Horizon Scanning in Oncology

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

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 89
ISSN online 2076-5940

Horizon Scanning in Oncology

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

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, July 2019

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Lynda McGahan, MSc
Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Nicole Grössmann, MSc
External review: Priv.-Doz. Dr. Nicole Skoetz
Evidence-Based Oncology

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

DSD: Horizon Scanning in Oncology No. 89
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abstract

Introduction

Several peripheral T-cell lymphomas (PTCL) express the tumour necrosis factor (TNF) receptor CD30, conferring cell survival and growth when activated through the NF-κB pathway. Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) comprising an anti-CD30 monoclonal antibody and a microtubule-disrupting agent, monomethyl auristatin E (MMAE). Once bound to CD30 on tumour cells, BV is internalized by endocytosis and the MMAE released into the cytosol disrupts the microtubule network causing cell death

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials.

Results of the ECHELON-2 trial

In the phase III, ECHELON-2 trial, 452 patients with untreated CD30-expressing PTCL were randomised 1:1 to receive BV (1.8 mg/kg IV) plus cyclophosphamide, doxorubicin, and prednisone (CHP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for six or eight 21-day cycles. At a median follow-up of 42.1 months, the median OS was not reached for either group. BV+CHP conferred longer progression-free survival (PFS) than CHOP (PFS: 48.2 months versus 20.8 months), reducing the risk of death or progression by 29%. Greater objective response (OR) and complete remission (CR) rates were reported in BV+CHP patients compared with CHOP (ORR: 83% versus 72%; CRR: 68% versus 56%). Durable OR was achieved at all levels of CD30 expression among BV+CHP recipients, including those with 10% CD30 expression. No clinically meaningful differences in generic or disease-specific quality of life (QoL) scores were observed between groups. Treatment-related AEs of any grade reported in 20% or more patients in the BV+CHP versus the CHOP group were was nausea, peripheral sensory neuropathy, neutropenia, diarrhoea, constipation, alopecia, pyrexia, vomiting, fatigue, and anaemia. Discontinuation due to AEs occurred in 6% of patients in the BV+CHP group and 7% of CHOP patients. AEs leading to death occurred in 3% of patients in the B+CHP group and 4% of patients in the CHOP group.

Conclusion

Overall, ECHELON-2 is the first phase 3, randomised, double-blind, active comparator study to demonstrate that compared with CHOP, BV+CHP increases PFS, OR and CR in previously untreated CD30-positive PTCL patients. While the PFS benefits were generally consistent across subtypes, the study was not powered to compare efficacy between individual histological subtypes and small sample sizes preclude definitively determining the treatment effect in non-systematic ALCL. No clinically meaningful differences were noted in QoL measures. The development of a clinically validated in vitro diagnostic for CD30 expression may ensure the appropriate selection of patients most likely to benefit from BV+CHP therapy. Further studies are needed to better define the efficacy of BV in non-ALCL histologies, optimal dosing to enhance disease control while limiting complications, optimal therapeutic sequence, and use as monotherapy versus in combination with immune checkpoint inhibitors or other immunomodulatory agents.

Table of Contents

List of Tables

1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is brentuximab vedotin?
A0022	Who manufactures brentuximab vedotin?
A0007	What is the target population in this assessment?
A0020	For which indications has brentuximab vedotin received marketing authorisation?
Health problem and current use	
A0002	What is peripheral T-cell lymphoma in the scope of this assessment?
A0004	What is the natural course of peripheral T-cell lymphoma?
A0006	What are the consequences of peripheral T-cell lymphoma for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of peripheral T-cell lymphoma?
A0003	What are the known risk factors for peripheral T-cell lymphoma?
A0024	How is peripheral T-cell lymphoma currently diagnosed according to published guidelines and in practice?
A0025	How is peripheral T-cell lymphoma currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of brentuximab vedotin on mortality?
D0005	How does brentuximab vedotin affect symptoms and findings (severity, frequency) of peripheral T-cell lymphoma?
D0006	How does brentuximab vedotin affect progression (or recurrence) of peripheral T-cell lymphoma?
D0011	What is the effect of brentuximab vedotin on patients' body functions?
D0012	What is the effect of brentuximab vedotin on generic health-related quality of life?
D0013	What is the effect of brentuximab vedotin on disease-specific quality of life?
Safety	
C0008	How safe is brentuximab vedotin in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying brentuximab vedotin?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of brentuximab vedotin?
A0021	What is the reimbursement status of brentuximab vedotin?

2 Drug description

Generic/Brand name/ATC code:

Brentuximab vedotin/Adcetris®/L01XC12

B0001: What is brentuximab vedotin?

anti-CD30 antibody conjugated with MMAE

Several peripheral T-cell lymphomas (PTCL) express the tumour necrosis factor (TNF) receptor CD30 that, upon activation through the NF-κB pathway, confers cell growth and survival. Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) comprising anti-CD30 monoclonal antibody and a microtubule-disrupting agent, monomethyl auristatin E (MMAE). Once bound to CD30 on tumour cells, BV is internalized by endocytosis and the MMAE released into the cytosol disrupts the microtubule network causing cell death [2, 3].

BV (1.8 mg/kg IV) every 3 weeks + CHP for 6–8 cycles

BV is available as single-use vials of 50 mg powder for reconstitution (5 mg/mL). It is administered as a 30-minute intravenous infusion (IV) at a dose of 1.8 mg/kg every three weeks, in combination with cyclophosphamide, doxorubicin and prednisone (CHP) chemotherapy, for six to eight cycles. Previously untreated PTCL patients receive granulocyte colony-stimulating factor (G-CSF) prior to their first cycle of BV+CHP [3, 4].

monitor AEs if given concomitantly with CYP3A inhibitors, avoid bleomycin; reduce or discontinue for safety/tolerability

Patients should be monitored for adverse events (AEs) when BV is given concomitantly with strong CYP3A inhibitors. BV is contraindicated with concomitant bleomycin due to pulmonary toxicity. Dose reduction may be necessary for patients with mild hepatic impairment, grade 2 motor neuropathy or grade 3 sensory neuropathy. BV is not for use in patients with severe renal or hepatic impairment and should be discontinued in patients with grade ≥3 motor neuropathy or progressive multifocal leukoencephalopathy (PMJ) [3].

A0022: Who manufactures brentuximab vedotin?

Seattle Genetics, Inc in collaboration with Takeda Pharmaceutical Company

3 Indication

A0007: What is the target population in this assessment?

previously untreated CD30-positive PTCL

Brentuximab vedotin (Adcetris®) is indicated, in combination with chemotherapy, for previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing PTCLs, including angioimmunoblastic T-cell lymphoma (AITL) and PTCL not otherwise specified (PTCL-NOS) [3].

4 Current regulatory status

A0020: For which indications has brentuximab vedotin received marketing authorisation?

FDA: licensed second-line for HL and sALCL from August 2011-2015

In August 2011, the US Food and Drug Administration (FDA) granted accelerated approval of BV for the treatment of Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or two prior multi-agent chemotherapy regimens in non-eligible ASCT candidates; and for sALCL after failure of at least one prior multi-agent chemotherapy. Approvals were based on the objective response rates (ORR) reported in two single-arm studies involving 102 HL patients and 58 sALCL patients [5, 6]. In August 2015, BV was approved for the treatment of patients with HL at high risk of relapse or progression post-ASCT based on progression-free survival (PFS) data from the phase 3 AETHERA trial involving 329 patients [7]. The FDA expanded approval of BV as first-line treatment for stage III or IV HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy in March 2018. Approval was based on PFS data from the open-label, phase 3 ECHELON-1 study involving 1,334 patients [8, 9].

FDA: expanded first-line in combination with AVD for stage III/IV HL in March 2018

FDA: licensed second-line for CTCL or CD30-expressing MF in November 2017

BV was granted FDA breakthrough therapy designation for the treatment of patients with primary cutaneous anaplastic large cell lymphoma (CTCL) or CD30-expressing mycosis fungoides (MF) following prior systemic therapy in November 2017. The approval was based on the ORR reported in the phase 3, ALCANZA trial involving 128 CTCL and CD30-expressing MF patients [9-12].

FDA: expanded first-line in combination with CHP for sALCL or CD30-expressing PTCL in November 2018

In November 2018, the FDA approved BV in combination with CHP chemotherapy for previously untreated sALCL or other CD30-expressing PTCL, including AITL and PTCL-NOS. Under the Real-Time Oncology Review Pilot Program, approval occurred less than two weeks following the submission of PFS and overall survival (OS) data from the phase 3 ECHELON-2 study involving 452 patients [3, 4, 13].

EMA: first-line in combination with AVD for CD30-positive stage IV HL; second-line for CD30-positive CTCL, sALCL, r/r HL or patients at risk of relapse/progression post-ASCT from 2012-2018

BV received marketing authorisation by the European Medicine Agency (EMA) in October 2012, and is approved for the treatment of patients with relapsed or refractory (r/r) CD30-positive HL or sALCL, CD30-positive HL at increased risk of relapse or progression following ASCT, and CD30-positive CTCL following systemic therapy. In December 2018, the marketing authorisation of BV was extended to include the treatment of previously untreated CD30-positive stage IV HL in combination with AVD [9, 14]. BV is not currently indicated as first-line therapy for sALCL or other CD30-epressing PTCL in Europe [15].

5 Burden of disease

A0002: What is peripheral T-cell lymphoma?

PTCL: heterogeneous group of T-cell NHL

Peripheral T-cell lymphoma (PTCL), a rare hematologic malignancy that develops from mature T-cells and natural killer (NK cells), accounts for approximately 10–15% of non-Hodgkin lymphomas (NHL). While approximately 28 histological subtypes have been identified, primary nodal PTCL accounts for more than 80% of European cases [16, 17]. It is commonly classified as PTCL-not otherwise specified (PTCL-NOS) (34%), angioimmunoblastic T-cell lymphoma (AITL) (28%), and anaplastic large cell lymphoma (ALCL) that subdivides as anaplastic lymphoma kinase (ALK)-positive and ALK-negative (6% and 9% of cases, respectively) [17]. Accounting for most PTCLs, PTCL-NOS represents a heterogeneous group of many not yet identified PTCL subtypes with no consistent immunophenotypic, genetic or clinical features [17]. The cellular membrane protein CD30 is strongly expressed on neoplasms but not on most normal cells, allowing for targeting by ADC-based BV therapy [18]. CD30 is uniformly expressed in ALCL while expression by other PTCL subtypes ranges from 43% to 57% [19].

