weeks as derived by the initial phase 1 studies. The efficacy of the agent was assessed using the Revised Response Criteria according to Cheson 2007. Survival and disease status were to be assessed every 3 months for a total of 2 years, every 6 months during years 3 to 5, and annually thereafter. By the time of analysis, all patients had discontinued therapy with a median observation time from first dose of 46.3 months. Results demonstrated an objective response rate (ORR) of 86% by independent review with a CR rate of 59%. A 4-year overall survival (OS) of 64% was also demonstrated, with a median progression-free survival (PFS) for patients with ALK-positive disease of 25.5 months compared with 20.0 months for those with ALK-negative disease. A total 18 patients underwent hematopoietic stem cell transplant (SCT) after discontinuing treatment; there were no differences in OS or PFS between patients who underwent allogeneic or autologous transplant. Treatment with BV was associated with a longer PFS than the patient's last prior therapy. In regard to adverse events (AEs) peripheral sensory neuropathy was identified more than 20% of the time, but was reversible and modifiable through dose modification. Other less common grade 3 AEs (≥5%) include: neutropenia, thrombocytopenia, peripheral sensory neuropathy, anemia, recurrent ALCL and fatigue. The researchers concluded that BV is highly active, leading to durable remissions when administered as monotherapy.[40]

The high response rate observed with BV supported investigation into its use earlier in the treatment pathway, including as potential first-line therapy. An initial phase 1 study by Horwitz, et al., integrated BV with chemotherapy in patients with CD30-positive mature T-cell and natural killer (NK)-cell neoplasms. BV was initially administered in the first arm of the study (N=20) as a single agent for 2 cycles to assess response using it as first-line therapy followed by cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for 6 cycles, and then BV was given for 8 cycles following completion of the CHOP regimen. However, in the second arm (N=6-12), there was an integration of the BV with chemotherapy consisting of cyclophosphamide, doxorubicin and prednisone (CH-P) to avoid overlapping neurologic toxicity of vincristine with BV. Part two of the study included an expanded cohort with 26 patients receiving 6 cycles of both CH-P and BV in combination followed by 10 additional cycles of BV. Results demonstrated an ORR of 100% and a CR rate of 88%. At the time of analysis, 77% of the patients studied remained in long-term follow-up with a median observation time of 38.7 months from the first dose. The 3-year OS was 80% with a 3-year PFS of 52% (median OS and PFS were not reached). The major significant toxicity found was peripheral neuropathy (any grade), found in 73% of patients with the vast majority of the patients having reversible neuropathy once the study drug was stopped. A total of 23 of 26 patients completed all the cycles of the BV plus CH-P, and 21 of the 26 patients received a median of 10 doses (range 1-10) of BV post-BV/CH-P combination therapy.[41] A previous study by Horwitz and colleagues assessed 35 patients, 13 of whom had adult T-cell lymphoma (ATCL) and 22 who had peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). BV 1.8 mg/kg was administered every 3 weeks until there was evidence for either disease progression or unacceptable toxicity. The response rate was highest in the ATCL population with an ORR of 54%, 5 CR and 2 PR. The ORR rate was 41% in the PTCL group with 8 CR and 6 PR. The ORR for the total patient population was 41% with a CR rate of 24%.[36] These studies essentially laid the groundwork

for the ECHELON-2 trial, a phase III trial of BV plus CH-P versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas, which is currently in the recruitment phase.[42]

Figure 4. Phase III Trial of Brentuximab Vedotin and CHP versus CHOP in the Frontline Treatment of Patients with CD30+ Mature T-cell Lymphomas (ECHELON-2)



[a]CT and PET scans required. [b]Additional CT scans every 6 months thereafter until progression per investigator, death, or analysis of primary endpoint, whichever comes first. [c]For patients with documented progression, continued follow-up for survival every 6 months until death or study closure, whichever comes first.
CT=computed tomography

Adapted from: *https://clinicaltrials.gov/ct2/show/NCT01777152?term=NCT01777152&rank=1*

Treatment of CD30-Expressing T-Cell Cutaneous Lymphomas and DLBCL

The role of CD30 in T-cell lymphomas that arise primarily from the skin is also a focus of significant research. These cutaneous lymphomas, including MF, primary cutaneous ALCL, and lymphomatoid papulosis, have been investigated in several clinical trials. Two pivotal studies have been conducted in this area.

