Brentuximab vedotin▼ reuse - core data

Brentuximab vedotin is indicated for the treatment of adult patients with relapsed or refractory (R/R) CD30+ Hodgkin lymphoma (HL):

1. following autologous stem cell transplant (ASCT)
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
3. at increased risk of relapse or progression following ASCT

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Brentuximab vedotin (ADCETRIS) Summary of Product Characteristics

Reuse of brentuximab vedotin in patients with CD30+ relapsed or refractory (R/R) Hodgkin lymphoma (HL)

Eligibility

- Relapsed CD30+ hematologic malignancy*
- Achieved CR or PR with brentuximab vedotin in a prior study
- Discontinued prior study with brentuximab vedotin when in remission
- Subsequent disease progression/relapse

Treatment (N=21)

- Brentuximab vedotin 1.2 or 1.8 mg/kg IV every 12 days
- No maximum number of cycles
- Frequency of restage per institutional SOC
- Best response assessed by investigator; based on Cheson 2007

Objectives

To investigate whether patients who previously responded to brentuximab vedotin could achieve another remission with retreatment

* The study also examined brentuximab vedotin retreatment in patients with anaplastic large cell lymphoma, however only data from HL patients are presented here
CR, complete remission; IV, intravenous; PR, partial remission; SOC, standard of care

Bartlett *et al*. *J Haem Onc* 2014;7:24; Cheson *et al. J Clin Oncol* 2007;579-586

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Reuse of brentuximab vedotin in patients with CD30+ R/R HL

Baseline patient characteristics

	HL N=21
Median age years (range)	30 (16, 65)
Gender M/F	10/11
Best response to brentuximab vedotin treatment – n (%) CR or PR SD PD	 20 (95%) 1 (5%) -
Median time from last BV treatment to first dose retreatment – months (range)	11.4 (4, 45)
Number of patients with intervening system therapies, n (%)	6 (21%)
ECOG – n (%) 0/1 2	 20 (95%) 1 (5%)
Median number of prior systemic therapies (range)	4 (2, 12)

BV, brentuximab vedotin; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial remission; SD, stable disease

Bartlett *et al*. *J Haem Onc* 2014;7:24

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Reuse of brentuximab vedotin in patients with CD30+ R/R HL

Efficacy results

Best response to retreatment	n (%) N=20*
ORR (CR+PR)	12 (60)
CR	6 (30)
PR	6 (30)
SD	4 (20)
PD	4 (20)

Time-to-event endpoint	Months (95% CI) N=20*
Median duration of response	9.2 (2.1,–)
Median duration of CR	9.4 (1.7–14.2)
Median PFS	9.9 (3.4–13.4)
Median OS	– (11.4,–)

*One patient had no post baseline response assessment
CI, confidence intervals; CR, complete remission; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial remission; SD, stable disease
Bartlett *et al*. *J Haem Onc* 2014;7:24

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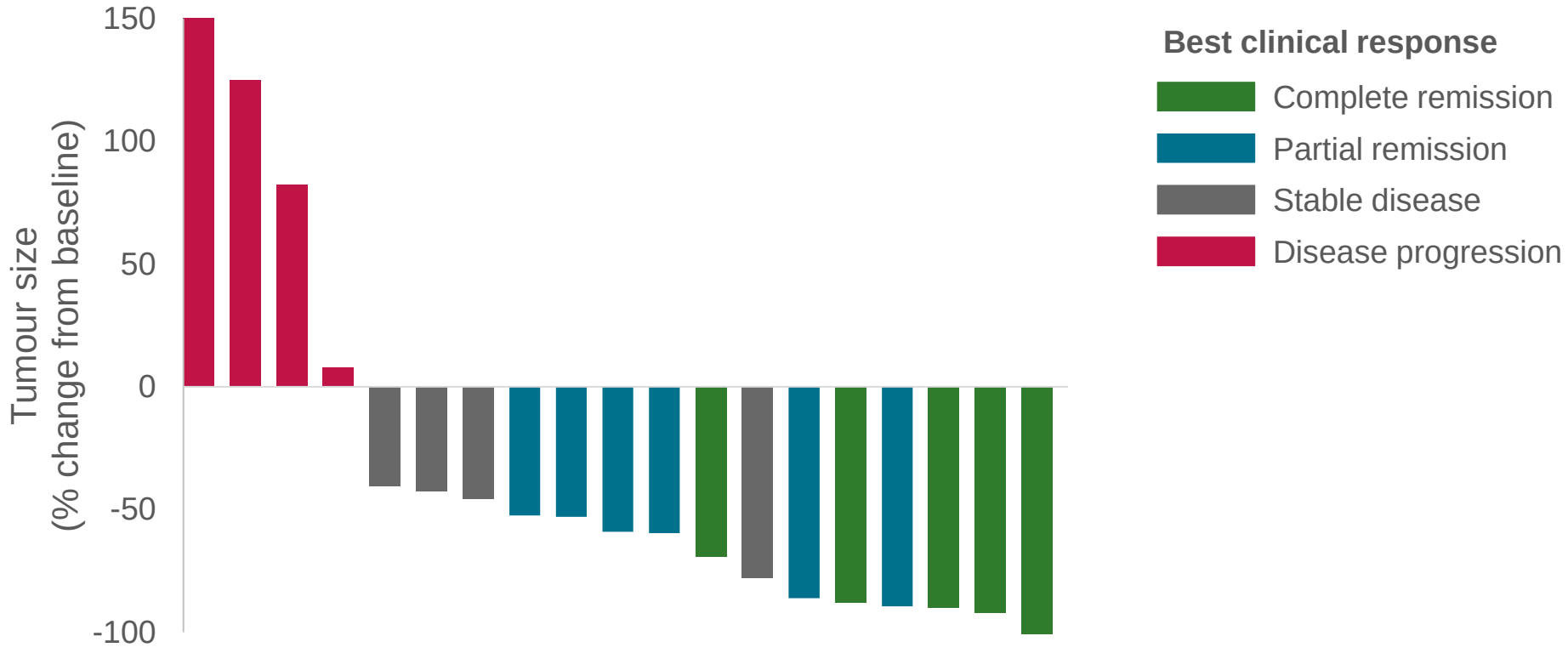
Reuse of brentuximab vedotin in patients with CD30+ R/R HL

Efficacy results: The majority of patients experienced reduction in measurable tumour volume*



Best change in the sum of the product of the diameter of target lesions over all stages.

*One patient had no baseline tumour measurement reported and is thus not included in the summary

Bartlett *et al*. *J Haem Onc* 2014;7:24

Reuse of brentuximab vedotin in patients with CD30+ R/R HL

Safety: Observed adverse events were generally similar to those seen in the phase II pivotal trials

	n, % (N=21)
Any event	**20 (95)**
Peripheral sensory neuropathy	12 (57)
Nausea	9 (43)
Diarrhoea	9 (43)
Fatigue	11 (52)
Headache	6 (29)
Peripheral motor neuropathy	6 (29)
Arthralgia	7 (33)
Dyspnoea	7 (33)
Pyrexia	7 (33)
Anaemia	6 (29)
Back pain	5 (24)
Cough	5 (24)
Dizziness	5 (24)

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Bartlett *et al*. *J Haem Onc* 2014;7:24

Reuse of brentuximab vedotin in patients with CD30+ R/R HL data summary

- Reuse of brentuximab vedotin provided an opportunity to achieve a second response in patients who previously achieved a complete or partial remission[1]
- With the exception of a higher rate of peripheral motor neuropathy, reuse was associated with a similar side effect profile to that observed in the pivotal trials[1]
- The recommended starting dose for reuse in patients with R/R HL who have previously responded to brentuximab vedotin is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every three weeks. Alternatively, treatment may be started at the last tolerated dose[2]

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1. Bartlett *et al*. *J Haem Onc* 2014;7:24 2. Brentuximab vedotin (ADCETRIS) Summary of Product Characteristics

Please refer to the summary of product characteristics for details on the full side-effect profile and drug interactions of brentuximab vedotin. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Takeda UK Ltd. on 01628 537900

NAVIGATE

Abbreviated Prescribing Information:

Adcetris▼ (brentuximab vedotin)

(Refer to Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 50 mg powder for concentrate for solution for infusion. **Indication:** treatment of adult patients with relapsed or refractory (R/R) CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; treatment of adult patients with R/R systemic anaplastic large cell lymphoma (sALCL); treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy. **Dosage & Administration:** Administration should be under the supervision of a physician experienced in the use of anti-cancer agents. Recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks (If the patient's weight is more than 100 kg, the dose calculation should use 100kg). Recommended starting dose for retreatment of patients with R/R HL or sALCL who have previously responded to treatment with Adcetris is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks or at the last tolerated dose. Recommended starting dose in patients with hepatic impairment or severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Continue treatment until disease progression or unacceptable toxicity. Patients with R/R HL or sALCL who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles. Patients with HL at increased risk of relapse or progression following ASCT, should start treatment following recovery from ASCT. These patients should receive up to 16 cycles. Patients with CTCL should receive up to 16 cycles. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored during and after infusion. **Dose Adjustments:** If neutropenia develops during treatment it should be managed by dose delays. If peripheral sensory or motor neuropathy emerges or worsens during treatment patients may require delay and dose reduction or discontinuation of Adcetris. *Elderly patients (≥65yrs):* dosing recommendations for patients aged 65 and older are the same as for adults. *Paediatric patients (<18 yrs): S*afety and efficacy has not yet been established. In nonclinical studies thymus depletion has been observed. **Contraindications:** Hypersensitivity to the active substance or excipients. Combined use of bleomycin and Adcetris causes pulmonary toxicity. **Warnings and Precautions:** Progressive multifocal leukoencephalopathy (PML) has been reported in patients who received Adcetris after receiving multiple prior chemotherapy regimens; patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Adcetris dosing should be held for any suspected case of PML and permanently discontinued if a diagnosis of PML is confirmed. Acute pancreatitis has been observed in patients treated with Adcetris. Patients should be monitored for abdominal pain suggestive of acute pancreatitis. Adcetris dosing should be held if acute pancreatitis is suspected and permanently discontinued if a diagnosis is confirmed. Pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported in patients receiving Adcetris. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation is required and patients treated appropriately. Consider holding Adcetris dosing during evaluation and until symptomatic improvement. Serious and opportunistic infections have been reported in patients treated with Adcetris. Patients should be carefully monitored during treatment. Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported. Monitor patients during and after infusion. Adcetris should be immediately and permanently discontinued if anaphylactic reaction occurs. Infusion should be interrupted if IRR occurs and appropriate management instituted. Infusion may be restarted at slower rate after resolution. Use premedication for subsequent infusions in instances of prior IRR. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome; these patients should be monitored and managed according to best medical practice. Adcetris may cause peripheral neuropathy which is reversible in most cases. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require delay and dose reduction or discontinuation of Adcetris. Refer to SmPC for dose adjustments if peripheral neuropathy develops. Grade 3 or 4 anaemia, thrombocytopenia and neutropenia can occur with Adcetris. Refer to SmPC for dose adjustments if neutropenia develops. Patients should be monitored for fever and managed according to best medical practice if febrile neutropenia develops. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with Adcetris with fatal outcomes. If SJS or TEN occurs, treatment with Adcetris should be discontinued and appropriate medical therapy administered. Gastrointestinal complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in the form of hepatotoxicity, has been reported. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Liver function should be tested before initiating the treatment and routinely monitored in patients receiving Adcetris. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of Adcetris. Any patient who experiences an event of hyperglycaemia should have their serum glucose monitored and managed appropriately. Monomethyl auristatin E (MMAE) clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations. The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. Adcetris should be used with caution in other CD30+ CTCL patients after consideration of the potential benefit-risk. Adcetris contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. **Pregnancy & lactation**: Women of childbearing potential should be using two methods of effective contraception during treatment with Adcetris and until 6 months after treatment. There are no data from the use of Adcetris in pregnant women. Animal studies have shown reproductive toxicity. There are no data as to whether Adcetris or its metabolites are excreted in human milk. **Fertility:** In non-clinical studies, Adcetris treatment has resulted in testicular toxicity, and may alter male fertility. Men being treated with Adcetris are advised not to father a child during treatment and for up to 6 months following the last dose. **Drug Interactions:** Co-administration of Adcetris: with strong CYP3A4 and P-gp inhibitors, such as ketoconazole, may increase the incidence of neutropenia; with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to Adcetris however, it appeared to reduce plasma concentrations of MMAE metabolites. Adcetris is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes e.g. midazolam. **Adverse Effects:** *Very common (≥10%):* Infection, upper respiratory tract infection, neutropenia, peripheral sensory neuropathy, peripheral motor neuropathy, cough, dyspnoea, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, pruritus, myalgia, arthralgia, fatigue, pyrexia, infusion-related reactions, weight decreased. *Common (≥1/100 to <1/10):* Herpes zoster, pneumonia, herpes simplex, oral candidiasis, anaemia, thrombocytopenia, hyperglycaemia, dizziness, alanine aminotransferase/ aspartate aminotransferase (ALT/AST) increased, alopecia, back pain, chills. *Uncommon (≥1/1000 to <1/100):* Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, tumour lysis syndrome, demyelinating polyneuropathy, pancreatitis acute, cytomegalovirus infection or reactivation, sepsis/ septic shock, febrile neutropenia, anaphylactic reaction, Stevens-Johnson syndrome/toxic epidermal necrolysis. *Frequency not known (cannot be estimated from the available data)*: Progressive multifocal leukoencephalopathy . Refer to the SmPC for details on full side effect profile and interactions. **Pharmaceutical Precautions:** Store vial in a refrigerator (2°C-8°C), protected from light. After reconstitution/dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C. **PI Date of Preparation:** January 2018. **PI approval code:** UK/ADC/1606/0038(3) **Legal category:** POM **Basic NHS Price & Marketing Authorisation:** £2,500 for each Adcetris 50mg vial (EU/1/12/794/001). **Further information is available from:** Takeda UK Ltd. Building 3, Glory Park, Glory Park Avenue, Wooburn Green, Buckinghamshire, HP10 0DF. Tel: 01628 537900 Fax: 01628 526617. Adcetris® is a registered trademark.

Adcetris has received a conditional marketing authorisation in Europe. A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required. The European regulatory agency will review new information on Adcetris at least every year and the summary of product characteristics will be updated as necessary.

Please refer to the summary of product characteristics for details on the full side-effect profile and drug interactions of Adcetris. Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Takeda UK Ltd 01628-537900