80% are primary nodal PTCL: 34% PTCL-NOS, 28% AITL, 6% ALK-positive and 9% ALK-negative ALCL

CD30 expression: uniform in ALCL; 43–57 % other subtypes

A0004: What is the natural course of peripheral T-cell lymphoma?

staged I–IV by invasiveness

PTCL develops when mature white blood cells, known as T-cells, undergo aberrant cell growth in lymphoid tissues outside of the bone marrow, such as the thymus, forming tumours in the mediastinum or lymphoid tissues. Virtually all cases of ALK-positive ALCL are due to genetic translocations involving ALK [20]. To facilitate treatment, NHL is staged from I through IV based on tumour location. Stage I cancer occurs in a single lymph node, region, organ, or site; stage II occurs in two or more lymph nodes on the same side of the diaphragm; stage III involves lymph node regions on both sides of the diaphragm, with or without partial involvement of an extranodal organ or site above or below the diaphragm; and stage IV has metastasized to bone marrow, spleen, liver, digestive system, skin or lungs [21].

malignant T-cells infiltrate bone marrow, liver, spleen, digestive system or skin

A0006: What are the consequences of peripheral T-cell lymphoma for the society?

50–70% present with stage III/IV advanced disease

Lymphoma is the most common blood cancer in Europe, and the fifth most common cancer after breast, lung, bowel and prostate cancers. Europe accounts for nearly 18–19% of all lymphoma mortality worldwide [22]. Comprising 5–10% of all lymphoid neoplasms, with the exception of ALK-positive ALCL and localized extranodal NK/T-cell lymphoma, PTCL is among the more aggressive lymphomas with poor prognosis [23]. Approximately 50% to 70% of patients present with stage III or IV advanced disease with peripheral, including mediastinal, and or abdominal lymphadenopathy. Five-year OS for patients with ALK-negative ALCL, PTCL-NOS, and AITL are approximately 34%, 35%, and 36%, respectively [24].

5-year OS: 35%

A0023: How many people belong to the target population?

NHL incidence: 7.6 in 100,000 people/year

PTCL incidence: 133–200 Austrians per year

PTCL accounts for approximately 10–15% of all NHL. The age standardized incidence rate for NHL in the European Standard Population was 15.5 per 100,000 persons per year in 2013 [25]. In Austria, 726 men and 607 women were diagnosed with NHL in 2016; and 354 men and 293 women died due to NHL (7.6 per 100,000 persons per year) [25]. Assuming this, approximately 133 to 200 Austrians may be

diagnosed with PTCL each year. PTCL is twice as common in men than women, and has a median age at diagnosis of 60 years [26].

A0005: What are the symptoms and the burden of disease or peripheral T-cell lymphoma?

PTCL symptoms: enlarged lymph nodes, fever, night sweats, weight loss, fatigue, dyspnoea, and skin rash

Symptoms of PTCL include enlarged lymph nodes in the neck, armpit or groin. Approximately 35% of patients experience B symptoms involving recurrent fever, night sweats, and weight loss. Other symptoms include loss of appetite, fatigue, dyspnoea, and skin rash. Most PTCL patients present with generalized lyphadenopathy, 38% have nodal disease only and 49% have nodal and extranodal disease. Hepatomegaly and splenomegaly occur in 17% and 24% of patients, respectively. Bone marrow involvement occurs in 20% of cases, as well as lactate dehydrogenase (LDH) elevation (37%), anaemia (27%) and thrombocytopenia (10%) [20, 26].

A0003: What are the known risk factors for peripheral T-cell lymphoma?

risk factors: autoimmune diseases, HIV/AIDS, HTLV-1, EBV, immunosuppressant's and pesticides

Risk factors for NHL include autoimmune diseases, human immunodeficiency virus – acquired immunodeficiency syndrome (HIV/AIDS), infection with human T-lymphotropic virus (HTLV-1) or Epstein-Barr virus (EBV), immunosuppressant medications, solvents, pesticides and fertilizers. Coeliac disease, psoriasis, and breast implants have been associated with an increased risk of ALCL [17, 27, 28].

IPI: risk of relapse

The International Prognostic Index (IPI) uses known risk factors to predict OS and guide clinical management. Age, stage III or IV disease, more than one lymph node involvement, elevated serum LDH and performance status are used to predict the risk of relapse [21].

A0024: How is peripheral T-cell lymphoma currently diagnosed according to published guidelines and in practice?

diagnosis: excisional lymph node biopsy; histology, immunophenotype, genetic features, CD30 expression

blood tests, CT, PET, MRI, BM biopsy

PTCL is diagnosed by a haematopathologist based on excisional lymph node biopsy. Classification is difficult due to the wide spectrum of morphologic features and lack of robust immunohistochemical markers. According to the World Health Organization classification (WHO), distinction among PTCL subtypes requires integration of the clinical features, morphology, immunophenotype, and genetics. Histologic examination of the biopsy usually shows atypical lymphoid cells, loss of mature T-cell antigens CD5 or CD7, clonal T-cell receptor gene rearrangements, and a proportion of PTCL express CD30 [17]. Gene expression profiling distinguishes PTCL-NOS from ALK-negative ALCL and AITL [23]. Additional diagnostic tests, including blood tests, computerized tomography (CT) scans, positron emission tomography (PET) scans, magnetic resonance imaging (MRI) and bone marrow biopsy may be useful to confirm diagnosis. Approximately 14% of PTCL cases are stage I, 17% are stage II, 26% are stage III, and 43% are stage IV at diagnosis [26].

6 Current treatment

A0025: How is peripheral T-cell lymphoma currently managed according to published guidelines and in practice?

no consensus regarding optimal therapy; anthracycline-based chemotherapy

PTCL are a heterogeneous group of mature, aggressive T-cell lymphomas and there is no general consensus regarding the optimal treatment regimen. Patients are stratified based on tumour expression of CD30, and are encouraged to participate in clinical trials. Newly diagnosed PTCL patients are typically treated with anthracycline-based chemotherapy regimens [21, 26]:

first-line: CHOP, CHEOP, EPOCH, hyper-CVAD, ASCT or radiotherapy as consolidation

- Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for patients >60 years of age or less medically fit
- Cyclophosphamide, hydroxydoxorubicin, vincristine, etoposide and prednisone (CHEOP) for patients ≤60 years of age
- Etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydoxorubicin (EPOCH)
- Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD)
- ASCT or radiation therapy may be used as consolidation depending on the lymphoma subtype.

7 Evidence

systematic literature search in 5 databases: 103 hits

A literature search was conducted on 19 April 2019 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "brentuximab vedotin", "Adcetris", "peripheral T-cell lymphoma", "PTCLs" and "CD30 positive". The manufacturer was also contacted and submitted 13 references, five of which had not already been identified by systematic literature search [29-33]. A manual search identified two statistical reports [22, 25], one FDA label [3], two EMA marketing authorization documents [14, 15], two clinical guidance documents [17, 26], two clinical trial documents [7, 8], and a cost document [34].

manual search: 15 additional references

overall: 118 references included: 2 studies

Overall, 118 references were identified. Included in this reported are:

- ECHELON-2, phase III [3, 4, 29, 30, 32, 35]
- Frontline BV with CHP for CD30-expressing PTCL, phase I [36, 37]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [38]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

external validity

The external validity of the included trials was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting [39].

ESMO-MCBS could not be assessed

The evaluation of the magnitude of "meaningful clinically benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was not applied, since it can only be used for the evaluation of solid tumour drugs [40].

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence, and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

ECHELON-2: BV+CHP versus CHOP for CD30-positive PTCL

ECHELON-2 (NCT02165397) is a multicentre, double-blind, double-dummy, randomised, placebo-controlled, interventional phase III trial involving 452 patients with previously untreated sALCL and CD30-expressing PTCL [4]. The study was designed to compare the safety and efficacy of BV+CHP versus CHOP for the treatment of CD30-positive PTCL using a double-dummy method of blinding where both treatment groups received a placebo. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved all patients who received any amount of BV or any component of CHOP.

ITT (n = 452): stratified by histological subtype and baseline IPI score

Eligible patients were 18 years or older, with newly diagnosed, centrally-confirmed CD30-positive (≥10% of cells) PTCL, measureable disease of 1.5 cm by CT, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Histologies were limited to ALK-positive sALCL (IPI ≥2), ALK-negative sALCL, PTCL-NOS, AITL, adult T-cell leukaemia or lymphoma (ATLL), enteropathy associated with T-cell lymphoma and hepatosplenic T-cell lymphoma. Patients were excluded if they had a history of another primary invasive cancer, haematological malignancy or previous treatment with BV. Study participants were stratified by histological subtype according to local pathology assessment (ALK-positive sALCL versus all other histologies, and baseline IPI score (0–1 versus 2–3 versus 4–5).

1.8 mg/kg IV BV+CHP versus placebo+CHOP

Patients were randomised 1:1 to BV+CHP or CHOP for six or eight 21-day cycles. All patients received cyclophosphamide (750 mg/m^2 IV) and doxorubicin (50 mg/m^2 IV) on day 1, and prednisone (100 mg once daily) on days 1 to 5 of each cycle, with either BV (1.8 mg/kg) and placebo vincristine (IV) (BV+CHP group) or vincristine (1.4 mg/m^2) and placebo BV (IV) (CHOP group) on day 1 of each cycle. Patients received granulocyte colony-stimulating factor (G-CSF) prior to their first BV+CHP cycle [35]. BV was reduced to a dose of 1.2 mg/kg for patients with mild hepatic impairment, grade 2 motor neuropathy or grade 3 sensory neuropathy; and discontinued in those with grade ≥3 motor neuropathy [3, 35]. Approximately 89% of BV+CHP patients and 81% of CHOP patients received six or more cycles. The median relative dose intensity was 99.2% (interquartile range (IQR) 93.6–100.0) for BV in the BV+CHP group and 99.1% (IQR 95.9–102.3) for vincristine in the CHOP group. Consolidative stem cell transplant or radiotherapy was permitted following treatment at the investigators' discretion [4].