In the first study by Kim, et al., patients with MF or SS with a history of least one systemic therapy failure were divided into three groups according to CD30+ status. Group A had low CD30 expression of less than 10% (43% of patients), Group B had intermediate CD30 expression between 10% to 50% (43% of patients), and Group C had high CD30 expression greater than 50% (13% of patients) on the total malignant infiltrates. BV was administered at the established dose of 1.8 mg/kg every 3 weeks for up to 8 cycles. If the patients achieved a PR, they were eligible to receive an additional 8 cycles of BV to a maximum of 60 total. If they achieved CR with up to 8 cycles, they received additional cycles of BV. Approximately 88% of patients enrolled had advanced-stage disease and around 90% of them had large cell transformation or the adverse prognostic features of folliculotropic MF. A substantial number had been heavily pretreated (range of treatments between 1 and 13) with the median number of prior systemic therapies having been 3. Of the 32 patients enrolled, 30 had efficacy evaluations. The global ORR in the total group of 30 patients was 70%, with the earliest stages (IB) showing response rates as high as 78%. However, only one patient achieved CR with the majority of responders achieving PR (67% of patients). Patients with <5% CD30 expression had a lower likelihood of global response (17%) compared to those with >5% CD30 expression (83%). The median time to treatment response was approximately 6.6 weeks, varying between 3 and 27 weeks. The 6-month and 12-month PFS were 79% and 54%, respectively. Event-free survival for those studied was 61% at 6 months and 28% at 12 months. When examining the modified severity-weighted assessment tool (mSWAT), which is an assessment of the body surface area of each type of lesion in the twelve areas of the body, the median best mSWAT reduction was 73% with 8 patients achieving an mSWAT reduction of more than 90%. As seen with other studies with this agent, peripheral neuropathy was the most significant AE with two-thirds of the patients experiencing peripheral neuropathy of any grade, and the majority of these events being grade 1 and grade 2; just one patient experienced a grade 3 event. Overall, the investigators concluded that BV demonstrated significant clinical activity in treatment-refractory or advanced MF/SS over a wide range of CD30 expression levels. The drug also demonstrated an encouraging duration of clinical benefit in the patients studied.[43]

Another study was a phase 2 trial of BV for CD30-positive cutaneous T-cell lymphoma (CTCL) and lymphomatoid papulosis by Duvic, et al. In this study, 48 evaluable patients received BV at a dose of 1.8 mg/kg every 21 days. Results demonstrated an ORR of 73% in the total patient population, with a 100% ORR for those with primary cutaneous ALCLs and lymphomatoid papulosis, and 54% rate for those with MF, irrespective of CD30 status. The CR was 35% for the overall patient population. Median time to response was 12 weeks for patients with MF and 3 weeks for those with lymphomatoid papulosis. Mediation duration of response was 32 weeks for those with MF and 26 weeks for the lymphomatoid papulosis population. The most common AEs were neuropathy (65%), fatigue (41%), and drug rash (27%). The investigators concluded that BV was active with a manageable safety profile in patients with CD30-positive CTCL, and the response rates compared favorably with previous treatment agents.[44]

Finally, another phase II study was performed by Yasenchak, et al., to evaluate combination therapy with BV and standard rituximab plus CHOP (RCHOP) as

frontline treatment for patients with high-intermediate (63% of patients) or high-risk (37%) diffuse large B-cell lymphoma (DLBCL), irrespective of CD30 status. Primary endpoints were CR and treatment tolerability with PFS as a key secondary endpoint. Patients were randomized to receive either BV 1.2 mg/kg plus RCHOP or BV 1.8 mg/kg plus RCHOP for up to 6 treatment cycles. Response was assessed using Cheson 2007. Results showed that the CR rate was 69% overall through assessment using positron emission tomography (PET). Patients with CD30-positive disease had a CR rate of 76% compared to a CR rate of 63% in those patients who were CD30-negative. The estimated PFS rate at 12 months was 82% in CD30-positive patients and 56% in those who were CD-negative; 60% of patients with CD30-negative, ABC-negative DLBCL progressed, versus 27% of patients who were CD30-positive and ABC-negative. Four patients with Epstein-Barr virus (EBV)-positive DLBCL were treated and all achieved CR, with 3 remaining in remission after a median 12-month follow-up. Overall, results demonstrated that adding BV to RCHOP results in a substantial CR rate, higher in those with CD30 expression, even in those with unfavorable ABC subtype and EBV-positive DLBCL.[45]

Brentuximab vedotin has demonstrated high responses and durable remissions in several types and subtypes of lymphoma, including CTCL, primary cutaneous ALCL and lymphomatoid papulosis. The ECHELON-2 study will indicate whether there is a potential role for BV in the frontline setting. There is promising data emerging for BV in other CD30-expressing B cell lymphomas, such as DLBCL and PMBL, further demonstrating the potential for the incorporation of BV into treatment paradigms across lymphoma subtypes and disease settings.[42]

