Takeda ONCOLOGY

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MEETING REPORT

How to best integrate targeted treatment in relapsed/refractory (R/R) Hodgkin lymphoma (HL)

Takeda sponsored satellite session

On Thursday 6th July 2017, following the Hartley Taylor Post ICML Lugano Lymphoma Highlights meeting, Takeda hosted a satellite session entitled “How to best integrate targeted treatment in relapsed/refractory (R/R) Hodgkin lymphoma (HL)” at The School of Oriental & African Studies, London.

The aim of the session was to discuss the use of targeted treatment of R/R HL in both the pre- and post-transplant setting, while giving consideration to the optimal sequencing of treatments. The following report summarises the key presentations and discussions from the meeting.

UK/ADC/1708/0060(1) Date of preparation: January 2018

Introduction

- In recent years, clinicians have had access to more sophisticated therapies compared to conventional chemotherapy to treat patients with R/R HL, including brentuximab vedotin (ADCETRIS▼)(BV) and, more recently, immune checkpoint inhibitors.
  - BV is indicated for the treatment of adult patients with R/R CD30+ HL: following at least two prior therapies when autologous stem cell transplant (ASCT) or multi-agent chemotherapy (MAC) is not a treatment option; following ASCT; or when a patient is at increased risk of relapse or progression following ASCT.[1]
  - Nivolumab is indicated for the treatment of adult patients with R/R HL after ASCT and treatment with BV.[2]
  - Pembrolizumab is indicated for the treatment of adult patients with R/R classical Hodgkin lymphoma (cHL) who have failed ASCT and BV, or who are transplant-ineligible and have failed BV.[3] However, it is not currently funded, and as such is not discussed in this document.
- A key challenge for clinicians is the sequence of therapies and appropriate individualised patient treatment and management.

Click on the following to learn more about the session:

Targeted treatment in the pre-transplant setting ›

Dr Graham Collins

Consultant Haematologist,
Oxford University Hospitals
NHS Foundation Trust, Oxford

Targeted treatment in the post-transplant setting ›

Prof Karl Peggs

Professor of Transplant Science
and Cancer Immunotherapy,
UCL Cancer Institute, London

What is the optimal sequencing of targeted treatments? ›

Dr Cathy Burton

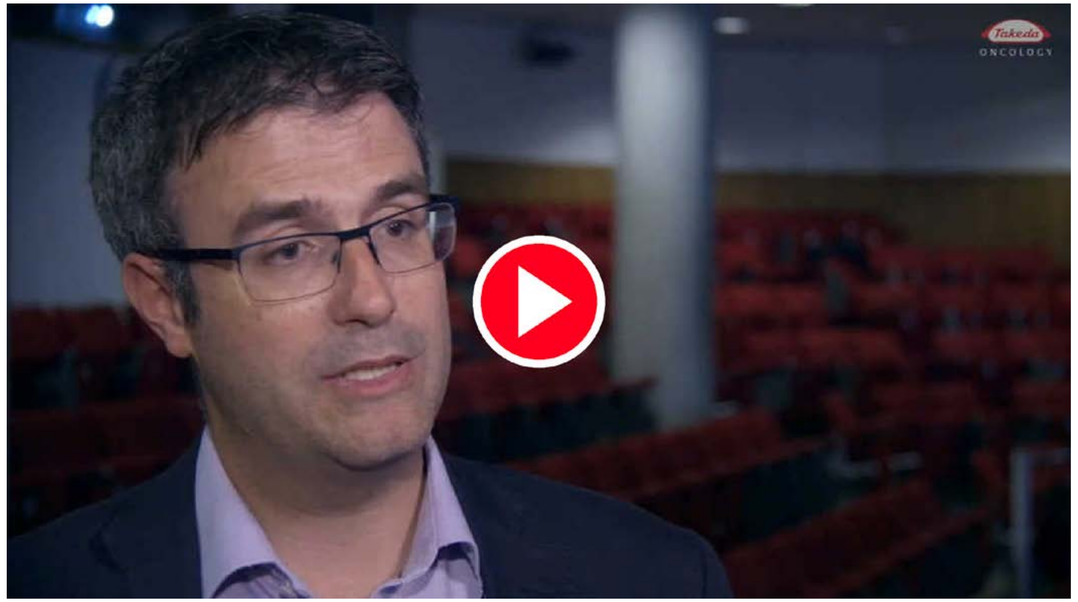
Consultant Haematologist,
Leeds Cancer Centre,
Leeds

Targeted treatment in the pre-transplant setting

Dr Graham Collins (GC)

Key takeaways

- BV is licensed and currently funded through the cancer drugs fund (CDF) as a treatment for patients pre-ASCT, with several studies supporting the efficacy and safety in this setting
- NICE has requested that additional retrospective data be collected to support a further NICE review for this patient population in 2018[4]
- Clinical trial data for nivolumab in this setting is limited and is not currently licensed or funded



Dr Graham Collins (GC)

In the pre-ASCT setting, BV is licensed following at least two prior therapies when ASCT or MAC is not an option.[1]

Targeted treatment in the pre-transplant setting

Dr Graham Collins (GC)

NICE recommendations for BV pre-ASCT

Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:

- they have relapsed or refractory disease after at least 2 previous therapies and they cannot have autologous stem cell transplant or multi-agent chemotherapy and
- the conditions of the managed access agreement are followed

Targeted treatment in the pre-transplant setting

Dr Graham Collins (GC)

Supporting Data

Three studies support the use of BV in the pre-transplant patient population.[5-7]

In a single arm phase IV study, BV showed activity in patients ineligible for stem cell transplant (SCT) or MAC, enabling 45% of this difficult-to-treat population to become SCT eligible.[6] An Italian retrospective analysis of 30 pre-treated patients supports the hypothesis that sensitivity to BV predicts a good outcome following ASCT.[7]

Real world data collated from the UK[5] is reflective of the earlier clinical evidence of patients receiving BV prior to SCT as a second line of salvage therapy.

The safety profile of BV in this setting was manageable and reflected the earlier phase II pivotal trial in R/R HL.[8]

Targeted treatment in the pre-transplant setting

Dr Graham Collins (GC)

UK data[5]

- Multicentre UK-wide retrospective study evaluating the efficacy of BV in R/R HL in the pre-transplant naive setting
- 96 patients evaluable for primary response assessment
- Median follow up from the start of BV: 12.0 months (0.4–56.7 months)
- Median of 4 cycles of treatment (range 1–9)
- Objective response rate (ORR) for all BV patients as assessed by the local treating physician was 56% (CR 29%, PR 27%)
  - 3rd Line ORR was 53% (CR 29%, PR 24%; n = 68)
  - 4th Line ORR was 65% (CR 43%, PR 22%; n = 23)
  - 5th Line ORR was 60% (CR 60%, PR 0%; n = 5)
- Median progression free survival (PFS) for all patients: 5.6 months (95% CI 4.4-12.2 months)
- Median overall survival (OS) for all patients: 37.2 months (95% CI 18.3 months – not reached)
- 3 patients developed dose limiting toxicities and did not undergo radiological assessment

GC... *There is more data now, looking at patients who are fit for a stem cell transplant but not suitable because they've not got a deep enough remission, and the take home message is that BV delivers around a third of patients to have a stem cell transplant, but it also enables another quarter to a third to have further treatment and then get to a stem cell transplant. So, it's an effective bridge.*

Targeted treatment in the pre-transplant setting

Dr Graham Collins (GC)

Case study:

GC highlighted the role of targeted therapy in the pre-transplant setting in a 23 year old female HL patient

Case history:

- The patient received first-line ABVD (six cycles) followed by radiotherapy, achieving complete remission (CR)
- She relapsed nine months later and received salvage chemotherapy with ESHAP but only achieved partial remission (PR)
- The patient received four doses of BV, achieving CR
- She then went on to receive a BEAM autograft

Outcome:

The patient remains in remission ten months following her autograft

ABVD - doxorubicin, bleomycin, vinblastine, dacarbazine; ESHAP - etoposide, methylprednisolone, cytarabine, cisplatin; BEAM - carmustine, etoposide, cytarabine, melphalan.

Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

Key takeaways

- 5-year follow-up to the phase II trial for BV in R/R HL post-ASCT patients identified a subset of patients who achieved long-term remission, thereby supporting the use of BV in this setting
- Clinical evidence, including long-term data, supports the reuse of BV.[8,9]
- Further consideration needs to be given to the management of patients and how many cycles of BV are given
  - Including when, or if, a patient achieving metabolic complete remission (mCR) should proceed to allo-SCT
- Treatment with PD-1/PD-L1 inhibitors offers clinicians further treatment options in patients who relapse following ASCT and BV
- Consolidation therapy with BV is not currently CDF funded, but there is a significant benefit for patients, particularly for those who are PET positive prior to their ASCT.[10]

Prof Karl Peggs (KP)

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Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

Treatment considerations

In the phase II study of BV in R/R HL post-ASCT, median OS, PFS and duration of response (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.[9] Patients with best response of PR or stable disease (SD) will inevitably relapse during follow-up. KP highlighted that a key challenge for clinicians is how they manage these patients. For example, in patients who achieve CR with BV, should a clinician move to allo-SCT or employ a 'watch and wait' approach? Furthermore, how does the introduction of other options such as BV reuse (now funded as a bridge to allo-SCT or DLI) and nivolumab, which offer the option of getting a response before allo-SCT, affect the decision to move to allo-SCT?

Some patients receiving BV post-ASCT who respond begin to see diminishing returns from therapy beyond cycle 6–8. This raises questions for clinicians: when do clinicians make the decision to move to allo-SCT?; how do you achieve a balance between conversion of patients with PR to CR versus the patient progressing from PR?

Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

Phase II study of BV in R/R HL post-ASCT: 5-year follow-up[9]

- 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 BV achieved long-term disease control and may be cured
- 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 BV was manageable, with 88% of patients who experienced peripheral neuropathy experiencing either resolution (73%) or improvement (14%) in symptoms

Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

NICE recommendation for BV following an ASCT

Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:

- they have relapsed or refractory disease after autologous stem cell transplant and
- the company provides brentuximab vedotin at the price agreed with NHS England in the commercial access agreement

NICE recommendation for nivolumab following an ASCT

Nivolumab is recommended, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma if:

- they have relapsed or refractory disease after autologous stem cell transplant and treatment with brentuximab vedotin and
- the company provides nivolumab with the discount agreed in the patient access scheme

Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

A significant advantage for clinicians is that funding is now available for BV in the reuse setting.[4]

The reuse of BV is based on a small data set (n=21; 20 patients CR/PR and 1 patient with SD).[11] The majority of patients achieve a disease response but, regardless of CR or PR, lose response over time and will require allo-SCT.

In the UK, management is polarised and clinicians may favour allo-SCT for consolidation. The challenge is whether patients with mCR should proceed to allo-SCT given reuse is a funded option, and other treatments are becoming immediately available in this setting.

Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

KP also discussed the role of BV as consolidation therapy following ASCT. The AETHERA trial was a phase III randomised, double-blind, placebo-controlled, multicentre study of BV vs placebo in R/R HL patients at risk of progression following ASCT.[10] Following progression 8 patients (15%) in the BV cohort and 73 patients (84%) in the placebo cohort received single agent BV as subsequent therapy.[10]

KP highlighted that, due to current NICE funding, clinicians may wait and use BV to salvage patients who relapse post-ASCT.

Further analysis from the AETHERA study examined subgroups of patients who may benefit further from consolidation therapy.[12] All patients who were pre-ASCT PET negative gained little benefit from BV consolidation therapy. Patients who were pre-ASCT PET negative with extranodal disease at relapse gained some benefit compared to placebo (hazard ratio (HR) 0.378, 95% CI 0.094-1.515). Patients who were PET positive with ≥2 risk factors had the greatest benefit from receiving BV as consolidation therapy (HR 0.448, 95% CI 0.264–0.759).[12,13]

Therapeutic issues: Consolidation post-ASCT setting

- Are we better placed to employ BV to salvage those who relapse post-ASCT, particularly if this now represents reuse?

Can we identify a group for a more targeted strategy?

Targeted treatment in the post-transplant setting

Prof Karl Peggs (KP)

Therapeutic issues: R/R HL post-ASCT setting

- UK practice has generally evolved to favour allograft as consolidation
  - Should a patient achieving mCR with BV proceed directly to an allograft?
  - If not, how many cycles of BV should be given?
  - Is reuse an option if a patient relapses?
- If you aim to allograft if PR, but defer in those attaining mCR:
  - How many cycles should you give before making the decision?
  - What is the balance between conversion of PR to CR, versus progression from PR?
- How does the availability of PD1/PD-L1 inhibitors impact these decisions?

KP... *One of the issues that we face as a clinical community is to work out how best to use agents such as brentuximab vedotin in this post transplant setting. We have two very nice data sets that in themselves give us useful information. The initial pivotal data of the use of BV in ASCT failure, tells us that the agent has activity, that we expect to see nice response rates in patients. The data in comparison in the AETHERA study, show us that if we use BV as a maintenance agent, we will see an advantage in terms of progression free survival.*

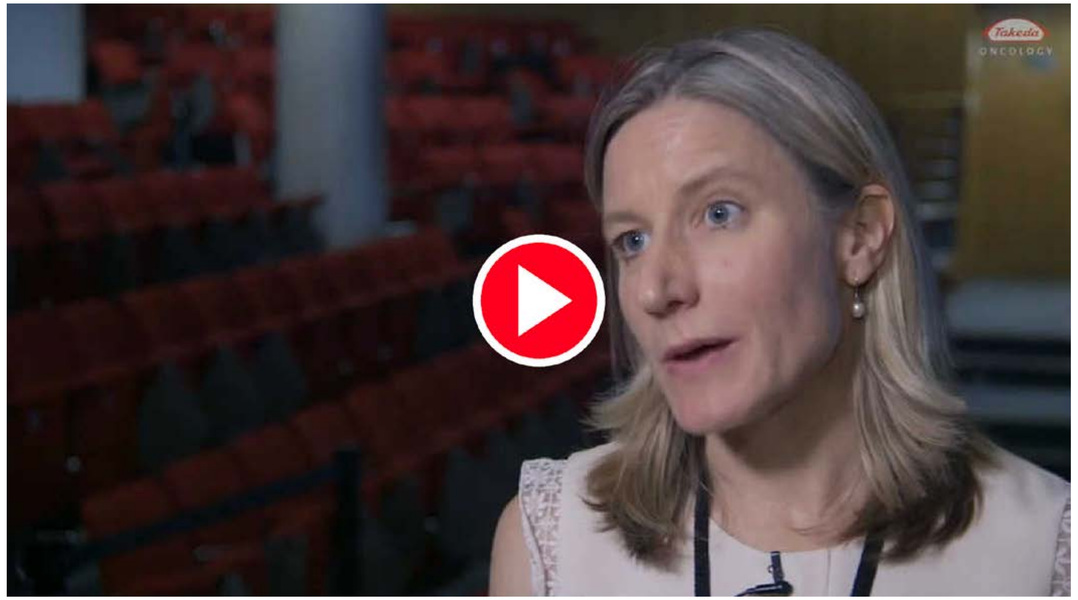
GC... *The particularly interesting thing we discussed was the data around reusing brentuximab vedotin. Now there has been data around reuse of BV in patients for some time but we've not been able to do it, because it's not been reimbursed. Whereas now it's gone through the NICE process, we do now have that option (in specific clinical circumstances).*

What is the optimal sequencing of targeted treatments?

Dr Cathy Burton (CB)

Key takeaways

- Sequencing of treatment in the post-ASCT setting is less straightforward than in the pre-ASCT setting
- The funding of BV reuse post-ASCT provides an additional viable treatment option in this setting as a bridge to allogeneic stem cell transplantation[4]
- It is important for clinicians to have clarity on the planned sequence of treatments and to discuss options with patients
- Recently introduced targeted therapies allow clinicians to provide a more individualised treatment approach
- Patient quality of life is a highly significant consideration for treatment sequencing, especially in patients who have responded, or have stable disease and are not symptomatic



Dr Cathy Burton (CB)

What is the optimal sequencing of targeted treatments?

Dr Cathy Burton (CB)

Clinicians need to have a treatment sequence in mind at the beginning of therapy.

- Treatment is more straight forward in the pre-ASCT setting; patients can receive salvage chemotherapy to achieve mCR, PET negative patients can proceed to transplant, and patients who do not achieve mCR (remain PET positive) can receive BV within licence as second-line salvage to enable a transplant.
- Post-ASCT the sequence needs to be more tailored on a patient-by-patient basis.

What is the optimal sequencing of targeted treatments?

Dr Cathy Burton (CB)

The cases CB discussed illustrate the various treatment options available to clinicians.

The cases presented highlight the need for tailoring the treatment sequence to each individual patient and the important role patient input plays in making treatment decisions.

Case study 1:

CB highlighted the importance of considering patient input into clinical decisions

Case history:

- The patient relapsed with HL after six years and received BV, achieving mCR after three cycles
- Advice was given to receive allo-SCT or continue with further cycles of BV, the patient elected to continue BV due to morbidity associated with allo-SCT
- The patient progressed and went on to receive bendamustine to achieve mCR, enabling bridge to allo-SCT

The faculty noted that a prompt mCR with BV would usually proceed to allo-SCT, but patient input needs to be considered

What is the optimal sequencing of targeted treatments?

Dr Cathy Burton (CB)

Case study 2:

CB highlighted another case study in which patient input influenced the treatment pathway

Case history:

- After initial HL treatment and relapse post-ASCT, the patient opted for active monitoring as they felt well and were not keen for further treatment
- Two years later (in 2014), following further progression, the patient received six cycles of BV and achieved mCR after four cycles
- The patient was advised to proceed to allo-SCT, but chose not to and continued BV treatment, receiving two further cycles
- The patient remained in remission for two years post BV but relapsed in May 2017
- The clinical choice between further chemotherapy, nivolumab or further BV, with the intention of taking the patient to allo-SCT, was considered. BV reuse was chosen as the patient had previously responded well and quickly to BV with a reasonable duration of response

What is the optimal sequencing of targeted treatments?

Dr Cathy Burton (CB)

CB... *The key message is considering what is the most appropriate treatment for an individual patient, but particularly knowing the treatment options, considering carefully the sequence of treatment and, in terms of targeted treatments, whether the reuse of BV or nivolumab is the best treatment for a particular patient.*

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References

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Prescribing information

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):* Safety 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°C8°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