89% of BV+CHP and 81% of CHOP patients received >6 cycles

death/progression at data cut-off: 219

Assuming a median PFS of 23.9 months for the BV+CHP group and 16.5 months for the CHOP group, an estimated 238 PFS events would give the trial 80% power to detect a hazard ratio (HR) for disease progression or death of 0.6895 at a one-sided significance of 0.025. Patients were enrolled between January 2013 and November 2016; by the data cut-off date for primary analysis, 219 PFS events had occurred. Excluding stem cell transplantation or radiotherapy for consolidation of response to initial therapy, 59 (26% of) BV+CHP patients and 94 (42% of) CHOP patients received subsequent anticancer therapies for residual or progressive disease. Approximately 23 (10% of) BV+CHP patients and 49 (22% of) CHOP patients received BV-containing subsequent therapy.

10% of BV+CHP and 22% of CHOP patients received subsequent therapy containing BV

primary endpoint: BICR-assessed PFS

secondary endpoints: BICR-assessed PFS for patients with sALCL, ORR, CRR, OS and safety

exploratory endpoint: relationship between CD30 expression, OR and DOR

The primary endpoint of PFS, defined as the time from randomisation until progression, subsequent anticancer chemotherapy or death, was assessed by blinded independent central review (BICR). Secondary endpoints were BICR-assessed PFS for patients with sALCL, ORR, complete remission rate (CRR), OS and safety. Exploratory analyses examined the relationship between CD30 expression, overall response (OR) and duration of response (DOR) [29]. Lymphoma response and progression were assessed according to the 2007 Revised Response Criteria for Malignant Lymphoma. Radiographical evaluations were submitted to BICR for masked review. CT and PET scans were performed at screening, after cycle 4, at the end of treatment, at 9, 12, 15, 18, 21 and 24 months, and every 6 months thereafter until progression or death. Safety outcomes were defined according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events, (CTCAE) version 4.03.

ITT: mean age 58 years, 63% male, 80% stage III/IV, 78% IPI ≥2

histology: 70% sALCL, 16% PTCL-NOS, 12% AITL, 2% ATLL, and 1% EATL

The ITT population (n = 452) had a median age of 58 years (range 45–67), 63% were male, 62% were Caucasian, 27% had stage 3 disease, 53% had stage 4 disease, and 78% had IPI ≥2. The population was comprised of 70% sALCL (48% ALK-negative, 22% ALK-positive), 16% PTCL-NOS, 12% AITL, 2% adult T-cell leukaemia or lymphoma (ATLL), and 1% enteropathy-associated T-cell lymphoma (EATL). Detailed patient characteristics including inclusion- and exclusion criteria can be found in **Fehler! Verweisquelle konnte nicht gefunden werden.** and study quality is described in **Fehler! Verweisquelle konnte nicht gefunden werden.** of the appendix, respectively. Clinical efficacy data are presented in Table 1 and AEs are listed in Table 2.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of brentuximab vedotin on mortality?

By the cut-off date for the primary analysis, 124 deaths had occurred; 51 (23%) in the BV+CHP group and 73 (32%) in the CHOP group. After a median follow-up of 42.1 months (95% CI 40.4–43.8), the median OS was not reached for either group. The 75th percentile OS was not reached for the BV+CHP group but was 17.5 months for the CHOP group. BV+CHP reduced the risk of death by 34% compared with CHOP (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.46–0.95; p = 0.0244). The OS benefit of BV+CHP over CHOP was consistent across histological subtypes based on the overlapping of confidence intervals with those of the ITT population [4, 35].

median OS: not reached in either group

75% percentile OS:
BV+CHP: not reached
CHOP: 17.5 months

OS benefit consistent across subtypes

D0006: How does brentuximab vedotin affect progression (or recurrence) of peripheral T-cell lymphoma?

At a median follow-up of 36.2 months, the primary endpoint of BICR-assessed median PFS was 48.2 months (95% CI 35.2–not estimable [NE]) in the BV+CHP group versus 20.8 months (95% CI 12.7–47.6) in the CHOP group (HR 0.71, 95% CI 0.54–0.93; p = 0.0110). The 3-year PFS was 57.1% (95% CI 49.9–63.7) for the BV+CHP group versus 44.4% (95% CI 37.6–50.9) for the CHOP group [4, 35].

median PFS:
BV+CHP: 48.2 months
CHOP: 20.8 months

3-year PFS:
BV+CHP: 57.1%
CHOP: 44.4%

Pre-specified analyses of PFS were similar to those of the primary analysis of PFS. The HR for BICR-assessed PFS for which consolidative stem cell transplantation or consolidative radiotherapy was censored was 0.71 (95% CI 0.53–0.94; p = 0.017) [4, 29]. BICR-assessed PFS for sALCL patients was consistent with results of the primary analysis (HR 0.59, 95% CI 0.42–0.84; p = 0.0031). The PFS analyses by subtype were generally consistent with the overall study results. ALK-positive sALCL had the lowest HR, ALK-negative sALCL, and PCL-NOS were similar to the ITT population, and AITL was above unity. However, the study was not powered to compare efficacy between individual histological subtypes [4].

PFS benefit generally consistent across histological subtypes

D0005: How does brentuximab vedotin affect symptoms and findings (severity, frequency) of peripheral T-cell lymphoma?

The secondary endpoint of BICR-assessed ORR in the ITT population was 83% (95% CI 77.7–87.8) in the BV+CHP group and 72% (95% CI 65.8–77.9) in the CHOP group (response rate difference [RRD] 11.1, 95% CI 3.4–18.7; p = 0.0032). Complete remission was reported in 68% (95% CI 61.2–73.7) of BV+CHP recipients and 56% (95% CI 49.0–62.3) of CHOP recipients (RRD 11.9, 95% CI 3.1–20.8; p = 0.0066). CRR and DOR in patients with AITL (p = 0.84, p = 0.30, respectively) and PTCL-NOS (p = 0.44, p = 0.90, respectively) were independent of the level of CD30 expression [30]. Durable OR was achieved at all levels of CD30 expression among BV+CHP recipients, including those with CD30 expression of 10% [29].

ORR ITT:
BV+CHP: 83%
CHOP: 72%

durable response at all levels of CD30 expression

CRR:
BV+CHP: 68%
CHOP: 56%

Excluding consolidation therapy for initial treatment, 26% of BV+CHP patients and 42% of CHOP patients received subsequent anticancer therapies for residual or progressive disease; 10% of the BV+CHP group and 22% of the CHOP group received subsequent therapy containing BV [4].

D0011: What is the effect of brentuximab vedotin on patients' body functions?

peripheral neuropathy, anaphylaxis, infusion reactions, infections, GI complications, TLS, SJS, and toxicities of the blood, liver, lung, and foetus

BV may cause peripheral neuropathy, anaphylaxis, infusion reactions, serious infections, tumour lysis syndrome (TLS), dermatologic reactions, gastrointestinal (GI) complications, and toxicities of the blood, liver, lung, embryo or foetus [3]. Approximately 52% of BV+CHP-treated patients experienced new or worsening peripheral neuropathy; 94% sensory and 16% motor, with a median onset of 2 months (range, <1–5) and a median time to improvement of 4 months (range, 0–45) [4]. Patients should be monitored for symptoms of neuropathy such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, burning, neuropathic pain or weakness. Infusions may be interrupted or discontinued in the case of infusion reaction or anaphylaxis.

monitor: CBC, liver enzymes, and bilirubin

prophylactic: G-CSF prior to BV+CHP

Serious febrile neutropenia, grade 3 or 4 thrombocytopenia may occur with BV. Patients require G-CSF prophylaxis prior to starting their first BV+CHP cycle, and complete blood count (CBC) monitoring prior to each BV dose. Liver enzymes and bilirubin should be checked periodically for hepatotoxicity. Patients with highly proliferating tumours should be monitored for tumour lysis syndrome; and those with new-onset central nervous system abnormalities or epidermal necrosis should discontinue BV in the case of progressive multifocal leukoencephalopathy (PML) or Stevens-Johnson syndrome (SJS). BV may cause embryo-foetal harm based on its mechanism of action. Females are advised to avoid pregnancy during BV treatment and for at least six months after the final dose.

D0012: What is the effect of brentuximab vedotin on generic health-related quality of life?

generic health-related QoL: no clinically meaningful difference in mean change in EQ-5D between groups

No clinically meaningful differences were noted in the mean change in EQ-5D from baseline over time between groups [29].

D0013: What is the effect of brentuximab vedotin on disease-specific quality of life?

disease-specific QoL: no clinically meaningful differences in functional, or global health scores or symptoms between groups

At baseline, the mean European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) functional, symptom, and global health scores were lower in the BV+CHP than the CHOP group. During treatment, the scores improved in both groups and returned to near normal values in long-term follow-up. No clinically meaningful differences were observed in the functional and global health scores between groups. With the exception of diarrhoea at cycle seven, none of the differences in the other symptom scores across cycles were clinically meaningful based on the published minimally important difference (MID) of ten. No clinically meaningful differences were found in the mean change in the Functional Assessment of Cancer Treatment Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) subscale scores between treatment groups during treatment [29].

