

Brentuximab vedotin (Adcetris®) with chemotherapy for CD30-positive peripheral T-cell lymphoma (PTCL)

General information [1]

Drug description	Indication
Brentuximab vedotin is an antibody–drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting drug monomethyl auristatin E.	Patients with previously untreated, CD30- positive PTCL; Eligible histologies were limited to ALK-positive systemic anaplastic large cell lymphoma (sALCL) with an IPI score of 2 or higher, ALK-negative sALCL, PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, adult T-cell leukaemia or lymphoma, enteropathy associated T-cell lymphoma, and hepatosplenic T-cell lymphoma

Current treatment [2]

NICE recommends cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy as first-line treatment for people with peripheral T-cell lymphoma.

Regulatory status

EMA [3]	FDA [4]
<p>Approval status for this indication: positive CHMP-opinion on 2020-03-26:</p> <ul style="list-style-type: none"> ❖ Brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated sALCL <p>Other indications:</p> <ul style="list-style-type: none"> ❖ Hodgkin lymphoma (HL) <ul style="list-style-type: none"> ○ indicated for adult patients with previously untreated CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine (AVD) ○ indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT ○ indicated for the treatment of adult patients with relapsed or refractory CD30+ HL: <ul style="list-style-type: none"> • following ASCT, or • following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. ❖ sALCL <ul style="list-style-type: none"> ○ indicated for the treatment of adult patients with relapsed or refractory sALCL ❖ Cutaneous T-cell lymphoma (CTCL) <ul style="list-style-type: none"> ○ indicated for the treatment of adult patients with CD30+ CTCL after at least 1 prior systemic therapy. <p>✓ Orphan status</p> <p>✓ Medicine under additional monitoring</p> <p>✓ Medicine received a conditional marketing authorisation¹</p>	<p>Approval status for this indication: approved:</p> <ul style="list-style-type: none"> ❖ Brentuximab vedotin is indicated for previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with CHP. <p>Other indications:</p> <ul style="list-style-type: none"> ❖ previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine ❖ cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation ❖ 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 ❖ sALCL after failure of at least one prior multi-agent chemotherapy regimen ❖ primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy .

Costs

1 vial of **Adcetris® 50 mg** powder for concentrate for solution for infusion = **€ 3,330.00** (ex-factory price) [5]
 Patients of the ECHOLON-2 trial (A+CHP group) received brentuximab vedotin 1.8 mg/kg intravenously on day 1 of each cycle for a median number of 6.0 treatment cycles.
 Assuming an average body weight of 70 kg, costs for 1 cycle → € 9,990.00 → 6 cycles = € 59,940.00.

Posology [6]

Primary prophylaxis with growth factor support, beginning with the first dose, is recommended for all patients with previously untreated sALCL receiving combination therapy.

Study characteristics [1, 7]

¹ The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine’s benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ECHELON-2 NCT01777152	452	A+CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone)	CHOP	PFS ²	double-blind, double-dummy, randomised, multicentre, multinational, placebo-controlled, active- comparator phase 3 study	CD30	Seattle Genetics Inc, Millennium Pharmaceuticals Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and National Institutes of Health National Cancer Institute Cancer Center	Link
Efficacy (I vs. C) ³							Safety (I vs. C) ⁴	
<p>Median PFS (per IRF for the ITT population): 48.2 months (95% CI 35.2–not evaluable) vs. 20.8 months (95% CI 12.7–47.6); HR 0.71 (95% CI 0.54–0.93), p=0.0110</p> <p>Median PFS (per IRF) for patients with centrally-confirmed sALCL: 55.7 months vs. 54.2 months; HR 0.59 (95% CI 0.42–0.84, p=0.003)</p> <p>3-year PFS: 57.1% (49.9–63.7) vs. 44.4% (37.6–50.9)</p> <p>OS:</p> <ul style="list-style-type: none"> ❖ HR 0.66 (95% CI 0.46–0.95), p=0.0244 ❖ as of the data cut-off date, 124 deaths occurred: 51 (23%) deaths vs. 73 (32%) deaths ❖ after a median follow-up of 42.1 months (95% CI 40.4–43.8), the median OS was not reached for either group. <p>CR rate and proportion of patients who achieved an objective response: statistically significantly higher in the A+CHP group than in the CHOP group (CR rate, p=0.0066; objective response, p=0.0032).</p> <p>Subgroup analysis for patients with locally-diagnosed sALCL:</p> <ul style="list-style-type: none"> ❖ OS: HR 0.54 (95% CI 0.34–0.87), p=0.0096 ❖ CR rate (by IRF) at the end of treatment: 71.0% vs. 53.2%, p=0.0004 ❖ ORR rate (by IRF) at the end of treatment: 87.7% vs. 70.8%, p<0.0001 							<p>Any AEs: n=221/223 (99%) vs. n=221/226 (98%)</p> <p>Grade ≥3 AEs: n=147/223 (66%) vs. n=146/226 (65%)</p> <p>SAEs: n=87/223 (39%) vs. n=87/226 (38%)</p> <p>Discontinuation⁵: n=14/223 (6%) vs. 15/226 (7%)</p> <p>Death⁶: n=7/223 (3%) vs. n=9/226 (4%)</p>	
Risk of bias (study level)								
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	Risk of bias			
yes	yes	yes	unclear ⁷	yes ⁸	low			
							First published: 03/2020 Last updated: 07/2020	

Abbreviations: AE=adverse event, ASCT=autologous stem cell transplant, auto-HSCT=autologous hematopoietic stem cell transplantation, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone, CTCL=cutaneous T-cell lymphoma, EMA=European Medicines Agency, FDA=Food and Drug Administration, HL=Hodgkin lymphoma, HR=hazard ratio, IRF=independent review facility, ITT=intention-to-treat, n=number, SAE=serious adverse event, sALCL=systemic anaplastic large cell lymphoma, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PTCL=peripheral T-cell lymphoma, QoL=quality of life

² according to blinded independent central review (BICR)

³ primary analysis data, trial is ongoing until 08/2020

⁴ primary analysis data, trial is ongoing until 08/2020

⁵ treatment discontinuation due to AEs

⁶ death due to AEs

⁷ primary analysis results reported, trial is currently ongoing

⁸ industry-funded

References:

1. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Volume 393, ISSUE 10168, P229-240, January 19, 2019. (2020-04-07).
2. National Institute for Health Research (NIHR). Brentuximab vedotin in addition to cyclophosphamide, doxorubicin, and prednisolone (CHP) for CD30+ mature T-cell lymphoma [Available from: <http://www.io.nihr.ac.uk/wp-content/uploads/2018/12/8929-Brentuximab-vedotin-for-CD30MTCL-V1.0-DEC2018-NON-CONF.pdf>].
3. European Medicines Agency (EMA). Medicines. Adcetris. [Available from: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/adcetris-o>].
4. U.S. Food and Drug Administration (FDA). Drugs@FDA: FDA-approved Drugs. Adcetris. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125388s100lbl.pdf].
5. Österreichischer Apotheker-Verlag. Warenverzeichnis online. [Available from: <https://warenverzeichnis.apoverlag.at/>].
6. European Medicines Agency (EMA). Adcetris: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_en.pdf].
7. Supplement to: Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2018; published online Dec 4.