Brentuximab vedotin (Adcetris®) in combination with doxorubicin, vinblastine and dacarbazine for previously untreated CD30+ Stage III or IV Hodgkin lymphoma

General information

Drug description [1]

Brentuximab vedotin (Adcetris®) is a CD30-directed antibody and microtubule inhibitor conjugate.

Indication [2]

Brentuximab vedotin (Adcetris®) is indicated for adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).

Incidence [3]

In Austria, in 2020, a total of 214 persons were newly diagnosed with HL. The age-standardised incidence rate[1] was 2.9 per 100,000 men and 2.0 per 100,000 women.

Current treatment [4]

For the treatment of advanced stage HL, Onkopedia recommends the following:

- Escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone) is considered as standard treatment for advanced stages of HL, followed by radiation therapy of PET-positive residues.
- Meta-analysis data clearly showed an increase in tumour control and OS of this combination therapy as compared with ABVD; hence, ABVD is not recommended as therapy of the first choice.
- Due to the results from the HD15 trial of the German Hodgkin Study Group, therapy cycles could be reduced from eight to six cycles. The reduced therapy was less toxic overall and more effective than the therapy including eight cycles.
- Results of the HD15 trial also showed that patients with PET-negative residual lymphoma had the same good prognosis without consolidative radiation as compared to patients with CR/CRu after chemotherapy.
- In patients with PET-positive residual lymphoma, local irradiation with 30 Gy should be applied. Due to the good prognosis of these patients (PFS at 4 years: 86.2%), stepping up systemic therapy (e.g., high-dose therapy) is not justified.
- Based on data from the HD15 trial, PET-driven therapy is considered as standard treatment for advanced stages of HL: patients who are PET-negative after 2 cycles receive only four cycles of escalated BEACOPP, patients with PET-positive residual lesions after 2 cycles should be treated with a total of six cycles escalated BEACOPP and - if necessary - irradiation of PET-positive residuals.

Regulatory status

EMA [2]

Approval status for this indication: On 14 September 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Adcetris®.

The CHMP adopted an extension to an existing indication to include treatment of Stage III HL:

- Adcetris® is indicated for adult patients with previously untreated CD30+ Stage **III or** IV HL in combination with AVD.

Other indications: Adcetris® is indicated:

- for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.
- for the treatment of adult patients with relapsed or refractory CD30+ HL:
  - following ASCT, or

FDA [1, 5]

Approval status for this indication: On 20 March 2018, the FDA approved brentuximab vedotin (Adcetris®) to treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL) in combination with chemotherapy.

- ✓ Priority review
- ✓ Breakthrough designation

Other indications: Adcetris® is indicated for the treatment of:

- Paediatric patients ≥2 years with previously untreated high-risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.
- Adult patients with cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.
- Adult patients with cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
- Adult patients with previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

[1] European Standard Population 2013.

• following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. ❖ in combination with cyclophosphamide, doxorubicin and prednisone for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL). ❖ for the treatment of adult patients with relapsed or refractory sALCL. ❖ for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy. ✓ **Orphan status**	❖ Adult patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen. ❖ Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy.

Manufacturer

Adcetris® is jointly developed by Seagen and Takeda.

Costs

Adcetris® powder for concentrate for solution for infusion 50 mg = € 3,884.00 (ex-factory price) [6]

Posology [7]

❖ Previously untreated HL
- The recommended dose in combination with chemotherapy (doxorubicin, vinblastine and dacarbazine) is 1.2 mg/kg administered as an IV infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles.
- Primary prophylaxis with growth factor support (G-CSF), beginning with the first dose, is recommended for all adult patients with previously untreated HL receiving combination therapy. Refer to the summary of product characteristics of chemotherapy agents given in combination with Adcetris® for patients with previously untreated HL.