Table 1: Efficacy results of ECHELON-2 [3, 4, 29, 32, 35]

Descriptive statistics and estimate variability	**Treatment group**	**BV+CHP (n = 226)**	**CHOP (n = 226)**
	Deaths, n (%) OS, m (95% CI)	51 (23) NR (NR–NR)	73 (32) NR (54.2–NR)
	PFS events, n (%) ITT (n = 452) BICR-assessed median PFS, m (95% CI) ITT 36 m PFS, m (95% CI) ITT Events Death Subsequent anticancer chemotherapy for residual or progression	95 (42) 48.2 (35.2–NR) 57.1 (49.9–63.7) 13 (6) 11 (5)	124 (55) 20.8 (12.7–47.6) 44.4 (37.6–50.9) 17 (8) 21 (9)
	PFS events, n (%) sALCL (n = 314) BICR-assessed median PFS, m (95% CI) sALCL	56 (34) 55.7 (48.2–NR)	73 (48) 54.2 (13.4–NE)
	ORR, % (95% CI), p-value	83 (78–88)	72 (66–78)
	CRR, % (95% CI), p-value	68 (61–74)	56 (49–62)
Effect estimate per comparison	*Comparison groups*	BV+CHP versus CHOP	
	BICR-assessed PFS (n = 452) (primary endpoint)	HR	0.71
		95% CI	0.54–0.93
		Log-rank test p-value	0.011
	PFS, sALCL (subgroup analysis, n = 314)	HR	0.59
		95% CI	0.42–0.84
		Log-rank test p-value	0.003
	PFS, ALK-positive sALCL (subgroup analysis, n = 98)	HR	0.29
		95% CI	0.11–0.79
		Log-rank test p-value	NA
	PFS, ALK-negative sALCL (subgroup analysis, n = 218)	HR	0.65
		95% CI	0.44–0.95
		Log-rank test p-value	NA
	PFS, AITL (subgroup analysis, n = 54)	HR	1.40
		95% CI	0.64–3.07
		Log-rank test p-value	NA
	PFS, PTCL-NOS (subgroup analysis, n = 72)	HR	0.75
		95% CI	0.41–1.37
		Log-rank test p-value	NA
	OS (n = 452) (secondary endpoint)	HR	0.66
		95% CI	0.46–0.95
		Log-rank test p-value	0.024
	Mean change in EQ-5D from baseline	Difference between groups	No meaningful difference
	EORTC QLQ-30 functional and global scores	Difference between groups	No meaningful difference
	Mean change in FACT/GOG-NTX	Difference between groups	No meaningful difference

Abbreviations: ALK = anaplastic lymphoma kinase, AITL = angioimmunoblastic T-cell lymphoma; BICR = blinded independent central review; CI = confidence interval; CRR = complete remission rate; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT/GOG-NTX = Functional Assessment of Cancer Treatment Gynecologic Oncology Group-Neurotoxicity; HR = hazard ratio; m = months; n = number; NA = not available; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; sALCL = systemic anaplastic large cell lymphoma

7.2.2 Safety

C0008: How safe is brentuximab vedotin in relation to the comparator(s)?

common AEs: nausea, peripheral neuropathy, diarrhoea, alopecia, pyrexia, vomiting, fatigue, and anaemia

In the safety population (n = 449), the most common AEs of any grade occurring in ≥20% of patients in the safety population, and more commonly reported in the BV+CHP than CHOP groups, respectively included nausea (46% versus 38%), peripheral sensory neuropathy (45% versus 41%), diarrhoea (38% versus 20%), alopecia (26% versus 25%), pyrexia (26% versus 19%), vomiting (26% versus 17%), fatigue (24% versus 20%) and anaemia (21% versus 16%). Approximately 52% BV+CHP patients and 55% of CHOP patients reported peripheral neuropathy, of which 50% and 64%, respectively, resolved within a median of 17 weeks. Constipation (29% versus 30%) was less commonly reported in BV+CHP than CHOP recipients [4].

common grade ≥3 AEs: neutropenia, infections, and peripheral neuropathy

Grade ≥3 AEs and SAEs were similar between groups (66% versus 65%, 39% versus 38%, BV+CHP versus CHOP groups, respectively). The incidence of grade ≥3 neutropenia was similar between groups (38% versus 38%, BV+CHP versus CHOP, respectively), and lower in patients receiving primary prophylaxis with G-CSF (13% versus 13%, G-CSF with BV+CHP or CHOP, respectively) [35]. Febrile neutropenia was reported in 18% of BV+CHP recipients and 15% of CHOP recipients. Grade ≥3 infections were reported in 19% of patients in the BV+CHP group and 14% of patients in the CHOP group. Approximately two BV+CHP recipients and one CHOP recipient experienced ongoing grade 3 peripheral neuropathy at the last follow-up. AEs that resulted in death occurred in seven (3% of) BV+CHP patients and nine (4% of) CHOP patients [4].

deaths due to AEs: BV+CHP: 3% CHOP: 4%

C0002: Are the harms related to dosage or frequency of applying brentuximab vedotin?

6% discontinued, 9% reduced dose, and 25% delayed BV+CHP due to AEs: peripheral neuropathy and infection

The median duration of treatment (DOT) was 18.1 months (range 3.0–34.0) for BV+CHP and 18.0 months (range 3.0–31.0) for CHOP. Patients in both groups received a median of six treatment cycles (range 1–8) [35]. SAEs occurring in >2% of BV+CHP recipients included febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), and sepsis (3%). In the BV+CHP group, AEs leading to dose delays occurred in 25% of patients, while 9% experienced AEs requiring dose reduction, primarily due to peripheral neuropathy. Approximately 6% of BV+CHP recipients and 7% of CHOP recipients discontinued treatment due to AEs, most commonly from peripheral neuropathy and infection [3, 4].

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of brentuximab vedotin?

susceptibles: elderly, hepatic or renal impairment

BV is not advised for use in patients with severe hepatic or renal impairment [3]. Patients with a history of another primary invasive cancer, haematological malignancy, peripheral neuropathy, symptomatic cardiac disease, or active infection were excluded from the trial population. Study participants had a median age of 58 years (range 44–67) with a good performance status (ECOG 0–1) and an IPI score of ≤3 [4]. Approximately 31% of BV+CHP-treated patients were older than 65 years of age. Among older patients, 74% had grade

common AEs in elderly: febrile neutropenia

≥3 AE and 49% had SAE. Of the patients less than 65 years of age, 62% experienced grade ≥3 AE and 33% had SAE. Febrile neutropenia occurred in 29% of patients older than 65 years of age and 14% of those less than 65 years of age [3].

BV may cause embryo-foetal harm

BV may cause embryo-foetal harm and potential for SAEs in nursing infants. Females are advised that breastfeeding is not recommended during BV+CHP treatment. Males and females are advised to use effective contraception during BV+CHP treatment and for at least six months following their last dose.

Table 2: Most frequent adverse events in ≥20% of the safety population [4]

Adverse Event (according to MedDRA version 21.0 and CTCAE version 4.03)	**B+CHP** (n = 223)		**CHOP** (n = 226)	
≥20% of patients	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Any AE	221 (99)		221 (98)	
Grade ≥ 3 AE	147 (66)		146 (65)	
SAE	87 (39)		87 (38)	
Discontinued due to AE	14 (6)		15 (7)	
Deaths due to AE	7 (3%)		9 (4)	
Nausea	103 (46)	5 (2)	87 (38)	4 (2)
Peripheral sensory neuropathy	110 (45)	8 (4)	92 (41)	6 (3)
Neutropenia	85 (38)	77 (35)	85 (38)	76 (34)
Diarrhoea	85 (38)	13 (6)	46 (20)	2 (1)
Constipation	64 (29)	2 (1)	67 (30)	3 (1)
Alopecia	58 (26)	0 (0)	56 (25)	3 (1)
Pyrexia	58 (26)	4 (2)	42 (19)	0 (0)
Vomiting	57 (26)	2 (1)	39 (17)	4 (2)
Fatigue	54 (24)	2 (1)	46 (20)	4 (2)
Anaemia	46 (21)	30 (13)	36 (16)	23 (10)

Abbreviations: AE = adverse event; CTCAE = Common Terminology for Cancer Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

7.3 Clinical effectiveness and safety – further studies

NCT01309789: First-line BV administered sequentially or in combination with chemotherapy for CD30-positive PTCL

NCT01309789 is a multicentre, open-label, dose escalation, phase 1 trial to evaluate the safety of BV as first-line treatment for CD30-positive PTCL administered either sequentially (n = 13) or in combination with chemotherapy (n = 26). The sequential treatment group received BV 1.8 mg/kg (two cycles, once every three weeks, IV), followed by CHOP (six cycles, once every three weeks, IV). The combination group received BV 1.8 mg/kg plus CHP (six cycles, once every three weeks, IV). Vincristine was omitted from combination treatment to reduce potential neurotoxicity. The combination treatment group included six patients with sALCL to determine the maximum-tolerated dose (MTD) of BV in combination with CHP. The initial dose of BV was 1.8 mg/kg; enrolment of patients would continue at that dose if one or fewer dose-limiting toxicities were observed. Patients with an OR at the end of treatment could receive single-agent BV for eight

to ten additional cycles. The sponsor terminated enrolment in the sequential-treatment group after observing patients who initially responded to BV experience disease progression while receiving CHOP.

primary endpoint: AE

secondary endpoints: ORR, CRR, PFS and OS

The primary endpoint was incidence of AEs. Secondary outcomes included ORR, CRR, PFS, and OS. For the sequential-treatment group, responses were assessed by CT/PET scan after two cycles of single-agent BV and again after six cycles of CHOP, according to the Revised Response Criteria for Malignant Lymphoma. For the combination-treatment group, responses were assessed by CT/PET after six combination treatment cycles. Scans were performed after subsequent single-agent BV maintenance treatment. Patients were assessed for survival and clinical progression every three months until death or study closure. AEs were summarised using MeDRA, version 14.0, and graded using (CTCAE) version 3.0.

cohort: 57 years of age, 44% stage IV

histology: 82% sALCL, 5% PTCL, 5% AITL, 5% ATLL, 3% EATL

The study population had a median age of 57 years (range 21–82), 51% were male, 67% were Caucasian, 44% had stage 4 disease, and 67% had IPI ≥2. The population was comprised of 82% sALCL (67% ALK-negative, 15% ALK-positive), 5% PTCL-NOS, 5% AITL, 5% ATLL, and 3% EATL. CD30 expression in the tumour cells of non-ALCL patients ranged from 20% to 98%. ALK-negative patients were older than ALK-positive patients (median age 60 versus 35 years).

sequential treatment:
ORR: 85%,
PFS rate: 77%
OS rate: 85%

combination treatment:
ORR: 100%
PFS rate: 71%
OS rate: 88%

After sequential treatment, eleven (85%) of 13 patients achieved an OR (CRR 62%; PRR 23%). Median PFS was 22.1 months (95% CI 8.8–NE), with a 1-year PFS rate of 77% (95% CI 44–92). Median OS was not reached, and the estimated 1-year OS rate was 85% (95% CI 51–96). After combination therapy, 26 (100%) of 26 patients achieved an OR (CRR 88%; PRR 12%). All seven non-ALCL patients achieved CR. Following a median of 21.4 months, median PFS had not been reached (95% CI 11.7–NE), and the estimated 1-year PFS rate was 71% (95% CI 49–85). Median OS was not reached, and the estimated 1-year OS rate was 88% (95% CI 68–96) [37]. At five years, neither the median PFS or OS was reached, estimated 5-year PFS and OS rates were 52% and 80%, respectively [36].

