Brentuximab vedotin▼ 5 year overall survival follow up – core data

This educational resource has been developed and funded by Takeda UK Ltd. and is intended for healthcare professionals only
Prescribing information can be found on slide 12

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

Phase II study of brentuximab vedotin in relapsed or refractory (R/R) Hodgkin lymphoma (HL) post-ASCT: overview

Eligibility

- R/R CD30+ HL*
- Age ≥12 years
- Measurable disease ≥1.5 cm
- ECOG performance status of 0–1
- Prior ASCT

Treatment (N=102)

- Brentuximab vedotin 1.8 mg/kg IV Q3wk
- Administered outpatient over 30 minutes
- 8 to 16 cycles for SD or better
- Restage** at cycles 2, 4, 7, 10, 13 16

Follow-up

Every 12 weeks for the first two years; every 6 months in years 3–5; every 12 months thereafter

Primary Endpoint: ORR by independent review facility
Secondary Endpoints: CR rate, DOR, PFS, OS, safety

* Histologically documented CD30-positive HL by central pathology review

** Revised response criteria for malignant lymphoma (Cheson 2007)

ASCT, autologous stem cell transplant; CR, complete remission; DOR, duration of response; ECOG, Eastern cooperative oncology group; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression free survival; SD, stable disease

Younes A, *et al. J Clin Oncol* 2012;30: 2183-2189.

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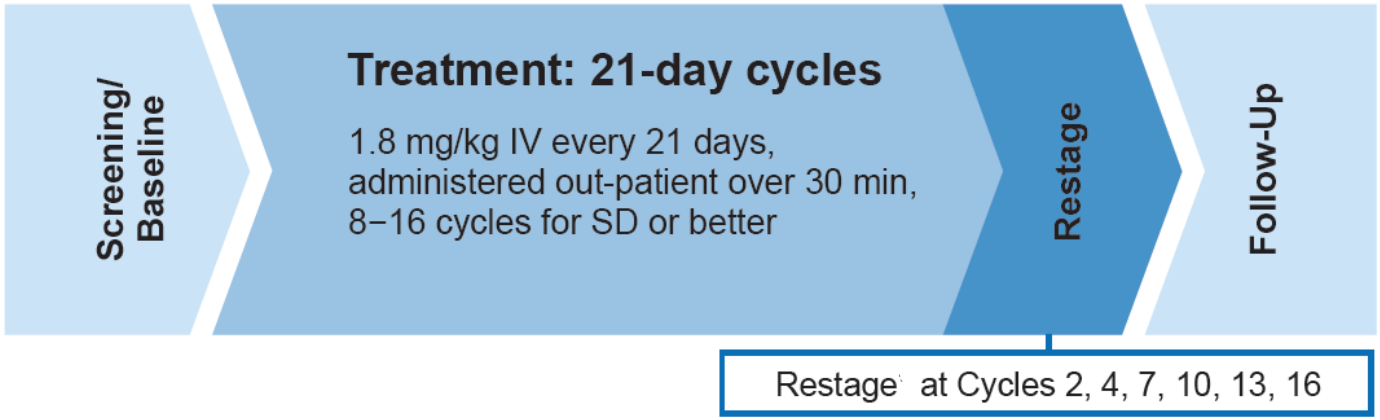
Phase II study of brentuximab vedotin in R/R HL post-ASCT: 5-year follow-up

Patients: 102 patients with R/R CD30+ HL after ASCT; median age 31 years (15–77), median of 3.5 (1–13) prior chemotherapy regimens, 71% refractory to frontline therapy, 42% refractory to most recent treatment, 71% relapsed ≤1 year post-ASCT

Dose and Schedule:



All patients completed treatment in August 2010, and were followed for PD/OS until end of study

Follow-up: Every three months for the first two years; every six months in years 3–5; every 12 months thereafter. Median observation time for all 102 patients from first dose was 35.1 months (1.8–72.9)

ASCT, autologous stem cell transplant; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; SD, stable disease