Warnings and precautions [1, 7]

❖ **Progressive multifocal leukoencephalopathy**
- JC virus infection resulting in progressive multifocal leukoencephalopathy and death can occur in patients receiving Adcetris®.

❖ **Peripheral neuropathy**
- Monitor patients for neuropathy and institute dose modifications accordingly.

❖ **Anaphylaxis and infusion reactions**
- If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion.

❖ **Hematologic toxicities**
- Monitor complete blood counts. Monitor for signs of infection. Manage using dose delays and growth factor support.

❖ **Serious infections and opportunistic infections**
- Closely monitor patients for the emergence of bacterial, fungal or viral infections.

❖ **Tumour lysis syndrome**
- Closely monitor patients with rapidly proliferating tumours or high tumour burden.

❖ **Hepatotoxicity**
- Monitor liver enzymes and bilirubin.

❖ **Pulmonary toxicity**
- Monitor patients for new or worsening symptoms.

❖ **Serious dermatologic reactions**
- Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs.

- **Gastrointestinal complications**
  - Monitor patients for new or worsening symptoms.
- **Hyperglycaemia**
  - Monitor patients for new or worsening hyperglycaemia. Manage with anti-hyperglycaemic medications as clinically indicated.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a foetus and to use effective contraception.
- **Pancreatitis**
  - Acute pancreatitis has been observed in patients treated with Adcetris®. Fatal outcomes have been reported.
  - Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Adcetris® should be held for any suspected case of acute pancreatitis.
  - Adcetris® should be discontinued if a diagnosis of acute pancreatitis is confirmed.
- **Febrile neutropenia**
  - Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 10^9/L, fever ≥ 38.5 °C; ref CTCAE v3) has been reported with treatment with Adcetris®. Complete blood counts should be monitored prior to administration of each dose of treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.
  - In combination therapy with AVD or CHP, advanced age was a risk factor for febrile neutropenia.When Adcetris® is administered in combination with AVD or CHP, primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all adult patients regardless of age.
- **Infusion site extravasation**
  - Extravasation during intravenous infusion has occurred. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.
- **Renal and hepatic impairment**
  - There is limited experience in patients with renal and hepatic impairment. Available data indicate that MMAE clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations.
- **CD30+ CTCL**
  - The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides and primary cutaneous anaplastic large cell lymphoma is not clear due to lack of high level evidence. In two single arm phase II studies of Adcetris®, disease activity has been shown in the subtypes Sézary syndrome, lymphomatoid papulosis and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Nevertheless, Adcetris® should be used with caution in other CD30+ CTCL patients after careful consideration of the potential benefit-risk on an individual basis.
- **Sodium content in excipients**
  - This medicinal product contains 13.2 mg sodium per vial, equivalent to 0.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Study characteristics [8-13]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up for PE	Characteristics	Biomarker	Funding	Publication(s)
ECHELON-1, Study C25003 NCT01712490	1,334 (1:1)	**A+AVD** (brentuximab vedotin, 1.2 mg/kg of body weight,	**ABVD** (doxorubicin 25 mg/m², bleomycin 10 U/m², vinblastine 6 mg/m², and dacarbazine	Modified PFS[2]	60.9 months	**ongoing**[3], open-label, international, randomised,	-	Millennium Pharmaceuticals (a wholly owned subsidiary of Takeda Pharmaceutical Company), and Seagen	ECHELON-1 [12]

[2] Defined as the time from randomisation to progression, death, or non-complete response and use of subsequent anticancer therapy) as per the independent review facility.
[3] The ECHELON-1 trial is currently ongoing; the estimated study completion date is January 2026.

		doxorubicin 25 mg/m² of BSA, vinblastine 6 mg/m², and dacarbazine 375 mg/m²) IV on days 1 and 15 of each 28-day cycle for up to 6 cycles	375 mg/m²) IV on days 1 and 15 of each 28-day cycle for up to 6 cycles			phase 3 trial			

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Male or female patients ≥18 years ❖ Treatment-naïve HL patients with Ann Arbor Stage III or IV disease. ❖ Histologically confirmed classical HL according to the current WHO Classification. ❖ ECOG PS ≤2 ❖ Patients must have had bidimensional measurable disease as documented by radiographic technique per the International Working Group Revised Criteria for Response Assessment for Malignant Lymphoma. ❖ Female patients who: • Were postmenopausal for at least 1 year before the screening visit, OR • Were surgically sterile, OR • If they were of childbearing potential, agreed to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of the study drug, OR • Agreed to practice true abstinence, when this was in line with the preferred and usual lifestyle of the subject. ❖ Male patients, even if surgically sterilized who: • Agreed to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR • Agreed to practice true abstinence, when this was in line with the preferred and usual lifestyle of the subject. ❖ Voluntary written consent ❖ Suitable venous access for the study-required blood sampling, including pharmacokinetic sampling. ❖ Clinical laboratory values as specified within 7 days before the first dose of the study drug: • Absolute neutrophil count ≥1,500/µL unless there was known HL marrow involvement. • Platelet count ≥75,000/µL unless there was known HL marrow involvement. • Total bilirubin, <1.5× the ULN unless the elevation was known to be due to Gilbert syndrome.	❖ Nodular lymphocyte predominant HL. ❖ Female patients who were both lactating and breastfeeding or who had a positive serum pregnancy test during the screening period or a positive pregnancy test on Day 1 before first dose of study drug. ❖ Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol. ❖ Known cerebral or meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy. ❖ Symptomatic neurologic disease compromising normal activities of daily living or requiring medications. ❖ Any sensory or motor peripheral neuropathy ❖ Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks before first study drug dose. ❖ Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy within 12 weeks of first study drug dose. ❖ Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin or any component of ABVD. ❖ Known human immunodeficiency virus positive. ❖ Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection. ❖ Diagnosed or treated for another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and had any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type were not excluded if they had undergone complete resection. ❖ Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug: • A left-ventricular ejection fraction <50%. • Myocardial infarction within 2 years of randomisation. • New York Heart Association Class III or IV heart failure.	❖ Male sex: 57% vs. 59% ❖ Median age: 35 vs. 37 years ❖ Age group • <60 years: 87% vs. 85% ≥60 years: 13% vs. 15% ❖ Ann Arbor stage at initial diagnosis: • Stage II: <1% vs. 0 • Stage III: 36% vs. 37% • Stage IV: 64% vs. 63% • Not applicable, unknown, or missing: <1% vs. <1% ❖ International Prognostic Score: • 0–1: 21% vs. 21% • 2–3: 53% vs. 53% • 4–7: 25% vs. 26% ❖ ECOG performance status • 0: 57% vs. 57% • 1: 39% vs. 39% • 2: 4% vs. 4% • Not obtained or missing: 0 vs. <1% ❖ Extranodal involvement at diagnosis • Yes: 62% vs. 62% o 1 extranodal site: 33% vs. 33% o >1 extranodal site: 29% vs. 29% • No: 33% vs. 34% • Unknown or missing: 5% vs. 4% ❖ Patients with any B symptom: 60% vs. 57% ❖ PET-2 status • Positive: 7% vs. 9% • Negative: 89% vs. 86%

[4] For detailed in- and exclusion criteria, please see Supplementary Appendix.