AE: PSN, nausea, anaemia, diarrhoea, PE, dyspnoea, febrile neutropenia, infection

sequential treatment:
grade ≥3 AE: 62%
SAE: 46%
discontinued: 15%

combination treatment:
grade ≥3 AE: 73%
SAE: 50%
discontinued: 23%

Sequential treatment-related AE of ≥ grade 3 severity occurred in eight (62%) of 13 patients, SAEs occurred in six (46%) of 13 patients, and two (15%) of patients discontinued treatment due to AEs. Combination treatment-related AEs of any grade (incidence ≥30), included peripheral sensory neuropathy (PSN) (69%), nausea (65%), fatigue (58%), diarrhoea (58%), alopecia (54%), dyspnoea (46%), constipation (38%), peripheral oedema (35%), and anaemia, chills, febrile neutropenia, upper respiratory tract infection, and myalgia (31% each). Grade 3 AE were observed in 73% of patients; febrile neutropenia (31%), neutropenia (23%), anaemia (15%), and pulmonary embolism (PE) (12%) occurred in at least 10% of patients. SAEs were reported in 50% of patients; febrile neutropenia (31%), pyrexia (8%), and cardiac failure (8%). Six (23%) of 26 patients discontinued treatment due to an AE, half during combination treatment and half during single-agent maintenance [37]. At 5 years, 18 (95%) of 19 BV+CHP recipients reported a resolution or improvement in the symptoms of treatment-related neuropathy [36].

8 Estimated costs

A0021: What is the reimbursement status of brentuximab vedotin?

€ 9,999.00 /cycle, additional costs for G-CSF, chemotherapy and genetic profiling

six cycles of BV: ~ € 59,994.00

In Austria, single-use vials of 50 mg BV powder for reconstitution, as a single-dose solution containing 5 mg/mL BV, are available at a cost of € 3,333.00 (ex-factory price) [34]. Based on a study dose of 1.8 mg/kg and assuming an average body weight of 70 kg, one dose of BV would cost approximately € 9,999.00, every three weeks in combination with CHP. Six cycles of BV+CHP would cost approximately € 59,994.00 plus the additional cost of CHP. BV is indicated for the treatment of previously untreated sALCL or other CD30-expressing PTCL, including AITCL and PTCL-NOS, in combination with CHP. Assuming approximately 133 to 200 Austrians may be diagnosed with PTCL each year, BV would cost approximately € 7,979,202.00 to € 11,998,800.00 (six cycles of treatment) annually with additional costs for G-CSF prophylaxis, chemotherapy and gene expression profiling.

9 Ongoing research

10 registered studies

Several studies are ongoing to investigate BV as monotherapy or in combination with other therapies, as induction, first-line, second-line, salvage or consolidation therapy for PTCL. In June 2019, searches of www.clinicaltrials.gov and www.clinicalrialsregister.eu using the search terms “brentuximab vedotin” and “peripheral T-cell lymphoma” yielded ten other registered studies (seven phase 2, one phase 1/2, and two phase 1 studies). Most studies were industry-sponsored or conducted in collaboration with industry.

7 phase 2 studies

Selected recently completed and ongoing phase 2 or 1 studies evaluating BV as induction therapy in combination with cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEP), first-line monotherapy in the elderly, first-line in combination with rituximab, as monotherapy for low CD30 expressing r/r PTCL, monotherapy for r/r PTCL following gemcitabine or BV, or in combination with lenalidomide or bendamustine for r/r PTCL:

- **NCT01805037:** is a phase 2, open-label, single-group, interventional study to evaluate the safety and effectiveness of combination BV and rituximab in CD30-positive and or EBV-positive lymphomas. Estimated study completion date January 2016.
- **NCT03113500:** is a phase 2, open-label, single-group, interventional trial to assess the safety and tolerability of cyclophosphamide, doxorubicin, etoposide, prednisone and BV (CHEP-BV) as induction therapy in CD30-positive PTCL patients, followed by BV consolidation. Estimated study completion date December 2019.
- **NCT03302728:** is a phase 1, open-label, single-group, dose-escalation, interventional study to investigate the combination of BV and lenalidomide for the treatment of r/r cutaneous T-cell lymphoma, and CD30-positive PTCL or HL. Estimated study completion date August 2021.

- **NCT02499627:** is a phase 2, multicentre, open-label, single-group, interventional trial designed to evaluate the efficacy and safety of combination bendamustine and BV as first salvage therapy in patients with r/r HL or PTCL. Estimated study completion date October 2021.
- **NCT0249731:** is a phase 2, multicentre, open-label, single-group, interventional study to evaluate the efficacy of BV as a single agent for the treatment of r/r CD30-positive PTCL. Estimated study completion date December 2021.
- **NCT03496779:** is a phase 2, multi-centre, open-label, single-group, interventional trial to determine the efficacy of BV in patients treated with gemcitabine for r/r PTCL in terms of ORR after four cycles of treatment. Estimated study completion date October 2022.
- **NCT02588651:** is a phase 2, open-label, single-group, interventional study to investigate BV monotherapy for r/r low CD30-expressiong (<10%) PTCL. Estimated study completion date December 2022.
- **NCT01716806:** is a phase 2, open-label, non-randomised, interventional study to evaluate the efficacy of first-line BV as monotherapy in CD30-expressing PTCL and in combination with other agents (bendamustine, dacarbazine or nivolumab) for HL in patients 60 years of age or older. Estimated study completion date September 2024.
- **NCT03947255:** is a phase 2, multicentre, open-label, single-group, interventional trial to assess the safety and efficacy of BV in patients with HL, sALCL or other CD3-expressing PTCL who experienced CR or PR with BV-containing regimen and subsequently experienced progression or relapse. Estimated study completion date December 2024.

10 Discussion

first-line: BV+CHP approved for sALCL or other CD 30-positive PTCL in US; currently not indicated in Europe

Between 2011 and 2018, both the FDA and the EMA licensed BV for the treatment of patients with CD30-positive r/r HL or sALCL, HL at increased risk of relapse or progression following ASCT, CTCL following systemic therapy, and previously untreated stage IV HL in combination with AVD [3, 14, 15]. Approvals were based on data from two phase 2 studies [5, 6], and three phase 3 trials, AETHERA [7], ALCANZA [9-12], and ECHELON-1 [8, 9]. In November 2018, the FDA licensed BV in combination with CHP as first-line treatment for sALCL or other CD30-expressing PTCL, including AITL and PTCL-NOS [13]. Under the Real-Time Oncology Review Pilot Program, approval occurred less than two weeks following the submission of PFS and OS data from the phase 3 ECHELON-2 study [4]. BV is not currently indicated as first-line therapy for sALCL or other CD30 expressing PTCL in Europe [15].

ECHELON-2, a randomised, double-blind, placebo-controlled, phase 3 trial compared the efficacy and safety of BV+CHP versus CHOP in 452 patients with previously untreated CD30-positive PTCL [4, 35]. At a median follow-up of 42.1 months, the median OS was not reached for either group. BV+CHP conferred longer PFS than CHOP (PFS at 36.2 months: 48.2 months versus 20.8 months), reducing the risk of death or progression by 29%. The 3-year PFS was 57.1% for BV+CHP versus 44.4% for CHOP. BICR-assessed PFS for sALCL patients was consistent with results of the primary analysis (55.7 months for BV+CHP versus 54.2 months for CHP). Greater OR and CR rates were reported in BV+CHP patients compared with CHOP (ORR: 83% versus 72%; CRR: 68% versus 56%). Durable OR was achieved at all levels of CD30 expression among BV+CHP recipients, including those with 10% CD30 expression. No clinically meaningful differences in generic or disease-specific QoL scores were observed between groups.

ECHELON-2: BV+CHP versus CHOP in previously untreated CD30-positive PTCL

PFS: BV increased PFS by 27.4 months

median OS NR

OR: BV increased OR regardless level of CD30 expression

Commonly reported AEs occurring in ≥20% of patients in the BV+CHP group included nausea, peripheral sensory neuropathy, neutropenia, constipation, alopecia, pyrexia, vomiting, fatigue, and anaemia. Grade ≥3 AEs and SAEs occurred in 66% and 38% of BV+CHP patients; and 3% died due to AEs. The most commonly reported grade ≥3 AEs in BV+CHP recipients were neuropathy (52%), neutropenia (38% versus 13% for those with G-CSF primary prophylaxis) and infections (19%). Peripheral neuropathy and infections lead to dose delay or reduction in 25% and 9% of BV+CHP patients, respectively.

grade ≥3 AEs: neuropathy, neutropenia, and infections

Results of the ECHELON-2 trial hold some limitations. To ensure the secondary endpoint of PFS in sALCL could be appropriately assessed, the trial was designed to enrol 75% of patients with sALCL, so approximately 70% of the ITT population was comprised of sALCL. The study is limited in that it was not powered to compare efficacy between individual histological subtypes and small subgroup sizes preclude definitively determining the treatment effect in non-systematic ALCL. HRs for PFS and OS for PTCL-NOS patients were <1, while those for AITL patients were 1.4 and 0.87, respectively, with wide confidence intervals. Further studies involving a larger number of AITL or non-sALCL patients are needed to increase the precision by which benefits can be assessed. However, the PFS and OS benefits conferred by BV+CHP over CHOP were generally consistent across histological subtypes with overlapping confidence intervals.

