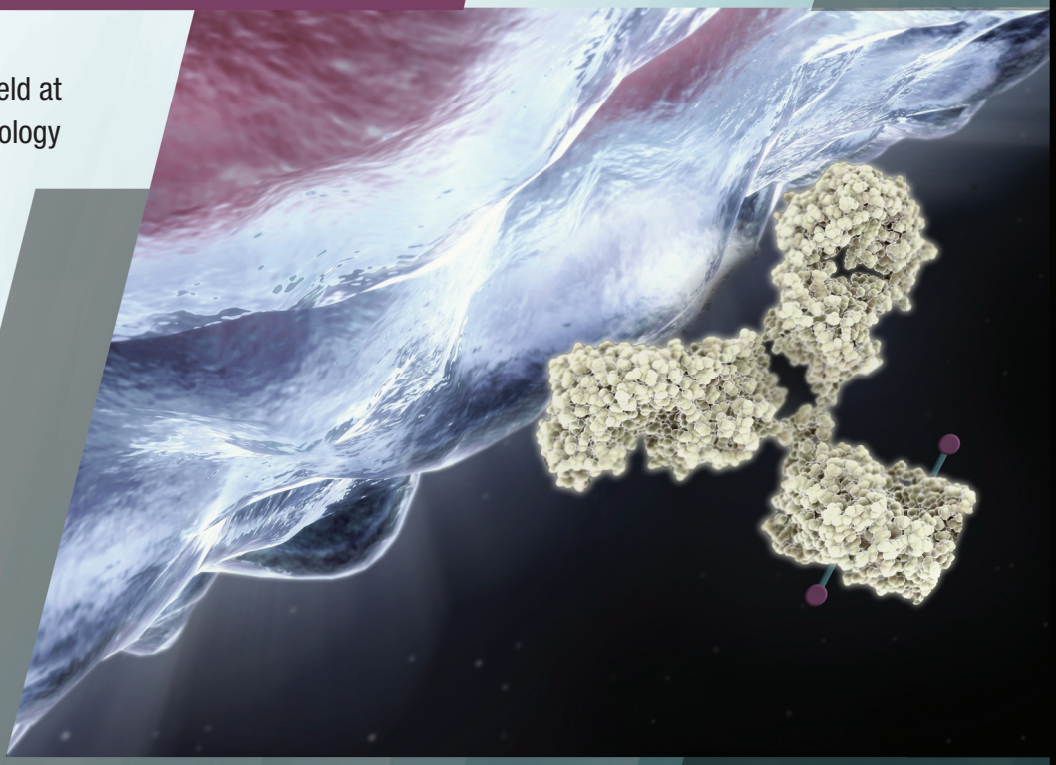
An Accredited e-Monograph

Key Issues in the Treatment of Lymphoma:

The Role of CD30 in Diagnosis and Management

Key proceedings from a live symposium held at the 20th Congress of the European Hematology Association (EHA) in Vienna, Austria



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Release Date: September 30, 2015

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PROGRAM OVERVIEW

With the advances made in frontline multiagent chemotherapy, Hodgkin lymphoma (HL) is deemed to be a highly curable disease. Nonetheless, advanced HL remains a challenge as 10% of patients will not achieve a complete remission and 20–30% of patients who initially responded will experience a relapse. This activity brings together leading world experts in lymphoma to discuss some of the most talked about issues and ongoing clinical trials in the treatment of HL today.

Since the initial description of monoclonal antibodies against Hodgkin and Reed-Sternberg (HRS) cells in HL, the CD30 antigen has attracted substantial scientific interest as a therapeutic target for malignancies that express this cell surface marker. As for other types of cancer, immunoconjugates or antibody-drug conjugates (ADCs) are part of a growing revolution in selective immunotherapeutic development for cancer, an ever-expanding clinical strategy that has led the way in addressing clinical barriers for HL and anaplastic large cell lymphoma (ALCL) as prime examples. Review what the experts are saying regarding the biology of CD30 and what the current data say about the efficacy of CD30 targeted therapeutic strategies in HL, and the evolving role in the treatment of B-cell and T-cell lymphoma.

TARGET AUDIENCE

This activity is designed for physicians, pharmacists, physician assistants, nurses, and other health care professionals who have an interest in enhancing their clinical skills in Hodgkin lymphoma.

LEARNING OBJECTIVES

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

- Outline the role of CD30 in HL and T-cell lymphomas based on the current science, and identify the critical pathobiological features of CD30+ lymphoid neoplasms
- Describe the immunohistochemical assessment of CD30 in patients with HL and T-cell lymphomas, and correlate the results of those assessments with prognosis in both types of lymphomas
- Formulate and implement a treatment plan for patients with HL, PTCL, or ALCL, taking into account disease histopathology, stage, and relevant patient characteristics
- Summarize results of clinical trials evaluating new and emerging agents or combinations of agents in the treatment of patients with CD30+ lymphomas, focusing on changes in recommended treatment sequencing that are evolving as a result of new data

AGENDA

Advances in CD30 Pathology – *Stefano A. Pileri, MD*

The Evolving Role of CD30 in B-cell and T-cell Lymphoma – *Francesco d'Amore, MD*

The Evolving Role of CD30 in Hodgkin Lymphoma – *Anas Younes, MD*

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Dr. Stefano Pileri has received honoraria related to formal advisory activities from Takeda Oncology and the development of educational materials from Medscape.

Dr. Anas Younes has received honoraria as a consultant from Bayer AG, Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Janssen Pharmaceuticals, Inc., Sanofi, Seattle Genetics, Inc., and Takeda Oncology. He has received grant support related to research activities from Curis, Inc., Johnson & Johnson Services, Inc., and Novartis AG.

