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EXPERT REVIEW

# Emerging Pharmacotherapy for Relapsed or Refractory Hodgkin's Lymphoma: Focus on Brentuximab Vedotin

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**Abstract:** Hodgkins' lymphoma (HL) which has relapsed post or is refractory to autologous bone marrow transplant presents an ongoing treatment challenge. Development of monoclonal antibodies (mAb) for the treatment of HL has aimed to replicate the success of mAb therapy in the treatment on Non Hodgkins Lymphoma. The identification of CD30 as a potential target for treatment has led to the development of a new antibody-drug conjugate, brentuximab vedotin (SGN-35), which conjugates monomethyl auristatin E to an anti-CD30 antibody to deliver targeted toxicity to the malignant Reed Sternberg cells of HL. This review describes CD30 as an antibody target, and focuses on the antibody-drug conjugate brentuximab vedotin, including current knowledge of the mechanism of action, preclinical, clinical and pharmacokinetic data available for Brentuximab Vedotin.

**Keywords:** brentuximab vedotin, SGN-35, Hodgkins Lymphoma, CD30, antibody-drug conjugate

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## Introduction

Hodgkins Lymphoma (HL) accounts for approximately 30% of all lymphoma.[1] It is a highly curable condition with a 5 year survival above 85%,[2] which is even higher in those patients with limited stage disease.[3]

Effective combination chemotherapy for HL began with the MOPP regimen (Mechlorethamine, Vincristine, Procarbazine and Prednisolone)[4] pioneered by the National Cancer Institute, Bethesda. This has been superceded by ABVD (Adriamycin, Bleomycin, Vinblastine and DTIC)[5,6] which was introduced in 1975[7] and is now widely regarded as the standard of care for first line treatment of HD in the United Kingdom and North America.[8] Recently published data shows ABVD and the newer escalated BEACOPP regimen, widely used in Europe, both achieve 85%–50% 10 year overall survival, although less toxicity is seen with ABVD.[9–12] The focus has now moved from further improving efficacy to reducing the late toxicity associated with some of these therapies.

Despite good initial responses to treatment, approximately 20%–30% of patients will relapse and require salvage therapy.[13] In younger fitter patients second line treatment of those with either refractory or relapsed disease involves high dose therapy and autologous stem cell transplant (ASCT) following salvage chemotherapy. Whilst ASCT may be curative, it will be ineffective in up to 50% of patients.[14]

For older or less fit patients ASCT is not a therapeutic option. For these patients or younger patients relapsing after a stem cell transplant there is a need for newer effective therapies. Within this context a range of drugs (including gemcitabine, vinorelbine and cisplatin) have shown activity, either as single agent or in combination.[15–18] Despite this there have been few studies directly comparing the many different regimens to help inform the choice of therapy.

## Identification of a Target for Monoclonal Antibody Therapy

The addition of antibody therapy to standard chemotherapy has resulted in a paradigm shift in the treatment of Non-Hodgkins Lymphoma (NHL).[19,20] In this context the CD20 antigen has proven a very effective target and as a consequence antigens associated with

HL have been sought. However, uniquely among cancers, the malignant cells of HL (Reed Sternberg (RS) cells) comprise only 1% of the tumour cells and are scattered throughout it. Surrounding the RS cells (and driven by cytokine secretion from them)[21,22] is a complex B and T cell rich environment which supports tumour growth and provides an inflammatory milieu in which the RS cells can evade immune attack.[23] Targeting the RS cells themselves would therefore seem a plausible method of reducing the overall tumour burden.

One potential therapeutic option would be to target the B cell tumour microenvironment with the use of the anti CD20 antibody Rituximab, however it has recently emerged that maintaining the B cell environment may be beneficial. Gene expression profiling has shown a correlation between an improvement in progression-free survival and disease-specific survival when there is a higher number of CD20+ B cells in the tumour.[24]

In this context the addition of rituximab to first line combination chemotherapy is currently under investigation in an ongoing clinical trial.[25]

In order to target the RS cells themselves monoclonal antibodies to various cell surface immunotargets have been investigated. The most attractive of these has been anti-CD30.

## CD30 as a Target

CD30 was discovered in 1982[26] and subsequently identified as a member of the TNF (tumour necrosis factor) superfamily.[27] It is expressed on all RS cells and functions as an integral membrane glycoprotein. CD30 is expressed in 98.4% HL cases,[28] and also in some other haematological malignancies, most notably Anaplastic Large Cell Lymphoma. Expression of CD30 is also highly restricted in normal tissue—it is only found in thymocytes during thymic development, decidual cells of the pregnant uterus and endometrium, pancreatic exocrine cells and a subset of activated lymphocytes (both B and T (CD4+ and CD8+) cells[29]—making it a good immunotherapy target that is unlikely to have many 'off target' side effects.

CD30 signaling appears to result in pleiotropic effects depending on the microenvironment within which the cell resides.[30,31] These effects are mediated by interaction of the long cytoplasmic domain of CD30 with members of the TNFR associated factor

(TRAF) family, which consequently activate NF κB,[32] responsible for anti-apoptotic gene induction. NF κB activation can however be pro-apoptotic in some cases, which may in part explain why the various anti-CD30 antibodies cause differing amounts of cell death in cell lines.[33]

As well as potentially stimulating direct cell death via CD30 activation, the use of therapeutic antibodies can potentially harness other mechanisms of cell death induction such as complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC).

## Anti-CD30 Antibody Development
Despite encouraging in-vitro results, the first anti-CD30 antibodies developed did not show significant therapeutic effects in vivo. SGN-30 (also called cAC10) is a chimeric antibody, consisting of the variable regions from a murine anti CD30 antibody (ac10) and the human regions of the gamma 1 heavy chain and lambda light chain. It was well tolerated in a phase 1 multidose study[34] with no maximum tolerated dose identified. The more significant adverse events (grade III/IV) all occurred at doses above 8 mg/kg and milder adverse events were not dose related. Unfortunately in a subsequent phase II study, no patient with HL achieved an objective response, although 29% HL patients had stable disease.[35]

When combined with the chemotherapy drugs Gemcitabine, Vinorelbine and liposomal Doxorubicin (GVD) in a randomized double blind phase II trial there were excess pulmonary adverse events in the GVD-SGN30 arm, including fatal pneumonitis, necessitating closure of the trial.[36]

MDX060 is a fully human anti CD30 antibody which also demonstrates minimal effect in vivo, despite promising in vitro data. Fewer than 10% of patients in the phase I and II trials responded objectively,[37] although there was an indication that higher doses may increase PFS.[38] Data regarding its effect in combination with chemotherapy have not been reported.

The second generation anti-CD30 antibodies (MDX-1401 and XmAb2513) have modified Fc regions to increase efficacy[39] but despite being well tolerated failed to reduce tumour burden significantly in phase I studies.[40,41]

In an attempt to increase the clinical activity of the anti-CD30 antibodies they were conjugated to toxins (Antibody Drug Conjugates; ADC's), using the 'naked' (unconjugated) antibody as a vehicle for toxin delivery to tumour cells. This has the advantage of potentially sparing the normal tissue from the effects of the cytotoxic agents. Although it is possible to conjugate radionuclides, RNAses and toxins to the antibodies, it is only the antibody/toxin combination that has been shown to have significant therapeutic effect without significant toxicity or the development of human anti-chimeric antibodies.

## Brentuximab Vedotin (SGN-35)
The ADC Brentuximab Vedotin is under development by Seattle Genetics Inc and its licensee Millennium: the Takeda Oncology Company. It consists of the anti-CD30 antibody cAC10 (SGN 30) conjugated to monomethyl auristatin E (MMAE). This is a synthetic analogue of dolastatin 10, a natural product isolated from Dolabella Auriculara (Indian Ocean sea hare) which acts as a potent anti-tubulin agent. The MMAE attaches to the antibody via a protease cleavable dipeptide bond. A valine-citrulline bond has been previously shown to exhibit superior linker stability over other linker technologies (eg, acid labile hydrazone linkers) with concurrently reduced toxicities during in vivo studies.[42] Once the antibody has bound to CD30 it is internalized and trafficked to lysosomes, where the dipeptide bond is cleaved by cathepsin, a lysosomal protease, releasing the MMAE into the cell. The free MMAE then binds to tubulin within the cell disrupting the microtubule network leading to G2/M cell cycle arrest and apoptosis.[43]

## Preclinical Studies
Initial production of SGN-35 conjugated 8 MMAE moieties to each mAB[42,43] however subsequent studies on cell lines and mouse CD30+ xenograft models showed that reducing the number of MMAE structures from 8 to 4 per monoclonal antibody molecule doubled the therapeutic index of the drug whilst maintaining efficacy in vivo.[44] Accordingly, SGN-35 has an average of 4 drug moieties per antibody molecule and no free MMAE in the formulation.

Initial studies showed that the addition of the conjugated toxin does not impact on the ability of the antibody to bind to CD30 in cell
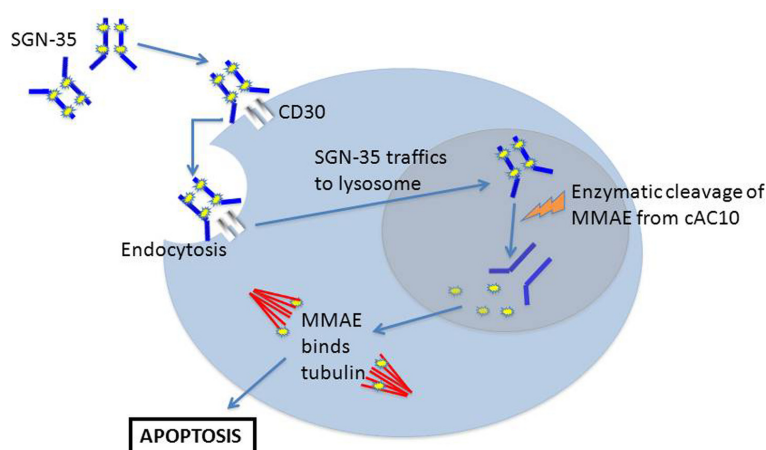
**Figure 1.** Mechanism of action.

lines—in vitro cytotoxicity studies showed high (up to 4 log) selectivity for CD30-positive cells after 96 hours exposure. The stability of the dipeptide linker was also confirmed, with less than 2% of the MMAE being released when the ADC was incubated with human serum over a 10 day period. When HL cell lines were exposed to the ADC, apoptosis and DNA fragmentation began within 12 hours of exposure to the drug.[43]

Brentuximab Vedotin performed well in further in-vitro studies, causing growth arrest and apoptotic cell death in CD30+ cell lines (HL and ALCL). It has been shown that Brentuximab Vedotin internalizes within 48 hours of binding to cell surface CD30 (faster in vivo than in vitro),[45] and that the release of the MMAE from the antibody occurs within 24 hours of the internalization allowing a much higher MMAE concentration within the cells than the ADC concentration administered.[46]

Interestingly the MMAE released into the cells after cleavage of the dipeptide linker seems to be able to diffuse out of viable HL cells and exert it's cytotoxic effect on bystander cells.[46] This may be very important in regression of a tumour such as HL where the malignant cells targeted constitute such a small percentage of the total tumour volume.

In animal models significant tumour regression was seen in mouse xenograft models of both HL and ALCL.[43] Table 1 highlights the key preclinical studies.

## Clinical studies
### Phase I
The results of the first multicentre phase I open label trial of Brentuximab Vedotin in relapsed/refractory HL have been published.[47] This study comprised 45 patients of which 42 had HL. They were heavily pretreated with an average of 3 previous lines of therapy (including ASCT in all eligible and consenting patients). Although there was no upper age limit for trial eligibility, the majority of the patients were young with a median age of 36, reflecting the demographics of this disease. Brentuximab Vedotin was administered once every 3 weeks at doses escalating from 0.2 mg/kg to 3.6 mg/kg in a standard dose-escalation trial design, followed by a cohort expansion phase to evaluate safety aspects further.

**Table 1.** Key preclinical trials for SGN-35 (to date).

| Study | Year | Key points |
|---|---|---|
| Francisco et al[38] | 2003 | Stable conjugation of MMAE to cAC10<br>Exposure to ADC induces apoptosis in CD30+ cells (in vitro) |
| Oflazoglu et al[47] | 2008 | SGN-35 effective with combination chemotherapy (in vitro) |
| Fromm et al[40] | 2010 | Demonstrated SGN-35 internalisation kinetics |
| Okeley et al[41] | 2010 | MMAE released within CD30+ cells.<br>Demonstrated bystander cell cytotoxicity |

1.8 mg/kg was found to be the maximum tolerated dose (MTD) and the dose limiting toxicities were febrile neutropenia, prostatitis and hyperglycaemia.

Of the total cohort an objective clinical response was seen in 35% patients (65% of these were complete remissions). Focusing on the HL patients in particular, an objective clinical response was seen in 21% (9/42) of the patients who had received ≤1.8 mg/kg, with a further 14 patients (33%) having stable disease. Of 28 patients who received doses of ≥1.2 mg/kg and were evaluable 46% obtained an objective response (25% complete response rate). When the MTD of 1.8 mg/kg dose is examined alone, 50% (6/12) of the HL patients attained an objective clinical response (with a further 5 patients having stable disease). Importantly the responding patients included those with bulky or widespread disease and 4 of these 6 patients achieved complete remission, rare for a single agent treatment in heavily pretreated relapsed/refractory HL patients.

For all patients (including 3 NHL patients) responding to the drug at any dose, the Kaplan Meier estimate for objective response duration was 17.3 months with a median progression free survival of 5.9 months.

There were 27 serious adverse events reported during the trial, of which 14 occurred at a dose of 1.8 mg/kg or lower. Of these 14 only 3 (hypercalcaemia, myocardial ischaemia and anaphylaxis) were felt to be related to the Brentuximab Vedotin. The most common adverse events were grade 1 and 2 constitutional symptoms (fatigue, pyrexia, nausea) as well as diarrhoea, neutropenia and peripheral neuropathy. Most of the significant (grade 3 or 4) laboratory abnormalities, including neutropenia and thrombocytopenia, occurred at the higher drug doses (1.8 mg/kg or above).

In total a significant number of patients (12; 27%) withdrew from the trial due to adverse events, including 2 each for fatigue and thrombocytopenia.

In total 36% patients treated with the higher doses of drug (including the 1.8 mg/kg dose) experienced peripheral neuropathy, consistent with treatment with an anti-tubulin agent. This was mostly low grade (I or II) and usually improved after drug cessation. The only grade 3 peripheral neuropathy occurred at a dose higher than the identified MTD.

A lower rate of human anti-chimeric antibodies (HACA) development than was seen with the unconjugated SGN-30 was reported in this trial, with only 2 of the 40 patients tested developing HACA. Both of these patients had a best clinical response of stable disease. As the incidence of HACA development in this trial is so low, no real conclusions can be drawn from this, however it will be of interest to monitor in future trials with this drug.

The addition of the toxin to the SGN 30 antibody can reasonably be assumed to account for the large difference in efficacy of the ADC compared to the SGN-30 antibody alone, and this study was the first to prove that the antibody could be efficiently used to deliver toxin to tumour cells selectively in vivo.

A further phase I study evaluated a more frequent (weekly) infusion regimen.[48] Brentuximab Vedotin was administered weekly at doses of 0.4–1.4 mg/kg for 3 out of 4 weeks in each cycle. 33 out of the enrolled 44 patients had relapsed or refractory HL (median of 3 prior lines of therapy and 62% had received a previous ASCT). 52% patients achieved an objective response (27% complete remissions). Compared with the 3 weekly dosing schedule, there was a marked increase in neuropathy with 10% of the patients experiencing grade 3 neuropathy at the higher doses. As a consequence the 3 weekly regimen has been adopted for further studies.

## Phase II
In a large phase II single arm multicenter study[49,50] 102 heavily pretreated patients were treated using the MTD dose of 1.8 mg/kg administered every 3 weeks. All had relapsed following ASCT and the median number of previous therapies was 4 (1–13). The majority (70%) of the patients had primary refractory disease. The median number of cycles of Brentuximab Vedotin received was 9 (1–16).

Adverse events reported in this trial were predominantly grades 1 and 2 with the commonest being peripheral sensory neuropathy (43%), fatigue (40%), nausea (35%), neutropenia (19%), diarrhea (18%) and pyrexia (16%). The more severe toxicities included grade 3 neutropenia (14%), peripheral sensory neuropathy (5%), fatigue and hyperglycemia (3% each) and grade 4 haematological toxicities (neutropenia (4%) and thrombocytopenia (1%)), pulmonary embolism and abdominal pain (1% each).

The overall response rate was 75% with 34% complete remission and 40% partial remission, and a median duration of response of 29 weeks (95% CI

**Table 2.** Key clinical trials for SGN-35 (to date).

| Study | Phase | Dosing | Histology | Total no of patients | No of HL patients | HL patients only | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ORR | CR | PR |
| Younes et al[42] | 1 | 3 weekly | HL, ALCL | 45 | 42 | 15 (36%) | 7 | 8 |
| Fanale et al[43] | 1 | weekly | HL, ALCL | 44 | 33 | 17 (52%) | 9 | 8 |
| Chen et al[45] | 2 (pivotal) | 3 weekly | HL | 102 | 102 | 76 (75%) | 35 | |

**Abbreviations:** HL, Hodgkins Lymphoma; ALCL, Anaplastic Large Cell Lymphoma; ORR, Overall response rate; CR, Complete Remission; PR, partial remission.

16–52). For patients with B symptoms at the start of treatment, 83% experienced a resolution of these symptoms by a median time of 3 weeks (range 1–16).

Based on this trial an accelerated approval application was submitted to the FDA and approved in August 2011. Table 2 highlights the key clinical trials.

## Potential for Retreatment

A case series presented at ASCO in 2010[51] describes patients relapsing following treatment with Brentuximab Vedotin and being re-treated with the drug. 7 patients had 8 re-treatments (6 of the 7 patients had HL) and all experienced tumour regression. Objectively there were 2 CR, 4 PR and 2 SD, showing that this ADC has the potential for repeated efficacy. A phase II re-treatment study is currently recruiting (NCT00947856, ClinicalTrials.gov).

## Pharmacokinetics

By performing various ELISA's with anti idiotype antibodies and anti-MMAE monoclonal antibodies (for both capture and detection), it was found that the ADC is very stable in mice with a dipeptide linker half-life of 144 hours. When repeated in cynomolgus monkeys, this half-life increased to 230 hours, raising hopes that it would be as stable in humans as in non-human primates.[52] The increased duration of stability of the dipeptide linker helps reduce the disparity between long monoclonal antibody half-lifes and short 'linker' half-lifes that complicates many ADC's, avoiding the problem of unconjugated monoclonal antibody binding to all potential targets and competing with conjugated antibody administered subsequently.

During the multicentre phase I trial, pharmacokinetic and pharmacodynamic data were collected.[47] This demonstrated that the amount of free MMAE is proportional to the dose of the ADC. Predictably, the

highest concentration of ADC was found immediately after drug infusion, however it took 2–3 days (estimated by non-compartmental methods) for the MMAE concentration to peak. The half-life of the ADC is 4–6 days (3–4 days for MMAE), consistent with the finding that steady state pharmacokinetics occurs after ~21 days. For the MTD of 1.8 mg/kg, concentration-time data gave a mean area-under-the-curve of 76.65 ug/mL for the ADC and 0.036 ug/mL for the MMAE, with a maximum mean concentration of 31.98 ug/mL for the ADC and 0.05 ug/mL for the MMAE. This was achieved at a median time of 0.089 days for the ADC and 2.09 days for the MMAE.

As TARC (thymus and activation related chemokine) levels have been previously correlated with HL activity[53] serum TARC levels were evaluated in the expansion phase of the phase 1 trial (12 patients). Levels of TARC reduced in all these patients, however with such a small number of patients evaluated it is difficult to extrapolate these results further. Although levels of various cytokines were analysed in the expansion phase of the trial, apart from decreases in interleukin-6 and TNF-α in 10 of the 12 patients no other results are reported.

## Combination with Chemotherapy

Using mouse xenograft models of HL Brentuximab Vedotin has been combined with chemotherapy. With ABVD and Gemcitabine, the effects appear synergistic. However with Vinorelbine no additional effect was evident.[54] This study provided a good rationale for taking the combination of Brentuximab Vedotin with certain chemotherapeutic agents into the clinical trial setting in the future, however given the high response rates achievable with first line therapy, this may be more suitable to either the relapsed/refractory HL population or more elderly patients who are unable to tolerate standard chemotherapy.

## Current Trials

The combination of Brentuximab Vedotin therapy with ABVD as frontline treatment is currently under investigation in a phase I study (NCT01060904, ClinicalTrials.gov). This aims to treat 70 patients and is now recruiting.

A current phase III trial using Brentuximab Vedotin in HL is currently recruiting. This is a multicenter double-blind placebo-controlled study: AETHERA (NCT01100502; SGN35-005, ClinicalTrials.gov) comparing Brentuximab Vedotin plus best supportive care versus placebo plus supportive care for patients at high risk of residual HL after ASCT. The primary outcome measure is progression free survival with a secondary endpoint of overall survival.

A phase II/III trial (NCT01196208, ClinicalTrials.gov) evaluating safety with Brentuximab Vedotin in HL is also available (expanded access).

At the time of writing, outside the US, Brentuximab Vedotin is available to patients on a named patient basis.

## Use in Other Diseases

As an anti-CD30 ADC, Brentuximab Vedotin has been trialed in systemic Anaplastic Large Cell Lymphoma (ALCL) alongside the trials of HL, with most of the phase I trials being open to patients with either condition.[47,48] ALCL is rare, accounting for 1%–2% of all NHL, and until now has been difficult to treat effectively. Recent phase II multicenter study results of Brentuximab Vedotin as treatment for relapsed/refractory systemic ALCL[55] has shown extremely promising results with 87% overall response rate and 57% CR rate. This is a significant advance and appears to be a breakthrough in the treatment of this condition.

It is possible that in the future, other hard to treat CD30+ diseases (eg, nasopharyngeal carcinoma) may benefit from the addition of this drug to existing treatments. A study is currently recruiting patients with ALCL, mycosis fungoides and extensive lymphomatoid papulosis for treatment with this drug (NCT01352520, ClinicalTrials.gov).

## Conclusion

Brentuximab Vedotin (SGN-35) is one of the most active ADC's ever reported and has the potential to represent a significant advance in the treatment of Hodgkins disease and ALCL. At a time when the vast majority of patients will respond to the standard first line combination chemotherapy, ABVD, it is likely that Brentuximab Vedotin will be a treatment of choice for patients with few other effective options either pre or post ASCT, providing significant benefit with minimal and manageable toxicities.

## Disclosures

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