ECHELON-2 limitations: insufficient power to compare individual histological subtypes

Generalizability of the results may be limited in that while most study participants had sALCL, good performance status (ECOG 0–2, an IPI≥2, and a median age of 58 years, PTCL-NOS accounts for most PTCL, represents a heterogeneous group, and the median age at diagnosis is 60 years [26]. Older patients may experience AEs of greater frequency and severity. Among the 31% of BV+CHP study participants ≥65 years of age, 74% experienced an AE of grade ≥3 severity, 49% experienced a SAE, and 29% had febrile neutropenia. Neutropenia rates may be underestimated as laboratory data were only captured at the start of each cycle. The impact of G-CSF may be limited by incomplete data on cytopenias and by the small number of patients that received primary prophylaxis [13]. While there is no general consensus regarding optimal treatment for PTCL, a more intensive CHEOP regimen may have been a suitable comparator for patients ≤60 years of age as CHOP is typically recommended for patients >60 years of age or less medically fit.

study generalizability limited: clinical patients most commonly PTCL-NOS, variable CD30 expression, older, AEs greater frequency and severity, may be treated with CHEOP

low risk of bias: randomised, double-blind, double-dummy, placebo-controlled

however, industry funded

ECHELON-2 is a phase 3 trial with few methodological limitations. There was no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were randomly assigned 1:1 to BV+CHP or CHOP using an interactive web-based response system (IWRS). A double-dummy method of blinding was used where patients in the BV group received placebo vincristine while those in the CHOP group received placebo BV. A pharmacist at each study site prepared BV, vincristine and their placebo replacements, and a pharmacy mask was enforced. The drugs were dispensed in a double-blind, double-dummy manner where patients, treating physicians, and the independent review committee were blinded to treatment. Selective outcome reporting is unlikely as the primary endpoint of PFS, secondary endpoints of PFS in sALCL patients, CRR, OS, ORR, QoL and AEs were reported as specified in the study record for the clinical trial. The risk of bias may be increased by industry involvement in funding the study, designing the trial, collecting, analysing and interpreting data and supporting manuscript preparation.

safety and efficacy results consistent with previous phase 1 study

The clinical efficacy and safety data from ECHELON-2 are consistent with a previously reported phase 1 trial where BV+CHP was well tolerated and resulted in OR, PFS, and OS rates of 100%, 71%, and 88%, respectively, as first-line for CD30-positive PTCL [36, 37]. Study populations were generally similar in age, stage, histology, and CD30-expression; however, none of the phase 1 patients received post-treatment consolidative ASCT. The most common AEs reported in both studies included PSN, nausea, fatigue, vomiting, diarrhoea, alopecia and dyspnoea. Grade ≥3 AEs most commonly reported in both studies included febrile neutropenia, neutropenia, peripheral neuropathy, infections, anaemia, and pulmonary embolism. While peripheral neuropathy may result in treatment delays or disruptions, majority resolve with time. Other potential toxicities include PML and pulmonary toxicity [3].

several ongoing studies evaluating BV monotherapy or in combination with other agents for CD30-positive PTCL at various stages

Several studies are underway to investigate BV as monotherapy or in combination with other therapies to treat various stages of CD30-positive PTCL. Recently completed or ongoing phase 2 or 1 studies are evaluating the safety and effectiveness of BV monotherapy for elderly patients with PTCL, combination BV+rituximab in lymphomas, the tolerability of CHEP-BV as induction therapy for PTCL, and combination BV+lenalidomide for r/r cutaneous T-cell lymphoma, PTCL or HL. Other phase 2 studies are investigating BV monotherapy for r/r CD30-positive or low CD30-expressing PTCL, combination bendamustine+BV as first salvage for r/r HL or PTCL, and BV following relapse on gemcitabinte or a BV-containing regimen.

€ 9,999.00/cycle, additional costs for G-CSF, chemotherapy and genetic profiling

six cycles of BV: ~ € 59,994.00

Administered as an intravenous infusion, the recommended dose of 1.8 mg/kg BV for a 70 kg person would cost approximately € 9,999.00, every three weeks in combination with CHP. Six cycles of BV+CHP would cost approximately € 59,994.00 plus the additional cost of CHP. Indicated for previously untreated sALCL or other CD30-expressing PTCL and assuming approximately 133 to 200 Austrians may be diagnosed with PTCL each year, BV would cost approximately € 7,979,202.00 to € 11,998,800.00 (six cycles of treatment) annually, with additional costs for G-CSF prophylaxis, chemotherapy and gene expression profiling.

CD30 expression: variable in PTCL; currently no threshold; diagnostic tool needed for patient selection

Questions remain regarding the patient population who would benefit most from BV+CHP therapy, and the relationship between the degree of CD30 expression and potential tumour response. The ECHELON-2 trial required ≥10% CD30 expression by immunohistochemical analysis; however, the optimal CD30 expression threshold remains uncertain. Data from ECHELON-2 are based on a population comprised 70% of ALCL patients; while ALCL universally expresses CD30, expression is variable in other PTCL subtypes. Estimates of CD30 expression range from 58–64% in PTCL-NOS, 63–75% in AITL, 0–55% in ATLL, 0–100%

in EATL, and 0–25% in hepatosplenic T-cell lymphoma. To better inform patient selection for BV+CHP, the FDA has requested that a clinically validated in vitro diagnostic for CD30 expression be developed [13].

ECHELON-2: phase 3 RCT demonstrates PFS benefit of BV+CHP over CHOP

no difference in QoL

efficacy in non-ALCL histologies, optimal dosing and therapeutic sequence, monotherapy versus in combination

Overall, ECHELON-2 is the first phase 3, randomised, double-blind, active comparator study to demonstrate that compared with CHOP, BV+CHP increases PFS, OR and CR in previously untreated CD30-positive PTCL patients. While the PFS benefits were generally consistent across subtypes, the study was not powered to compare efficacy between individual histological subtypes and small sample sizes preclude definitively determining the treatment effect in non-systematic ALCL. No clinically meaningful differences were noted in QoL measures. The development of a clinically validated in vitro diagnostic for CD30 expression may ensure the appropriate selection of patients most likely to benefit from BV+CHP therapy. Further studies are needed to better define the efficacy of BV in non-ALCL histologies, optimal dosing to enhance disease control while limiting complications, optimal therapeutic sequence, and use as monotherapy versus in combination with immune checkpoint inhibitors or other immunomodulatory agents.

11 References

[1] European Network for Health Technology Assessment (EUnetHTA). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals. Version 3.0. 2013 [cited 2015-10-30];Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] D. Chihara and Y. Oki. Brentuximab vedotin for treatment of systemic T-cell lymphoma. Expert Opinion on Biological Therapy. 2014;14(10):1519-1526. DOI: https://dx.doi.org/10.1517/14712598.2014.953048.

[3] U.S. Food and Drug Administration Drugs@FDA Adcentris® Label Information. 2019 [cited 2019-05-10];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125388s099lbl.pdf.

[4] S. Horwitz, O. A. O'Connor, B. Pro, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet (london, england). 2019;393(10168):229-240. DOI: 10.1016/S0140-6736(18)32984-2.

[5] A. Younes, N. L. Bartlett, J. P. Leonard, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010;363(19):1812-1821. Epub 2010/11/05. DOI: 10.1056/NEJMoa1002965.

[6] B. Pro, R. Advani, P. Brice, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol. 2012;30(18):2190-2196. Epub 2012/05/23. DOI: 10.1200/jco.2011.38.0402.

[7] C. H. Moskowitz, A. Nademanee, T. Masszi, et al. Brentuzimab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853-1862.

[8] J. M. Connors, W. Jurczak, D. J. Strauss, et al. Brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine (A+AVD) as frotline therapy demonstrates superior modified progression-free survival versus ABVD in patients with previously untreated stage III or IV Hodgkin lymphoma (HL): the phase 3 Echelon-1 study. Blood. 2017;130(6).

[9] C. Van Der Weyden, M. Dickinson, J. Whisstock, et al. Brentuximab vedotin in T-cell lymphoma. Expert Review of Hematology. 2019;12(1):5-19. Epub 2018/12/12. DOI: 10.1080/17474086.2019.1558399.

[10] M. Duvic, M. T. Tetzlaff, P. Gangar, et al. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis. J Clin Oncol. 2015;33(32):3759-3765. Epub 2015/08/12. DOI: 10.1200/jco.2014.60.3787.

[11] Y. H. Kim, S. Whittaker, S. M. Horwitz, et al. Brentuximab vedotin demonstrates significantly superior clinical outcomes in patients with CD30-expressing cutaneous T cell lymphoma versus physician's choice (Methotrexate or Bexarotene): the phase 3 alcanza study. Blood. 2016;128(22).

[12] H. M. Prince, Y. H. Kim, S. M. Horwitz, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017;390(10094):555-566. Epub 2017/06/11. DOI: 10.1016/s0140-6736(17)31266-7.

[13] N. C. Richardson, Y. L. Kasamon, H. Chen, et al. FDA Approval Summary: Brentuximab Vedotin in First-Line Treatment of Peripheral T-Cell Lymphoma. Oncologist. 2019;26:26. DOI: https://dx.doi.org/10.1634/theoncologist.2019-0098.

[14] European Commission Approves ADCETRIS® (brentuximab vedotin) with AVD, the first new treatment in decades for adults with previously untreated CD30+ stage IV Hodgkin lymphoma. 2019 [cited 2019-06-01];Available from: https://www.takeda.com/newsroom/newsreleases/2019/european-commission-approves-adcetris-with-avd-for-adults-with-previously-untreated-cd30-stage-iv-hodgkin-lymphoma/.

[15] European Medicines Agency Adcentris® EPAR - Summary of Product Characteristics. 2019 [cited 2019-06-01];Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris.

[16] H. Ma, A. Davarifar and J. E. Amengual. The Future of Combination Therapies for Peripheral T Cell Lymphoma (PTCL). Current hematologic malignancy reports. 2018;13(1):13-24. DOI: https://dx.doi.org/10.1007/s11899-018-0432-3.

[17] F. d'Amore, P. Gaulard, L. Trumper, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2015;available from: https://www.esmo.org/Guidelines/Haematological-Malignancies/Peripheral-T-Cell-Lymphomas.

[18] X. Chen, L. A. Soma and J. R. Fromm. Targeted therapy for Hodgkin lymphoma and systemic anaplastic large cell lymphoma: Focus on brentuximab vedotin. Onco Targets Ther. 2014;7:45-56. DOI: 10.2147/OTT.S39107.