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Advances in CD30 Pathology

Stefano A. Pileri, MD

The cluster of differentiation 30 (CD30) antigen, also known as Ki-1, belongs to the tumor necrosis factor receptor superfamily and is physiologically expressed by activated B and T lymphocytes.[1] A gene located on the short arm of chromosome 1 encodes CD30. CD30 is constitutively expressed by a series of tumors that includes classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma (PMBCL), the anaplastic variant of diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphomas (ALCL) of both ALK-positive and ALK-negative types, aggressive mastocytosis, and embryonic carcinoma. However, it can also be variably expressed in many other types of tumor, especially of lymphoid origin.[2-4]

Development of Antibodies to Detect CD30

Several antibodies have been developed that recognize the CD30 antigen. The Ki-1 monoclonal antibody was the prototype and was generated in the early 1980s.[5] The Ki-1 antibody was originally thought to be specific for the Reed-Sternberg cells of Hodgkin lymphoma; however, its extensive application quickly revealed that it reacted with tumors other than Hodgkin lymphoma. Notably, this led to the discovery of anaplastic large cell lymphoma. The main limitation of the Ki-1 monoclonal antibody was the need for fresh or frozen material, limiting its utility in formalin-fixed samples. This limitation was overcome by the generation of the Ber-H2 monoclonal antibody a few years later.

The Ber-H2 antibody detects an epitope of the CD30 molecule that is conserved during formalin fixation.[6] Notably, the staining patterns of the Ki-1 and the Ber-H2 antibodies are almost identical. Both antibodies stain B and T lymphocytes located respectively at the edge of germinal centers and in the paracortex.[6] When applied to other organs, the Ber-H2 antibody also stains ganglion and Purkinje cells as well as exocrine pancreatic cells. Currently, the Ber-H2 antibody is the gold standard for CD30 detection in most pathology labs.

Ber-H2 antibody has a distinctive staining pattern that is characterized by dot-like positivity close to the nucleus and strong staining at the cytoplasmic membrane. This staining pattern corresponds with the normal synthesis of the CD30 molecule, which is assembled in the Golgi apparatus. Following glycosylation, the molecule moves to the cytoplasmic membrane. As it has a transmembranic location, a large part of the external domain of the molecule is shed into the peripheral blood where it can be assessed quantitatively. Importantly, the epitopes detected by the Ber-H2 and SGN-30 monoclonal antibodies, although located on the external domain of the molecule, are not involved in the shedding phenomenon.[7,8]

Pathological Application of Anti-CD30 Antibodies

As previously mentioned, CD30 is expressed in several types of tumors, especially those of lymphoid origin. Table 1 (see page 4) summarizes key pathological information about the expression of CD30. In order to identify the utility of CD30 immunohistochemistry (IHC) as a tool for clinical practice, a study compared semi-quantitative immunohistochemistry with messenger ribonucleic acid (mRNA) assessment by microarray. The results of the analysis demonstrate that IHC is a valuable tool in clinical practice to assess CD30 expression at least for PTCL.[9] Guidelines from the National Comprehensive Cancer Network as well as the most recent World Health Organization (WHO) Classification stress the importance of CD30 in the diagnosis of certain tumors.[10,11]

Therapeutic Application of Anti-CD30 Antibodies

The discovery of the expression of CD30 in a number of lymphoid tumors along with its restricted expression in normal human tissues prompted exploration of the use of CD30 as a therapeutic target. Initial studies with the Ber-H2 antibody revealed that the naked antibody was not associated with tumor regression in patients with refractory Hodgkin lymphoma.[35] Subsequent studies focused on conjugating the Ber-H2 antibody with toxic agents such as saporin. Results from a study using the Ber-H2 antibody conjugated with saporin showed a significant reduction of up to 50% in patients refractory to all available treatments for Hodgkin lymphoma.[35] Repeat administrations of the antibody-conjugate were not possible owing to the mouse monoclonal backbone leading to the development of antibodies to the treatment. Additionally, the saporin molecule was associated with undesirable side effects. As a result, new monoclonal antibodies as well as toxins were investigated further.

The discovery of SGN-30, a humanized monoclonal antibody constructed from the variable regions of the anti-CD30 murine monoclonal antibody AC10 and the human gamma 1 heavy chain and kappa light chain constant regions, overcame the limitations of the Ber-H2 antibody. Similar to Ber-H2, the naked antibody was not particularly effective and hence, a new antibody, SGN-35 (brentuximab vedotin) was developed in which the SGN-30 antibody was conjugated to the tubulin-polymerization inhibitor monomethyl auristatin E. Initial studies have supported the role for brentuximab vedotin in various lymphomatoid tumors.[36,37]

Correlating CD30-positivity to Treatment Response

An interesting phenomenon has been observed in some studies where patients who do not appear to have detectable CD30-positive cells still respond to brentuximab vedotin.[16,37] In the study by Jacobsen and colleagues,[16] a disconnect between the presence of CD30 positivity determined by visual inspection (1% of neoplastic cells) and CD30 expression detected by computer-assisted inspection (34% of neoplastic cells) was observed. Thus highlighting a potential pitfall in the detection of CD30 positivity.

Several theories have been put forward to address the paradoxical situation of efficacy of brentuximab vedotin in the apparent absence of CD30-positivity. The first is the crossfire effect.[38,39] In studies of mixed cell cultures it has been shown that the cell lysis associated with tumor cell death results in release of monomethyl auristatin E into the

Table 1. Summary of CD30 Detection in Tumors of Lymphoid Origin

Tumor type	Staining	Subtypes detected	Cases (%)	Cells (%)	Other
Classical Hodgkin lymphoma	Pronounced membrane-bound staining with weaker cytoplasmic staining of Reed-Sternberg cells[6]	All forms of classical Hodgkin lymphoma	98.4%[12]	≥20%[12]	N/A
Primary mediastinal B-cell lymphoma	CD30 is expressed in >80% of cases of PMBCL, though expression is weak and variable[4,13]	N/A	69% – 86%[4,14]	Variable[4,14]	Staining may be limited to the lymphomatous cells[4]
Anaplastic variant of DLBCL	CD30 is expressed in approximately 14% – 25% of DLBCL patients[15,16]	N/A	4% – 26%[17-19]	Variable[17-19]	CD30 expression defines a subgroup of DLBCL that may have a favorable clinical outcome and distinct gene expression signature[15]
Anaplastic large cell lymphoma	All tumor cells are CD30 positive[2] strong staining of the membrane and Golgi apparatus. CD30 expression is independent of the presence or absence of the ALK protein[20]	All forms of ALCL including rare forms[2]	100%[10]	Almost all[10,21]	
PTCL, NOS	Moderate to strong staining observed in >50% of cases[22]	N/A	>60%[22]	>20%[20,23]	Due to the variability in CD30 expression within a single sample it is important to assess staining across the full slide section
AITL	Moderate to strong staining observed in ~21% of cases, weak staining observed in ~21% cases[22]	N/A	<50%[22]	10% – 30%[24,25]	Due to the variability in CD30 expression within a single sample it is important to assess staining across the full slide section
ENTL	Moderate to strong staining observed in 70% of cases[22]	N/A	31% – 75%[26-30]	>50%[26]	Due to the variability in CD30 expression within a single sample it is important to assess staining across the full slide section
MF	Weak staining observed in ~50% of cases[22]	N/A	11%[31]	>10%[31]	Due to the variability in CD30 expression within a single sample it is important to assess staining across the full slide section
Transformed MF	Moderate staining observed in 100% of cases[22]	N/A	24% – 100%[32-34]	5% – >60%[34]	Due to the variability in CD30 expression within a single sample it is important to assess staining across the full slide section
EATL type 1	Moderate to strong staining observed in 100% of cases[22]	N/A	100%[22]	N/A	Due to the variability in CD30 expression within a single sample it is important to assess staining across the full slide section
EATL type 2	No staining observed[22]	N/A	0%[22]	N/A	N/A

AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large-cell lymphoma; ALK=anaplastic lymphoma kinase; DLBCL=diffuse large B-cell lymphoma; EATL=enteropathy-associated T-cell lymphoma; ENTL=extranodal NK/T-cell lymphoma; NA=not applicable; PMBCL= primary mediastinal B-cell lymphoma; PTCL, NOS=peripheral T-cell lymphoma, not otherwise specified.

local environment.[38] As a result, the toxin can induce cell death in the surrounding cells up to 2- to 3-cell diameters away from the original CD30-expressing cell.

The second theory is the influence of the microenvironment. Certainly, in some cases, there is non-neoplastic microenvironmental expression of CD30. This is clearly the case in angioimmunoblastic T-cell lymphoma (AITL). AITL is rich in CD30-positive Epstein-Barr virus (EBV)-infected B blasts, and their presence in the tumor microenvironment can contribute to the crossfire effect. However, in other tumors, where only the anaplastic cells express CD30, the contribution of the microenvironment may be more debatable.

Lastly, the limitations of IHC may also contribute to the situation. In the analysis by de Jong and colleagues,[40] significant interlaboratory variability was observed for 3 molecules (BCL6, IRF4, and CD10). It is likely that this is also the situation for CD30 detection. Another important issue revolves around optimal formalin fixation protocols. Comparison of different formalin-fixation protocols has revealed that over-exposure to the fixation solution can lead to suboptimal results. It is recommended that slides be fixed in 10% buffered formalin (Lillie's protocol) for no longer than 24 hours.

Antigen retrieval plays another important role in optimizing and standardizing CD30 IHC. While many different approaches have been reported in the literature, the best results were provided by heating sections either in a microwave (3 cycles, 5 minutes each, 900 watt microwave oven) or in a pressure cooker (4 minutes when at pressure) in 1 mM EDTA pH 8.0.[41] Alternatively, an automated antigen retrieval system can be used, and their use contributes to standardization. One caveat is the sensitivity of detection being variable between detection systems making it difficult to compare results across different laboratories. There is evidence to suggest that the best results are obtained with detection methods based on a polymer backbone that carries a large amount of the marker molecule. Lastly, digital imaging analysis can also contribute to standardization of results by assessing the staining pattern in an objective manner. Importantly, digital imaging systems can assess staining intensity, location of the intensity, and the percentage of the positive cells.

While it remains unclear how best to answer the question of CD30-negativity and response to treatment with anti-CD30 antibodies, a study is currently underway to compare CD30 expression by gene expression profiling, FACS analysis, and IHC on the same samples. Samples include CD30-positive and CD30-negative cell lines and a xenograft model of EBV-positive post-transplant lymphoproliferative disorder. Additionally, we are investigating the optimal fixation protocol and antigen retrieval/detection methods.

The Evolving Role of CD30 in B-cell and T-cell Lymphoma

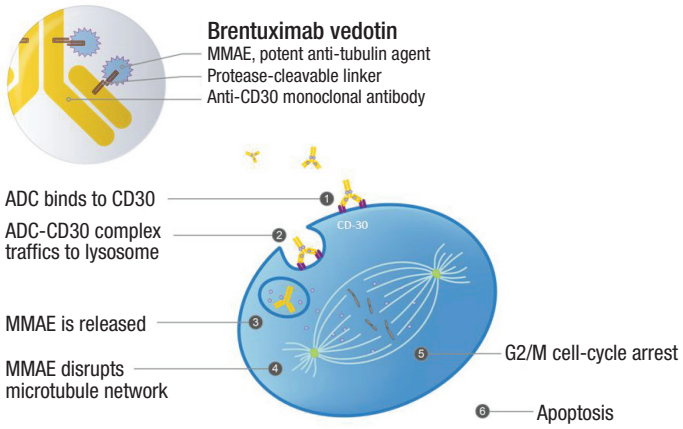
Francesco d'Amore, MD

Overview of Brentuximab Vedotin

As mentioned previously, the naked SGN-30 antibody was not an effective treatment for patients with Hodgkin lymphoma, although limited activity was observed in patients with cutaneous ALCL.[42] As a result, the SGN-35 antibody-drug conjugate, brentuximab vedotin, was developed. Antibody-drug conjugates incorporate cytotoxic drugs with stable linkers to an antibody. Once the antibody-drug conjugate is internalized by the target cell, the drug is released.[43] Figure 1 shows the structure of brentuximab vedotin.

Until recently, the antibody was regarded as a carrier of the auristatin molecule to the tumor cells, but there is data suggesting that the binding of the antibody to the CD30 antigen may induce intracellular signaling of the NF-kappa B pathway, thereby directly contributing to the anti-tumoral effect.[43-45] Furthermore, the effect appears to be independent of the immune evasion mechanisms mediated by the intratumoral inflammatory cells.[44]

Figure 1. Structure and Mechanism of Action of Brentuximab Vedotin

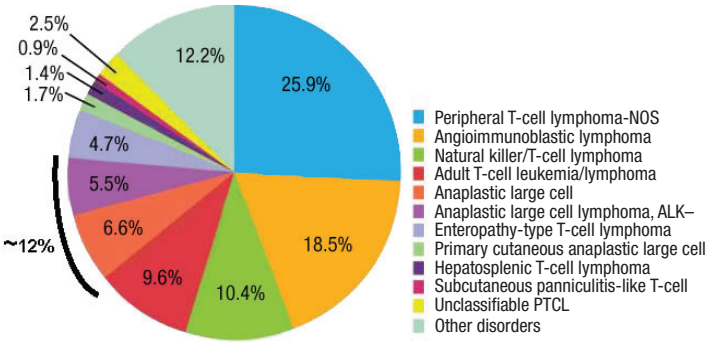


MMAE=monomethyl auristatin E
Adapted from Younes, et al.[36]

Role of Brentuximab Vedotin in Anaplastic Large-cell Lymphoma

Anaplastic large cell lymphomas represent 10% to 12% of all peripheral T-cell lymphomas (Figure 2).[46] ALK-positive cases are more common in the pediatric setting and in younger adults, whereas ALK-negative cases are consistently present in cutaneous anaplastic large cell lymphoma and in older patients.

Figure 2. Incidence of Peripheral T-cell Lymphomas



Adapted from Vose, et al.[46]

In 2012, Pro and colleagues published the data from the pivotal trial of brentuximab vedotin in relapsed/refractory systemic ALCL.[47] Patients >12 years of age with measurable disease by fluoro-deoxy glucose (FDG)-avidity by positron emission tomography (PET) were enrolled. Brentuximab (1.8 mg/kg intravenous [IV]) was administered every third week for a minimum of 8 cycles and a maximum of 16 cycles. Restaging using the RECIST criteria[48] was carried out at Cycle 2, 4, 7, 10, 13, and 16. The trial accrued 58 patients with a median age of 52 years. The majority of the patients were ALK negative (72%), 62% of the patients were refractory to front-line therapy, 50% were refractory to their most recent treatment, 22% to any prior treatments, and 26% of the patients had received an autologous transplant. In general, brentuximab vedotin was well tolerated. Table 2 shows the Grade 3 or 4 adverse events observed in the study.

Table 2. Adverse Events Occurring in Patients with Anaplastic Large-cell Lymphoma Treated with Brentuximab Vedotin[47]

Preferred Term, %	All Grades	Grade 3	Grade 4
Peripheral neuropathy	57	17	0
Nausea	40	2	0
Fatigue	38	3	2
Pyrexia	34	2	0
Diarrhea	29	3	0
Rash	24	0	0
Constipation	22	2	0
Neutropenia	21	12	9

Peripheral neuropathy was one of the most relevant adverse events. In the patients that developed peripheral neuropathy, 81% saw some clinical improvement in their symptoms, while 48% saw a complete resolution of their symptoms. The median time to resolution of peripheral neuropathy symptoms was around 10 weeks.

Brentuximab treatment resulted in a significant number of profound responses in a heavily pretreated population — of which more than half were complete responses (CRs).[47] The overall response rate (ORR) was 88% for ALK-negative patients and 81% for ALK-positive patients. After 24 months of follow-up, no difference in ORR or CR was noted between ALK-negative and ALK-positive cases. The median duration of objective responses was over 13 months, and in patients with CR, the median duration of response was not reached at the time of the analysis. Progression-free survival (PFS) for patients achieving a CR was a median of 14.6 months. Overall survival (OS) for the entire cohort was estimated at 63% at 24 months, with no significant difference in OR or PFS according to ALK status of the patients. Compared with most recent therapy, brentuximab vedotin significantly increased PFS (5.9 months vs 14.3 months; hazard ratio [HR] 0.48; $P = .001$). Additionally, 8 cycles of brentuximab vedotin followed by allogeneic (Allo)- or autologous (Auto)-stem cell transplantation (SCT) resulted in durable responses with the median PFS not reached at the time of the analysis. In patients unable to undergo SCT, brentuximab vedotin resulted in a median PFS of 18.4 months. Overall, patients received a median of 7 cycles (range 1–16) of brentuximab vedotin, and better responses were seen in those patients that received more cycles of therapy.[49]

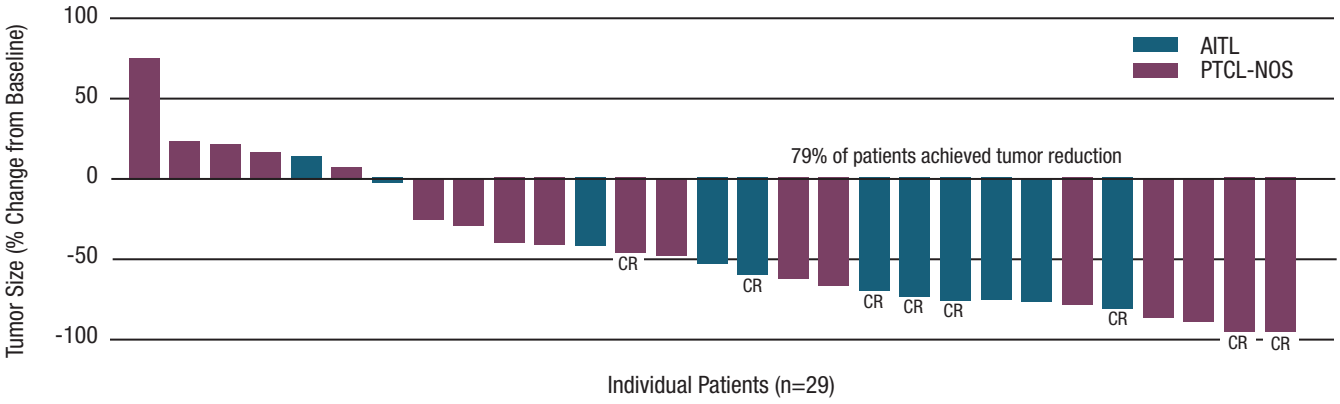
Recently, Dr. Bartlett and colleagues,[50] reported that retreatment with brentuximab vedotin after relapse resulted in a second response. This was a Phase 2 study where patients who had previously achieved an objective response (complete or partial remission) with prior brentuximab vedotin treatment were retreated. Although the number of ALCL patients was small (n = 8) 5 of them achieved a CR, 2 a partial response (PR), and one patient had progressive disease. The adverse event (AE) profile was similar to that seen in the pivotal trials, with the exception of peripheral neuropathy, a known cumulative dose event. Grade 3 or higher events were observed in 48% of patients; these were generally transient and managed by dose modifications or delays.[50]

In summary, brentuximab has significant activity in ALK-positive and ALK-negative ALCL, results in durable responses in patients who subsequently undergo SCT, and re-treatment is possible, achieving good responses in the majority of patients with ALCL.[47,49,50]

Role of Brentuximab Vedotin in Patients with CD30-positive Peripheral T-cell Lymphoma

In a Phase 2 study of patients with relapsed/refractory CD30-positive PTCL, treatment with brentuximab vedotin resulted in an overall response (CR+PR) of 41% for mature T/NK-cell lymphomas (n = 34), 54% for patients with AITL (n = 13), and 33% for patients PTCL-NOS.[51] Tumor reduction was observed in 79% of patients (Figure 3).

Figure 3 Waterfall Plot of Best Overall Response for Patients with Relapsed/Refractory CD30-Positive Peripheral T-cell Lymphoma



Adapted from Horwitz, et al.[51]

Importantly there was no correlation between the level of CD30 expression and the effect on the tumor.[51] The safety profile of brentuximab vedotin was similar to that seen in previous studies. Adverse events of Grade ≥3 were neutropenia (14%), peripheral sensory neuropathy (9%), and hyperkalemia (9%).

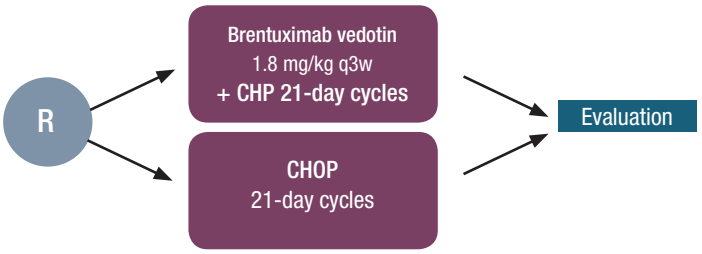
A Phase 1 study of patients with treatment-naïve CD30-positive PTCL compared treatment with 6 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) followed by 8 cycles of brentuximab vedotin with 6 cycles of cyclophosphamide, doxorubicin, prednisone and brentuximab vedotin (BV+CHP) followed by 10 cycles of brentuximab vedotin.[52] The maximum tolerated dose was 1.8 mg/kg in the combination. The patients were divided into ALCL and non-ALCL. The combination treatment was more effective than the sequential treatment with regard to best overall response (Table 3). Grade 3/4 adverse events occurred in 3/13 (62%) patients. In the combination group, Grade 3/4 adverse events occurring in ≥10% were febrile neutropenia (31%), neutropenia (23%), anemia (15%), and pulmonary embolism (12%).[52]

Table 3. Best Response After Sequential of Combination Therapy[52]

			Combination					
	Sequential ALCL		ALCL		Non-ALCL		Total	
	(n = 13)		(n = 19)		(n = 7)		(n = 26)	
Response	N	%	N	%	N	%	N	%
Objective response	11	85	19	100	7	100	26	100
Complete response	8	62	16	94	7	100	23	88
Partial response	3	23	3	16	0	0	3	12
Stable disease	0	0	0	0	0	0	0	0
Progressive disease	2	15	0	0	0	0	0	0

Based on the outcomes of the Phase 1 study, a Phase 3 trial is currently underway called ECHELON-2 (NCT01777152).[53] The study is a double-blind, randomized, multicenter, Phase 3 clinical trial to compare the efficacy and safety of brentuximab vedotin in combination with CHP with the standard-of-care CHOP in patients with CD30-positive mature T-cell lymphomas. Centers can decide whether they want to do an upfront Auto-SCT. It is center-stratified and is planned to accrue over 300 patients making it the largest randomized T-cell trial in the upfront setting ever performed. The primary endpoint of the study is PFS per independent review facility. Secondary endpoints include PFS in patients with systemic ALCL; complete remission rate at end of treatment; overall survival; objective response rate at end of treatment; and type, incidence, severity, seriousness, and relatedness of adverse events.

Figure 4. Study Design of the ECHELON-2 Study



The prognosis of advanced cutaneous T-cell lymphoma (CTCL), including Sézary syndrome and mycosis fungoides (MF), is poor. So far, no curative option apart from allogeneic stem cell transplantation is available. Large cell transformation often identifies cases with a more aggressive clinical course, and large tumor cells may express CD30. Earlier this year, Mehra and colleagues[54] published their findings from a case series of 4 patients (3 transformed MF, 1 Sézary syndrome) who were treated with brentuximab vedotin. Two patients achieved a response allowing them to go on to receive an Allo-SCT.

Role of Brentuximab Vedotin in Patients with Relapsed Diffuse Large B-cell Lymphoma

A Phase 2, open-label study evaluated the efficacy of brentuximab vedotin in patients with relapsed/refractory CD30-positive non-Hodgkin lymphoma.16 The study included a planned subset analysis of patients with DLBCL (n = 49) as well as patients with other B-cell NHLs (n = 19). For the patients with DLBCL, the ORR was 44%, including 8 (17%) CRs. The median duration of response is 16.6 months (range, 2.7 to 22.7+ months). Notably, there was no statistical correlation between response and level of CD30 expression; however, all responding patients had quantifiable CD30 by computer-assisted assessment of IHC.[16]

Analysis of CD30 levels in patients with post-transplant lymphoproliferative disorders of DLBCL revealed that 81% of patients express high levels of CD30, and like MF, the high expression of CD30 is associated with better outcomes.[55]

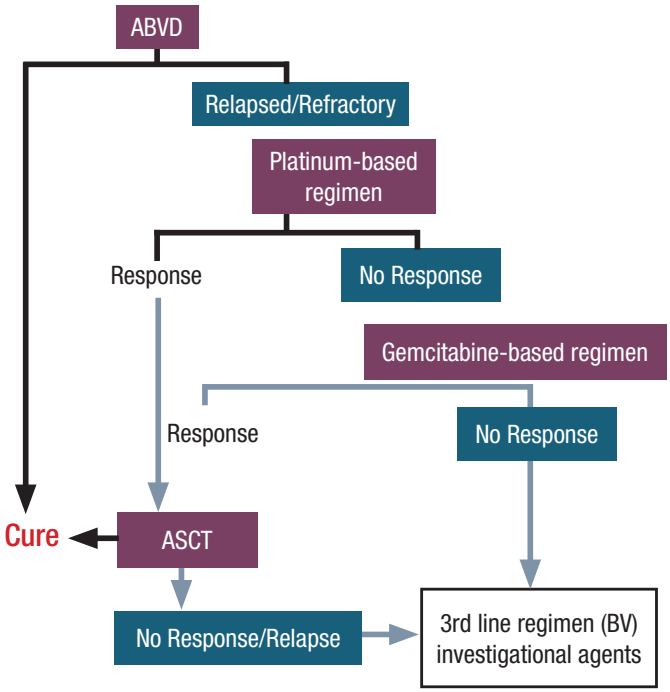
The Evolving Role of CD30 in Hodgkin Lymphoma

Anas Younes, MD

Treatment of Relapsed/Refractory Hodgkin Lymphoma

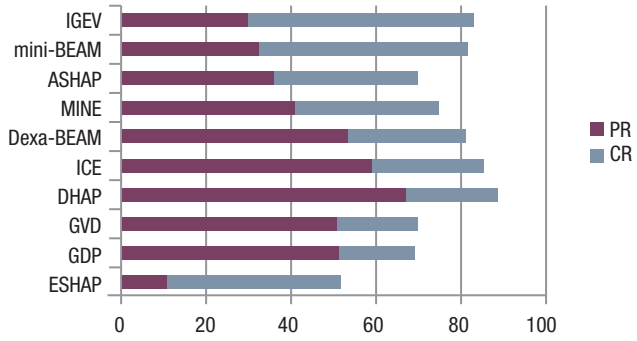
The treatment of patients with HL is based on the stage of the disease and the presence of adverse prognostic factors. Figure 5 presents a common treatment paradigm for relapsed/refractory HL.

Figure 5. Treatment of Relapsed/Refractory Lymphoma



As shown in Figure 5, a suitable treatment to start with is the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). An alternate option is bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). However, ABVD alone can achieve a cure in as many as 70% of patients.[56] For patients who relapse after ABVD, numerous combinations of chemotherapy are available as second-line options (Figure 6). No head-to-head comparisons have been conducted comparing the effectiveness of these agents, so the choice of second-line therapy remains a physician preference.

Figure 6. Second-line Treatment Options for Relapsed/Refractory Hodgkin Lymphoma



An initial second-line choice would be ICE, and if the patient responds, then the next logical step would be consolidation with Auto-SCT. If there is no response or suboptimal response (PR or less or PET-positive disease) the option is to switch to another regimen, usually gemcitabine-based. If the patient is not a candidate for transplantation, then brentuximab vedotin is a suitable option. Alternatively, one could consider entry into a clinical trial. Ultimately the goal of treatment should be complete response followed by Auto-SCT, and then in the best-case scenario, cure of about 50% to 60% of the patients.

For patients who relapse after Auto-SCT, survival outcomes are poor and significant differences in overall survival (OS) are seen correlated with time-to-relapse after transplant. Survival times range from less than 1 year to more than 4 years.[57,58] The clear differences in survival have prompted the FDA and other organizations to declare that treatments to address the unmet medical need in early-relapse patients are desperately needed.

Role of Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

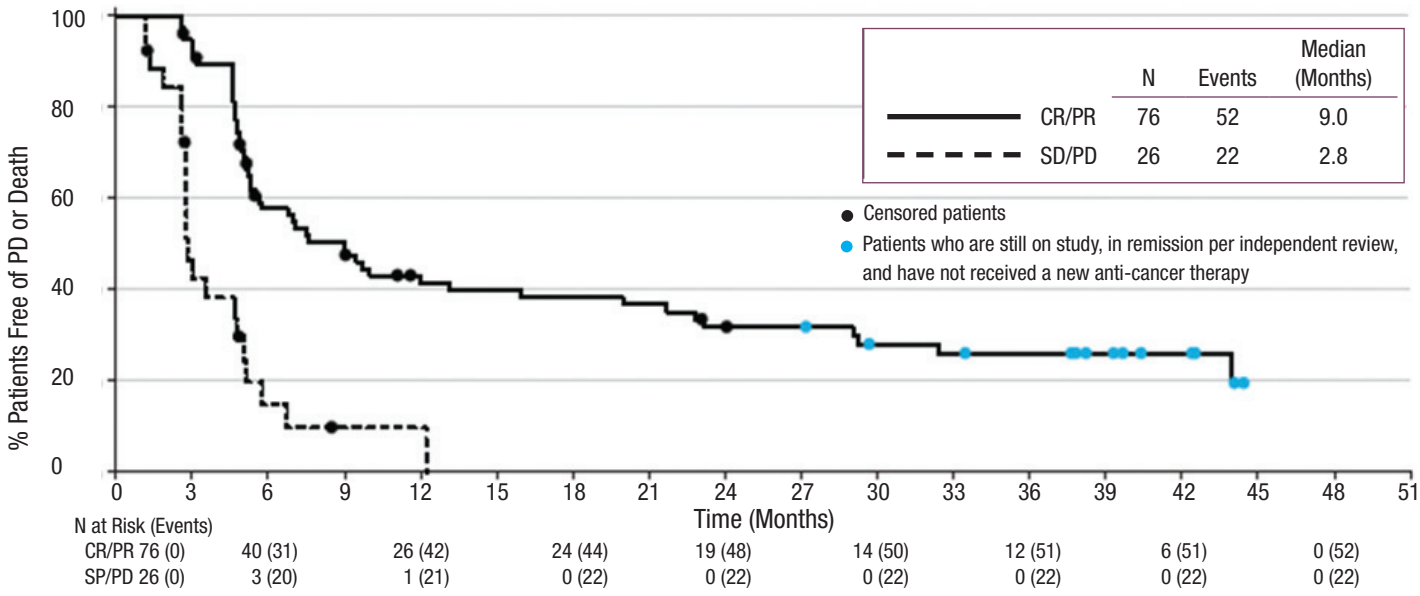
A proof of concept, Phase 1 clinical trial that predominantly enrolled patients with relapsed/refractory HL, but also included patients with CD38 relapsed lymphomas, was initiated. The dose-ranging study started with a dose of 0.1 mg/kg increasing up to 2.7 mg/kg, before selecting the 1.8 mg/kg dose of brentuximab vedotin. Compared with the naked SGN-30 antibody, brentuximab vedotin showed remarkable responses — 86% of patients achieved tumor reductions — prompting a Phase 2 study in patients with HL.

The pivotal Phase 2 study enrolled patients >12 years of age with measurable disease assessed by PET FDG-avidity.[59] Brentuximab (1.8 mg/kg IV) was administered every third week for a minimum of 8 cycles and a maximum of 16 cycles. Restaging using the RECIST criteria[48] was carried out at Cycle 2, 4, 7, 10, 13, and 16. The vast majority of patients had shrinkage of their tumor. Only, 2 of 98 patients had true progression and 74% of achieved a PR or CR.[59] Importantly, in this study, CR was defined by PET results, which is why some responses were less than 100%. In this heavily pretreated population of patients with bulky disease and multiple relapses the quality of responses was remarkable, with 94% of patients achieving tumor reduction. Furthermore, the patients who achieved a CR had durable remissions.[59] The most common Grade ≥3 AEs occurring were peripheral sensory neuropathy (8%), and laboratory abnormalities including neutropenia (20%), thrombocytopenia (8%), and anemia (6%). In an update published this year, prolonged remissions up to 4 years have been observed, suggesting that patients who achieve a CR can remain in CR (Figure 7).[60] Based on the results from this study, patients who have relapsed after Auto-SCT and have subsequently been treated with brentuximab vedotin and have achieved a CR, it may be reasonable to consider observation instead of proceeding to consolidation with Allo-SCT. Given the toxicity of Allo-SCT and the durable responses seen with brentuximab vedotin, delaying Allo-SCT until absolutely required may be a valuable option. If patients do relapse, Allo-SCT remains a viable treatment option.

Similar to ALCL, retreatment of patients with brentuximab vedotin does result in tumor volume reductions and can be considered for those patients who have previously responded to brentuximab vedotin.[50]

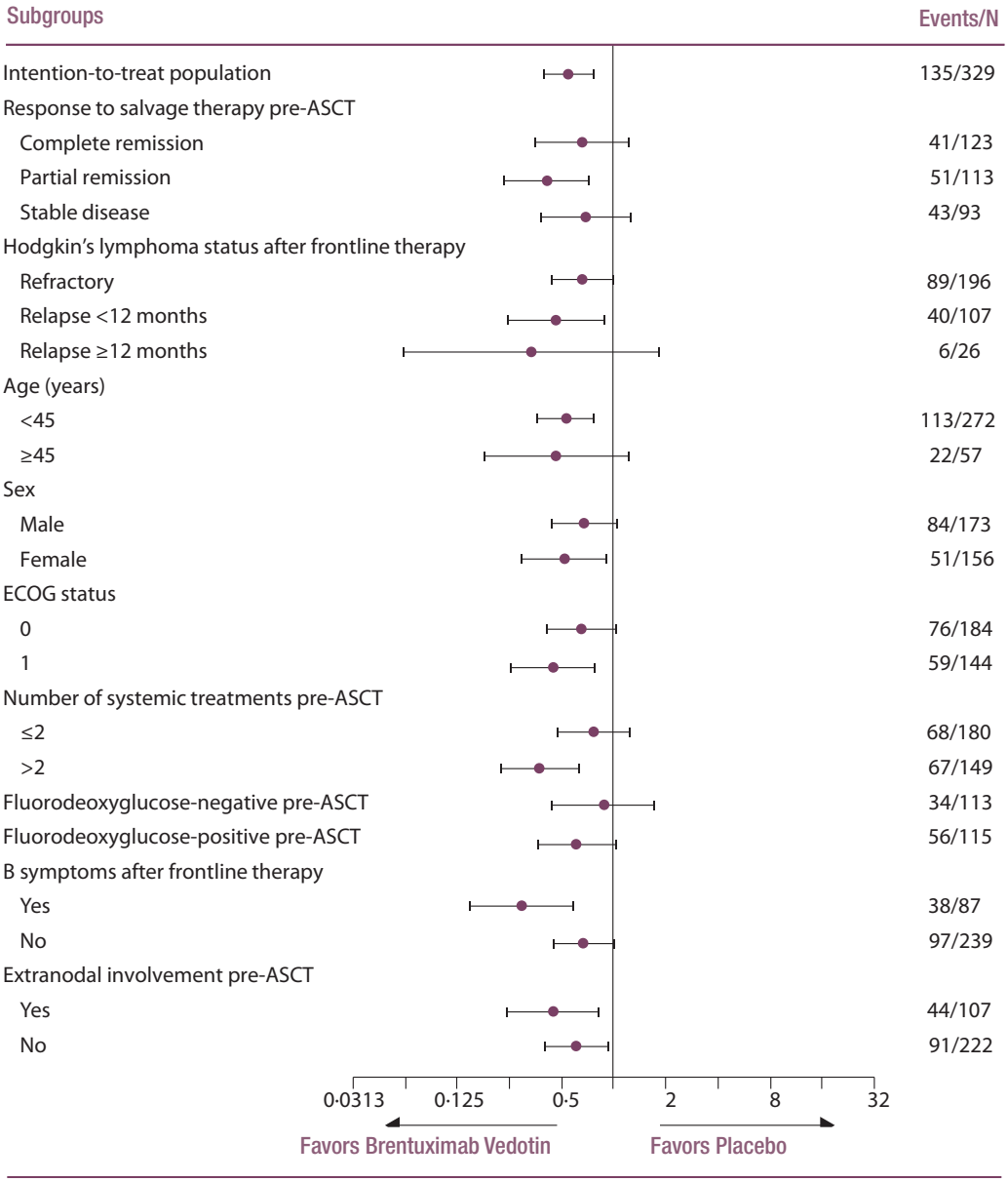
Recently, the results from the Phase 3 ATHERA study were published.[61] The ATHERA study was a randomized, double-blind, placebo-controlled study that investigated whether brentuximab vedotin improved PFS when given as early consolidation after Auto-SCT. Patients with unfavorable-risk relapsed or primary refractory classic HL who had undergone Auto-SCT were randomized to receive 16 cycles of 1.8 mg/kg brentuximab vedotin or placebo IV every 3 weeks, starting 30 to 45 days after Auto-SCT. Progression-free survival by was significantly improved in the brentuximab vedotin arm compared with the placebo arm (hazard ratio [HR] 0.57, 95% CI 0.40-0.81; *P*=.0013). This effect was conserved across prespecified subgroups (Figure 8) (see page 10).

Figure 7. Three-year Follow-up Data and Characterization of Long-Term Remissions from an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory HL



Adapted from Gopal, et al.[60]

Figure 8. Benefits of Brentuximab Vedotin on Progression-free Survival are Conserved Across Subgroups



In the pre-transplant setting, there are several potential approaches to using brentuximab vedotin, one approach is using it in sequence.[62] The rationale for this approach is to reduce unnecessary exposure to chemotherapy. Initially patients received single-agent brentuximab vedotin and once they achieved a CR, stem cells were harvested and patients underwent Auto-SCT. Patients who did not achieve a CR received ICE and subsequently went on to Auto-SCT. In the Moskowitz study,[62] 12 patients (27%, 95% CI 13-40) were PET-negative and proceeded to HDT/ASCT after brentuximab vedotin. Thirty-three (73%, 95% CI 60-86) patients were PET-positive after brentuximab vedotin; and 32 PET-positive patients received ICE, 22 (69%, 95% CI 53-85) of whom were PET-negative. Overall, 34 patients (76%, 95% CI 62-89) achieved PET-negativity. A similar approach using a different dosing schedule of brentuximab reported similar findings.[63]

Another approach is to combine brentuximab vedotin with bendamustine.[64] In a small Phase 1/2, single-arm, 2-stage, open-label study, patients received 1.8 mg/kg brentuximab vedotin on Day 1 with 90 mg/m^2 bendamustine on Days 1 and 2 of 3-week cycles for up to 6 cycles. Patients could undergo Auto-SCT any time after Cycle 2 and post-transplant resume treatment with brentuximab vedotin as monotherapy for up to 16 total doses. The CR rate of the combination was 82% and the overall ORR was 94%. The majority of CRs were achieved after 2 cycles of combination therapy. Stem cell mobilization and collection was considered adequate in all 24 patients who underwent the procedure.

Role of Brentuximab Vedotin in Patients with Treatment-Naïve Hodgkin Lymphoma

Owing to the effectiveness and tolerability of brentuximab vedotin in patients with relapsed/refractory HL, current research is investigating the role of this agent in the front-line setting. In this regard, a Phase 1 study has been completed comparing ABVD with ABVD + BV.[65] During the trial it became clear that the combination of ABVD + BV was associated with excess pulmonary toxicity (44%), and as a result the protocol was amended to exclude bleomycin. The exclusion of bleomycin resulted in no pulmonary adverse events. It is important to note that there is a black box warning stating that brentuximab vedotin should not be combined with bleomycin-containing regimens.[66] Importantly, excluding bleomycin from the treatment regimen did not result in diminished treatment response, with 95% of patients receiving ABVD + BV achieving a CR by the end of treatment, and 96% of patients receiving AVD + BV achieving a CR.[65] Long-term follow-up of the study suggests that patients receiving the bleomycin-free regimen have a PFS of 92% and an OS of 100%.[67]

The results of the Phase 1 study were promising and have initiated a flurry of research into various treatment combinations as well as research into whether brentuximab should be administered sequentially or concurrently with chemotherapy. Some of these questions will be answered by the Phase 3 ECHELON-1 study currently underway (NCT01712490).[68] ECHELON-1 is an open-label, randomized, 2-arm, multicenter, Phase 3 study with the primary objective of comparing effects of AVD + BV with ABVD on the modified PFS in newly diagnosed patients with advanced classical HL. The estimated completion date for the study is March 2020.

Future Directions in the Treatment of Hodgkin Lymphoma

The advent of targeted therapies as well as agents with lower toxicity has opened the door to a multitude of new treatment combinations. As a result, numerous studies are underway examining combinations that build on the backbone of brentuximab vedotin and combine agents with complementary actions. These include agents that target the histone deacetylases, the PI3K/mTOR pathway, and the immune checkpoint agents, primarily PD1 and its ligand PDL1.

Two recent clinical trials targeting PD-1/PD-1-ligand interactions have been reported. In a clinical trial utilizing nivolumab, 23 patients with relapsed or refractory HL were treated every 2 weeks with 3 mg/kg of the antibody.[69] The majority of these patients had previously received an Auto-SCT, and most had received previous brentuximab vedotin. Nivolumab was associated with an overall response rate of 87%. In a second trial utilizing the anti-PD-1 monoclonal antibody pembrolizumab, an overall response rate of 53% in heavily pretreated patients was reported.[70]

Conclusions

In the past 5 years, significant inroads into the treatment of CD30 positive lymphomas such as HL, PTCL, and ALCL have demonstrated that this pathway is a suitable treatment target. This activity reviewed CD30 pathology, the pitfalls, the diagnoses, as well as the efficacy of target treatment if cells are CD30 positive or even when cells are CD30 negative. The focus of treatment now is determining how to combine these new most effective molecules in order to achieve the best possible outcomes for these lymphomas. Using these future combinations we may be able to prevent patients having to receive toxic and less effective high-dose chemotherapy and autologous or allogeneic transplant.

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