Chen R, *et al. Blood* 2016;128:1562–1566

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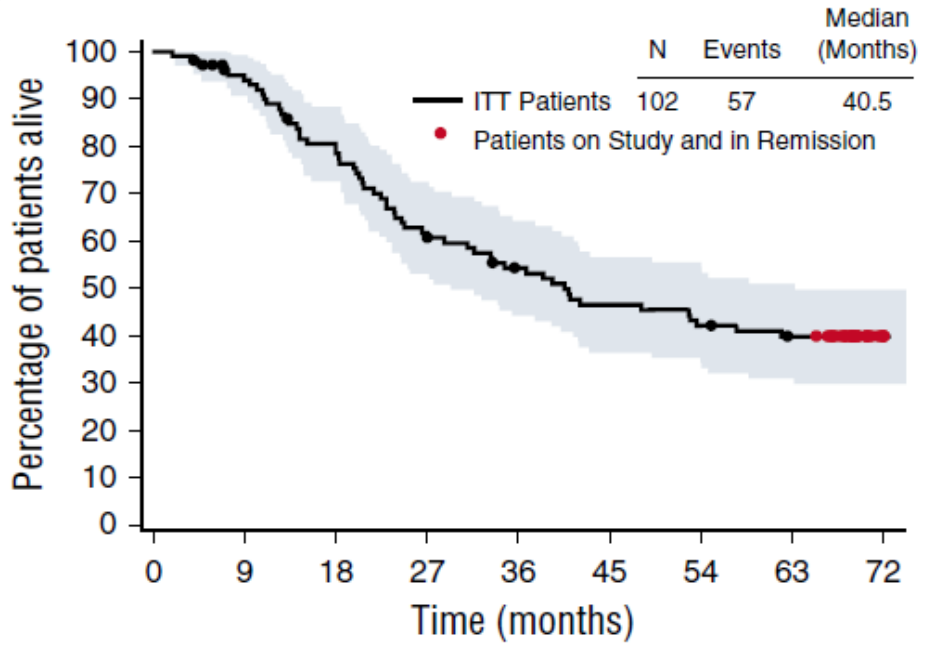
Phase II study of brentuximab vedotin in R/R HL post-ASCT: 5-year follow-up

Efficacy:

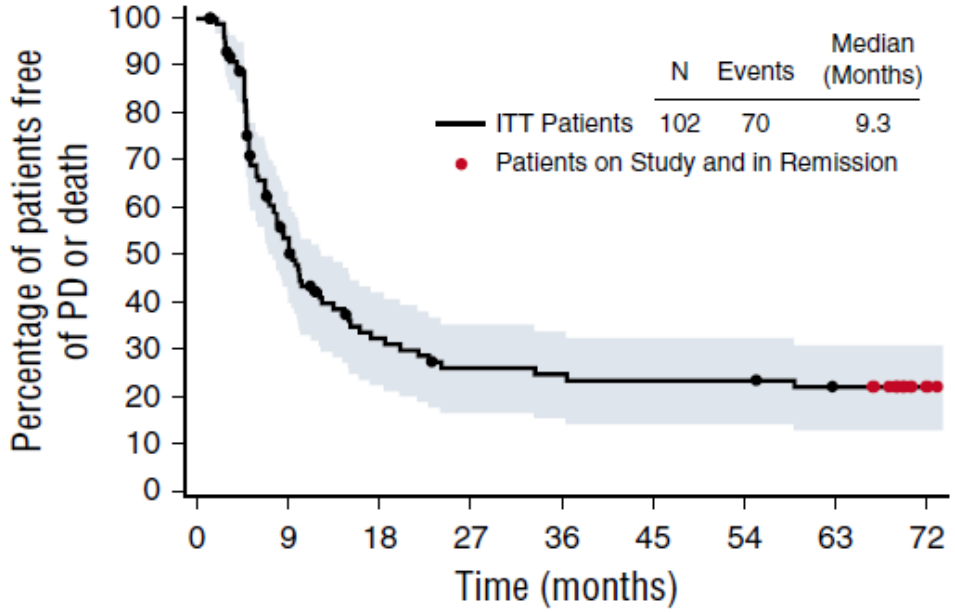
OS at 5 years



Median OS: 40.5 months
(95% CI: 28.7, 61.9 [1.8–72.9+])

5-yr OS: 41%
(95% CI: 31–51%)

PFS at 5 years



Median PFS: 9.3 months
(95% CI: 7.1, 12.2)

5-yr PFS: 22%
(95% CI: 13–31%)

ASCT, autologous stem cell transplant; CI, confidence interval; ITT, intention to treat; OS, overall survival; PD, progressive disease; PFS, progression-free survival

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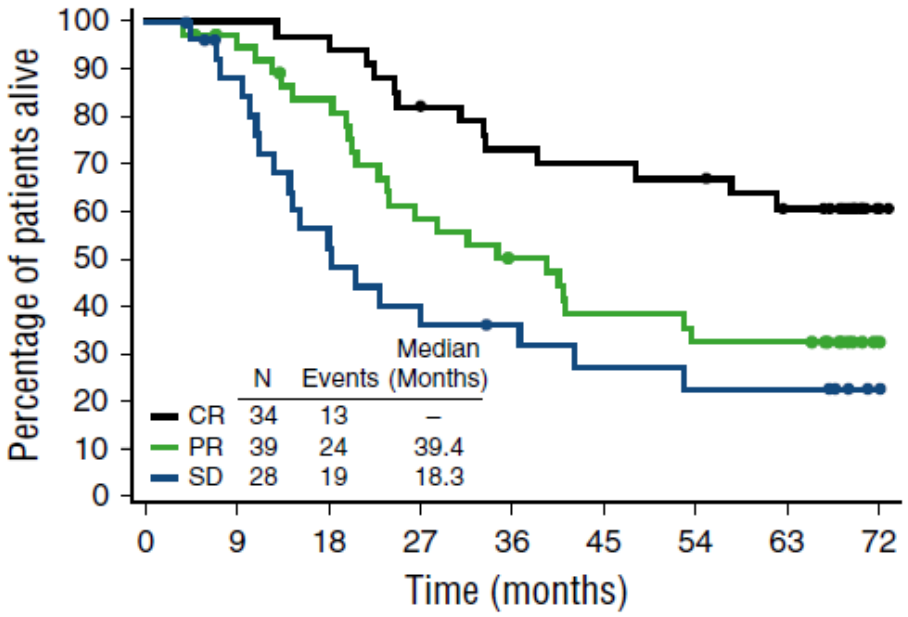
Phase II study of brentuximab vedotin in R/R HL post-ASCT: 5-year follow-up

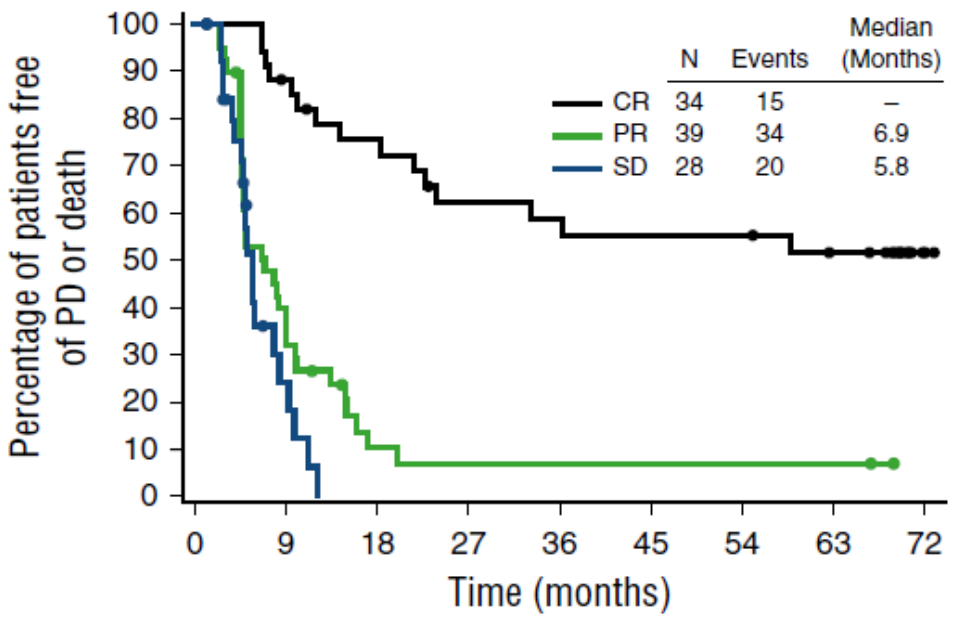
Efficacy: Median OS, PFS and DOR were not reached in patients who achieved CR (n=34), with 13 CR patients (38% of all CR patients) remaining in follow-up and in remission at study closure

OS by best response



5-yr OS: 64%
(95% CI: 48%, 80%)

PFS by best response



5-yr PFS: 52%
(95% CI: 34%, 69%)

CR, complete remission; DOR, duration of response; OS, overall survival; PFS, progression-free survival; PR, partial remission; SD, stable disease

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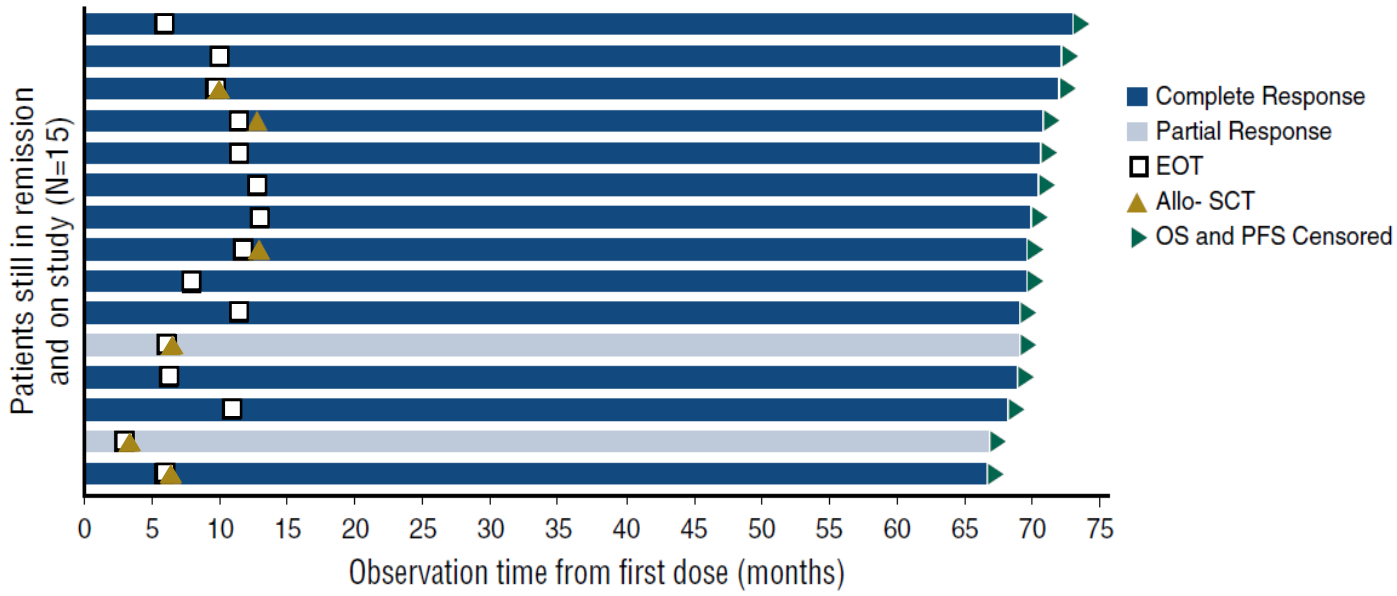
Phase II study of brentuximab vedotin in R/R HL post-ASCT: 5-year follow-up

Efficacy:

- Of the 28/34 CR patients who did not receive consolidative alloSCT:
  - 14 relapsed
  - 10 are in remission
  - Four came off study prior to closure
- 15/102 patients remained in follow-up and in remission at end of study, with a median observation time of 69.5 months (66.5–72.9)
  - 13 CR and two PR
  - 4/13 CR and both PR patients received an allo-SCT (total of six patients)
  - 9/13 CR patients received no further treatment

Patients in follow-up and in remission at end of study



AlloSCT, allogeneic stem cell transplant; CR, complete remission; EOT, end of treatment; OS, overall survival; PFS, progression free survival; PR, partial remission

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Phase II study of brentuximab vedotin in R/R HL post-ASCT: 5-year follow-up

Efficacy:

- The majority of CR patients had achieved CR by the end of cycle seven
- 77/102 patients received at least 1 subsequent treatment following brentuximab vedotin
- 44/77 received multi-agent therapy, 42/77 single agent, 22/77 received SCT and 8/22 received alloSCT
- 13/77 received brentuximab vedotin re-treatment (10 as single-agent and three in a multi-agent regimen); a 2nd response was reported in 60% (30% CR) of HL patients with median DOR of 9.2 months
- Six patients received treatment with a PD-1 pathway inhibitor (five as single-agent and one in a combination)

Time to best response for patients in long term remission	CR (n=13)	PR (n=2)	Total (n=15)
Visit of earliest best response[a] (day 15–21), n (%)			
Cycle 2	2 (15)	2 (100)[b]	4 (27)
Cycle 4	5 (38)	0	5 (33)
Cycle 7	3 (23)	0	3 (20)
Cycle 10	2 (15)	0	2 (13)
Cycle 16	1 (8)	0	1 (7)

[a]Response assessed per Cheson et al. 2007

[b]Patients discontinued per Investigator decision, proceeded to allo-SCT

AlloSCT, allogeneic stem cell transplant; CR, complete remission; DOR, duration of response; PR, partial remission; SCT, stem cell transplant

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Phase II study of brentuximab vedotin in R/R HL post-ASCT: 5-year follow-up

Safety: Patients received a median of nine cycles (1–16) of brentuximab vedotin
Grade ≥3 AEs in ≥5% of patients were 20% neutropenia, 8% sensory PN, 8% thrombocytopenia, 6% anaemia

Reason for treatment discontinuation, n (%)*	CR (n=34)	PR (n=39)
Completed treatment	12 (35)	4 (10)
PD	4 (12)	23 (59)
AE	9 (26)	5 (13)
Investigator decision	7 (21)	4 (10)
Patient decision	2 (6)	3 (8)

Treatment-emergent PN	N=102
Patients experiencing PN, n (%)	56 (55%)
PN outcome, % Complete resolution Improvement	n=56 73% 14%
Ongoing PN Grade ≤2 at last follow-up, n (%)	15 (27%)
Grade ≥3 PN at last follow-up	0

*1 patient was not evaluable for response

AE; adverse events; CR, complete remission; PD, progressive disease; PN, peripheral neuropathy; PR, partial remission

Chen R, *et al. Blood* 2016;128:1562–1566

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5-year overall survival R/R HL data summary

- 5-year follow-up from the phase II trial in this heavily pre-treated population identified that a subset of patients with R/R HL who obtained CR with single-agent brentuximab vedotin achieved long-term disease control
- For the overall population (102 patients), 5 year OS rate was 41% (95% CI 31–51) and PFS rate was 22% (95% CI: 13–31)
- For patients achieving CR (34 patients), median OS and PFS were not reached, with 13 patients remaining in follow-up and CR at study closure
- The safety profile of brentuximab vedotin was manageable, with 88% of patients who experienced peripheral neuropathy experiencing either resolution (73%) or improvement (14%) in symptoms

CI, confidence intervals; CR, complete remission; OS, overall survival; PFS, progression free survival

Chen R, *et al. Blood* 2016;128:1562–1566

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