[19] M. Gleeson. Moving to a higher echelon in CD30-positive T-cell lymphoma. Lancet. 2019;393(10168):201-202. DOI: https://dx.doi.org/10.1016/S0140-6736(18)33127-1.

[20] N. Tsuyama, K. Sakamoto, S. Sakata, et al. Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. J Clin Exp Hematop. 2017;57(3):120-142. Epub 2017/12/28. DOI: 10.3960/jslrt.17023.

[21] Leukemia & Lymphoma Society: Peripheral T-cell Lymphoma Facts. [cited 2019-06-04];Available from: https://www.llscanada.org/sites/default/files/file_assets/peripheraltcelllymphomafacts.pdf.

[22] Lymphoma Coalition Europe: Lymphoma in Europe. [cited 2019-06-04];Available from: https://www.lymphomacoalition.org/lymphoma-in-europe.

[23] P. P. Piccaluga, V. Tabanelli and S. A. Pileri. Molecular genetics of peripheral T-cell lymphomas. International Journal of Hematology. 2014;99(3):219-226. DOI: https://dx.doi.org/10.1007/s12185-014-1522-1.

[24] M. A. Lunning. Treatment of Peripheral T-Cell Lymphoma: Many Shades of Gray. Oncology (Williston Park). 2015;29(8):545-550.

[25] Statistik Austria. Krebserkrankungen [cited 2019-04-24];Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/index.html.

[26] A. S. Freedman and J. C. Aster. Initial treatment of peripheral T cell lymphoma. UpToDate [Internet]. 2019;Available from: https://www.uptodate.com Subscription required.

[27] A. J. Ferreri, S. Govi, S. A. Pileri, et al. Anaplastic large cell lymphoma, ALK-negative. Critical Reviews in Oncology-Hematology. 2013;85(2):206-215. DOI: https://dx.doi.org/10.1016/j.critrevonc.2012.06.004.

[28] Y. Oki and A. Younes. Brentuximab vedotin in systemic T-cell lymphoma. Expert Opinion on Biological Therapy. 2012;12(5):623-632. Epub 2012/03/21. DOI: 10.1517/14712598.2012.670216.

[29] T. Oncology. E2 Slide Resource Library. 2019;Available directly from manufacturer.

[30] R. Advani, S. Horwitz, S. Iyer, et al. Response to A+CHP by CD30 Expression in the ECHELON-2 Trial. ASCO Poster. 2019;Available from the manufacturer.

[31] D. Jagadeesh, S. Horwitz, N. Bartlett, et al. Response to Brentuximab Vedotin by CD30 Expression: Results from Five Trials in PTCL, CTCL, and B-cell Lymphomas. ASCO Poster. 2019;Available from manufacturer.

[32] S. Horwitz, O. O'Connor, B. Pro, et al. The Phase 3 ECHELON-2 Trial: Results of a Randomised, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30- Expressing PTCL. ASH 2019 presentation. 2018;Available from manufacturer.

[33] S. Garciaz, M. Loschi, A. De Masson, et al. Brentuximab vedotin as a bridge to allogeneic stem-cell transplantation for refractory or relapsing patients with CD30 positive anaplastic or T-cell non-Hodgkin lymphomas: a study on behalf of the SFGM-TC. Leukemia & Lymphoma. 2019;https://doi.org/10.1080/10428194.1599112.

[34] N. Grössmann, E. Rothshedl and S. Wolf. Horizon Scanning in Oncology 39th Prioritization -2nd quarter 2019. 2019;Available from: http://eprints.hta.lbg.ac.at/1189/1/HSO_39th_Prioritisation.pdf.

[35] S. Horwitz, O. A. O'Connor, B. Pro, et al. Supplementary Appendix to: 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. Lancet (london, england). 2019;393(10168):229-40. 2019.

[36] M. A. Fanale, S. M. Horwitz, A. Forero-Torres, et al. Five-year outcomes for frontline brentuximab vedotin with CHP for CD30-expressing peripheral T-cell lymphomas. Blood. 2018;131(19):2120-2124. Epub 2018/03/07. DOI: 10.1182/blood-2017-12-821009.

[37] M. A. Fanale, S. M. Horwitz, A. Forero-Torres, et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. Journal of clinical oncology. 2014;32(28):3137-3143. DOI: https://dx.doi.org/10.1200/JCO.2013.54.2456.

[38] European Network for Health Technology Assessment. Internal validity of randomized controlled trials. 2013;Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[39] European Network for Health Technology Assessment. EUnetHTA guidelines. Levels of evidence. Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals. . February 2013;Available from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Applicability.pdf.

[40] C. Wild, N. Grössmann, P. V. Bonanno, et al. Utilisation of the ESMO-MCBS in practice of HTA. Ann Oncol. 2016;27(11):2134-2136.

12 Appendix

Table 3: Administration and dosing and of BV+CHP or CHOP [3, 4]

	BV + CHP	CHOP
Administration mode	BV IV over 30 minutes, approximately 1 hour after CHP [3]	Double-blind, double-dummy [4]
Description of packaging	50 mg white lyophilized powder in a single-dose vial for reconstitution with 10.5 mL of sterile water for injection USP (solution of 5 mg/mL BV); withdraw required volume and transfer into IV bag containing 100 mL of 0.9% sodium chloride injection, 5% dextrose injection or lactated ringer's injection (final concentration of 0.4-1.8 mg/mL BV) [3].	Double-blind, double-dummy; BV, vincristine and placebo replacements prepared by onsite pharmacist [4]
Total volume contained in packaging for sale	50 mg of BV powder in individually-boxed single-dose vials [3]	Double-blind, double-dummy; [4]
Dosing	Brentuximab vedotin (1.8 mg/kg IV, maximum 180 mg) + cyclophosphamide (750 mg/m² IV) + doxorubicin (50 mg/m² IV) + placebo vincristine IV on day 1 + prednisone (100 mg oral) daily on days 1-5 of each 21-day cycle, for 6-8 cycles. Previously untreated PTCL patients received G-CSF prior to first BV + CHP cycle. Reduce dose to 1.2 mg/kg for patients with mild hepatic impairment (Child-Pugh A), grade 2 motor neuropathy, or grade 3 sensory neuropathy. Discontinue in patients with grade ≥3 motor neuropathy or PML [3, 35].	Placebo brentuximab vedotin + cyclophosphamide (750 mg/m² IV) + doxorubicin (50 mg/m² IV) + vincristine (1.4 mg/m², maximum 2 mg IV) on day 1 + prednisone (100 mg oral), once daily on days 1-5, of each 21-day cycle, for 6-8 cycles [4].
Median treatment duration	89% received 6-8 cycles [4].	81% received 6-8 cycles [4].
Contraindications	Not for use in patients with severe renal (CrCL<30 ml/min) or hepatic (Child-Pugh B or C) impairment. BV is contraindicated with concomitant bleomycin due to pulmonary toxicity [3].	Not for use in patients with severe renal (CrCL<30 ml/min) or hepatic (Child-Pugh B or C) impairment. BV is contraindicated with concomitant bleomycin due to pulmonary toxicity [3].
Drug interactions	Closely monitor AEs if given concomitantly with strong CYP3A4 inhibitors. Co-administration with ketoconazole increased exposure to MMAE increasing risk of AE [3].	Double-blind, double-dummy; [4]

Abbreviations: AE = adverse event; BV = brentuximab vedotin; CrCL = creatinine clearance; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP = CHOP without vincristine; G-CSF = granulocyte colony-stimulating factor; MMAE = monomethyl auristatin E; PML = progressive multifocal leukoencephalopathy; USP = United States Pharmacopeia

Table 4: Characteristics of the ECHELON-2 trial [4]

Title: Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial [4, 35]			
Study identifier	NCT01777152, EudraCT 2012-002751-42, SGN35-014, ECHELON-2		
Design	International (17 countries), multicentre (132 sites), double-blind, double-dummy, randomised, placebo-controlled, interventional phase III		
	Duration of main phase: Duration of enrolment: Duration of extension phase:		Patients received 21-day cycles of BV+CHP or CHOP for 6 or 8 cycles at the investigator's discretion. The data cut-off for primary analysis was August 15, 2018. January 24, 2013 – Nov 7, 2016, 601 patients were enrolled. CT scans were required at 9, 12, 15, 18, 21, and 24 months after initiating study treatment, and every 6 months thereafter until progression, death, or analysis of the primary endpoint up to 7 years post-treatment.
Hypothesis	Superiority The study was designed to compare the efficacy and safety of brentuximab vedotin in combination with CHP (A+CHP) versus standard CHOP for the treatment of untreated patients with CD30-positive PTCL.		
Funding	Seattle Genetics, Inc.		
Treatments groups	BV+CHOP (6-8 cycles) (n = 226 efficacy; n = 223 safety)		Brentuximab vedotin: 1.8 mg/kg IV (day 1) Cyclophosphamide: 750 mg/m² IV (day 1) Doxorubicin: 50 mg/m² IV (day 1) Placebo vincristine IV (day 1) Prednisone: 100 mg orally on days 1-5 of each 3-week cycle
	CHOP (6-8 cycles) (n = 226 efficacy; n = 226 safety)		Placebo brentuximab vedotin (day 1) Cyclophosphamide: 750 mg/m² IV (day 1) Doxorubicin: 50 mg/m² IV (day 1) Vincristine: 1.4 mg/m² (maximum 2 mg) IV Prednisone: 100 mg orally on days 1-5 of each 3-week cycle
	Notes		Consolidative stem cell transplantation or radiotherapy after treatment was permitted at the investigator's discretion
Endpoints and definitions	Progression-free survival Primary endpoint	PFS	Time from randomisation until progression, subsequent anticancer chemotherapy, death or study closure, for up to 5 years post-treatment, as assessed by BICR.
	Progression-free survival Secondary endpoint	PFS	Time from randomisation until progression, subsequent anticancer chemotherapy, death or study closure, for up to 5 years post-treatment, as assessed by BICR, in patients with centrally confirmed sALCL
	Complete remission rate Secondary endpoint	CRR	At end of treatment, as assessed by BICR.
	Overall survival Secondary endpoint	OS	Time from randomisation until death or study closure, up to 7 years post-treatment
	Objective response rate Secondary endpoint	ORR	Proportion of patients who achieved an objective response, according to BICR, at the end of treatment.
	Adverse events Secondary endpoint	AEs	AEs graded by CTCAE version 4.03, up to one month following last dose.
	Efficacy by CD30 expression Exploratory endpoint	–	The relationship between CD30 expression and overall response and DOR
Database lock	Last update posted October 11, 2018		
Results and Analysis			