• ALT or AST, <3× ULN. AST and ALT could be elevated up to 5 times the ULN if their elevation could be reasonably ascribed to the presence of HL in liver. • Serum creatinine, <2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance >40 mL/minute. • Haemoglobin, ≥8 g/dL	• Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.	• Unknown or unavailable: 4% vs. 5%

Efficacy (I vs. C)	**Safety** (I vs. C)
Cut-off date for the 5-year analyses: 14 September 2020; median follow-up time was 60.9 months **Estimated 5-year PFS per investigator assessment in the ITT population**: 82.2% (95% CI 79.0–85.0) vs. 75.3% (95% CI, 71.7–78.5); HR 0.68 (95% CI, 0.53–0.87); p=0.0017 **PFS in PET-2-negative patients**: 84.9% (95% CI, 81.7–87.6) vs. 78.9% (95% CI, 75.2–82.1) **PFS in PET-2-positive patients:** 60.6% (95% CI, 45.0–73.1) vs. 45.9% (95% CI, 32.7–58.2) Patients who received at least one **subsequent anticancer therapy**: 20% vs. 24% Patients who had **high-dose chemotherapy plus an autologous HSCT**: 6% vs. 9% **Cutoff date for the OS analysis: 1 June 2021; median follow-up time was 73.0 months** **Number of deaths**: 39 vs. 64 **OS**: HR for death 0.59 (95% CI, 0.40-0.88); p=0.009 **6-year OS estimates**: 93.9% (95% CI, 91.6-95.5) vs. 89.4% (95% CI, 86.6-91.7) **Subgroups**: more favourable estimates of the treatment effect with A+AVD than ABVD C among patients <60 years of age, those with stage IV disease, among those in the high-risk IPS subgroup, and among those in North America; less favourable estimates of the treatment effect with A+AVD than with ABVD among patients ≥60 years of age, among women, and among patients in the low-risk IPS subgroup. **6-year rates of PFS estimates by investigator assessment in the ITT population** (median follow up 72.6 months): 82.3% (95% CI, 79.1-85.0) vs. 74.5% (95% CI, 70.8-77.7); HR 0.68 (95% CI, 0.53-0.86)	**Cut-off date for the 5-year analyses: 14 September 2020; median follow-up time was 60.9 months** **Peripheral neuropathy:** n=443/662 (67%) vs. n=286/659 (43%) **Ongoing peripheral neuropathy at 5 years:** n=127/662 (19%) vs. n=59/659 (9%) **Secondary malignancies:** n=19/662 (3%) vs. n=29/659 (4%) **On-treatment treatment-related deaths[5]:** n=8 vs. n=7

Patient-reported outcomes

According to the study protocol, PRO per EORTC-QLQ-C30, PRO per FACIT-Dyspnea 10, PRO per FACT-Ntx and patient-reported health utility values per EQ-5D were defined as secondary and exploratory endpoints, respectively. Currently, results are not available.

ESMO-MCBS for Haematological Malignancies Version 1.0 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	-	93.9% vs. 89.4%	0.59 (0.40-0.88)	Increase in 5-year survival ≥10% (if >20% patients have reached 5 years OS)	4	-	-	-	4

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear[6]	-	no[7]	unclear[8]	yes[9]	**high risk**

[5] A+AVD group: Cardio-respiratory arrest, histiocytosis haematophagic, respiratory failure, unknown, multiple organ dysfunction syndrome, myocardial infarction, neutropenic sepsis, septic shock (one patient each). ABVD group: Pneumocystis jirovecii pneumonia, pneumonia, cardiac arrest, pulmonary toxicity, pneumonitis, respiratory disorder (one patient each).

[6] The randomisation scheme was generated by the sponsor. Before administration of study drugs, a randomisation number was assigned to each patient. The information about the sequence generation process is insufficient.

[7] ECHELON-1 is an open-label trial.

[8] The trial is currently ongoing; final analysis data is not available yet.

[9] Data were verified and analysed by the sponsors and sponsor statisticians and interpreted by academic authors and representatives of the sponsor; medical writing was supported by funding from the sponsor.

unclear risk		high risk	unclear risk	high risk	

Ongoing trials [16]

NCT number/trial name	Description	Estimated study completion date
NCT01712490/ ECHELON-1	Please see above.	01/2026
NCT03907488	A phase III, randomized study of nivolumab plus AVD or Brentuximab Vedotin plus AVD in patients (≥12 years) with newly diagnosed advanced stage classical HL.	03/2024
NCT02661503/ HD21	HD21 for advanced stages treatment optimization trial in the first-line treatment of advanced stage HL; comparison of 6 cycles of escalated BEACOPP with 6 cycles of BrECADD	09/2025

Available assessments

- In December 2020, CADTH published a "pERC Final Recommendation", a "Final Economic Guidance Report" and a "Final Clinical Guidance Report" for brentuximab vedotin for the treatment of previously untreated patients with stage IV HL in combination with doxorubicin, vinblastine, and dacarbazine [17].
- In June 2019, an efficacy assessment was published by G-BA [18].
- The National Institute for Health Research published "Brentuximab vedotin (Adcetris) for treatment-naïve Hodgkin's Lymphoma" in April 2017 [19].
- No assessments were identified via NICE and ICER.

Other aspects and conclusions

- In September 2023, the **CHMP** adopted an **extension to an existing indication** to include treatment of Stage III HL: Adcetris® is indicated for adult patients with previously untreated CD30+ Stage **III or** IV HL in combination with AVD. On 20 March 2018, the FDA approved brentuximab vedotin (Adcetris®) to treat adult patients with previously untreated stage III or IV cHL in combination with chemotherapy.
- **ECHELON-1** (NCT01712490) is an **ongoing**, international, open-label, randomised, phase 3 trial, assessing the safety and efficacy of front-line A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) versus ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in patients with stage III or IV cHL. Patients aged ≥18 years with an ECOG PS of ≤2, with previously untreated stage III or IV cHL, histologically confirmed according to the current WHO classification were included. Patients with nodular lymphocyte predominant HL, with known cerebral or meningeal disease, including signs or symptoms of PML and a pulmonary diffusion capacity > 25% lower than the normal predicted value were excluded.
- The primary endpoint was **modified PFS**; at a median follow-up of 60.9 months, **5-year PFS was 82.2%** (95% CI 79.0–85.0) with A+AVD **and 75.3%** (95% CI, 71.7–78.5) with ABVD; HR 0.68 (95% CI 0.53–0.87); p=0.0017. **Median PFS** data was not reported.
- Currently, there is **no data available** regarding the **patient-reported outcome endpoints** defined in the study protocol.
- The **ESMO-MCBS** for Haematological Malignancies was applied, resulting in a final adjusted magnitude of clinical benefit of 4.
- The **risk of bias** of ECHELON-1 was considered **high**, which is based on the insufficient information on the sequence generation process, the open-label design of the trial and the participation of the sponsor in data analysis and -interpretation.
- Besides ECHELELON-1, **two further phase 3 trials**, evaluating the efficacy and safety of brentuximab vedotin in patients with stage III and IV HL, were identified.
- Final analysis data of ECHELON-1, including median PFS and PROs data, is required to confirm the efficacy and safety of brentuximab vedotin for this patient population.

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Abbreviations: A+AVD=brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine, ABVD=Adriamycin, Bleomycin, Vinblastin, Dacarbazin, AE=adverse event, AJ=adjustment, ALT=Alanine aminotransferase, ASCT=autologous stem cell transplant, AST=aspartate aminotransferase, BEACOPP=bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, cHL=classical Hodkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CRu=complete responses unconfirmed, EMA=European Medicines Agency, EORTC=European Organization for Research and Treatment of Cancer, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACIT=Functional Assessment of Chronic Illness Therapy, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HL=Hodkin lymphoma, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IPS=International Prognostic Score, ITT=intention-to-treat, IV=intervention, MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PET=positron emission tomography, PFS=progression-free survival, PM=preliminary grade, PTCL=peripheral T-cell lymphoma, QoL=Quality of Life, SAE=serious adverse event, sALCL=systemic anaplastic large cell lymphoma, ST=standard treatment, ULN=upper limit of normal, WHO=World Health Organisation.

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