The Evolving Role of Targeted Therapy for Patients with CD30-Positive Hodgkin Lymphoma

Anas Younes, MD

Hodgkin Lymphoma: Characteristics for Therapy

Current cancer statistics published annually in the United States estimate that approximately 8,500 new cases (4,790 men, 3,710 women) of HL will be diagnosed in 2016 with 1,120 deaths expected to occur from this hematologic malignancy (640 in men, 480 in women).[46] HL is staged traditionally from one to four, with early disease (stage I/II) classified by the presence of favorable or unfavorable characteristics.[9,47] This designation is based upon prognostic factors that may vary according to the classification system.

Table 1. Regional Variations in Defining Early Stage HL and Treatment Options

Early (limited) stage I/II HL				
EORTC		GHSG		North America
Favorable	Unfavorable	Favorable	Unfavorable	
	1. Bulky mediastinal mass		1. Bulky mediastinal mass	No bulk No B symptoms
	2. Elevated ESR		2. Elevated ESR	
	3. Nodal regions ≥ 4		3. Nodal regions ≥ 3	
	4. Age ≥ 50 years		4. Extra-nodal disease	

EORTC=European Organisation for the Research and Treatment of Cancer; GHSG=German Hodgkin Study Group; ESR=European Study Group.

Table courtesy of A. Younes, MD

Standard Therapy for Hodgkin Lymphoma

Standard therapy for patients with HL has been salvage chemotherapy followed by consolidation with high-dose therapy and autologous SCT (ASCT), curing approximately 50% of patients using these regimens.[48] The previous standard of care was established by a study from Engert, et al., (HD10 study), comprising 4 treatment groups who received 4 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy plus 30 Gy of involved-field radiation therapy (Group 1); 4 cycles of ABVD plus reduced-dosage of radiation therapy at 20 Gy, (Group 2); 2 cycles of ABVD but with the standard radiation dose of 30 Gy (Group 3); and 2 cycles of ABVD plus reduced 20 Gy radiation dose (Group 4); 1,370 patients were randomized into this trial, with a primary endpoint of freedom from treatment failure and secondary endpoints of efficacy and toxicity of therapy. At 5 years, the rates of freedom from treatment failure were 93% with the 4-cycle ABVD regimen and 91.1% in patients who received only 2 cycles of ABVD. Adding in the effects of the standard and lower radiation doses, there were also no significant differences in freedom from treatment failure or OS.[49] In summary, the treatment of early-stage HL should be based on risk classification. (*Table 2*) For early favorable HL, the standard of care would be 2 cycles of ABVD plus 20 Gy of radiation therapy. Early unfavorable

Table 2. Treatment of Early Stage HL Based on Risk Classification

		Stage III/IV	Stage I/II	
			I/II Bulky Mediastinal	I/II No Bulk
Stage Grouping	North America	Advanced stage includes Stage I/II bulky disease		Early stage
	GHLSG	Advanced stage	Early-stage unfavorable	Early-stage favorable
Treatment Options	North America	ABVD x 6-8 ± XRT	ABVD x 6-8 + 36 Gy IF-XRT	ABVD x 4 + 30 Gy IF-XRT / ABVD x 2 + 20 Gy IF-XRT
	GHLSG	Esc BEACOPP x 6 ± XRT	Esc BEACOPP x 2 + ABVD x 2 + 30 Gy IF-XRT	ABVD x 2 + 20 Gy IF-XRT

GHLSG=German Hodgkin Lymphoma Study Group; ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; Esc=escalated; IF-XRT=involved-field radiation therapy

Adapted from Younes A. *J Clin Oncol*. 2012;30(9):895-896.

disease should be treated with 4 cycles of ABVD plus 30 Gy of radiation therapy. If bulky mediastinal mass is present in HL, North American classification recommends 6 cycles of ABVD plus 30 Gy of radiation therapy. The presence of bulky mediastinal mass in a patient with stage I/II disease is included with early unfavorable disease, and this can also be treated with 2 cycles of an escalated combination regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP), followed by 2 cycles of ABVD and 30 Gy of radiation therapy; this was based on a randomized trial reported by the German Hodgkin Lymphoma Study Group (GHLSG/GHSG).[50]

Chemotherapy for Hodgkin Lymphoma

There is now a trend developing to spare the patient from the need for radiation therapy (RT) and using chemotherapy alone as an approach for early-stage HL. This is based upon the use of interim PET scanning; treating the patient with ABVD and performing PET, and depending on the imaging results, administering chemotherapy with or without RT. In the Randomised Phase III Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease (RAPID trial), 602 patients with newly-diagnosed stage IA or stage IIA HL received 3 cycles of ABVD and then underwent PET scanning. If PET findings were negative, patients were randomized to receive involved-field (IF) RT or no further treatment. Patients who had positive findings on PET received one more cycle of ABVD combined with RT. This trial primarily assessed for noninferiority of no further treatment compared to more ABVD in combination with RT. Results demonstrated negative PET findings in 426 of these patients (74.6%), 420 of whom were randomly assigned to further study groups (209 to RT vs 211 to no further therapy). At a median of 60 months' follow-up, there were 8 instances of disease progression in the RT cohort, and 8 patients had died; three deaths were due to disease progression. In the group of patients who received no further therapy, 20 experienced disease progression; 4 patients had died, with two deaths attributed to disease progression. The 3-year rate of PFS was 94.6% in patients who had received RT vs 90.8% in the group that received no further therapy. Overall, the results demonstrated slight favorability toward those who received ABVD and RT; withholding further treatment failed to demonstrate non-inferiority with regard to PFS. However, prognosis was favorable for all patients, including those who received no further treatment.[51]

However, nearly a third (30%) of patients with HL relapse or do not respond to first-line therapy.[48] For advanced-stage HL, the usual standard of care is ABVD, based on data that compared ABVD with the earlier treatment regimen of mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) versus MOPP/ABVD.[52] ABVD is simpler to administer, less toxic than MOPP, and has therefore became standard of care for more than 40 years. One recent randomized trial compared ABVD with the Stanford V regimen, consisting of a combination of doxorubicin, vinblastine, mechlorethamine, vincristine,

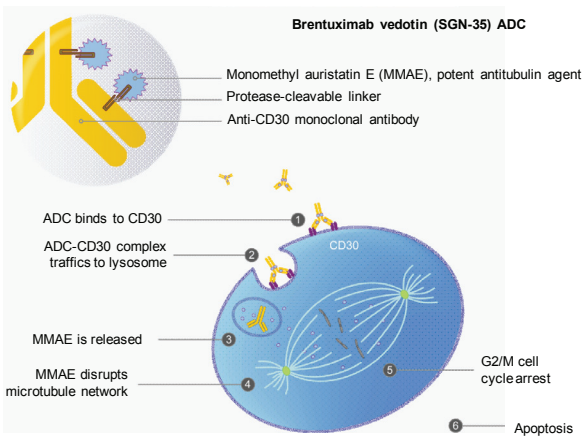
bleomycin, etoposide, and prednisone. The primary endpoint was failure-free survival (FFS) in terms of time to progression, relapse, or death, and results demonstrated no significant difference in ORR between the 2 cohorts; the CR were 73% for ABVD and 69% for Stanford V.[53] Another regimen that was studied against ABVD was BEACOPP. In one study comparing ABVD to BEACOPP in patients with Stage IIB, III or IV HL, the 7-year rate of freedom from first progression was 73% among patients who had received initial treatment with ABVD versus 85% among those who had received initial treatment with BEACOPP, and the 7-year rate of event-free survival was 71% and 78%, respectively. However, following treatment completion, the 7-year rate of freedom from second progression was 82% in the ABVD group and 88% for those who received BEACOPP; the 7-year rate of OS was similar at 84% and 89%, respectively.[54]

One important study assessing optimal chemotherapy for patients with HL was the Response-Adapted Therapy in Advanced-Stage Hodgkin Lymphoma (RATHL) study involving 214 patients with newly diagnosed HL. This trial also evaluated the impact of PET with computerized tomography (PET-CT) on managing therapy with ABVD versus BEACOPP/escalated BEACOPP (eBEACOPP). Following baseline PET-CT (PET1), all patients received 2 cycles of ABVD and then underwent interim PET-CT (PET2). PET2 scan results were negative in 954 patients (84%), and within this group, 469 patients were randomized to ABVD and 466 to AVD, skipping the more toxic bleomycin for an additional 4 cycles; 33 patients (4%) also received consolidation radiotherapy. In comparison, patients with positive PET scans proceeded to intensification with either 4 cycles of BEACOPP (n=96) or 3 cycles of eBEACOPP (n=78) and received a third scan (PET3), after which patients with negative PET3 completed a further 2 cycles of BEACOPP or 1 cycle of eBEACOPP. The primary endpoint was PFS for PET-negative randomized patients and the endpoint for the second randomization was ORR following administration of BEACOPP. The overall 3-year PFS rate was 83% and the 3-year OS rate was 95% for patients in all of the therapy cohorts. Patients with positive PET2 findings received intensified therapy with eBEACOPP and 74% subsequently achieved a negative PET3 study. No difference was observed between the nonrandomized comparison of eBEACOPP and BEACOPP treatment. At 3-years follow-up, results were comparable in patients who received either ABVD or AVD who had a negative interim PET scan. Three-year PFS rates were 85.4% in patients who received ABVD compared to 84.4% who received AVD. OS rates in PET-negative patients showed no difference between these two treatments; 3-year OS rates were 97.1% in the ABVD cohort and 97.4% with AVD.[55,56] Pulmonary toxicity was higher in the ABVD group, and the PFS and OS results suggest that the more toxic bleomycin can be removed from the therapy regimen without compromising its effectiveness.[55,57] In contrast, in the cohort of patients who were PET-positive after 2 cycles of ABVD, switching to eBEACOPP improved response, with a 3-year PFS rate of 71.1% and OS rate of 82.8%.[55,58]

There remains a question as to whether or not intensification to BEACOPP should be part of standardized therapy for more advanced HL. While there is evidence that BEACOPP is the more effective regimen in patients with advanced disease, it is also associated with more toxicity than ABVD. While ABVD is better tolerated, data suggest is may be less effective.[58] In cases of patients who do not respond completely to chemotherapy, the use of salvage therapy and SCT may be considered, as noted earlier. However, for those whose disease relapses or progresses after autologous transplant, outcomes may be poor. A database study of 756 patients with HL who had received SCT by Arai, et al., found that the median OS was 4.6 years in patients whose time to relapse was >12 months. However, if disease progressed in a very short 3-month period, the median survival was reduced to only 0.7 months. In addition, the median post-progression survival overall for the total group of patients relapsing after SCT was only 1.3 years.[59] Considering the toxicities of intense chemotherapy regimens and the poor survival associated with SCT, the research and development of new agents that can be incorporated into the backbone of HL therapy is critical to improving patient outcomes and survival.[58]

Targeted Therapy for Hodgkin Lymphoma

Figure 5. Brentuximab Vedotin: Mechanism of Action



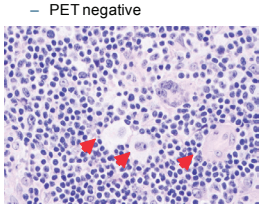
Younes A, et al. *N Engl J Med*. 2010;363:1812-1821.
Graphic courtesy of A Younes, MD

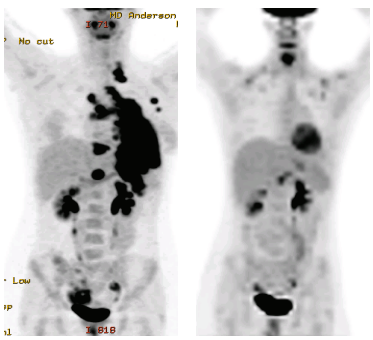
New options for treatment beyond standard and intensified chemotherapy became a reality with the development of brentuximab vedotin.[58] As noted earlier, BV is an anti-CD30 chimeric antibody that is conjugated to the anti-tubulin agent MMAE. The resulting ADC binds to CD30 on the cell surface, is rapidly internalized, and then releases the toxin in the lysosomes. The toxin binds to microtubules, leading to cell cycle arrest in the gap2/mitosis (G2/M) phase and subsequent cell death.[60]

A phase I trial of brentuximab vedotin involved 45 patients with relapsed or refractory CD30-positive HL or ALCL who received the agents ever 3-week at doses ranging from 0.3 to 3.6 mg/kg. Response was observed in 17 patients, including 11 CRs. Among 12 patients who received the maximum tolerable dose of 1.8 mg/kg, half achieved a response. The median duration of response was 9.7 months, and tumor regression was seen in 36 of 42 evaluable patients (86%). AEs that occurred most commonly included fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. The researchers concluded that BV induced durable responses and resulted in tumor regression for most patients treated.[60]

Figure 6. Relapsed HL Patient Treated with Brentuximab Vedotin

- 21-year-old female
- HL diagnosed 2003
  - ABVD + XRT to mediastinum
  - ICE
  - BEAM→ASCT
  - HDAC-inhibitor
- SGN-35 2.7 mg/kg x 8 cycles
  - Best clinical response: CR
  - CT 93% reduction, PET-
  - PET negative



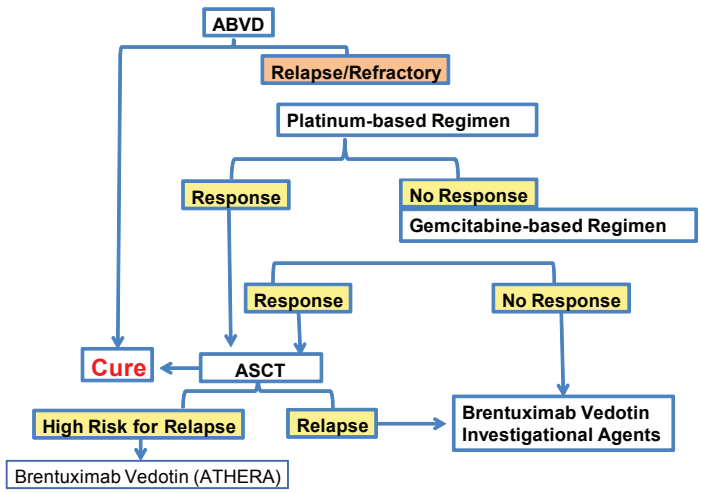


Younes A, et al. *N Engl J Med*. 2010;363:1812-1821.
Graphic courtesy of A Younes, MD

The current recommended dose of 1.8 mg/kg of BV was then used in a pivotal phase II, multinational trial of 102 patients with relapsed or refractory HL after ASCT. Results in this study demonstrated an ORR of 75% with CR observed in 34% of patients. The median PFS for the total patient population was 5.6 months, and the median duration of response for patients who achieved a CR was 20.5 months; 94% of patients treated achieved tumor reduction. At 1.5 years post-completion, a total of 31 patients were still alive and free of disease progression. The most common AEs seen with the agent were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea.[61] Data from this study was updated by Gopal, et al., where a total of 47% of patients who had achieved CR with BV remained progression-free after a median of 53 months' follow-up; the 3-year OS and PFS rates were 73% for this patient group. This analysis found that younger age, good performance status, and lower disease burden at baseline were associated with CR and a prognostic indicator of longer survival.[62]

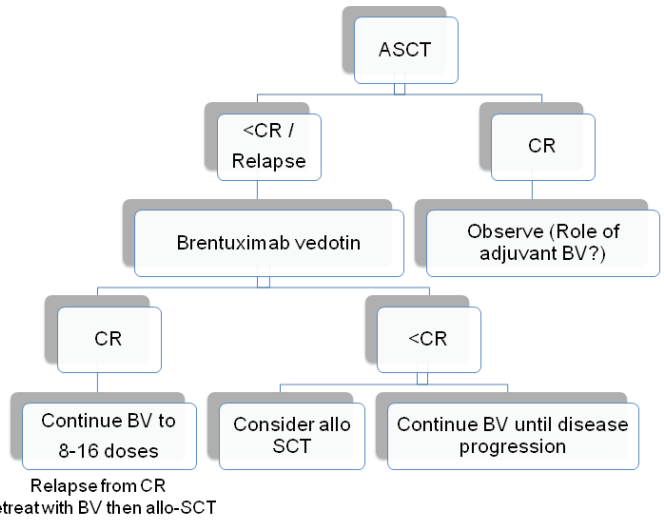
Incorporating all of these data, potential algorithms for treatment of relapsed/refractory HL and for those who relapse post-ASCT may be proposed:

Figure 7. Relapsed/Refractory HL Treatment Algorithm



Graphic courtesy of A. Younes, MD, reflecting his professional opinion

Figure 8. Proposed Algorithm for Treating Patients Post ASCT



Graphic courtesy of A. Younes, MD, reflecting his professional opinion

Once a given agent has demonstrated a high response rate in the relapsed/refractory disease setting, the trend is to move the drug to the frontline and "first-relapse" settings. A phase I dose escalation study evaluated BV combined with ABVD or AVD for newly-diagnosed patients with HL. Patients in the study (n=51) had stage IIa bulky disease, IIB, III, or IV. Patients were treated with BV in doses ranging from 0.6 mg/kg to 1.2 mg/kg, with either ABVD or AVD. Early efficacy results from this trial demonstrated that 21 of 22 (95%) who received BV and ABVD achieved CR, as did 24 of 25 (96%) of those who received BV and AVD; 100% of those who received BV/ABVD had PET-negative results following treatment, compared to 92% of those who received BV/AVD. However, 44% of patients who received ABVD had pulmonary toxicity compared to none who received AVD, leading to a conclusion that BV should not be given with bleomycin, especially as first-line therapy for treatment-naive patients. That said, the 1.2 mg/kg dose of BV in combination with AVD every 2 weeks was found to be generally well-tolerated.[63] Longer term results testing BV with chemotherapy will be coming in the future from the ECHELON-1 trial, which is investigating BV in combination with either 6 cycles of ABVD or AVD in patients with advanced stage 3 and 4 HL.[42]

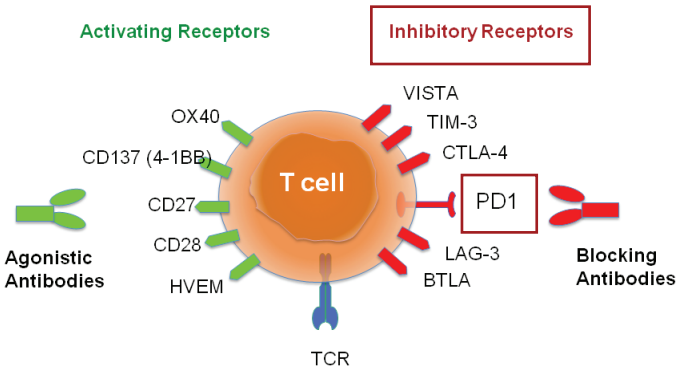
Another approach to treatment is to combine BV and first-line salvage therapy before transplant. A trial by Moskowitz, et al., studied patients with relapsed or refractory HL who had previously failed one doxorubicin-containing chemotherapy regimen. Patients received weekly infusion of BV 1.2 mg/kg on specific days for two 28-day cycles. Following therapy, they underwent PET scanning. Patients who achieved PET-negative status went directly to consolidation with high-dose therapy (HDT) and ASCT. Those whose abnormalities persisted on PET received 2 cycles of augmented ifosfamide, carboplatin, and etoposide (augICE) before consideration for HDT/SCT. AugICE consisted of: two doses of ifosfamide 5000 mg/m^2 in combination with mesna 5000 mg/m^2 continuous infusion over 24 hours on days 1 and 2; one dose of carboplatin with a target area under the curve (AUC) of 5 on day 3; and 3 doses of etoposide 200 mg/m^2 every 12 hours on day 1. Results in 45 enrolled patients showed that following BV administration, 12 patients (27%) were PET-negative and proceeded to HDT/ASCT; 33 patients (77%) were PET-positive, and of this group, 32 received augICE, with 22 then becoming PET-negative (one patient withdrew from the study). Overall, 34 total patients achieved PET-negativity; 44 patients who completed treatment via the approved protocol proceeded to HDT/ASCT. The researchers concluded that PET-adapted sequential salvage therapy with BV, followed by augICE resulted in a high proportion of patients in this population achieving PET-negativity, potentially optimizing the chance of cure after HDT/ASCT.[48]

Brentuximab vedotin has also been studied for use following ASCT. In the AETHERA trial, 329 patients with unfavorable-risk relapsed or refractory HL who had previously undergone autologous stem cell transplant were enrolled at 78 sites in North America and Europe. Patients were randomly assigned to receive 16 cycles of BV 1.8 mg/kg or placebo intravenously every 3 weeks, starting 30-45 post-ASCT. Randomization was stratified according to best clinical response following salvage chemotherapy (CR, PR, or stable disease) and time to relapse, including primary refractory HL versus relapsed disease less than 12 months after completion of frontline therapy, versus relapse 12 months or more post-treatment. The primary endpoint was PFS defined as the time from patient randomization to tumor progression or death. Results demonstrated that patients who received BV had significantly improved PFS (42.9 months) compared to those who received placebo (24.1 months). The study recorded consistent benefit of BV consolidation across the subgroups studied. The most frequent adverse events in the BV-treated group were peripheral sensory neuropathy and neutropenia. At the time of analysis, 28 of 167 patients (17%) in the BV cohort had died compared to 25 of 160 patients (16%) in the placebo group. The investigators concluded that early consolidation with BV following ASCT improved PFS in patients with HL who have a greater risk for relapse or progression after transplantation.[64]

Future Combination Therapy for Hodgkin Lymphoma

Now that brentuximab vedotin has been shown to be one of the most active agents for the treatment of patients with HL, it is being tested in combination with other targeted drugs and regimens beyond standard chemotherapy, including phosphoinositide 3-kinase (PI3K) inhibitors, mechanistic target of rapamycin (MTOR) inhibitors, and most recently, immune checkpoint inhibitors.[65] T-cells can target and destroy tumor cells through antigen recognition and endogenous immunologic mechanisms, which can be activated or inactivated through regulation by multiple proteins and receptors expressed on the T-cell surface. Activating proteins include CD27, CD28, 4-1BB, CD137, and OX40 (shown in green in the graphic at top right). Inactivating receptors include PD-1, CTLA-4, and TIM-3 (shown in red).[66]

Figure 9. Checkpoint Inhibitors Activate T-Cells by Blocking Inhibitory Receptors



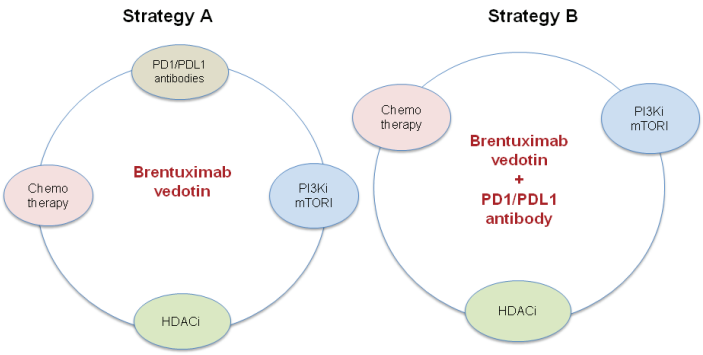
Adapted from Batlevi CL, et al. *Nat Rev Clin Oncol*. 2016;13(1):25-40.

One area of great interest and research in HL surrounds immune checkpoint inhibition. The programmed death 1 (PD-1) functions as a checkpoint that limits T-cell mediated immune responses. When programmed death ligand 1 or 2 (PD-L1/2) binds the PD-1 receptor on T cells, it inhibits their activation. Tumor cells upregulate expression of PD-L1 and PD-L2 to evade the immune system, thus anti-PD-1 monoclonal antibodies block the interaction of PD-1 with PD-L1/L2, releasing inhibition of T-cells and restoring the immune response against cancer cells.[67,68] In classical HL, there are a small number of malignant cells termed Reed-Sternberg cells, which have demonstrated overexpression of PD-L1.[68]

There is current data surrounding two PD-1-blocking IgG4 antibodies that have been tested in clinical trials, nivolumab and pembrolizumab. Nivolumab was studied in a phase I trial of 23 patients with HL enrolled with disease relapse following ASCT. Response was achieved in 20 patients (87%), including 4 patients (17%) who had a CR and 16 patients (70%) with a PR. The remaining two patients (13%) had stable disease following treatment with nivolumab.[68] Nivolumab was approved by the United States Food and Drug Administration (FDA) for treatment of relapsed or refractory HL in May 2016 on the basis of data demonstrating an ORR of 65% found in 62 of 95 patients enrolled in two single-arm trials.[69] Pembrolizumab was studied in a phase II trial in patients with relapsed/refractory classical HL. Interim data was reported at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting following 60 patients reaching first response assessment in cohorts 1 and 2 (cohort 1 consisted of patients treated after ASCT and subsequent BV therapy; cohort 2 consisted of patients who were ineligible for ASCT due to chemo-resistance and failed BV treatment). The ORR was 70% among the 30 patients in cohort 1 with 6 patients (20%), achieving CR, 15 patients (50%) reporting PR and 6 (20%) having stable disease following therapy. The ORR among the three patients in cohort 2 was 80%, with 8 patients (27%) achieving CR, 16 patients (53%) reporting PR, and 6 (20%) having stable disease as best response. The study is ongoing, with continuing accrual of patients for cohort 3, consisting of patients with relapsed/refractory classical HL being treated after ASCT but have not received BV.[70]

The therapeutic landscape for the treatment and management of patients with Hodgkin lymphoma continues to evolve, with ongoing trials investigating the combination of brentuximab vedotin with checkpoint inhibitors, and other targeted agents to improve outcomes for patients with lymphoma.[65]

Figure 10. Hodgkin Lymphoma: Future Treatment Strategies



Adapted from Stathis A, Younes A. *Ann Oncol*. 2015;26(10):2026-2933.

Conclusion

Investigation into CD30 as a target and pathway for management of lymphomas has advanced substantially over the past several years. Multiple studies have demonstrated effectiveness of anti-CD30 therapy in the treatment of CD30-positive HL and non-HL. This activity delineated the variety of tumors expressing CD30, the use of anti-CD30 drug conjugates, including in combination with standard chemotherapy, and the potential for future uses in additional drug combinations. Next steps are already underway in researching additional targeted therapies that may potentially be used with anti-CD30 treatment to improve management of patients with CD30-positive lymphomas, while reducing treatment-related toxicity. Future research and therapy will focus on honing the most effective combinations to improve treatment and overall outcomes for patients with lymphomas.

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