Title: Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial [4, 35]

Study identifier	NCT01777152, EudraCT 2012-002751-42, SGN35-014, ECHELON-2			
Analysis description	**Primary Analysis** ITT: efficacy analyses included all patients randomised unless otherwise specified. Safety analyses included patients who received any amount of BV or any component of CHOP. BICR-assessed PFS, CRR, OS, and ORR were tested statistically using a two-sided α of 0.5, CIs at two-sided 95% level, results favouring treatment with $p<0.05$ are significant at the one-sided 0.025 level. Missing data were not imputed; subjects with missing values of a variable other than PFS or OS were excluded from the analysis of that endpoint. Primary efficacy analysis was a stratified log-rank test (by randomisation stratification factors) to compare the difference in BICR-assessed PFS between treatment groups. HR was estimated based on the stratified Cox regression model. PFS was also summarised using Kaplan-Meier. Similar methods were used for secondary efficacy endpoints of PFS in patients with sALCL and OS. PFS and OS median follow-up was calculated using the reverse Kaplan-Meier methods. The proportion of patients with an objective response and complete remission between groups was tested using the Cochran-Mantel-Haenszel test, stratified by the randomisation stratification factors. Assuming a median PFS of 23.9 m for the BV+CHP group and 16.5 m for the CHOP group, an estimated 238 PFS events provided an 80% power to detect a HR for disease progression or death due to any cause of 0.6895 at a one-sided significance level of 0.025; planned enrolment of 450 patients, targeting 75% (±5%) of patients with sALCL to ensure the secondary endpoint could be assessed.			
Analysis population	Inclusion	✪ Adults with untreated CD30-positive (≥ 10% of cells by local review) mature T-cell lymphomas according to the WHO 2008 classification ✪ Histologies included ALK-positive sALCL with IPI score ≥ 2, ALK-negative sALCL, PTCL-NOS, AITL, ATLL, EATL, and hepatosplenic T-cell lymphoma ✪ FDG-avid disease by PET, measurable disease of at least 1.5 cm by CT ✪ ECOG performance status ≤ 2 ✪ ALT and AST ≤ 3X ULN or ≤ 5X ULN for subjects with hepatic involvement, serum creatinine ≤ 2X ULN, ANC ≥ 1000/µL, or platelet count ≥ 50,000/µL		
	Exclusion	✪ History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years ✪ Current diagnosis of primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas or mycosis fungoides ✪ History of PML ✪ Cerebral/meningeal disease related to the underlying malignancy ✪ Prior treatment with brentuximab vedotin ✪ Baseline peripheral neuropathy ≥ 2 per NCI-CTCAE 4.03 or demyelinating Charcot-Marie-Tooth syndrome ✪ Left ventricular ejection fraction ≤ 45%, symptomatic cardiac disease or myocardial infarction within the past 6 months, or previous treatment with complete cumulative doses of anthracyclines ✪ Active grade 3≥ viral, bacterial or fungal infection within two weeks prior to the first dose of study treatment; HIV, or hepatitis B or C		
	Characteristics	B+CHP (n = 226)	CHOP (n = 226)	Total (n = 452)
	Age, years Median (IQR) ≥ 65, n (%)	 58.0 (45-67) 69 (31)	 58.0 (44-67) 70 (31)	 58.0 (44-67) 70 (31)
	Male, n (%)	133 (59)	151 (67)	142 (63)
	Median time from diagnosis (months)	0.8	0.9	0.9
	Race, n (%) Asian African American Caucasian Hawaiian or Pacific Islander Other or unknown	 45 (20) 12 (5) 139 (62) 1 (0) 29 (13)	 54 (24) 6 (3) 142 (63) 0 (0) 24 (11)	 50 (22) 9 (4) 141 (63) 1 (0) 27 (12)

Title: Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial [4, 35]				
Study identifier	NCT01777152, EudraCT 2012-002751-42, SGN35-014, ECHELON-2			
	ECOG performance-status, n (%)			
	0	84 (37)	93 (41)	89 (39)
	1	90 (40)	86 (38)	88 (39)
	2	51 (23)	47 (21)	49 (22)
	Diagnosis, n (%)			
	sALCL	162 (72)	154 (68)	158 (70)
	ALK-positive	49 (22)	49 (22)	49 (22)
	ALK-negative	113 (50)	105 (46)	109 (48)
	PTCL-NOS	29 (13)	43 (19)	36 (16)
	AITL	30 (13)	24 (11)	27 (12)
	ATLL	4 (2)	3 (1)	4 (2)
	EATL	1 (0)	2 (1)	2 (1)
	Disease stage at diagnosis, n (%)			
	1	12 (5)	9 (4)	11 (5)
	2	30 (13)	37 (16)	34 (15)
	3	57 (25)	67 (30)	62 (28)
	4	127 (56)	113 (50)	120 (53)
	IPI score, n (%)			
	0	8 (4)	16 (7)	12 (6)
	1	45 (20)	32 (14)	39 (17)
	2	74 (33)	78 (35)	76 (34)
	3	66 (29)	66 (29)	66 (29)
	4	29 (13)	25 (11)	27 (12)
	5	4 (2)	9 (4)	7 (3)
	% CD30 expression, per BICR			
	Mean (SD)	81 (28)	78 (31)	80 (30)
	Range	0–100	0–100	0-100
	% CD30 expression, ALCL, per BICR			
	Mean (SD)	95 (11)	93 (14)	94 (13)
	Range	0–100	0–100	0-100
	% CD30 expression, non-ALCL, BICR			
	Mean (SD)	47 (30)	46 (31)	47 (31)
	Range	5–100	0–100	0-100
Applicability of evidence				
Population	ECHELON-2 was conducted in patients with newly diagnosed, CD30-positive PTCL with good performance status (ECOG 0–1), and an IPI score of ≤3. Generalizability of the results may be limited in that most study participants had sALCL and a median of 58 years while PTCL-NOS accounts for most PTCL, represents a heterogeneous group, and the median age at PTCL diagnosis is 60 years. Older patients may experience AEs of greater severity; of the 31% of BV+CHP patients ≥65 years of age, 74% experienced an AE of ≥3 severity, 33% had a SAE and 29% had febrile neutropenia.			
Intervention	The dosage and administration of BV used in ECHELON-2 is consistent with that recommended for previously untreated PTCL. Dose reductions were allowed for patients with mild hepatic impairment, grade 2 motor neuropathy or grade 3 sensory neuropathy. Consolidative therapy was permitted.			
Comparators	PTCL is a heterogeneous group of mature T-cell lymphomas for which there is no general consensus regarding the optimal treatment regimen. Newly diagnosed PTCL patients are typically treated with anthracycline-based chemotherapy regimens. CHOP is often recommended for patients >60 years of age or less medically fit, whereas CHEOP may be recommended for patients ≤60 years of age. While study participants were a median of 58 years of age, CHOP was used as the comparator.			
Outcomes	Neutropenia rates may be underestimated because laboratory data were captured only at the start of each cycle. Evaluation of the impact of G-CSF was limited by the incomplete data on cytopenias, and by the small number of patients who received primary prophylaxis.			
Setting	ECHELON-2 is a multination study conducted in 132 sites across Australia, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Poland, Republic of Korea, Romania, Spain, Taiwan, United Kingdom, and United States.			

Abbreviations: AITL = angioimmunoblastic T-cell lymphoma; ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; AITL = angioimmunoblastic T-cell lymphoma; ATLL = adult T-cell leukaemia/lymphoma; BICR = blinded independent central review; BV+CHP = brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP = CHOP without vincristine; CI = confidence interval; CRR = complete remission rate; CT = computed tomography; DOR = duration of response; EATL = enteropathy-associated T-0cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; HIV = human immunodeficiency virus; HR = hazard ratio; IPI = International Prognostic Index; IQR = interquartile range; ITT: intent-to-treat; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR = overall response rate; OS = overall survival; PET = positron emission tomography; PML = progressive multifocal leukoencephalopathy; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; sALCL = systemic anaplastic large cell lymphoma; ULN = upper limit of normal; WHO = World Health Organization

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [38]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomised 1.1 to BV+CHP or CHOP using an IWRS that assigned a unique patient randomisation number and did not specify actual treatment assignment. Randomisation was stratified by histological subtype according to pathology assessment (ALK-positive sALCL versus other histologies) and IPI score (0-1 versus 2-3 versus 4-5).		yes
Adequate allocation concealment: centralised randomisation and allocation; blinded study medication was administered based on assignment from the IWRS. BV and vincristine were dispensed in a double-blinded, double-dummy manner. The pharmacist at each study site prepared BV, vincristine and their placebo replacements and a pharmacy mask was enforced.		yes
Blinding:	**Patient:** centralised randomisation and allocation; BV and vincristine were dispensed in a double-blind, double-dummy manner and patients were masked to treatment assignment.	yes
	Treating physician: centralised randomisation and allocation; BV and vincristine were dispensed in a double-blind, double-dummy manner and investigators were masked to treatment assignment.	yes
	Outcome assessor: centralised randomisation and allocation; BICR were masked to treatment assignment, and assessed efficacy and safety at interim analysis.	yes
Selective outcome reporting unlikely: primary endpoint of PFS, secondary endpoints of PFS in patients with sALCL, CRR, OS, ORR and AEs were reported as per protocol.		yes
No other aspects which increase the risk of bias: industry funded the study, designed the trial, collected, analysed and interpreted the data, and supported manuscript preparation.		yes
Risk of bias – study level		low-risk

Abbreviations: BICR = blinded independent review committee; BV+CHP = brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CRR = complete remission rate; IPI = International Prognostic Index; IWRS = interactive web response system; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma