26 March 2020
EMA/CHMP/213609/2020
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Adcetris

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0070

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

A+CHP brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, and prednisone

ADC antibody drug conjugate

AE adverse event

AITL angioimmunoblastic T-cell lymphoma

ALK anaplastic lymphoma kinase

ALT alanine aminotransferase

ANC absolute neutrophil count

AST aspartate aminotransferase

ADA antidrug antibodies, same meaning as ATA

ATA antitherapeutic antibodies

ATLL adult T-cell leukemia/lymphoma

AUC area under the concentration-time curve

β-hCG beta human chorionic gonadotrophin

CBC complete blood count

Ceoi concentration at the end of infusion

CFR Code of Federal Regulations

CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone

CHP cyclophosphamide, doxorubicin, and prednisone

Cmax maximum concentration

CNS central nervous system

CR complete remission

CRF case report form

CSR clinical study report

CT computed tomography

$C_{trough}$ trough concentration

EATL enteropathy-associated T-cell lymphoma

ECG electrocardiogram

ECOG Eastern Cooperative Oncology Group

eCRF electronic case report form

EFS event-free survival

EMA European Medicines Agency

EOT end of treatment

EQ-5D-3L European Quality of Life 5-Dimensions 3-Level Questionnaire

FACT/GOG-NTX Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity

FDA Food and Drug Administration

FDG fluorodeoxyglucose

GCP Good Clinical Practice

HEENT head, eyes, ears, nose, and throat

HIPAA Health Information Portability and Accountability Act

HIV human immunodeficiency virus

HSTCL hepatosplenic Tcell lymphoma

HR hazard ratio

HRA Health Regulatory Authority

HTLV-1 human T-cell leukemia virus-1

ICH International Council for Harmonisation

IV intravenous

IPI International Prognostic Index

IEC Independent Ethics Committee

IND investigational new drug

IRB Institutional Review Board

IRF independent review facility

ITT intent to treat

IWRS interactive web response system

JCV John Cunningham virus

LDH lactate dehydrogenase

MF mycosis fungoides

MMAE monomethyl auristatin E

MRI magnetic resonance imaging

MRU medical resource utilization

MTD maximum tolerated dose

MUGA multi-gated acquisition

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

NE not estimated

NHL non-Hodgkin lymphoma

NK natural killer

ORR objective response rate

OS overall survival

PCR polymerase chain reaction

PD pharmacodynamics

PD progressive disease

PET positron emission tomography

PFS progression-free survival

PK pharmacokinetics

PML progressive multifocal leukoencephalopathy

PR partial remission

PRO patient-reported outcome

PTCL peripheral T-cell lymphoma

QoL quality of Life

SAE serious adverse event

sALCL systemic anaplastic large cell lymphoma

SAP statistical analysis plan

SCT stem cell transplant

SMQ standardised MedDRA query

Tmax time at which the maximum concentration occurs

TTO time trade-off

ULN upper limit of normal

USAN United States adopted name

USP United States Pharmacopeia

WHO World Health Organization

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 19 June 2019 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include in combination with cyclophosphamide, doxorubicin, and prednisone treatment of adults with previously untreated CD30+ PTCL for Adcetris; as a consequence, section(s) 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are being updated to reflect the PTCL indication. The Package Leaflet (PL) is updated in accordance. Version 15.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information relating to orphan designation*

Adcetris was designated as an orphan medicinal product EU/3/08/595 on 15 January 2009.

Adcetris was designated as an orphan medicinal product in the following indication: ALCL. The designation was amended from the condition ALCL to PTCL on 21 August 2019.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0232/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0232/2017 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition

related to the proposed indication.

### *Protocol assistance*

The MAH received Protocol Assistance at the CHMP (EMA/288880/2012; EMA/559606/2012; EMA /628945/2014).

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Jan Mueller-Berghaus

| Timetable | Actual dates |
|---|---|
| Submission date | 19 June 2019 |
| Start of procedure: | 20 July 2019 |
| CHMP Co- Rapporteur's preliminary assessment report circulated on: | 16 September 2019 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 17 September 2019 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 17 September 2019 |
| PRAC RMP advice and assessment overview adopted by PRAC on: | 3 October 2019 |
| CHMP Joint Rapporteur's updated assessment report circulated on: | 11 October 2019 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 17 October 2019 |
| MAH's responses submitted to the CHMP on: | 26 November 2019 |
| CHMP Joint Rapporteur's assessment report on the MAH's responses circulated on: | 7 January 2020 |
| 2nd Request for supplementary information and extension of timetable adopted by the CHMP on: | 30 January 2020 |
| MAH's responses submitted to the CHMP on: | 21 February 2020 |
| A SAG meeting to address questions raised by the CHMP took place on: | 5 March 2020 |
| CHMP Joint Rapporteur's assessment report on the MAH's responses circulated on: | 13 March 2020 |
| An Oral explanation took place on | 25 March 2020 |
| CHMP opinion adopted on: | 26 March 2020 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

#### *Disease or condition*

Peripheral T cell lymphomas (PTCLs) are a group of uncommon and heterogeneous malignant lymphoproliferative disorders that originate from post-thymic (peripheral) T cells or mature natural killer (NK) cells, which according to the recent (2016) WHO classification are recognized as separate entities.

The originally acclaimed indication was: ADCETRIS in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) is indicated for adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL).

Following the assessment, the final agreed indication was: ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

#### *Epidemiology*

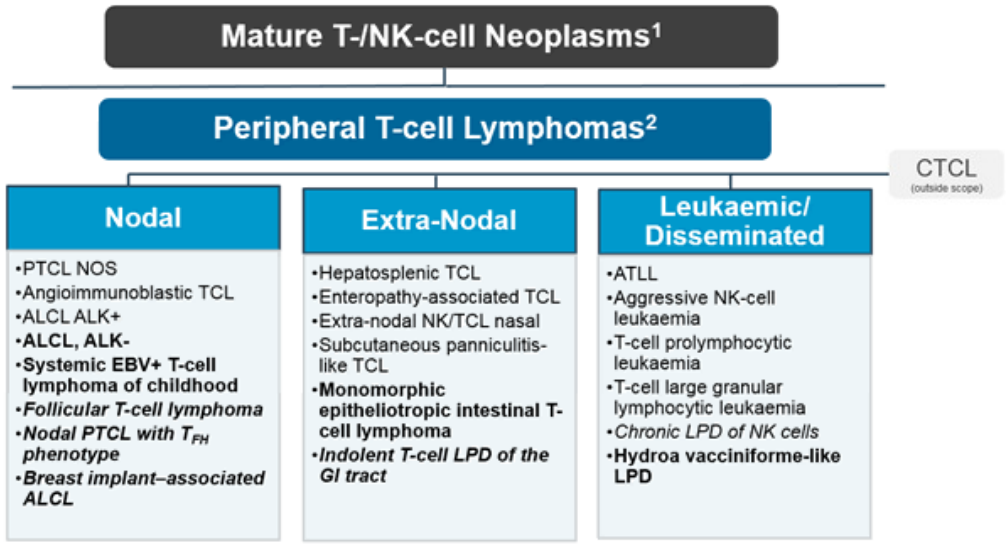
PTCL is a very rare condition with an estimated incidence of < 1 case per 100,000 people, which represent 10%–15% of all non-Hodgkin's lymphomas. The male/female ratio is 2:1 and the median age at diagnosis is between 50 and 70 years but may vary between subtypes (e.g. for hepatosplenic T cell lymphoma (HSTCL) the median age is 34 years). The most frequent occurring PTCL entities in the EU are (Vose 2008):

- Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS), 34.3%;
- Angioimmunoblastic T cell lymphoma (AITL), 28.7%, this subtype is associated with infection by the HTL virus, type I;
- Anaplastic large cell lymphoma, primary systemic type (sALCL); ALK- 9.4%, ALK+ 6.4%. This subtype has a CD30 cell expression of ≥75% per definition;
- Enteropathy associated T cell lymphoma (EATL), 9.1%. EATL is seen in patients with untreated celiac disease.

The International Prognostic Index (IPI) is the most commonly used prognostic tool in nodal PTCL (PTCL-NOS, AITL and ALCL).

#### *Biologic features*

Peripheral T cell lymphomas (PTCLs) are a group of heterogeneous malignant lymphoproliferative disorders that originate from post-thymic T cells or mature natural killer (NK) cells. Taking into account the differences in disease biology the WHO 2016 classifies these disorders as separate disease entities.




Provisional entities are in *italics*, changes from 2008 classification are in **bold**.
Excerpted from Swerdlow et al. (Swerdlow, Campo et al. 2016).
ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NK, natural killer; pcALCL, primary cutaneous ALCL; PTCL-NOS, peripheral T-cell lymphoma – not otherwise specified; TFH, T follicular helper; TCL, T-cell lymphoma.

**Figure 1 PTCL classification**

CD30 - a member of the tumor necrosis factor receptor superfamily- is expressed on a small subset of activated T and B lymphocytes, and a variety of lymphoid neoplasms, with the highest expression in classical HL and ALCL (ALCL is defined by CD30 cell expression of 75% or higher). CD30 expression in various intensity has also been described in more than half of the patients with PTCL-NOS, AITL, ENKTL (not included in study), EATL and ATLL (Bossard 2014, Weyden 2017).

**Table 1. Immunohistochemical CD30 expression in PTCL subtypes (Bossard 2014)**

| % of CD30+ tumor cells | ALCL ALK+ (N = 61) | ALCL ALK− (N = 19) | PTCL NOS (N = 141) | AITL (N = 97) | ENKTL (N = 28) | EATL (N = 14) | ATLL (N = 9) | HSTL (N = 7) |
|---|---|---|---|---|---|---|---|---|
| **Score 0** | 0 | 0 | 59 | 36 | 15 | 7 | 4 | 7 |
| <5% | | | 42% | 37% | 53.5% | 50% | 44% | 100% |
| **Score 1** | 0 | 0 | 37 | 46 | 2 | 0 | 1 | 0 |
| 5-24% | | | 26% | 47% | 7% | | 11% | |
| **Score 2** | 3 | 0 | 13 | 10 | 3 | 0 | 3 | 0 |
| 25-49% | 5% | | 9% | 10% | 11% | | 33% | |
| **Score 3** | 1 | 0 | 14 | 5 | 4 | 1 | 1 | 0 |
| 50-75% | 2% | | 10% | 5% | 14% | 7% | 11% | |
| **Score 4** | 57 | 19 | 18 | 0 | 4 | 6 | 0 | 0 |
| >75% | 93% | 100% | 13% | | 14% | 43% | | |
| Total positive cases (scores 1-4) | 61 | 19 | 82 | 61 | 13 | 7 | 5 | 0 |
| | 100% | 100% | 58% | 63% | 46% | 50% | 55.5% | |
| Strongly positive cases (scores 3-4) | 58 | 19 | 32 | 5 | 8 | 7 | 1 | 0 |
| | 95.1% | 100% | 23% | 5% | 28.5% | 50% | 11% | |

## *Clinical presentation, diagnosis and stage/prognosis*

Most patients with PTCL present with generalized lymphadenopathy, and the skin and gastrointestinal tract are the most commonly involved extranodal sites. Infiltration of bone marrow, liver and/or spleen may be seen. Symptoms such as B-symptoms, eosinophilia, pruritus, haemophagocytosis, thrombocytopenia and anemia may be observed.

Diagnosis and classification are made based on histology, immunophenotype, molecular genetic data

and clinical data.

The prognosis of PTCL is highly dependent on subtype and IPI score, see Table 2. The subtype ALCL ALK+ (5 year OS 70%) usually has a better prognosis compared to the other subtypes. Also, ALK− ALCL (5 year OS 49%) appears to be have a better prognosis than that reported for PTCL-NOS and AITL (both 5 year OS 32%). EATL has a poor prognosis (5 year OS 20%). ATLL prognosis (5 year OS 14%) is dependent on the clinical variant, ranging from very poor prognosis (several months) to sometimes quite indolent. HSTCL has one of the worst prognoses among PTCLs with 5-year OS rates of less than 10%.
In summary, there is an unmet need in PTCL due to the toxicity of the regimens used for treatment and due to the low long-term survival rates in most PTCL subtypes.

**Table 2. PTCL subtype survival by histologic type and IPI (Vose 2008)**

**Table 3.** Survival by Histologic Type and the IPI

| | 5-Year OS | | | 5-Year FFS | | |
|---|---|---|---|---|---|---|
| Diagnosis | % | IPI 0/1 | IPI 4/5 | % | IPI 0/1 | IPI 4/5 |
| PTCL-NOS | 32 | 50 | 11 | 20 | 33 | 6 |
| Angioimmunoblastic | 32 | 56 | 25 | 18 | 34 | 16 |
| Nasal NKTCL | 42 | 57 | 0 | 29 | 53 | 0 |
| Extranasal NKTCL | 9 | 17 | 20 | 6 | 21 | 20 |
| ATLL | 14 | 28 | 7 | 12 | 26 | 0 |
| ALCL, ALK+ | 70 | 90 | 33 | 60 | 80 | 25 |
| ALCL, ALK− | 49 | 74 | 13 | 36 | 62 | 13 |
| Enteropathy-type | 20 | 29 | 14 | 4 | 7 | 14 |
| Primary cutaneous ALCL | 90 | 100 | NA | 55 | 62 | NA |
| Hepatosplenic | 7 | 0 | 0 | 0 | 0 | 0 |
| Subcutaneous panniculitis-like | 64 | 60 | 0 | 24 | 30 | 0 |

Abbreviations: IPI, International Prognostic Index; OS, overall survival; FFS, failure-free survival; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large-cell lymphoma; NA, not applicable.

## *Management*

The treatment of newly diagnosed PTCL patients depends on subtype, age, IPI and comorbidities. Most PTCL patients are treated in a trial. Outside of a trial the following is advised (subtypes limited to those included in the pivotal study):

- Nodal PTCL (PTCL-NOS, AITL and ALCL): The combination of Cyclophosphamide, Hydroxydaunorubcin, Oncovin (vincristine) and prednisone (CHOP) is the most commonly used regimen. For fit patients ≤60 years CHOEP (i.e. CHOP plus etoposide) is recommended, as population-based studies indicate that CHOEP gives an EFS benefit compared to CHOP, but no OS benefit has been shown. Based on level III evidence autologous SCT is advised in fit patients (most beneficial in first CR relative to second or subsequent CR or PR). The few patients with truly localized disease should receive a shortened chemotherapy schedule followed by local radiotherapy. In low-risk (IPI 0-2) ALCL ALK+ patients, consolidation with autologous stem cell transplantation (auto-SCT) is not recommended due to the favourable prognosis at baseline.
- Extranodal PTCL:
    - EATL: This subtype has poor outcomes on CHOP and more intensive regimens are recommended (e.g. IVE/MTX, CHOEP 14). Fit patients who achieve first remission may benefit from autoSCT.
    - HSTCL: There are limited data available on the treatment of this subtype, but intense regimens such as ICE, IVAC or dose-dense CHOEP/EPOCH have been proposed. AutoSCT consolidation in fit patients is recommended, since it may offer the only chance for durable

remission.

- Widespread PTCL:
    - ATLL: Therapy is usually offered to patients with acute, lymphoma-type, or unfavourable chronic type. It is unclear what the best treatment for ATLL is, but VCAP-AMP-VECP has been proposed.

Response duration of first line therapy is often short and relapses are frequent. There is no standard of care for r/r PTCL besides brentuximab vedotin for r/r ALCL patients. Furthermore, it is currently recommended that fit patients who respond to therapy (preferably in first CR) should proceed to autologous SCT, as response duration upon first line therapy is often modest and relapses are frequent. For patients not able to proceed to SCT, responses to subsequent therapy are often of short duration.

A treatment bridging to transplant could be offered but not all patients may be fit enough to undergo this. For these patients, responses to subsequent therapy are often of modest duration.

*Subtypes excluded from the study*

Natural killer/T-cell lymphoma (NKTCL) is the 6$^{th}$ most common subtype in the EU. This subtype has been described to express CD30. Treatment has shown promising results on L-asparaginase containing regimens. Radiotherapy can be added in case of stage I-II (usually nasal) disease. Stage III-IV patients should proceed to autoSCT if CR is reached. Subcutaneous panniculitis-like T cell lymphoma is a very rare entity often presenting with an associated haemophagocytic syndrome (HPS). Patients with the alpha/beta variant have more indolent disease, patients with the gamma/delta variant have poor prognosis and should be treated with aggressive, anthracycline-based chemotherapy.

There is an unmet need in PTCL due to the low long-term survival rates in all PTCL entities and the toxicity of the treatment regimens.

### 2.1.2. About the product

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell MMAE is released via proteolytic cleavage and degradation of the drug linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

### 2.1.3. The development programme/compliance with CHMP guidance / scientific advice

The development programme was discussed with the CHMP in the context of Scientific Advice / protocol Assistance procedures, (see above) regarding the proposed study population, the appropriateness of the control arm; the primary endpoint PFS and secondary endpoints, sample size calculation, the possibility of unblinding at time of documented progression; considerations on the HR assumption.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the

CHMP.

## 2.2.1. Ecotoxicity/environmental risk assessment

The applicant provided an updated ERA.

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric antibody cAC10, specific for human CD30, 2) the antimicrotubule agent monomethylauristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. cAC10 has a structure typical of the human immunoglobulin G1 (IgG1) subclass. Estimated $PEC_{surface\ water}$ is 3.69 ng $L^{-1}$. A refined $F_{pen}$ ($4.1\times10^{-5}$) was used to calculate this PEC, based on a worst-case combined incidence rate of $8.8\times10^{-4}$ for the following four indications: Hodgkin's lymphoma (HL), systemic Anaplastic large cell lymphoma (sALCL), Cutaneous T-cell lymphoma (CTCL) and Peripheral T-cell lymphoma (PTCL). The incidence rates for HL, sALCL and CTCL were published in EMA/COMP public summaries of opinion (PSO) on orphan designation for brentuximab vedotin. The incidence rate for PTCL originates from the current application and corresponds to incidence rates for PTCL as cited in the Orphan Designation PSO's for other active substances (e.g. EMA/694349/2017). Further, a worst-case dose estimation and a full one year prescribed treatment regime were assumed to calculate the cited $F_{pen}$.

The size of the molecule (molecular weight estimated at 153,352 Da) excludes bioaccumulation. A determination of log $K_{ow}$ of this substance has not been performed and is not needed. The PBT assessment is therefore concluded. Brentuximab vedotin is not PBT, nor vPvB.

| **Substance (INN/Invented Name):** brentuximab vedotin | | | |
|---|---|---|---|
| **CAS-number (if available):** 914088-09-8 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential* – log $K_{ow}$ | | not performed | – |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | log $K_{ow}$ not necessary due to size of molecule. $M_w$ = 153,352 Da | not B |
| **PBT-statement :** | The compound is considered as not PBT nor vPvB | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ Refined $F_{pen}$, based on EMA/COMP published incidence rates | $3.69\times10^{-3}$ | µg/L | < 0.01 threshold |

## 2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of brentuximab vedotin.

## *2.3. Clinical aspects*

## 2.3.1. Introduction

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The pivotal study supporting the current application was ECHELON-2 (SGN35-014)

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

| Study No. Phase | Design | Study Objective | Diagnosis | Dosage (BV) Frequency Duration [a] | Primary Endpoint | Planned/ Treated/ Analyzed [b] | M:F Median age (Range) | Study Dates [c] | Sites/ Regions |
|---|---|---|---|---|---|---|---|---|---|
| SGN35-011 Phase 1 | Open-label, nonrandomized, 3-arm, with CHOP/CH-P | Safety | CD30+ mature T-cell and NK-cell neoplasms (treatment naïve) | 1.2 or 1.8 mg/kg IV q3wk 16 cycles | AEs: laboratory abnormalities | 52/39/39 | 51%:49% 57 (21-82) | Feb 2011– Apr 2015 | 10 US, W Europe |
| SGN35-012 Phase 2 | Open-label, nonrandomized, 3-part, single-agent or with rituximab | Efficacy and safety | NHL, including DLBCL | 1.8 mg/kg IV q3wk NA | Parts A and C: ORR Part B: AEs; laboratory abnormalities | 160/172/172 | 60%:40% 63 (16-91) | Aug 2011– Jun 2015 | 33 US, Canada |
| SGN35-014 Phase 3 | Randomized, double-blind 2-arm, A+CHP versus CHOP | Efficacy and safety | CD30+ mature T-cell lymphomas (treatment-naïve) | 1.8 mg/kg IV q3wk 6-8 cycles | PFS | 450/452/452 | 63%:37% 58 (18-85) | Jan 2013– Oct 2018 [d] | 132/ US, Asia, Canada, Europe, Israel |

## 2.3.2. Pharmacokinetics

An overview of the clinical pharmacology of brentuximab vedotin as monotherapy was already provided in the assessment reports for the original MAA. Reference PK results for brentuximab vedotin antibody-drug conjugate (ADC) and monomethyl auristatin E (MMAE) at time of initial registration in patients with CD30 positive haematological malignancies are shown in Table 3. Additional pharmacokinetic and pharmacodynamic results were reported in the previously submitted dossiers based on the phase 3 ALCANZA and ECHELON-1 trials.

**Table 3. Geometric Mean (%CV) PK parameters of ADC and MMAE following first dose of brentuximab 1.8 mg/kg as single agent in studies SG035-0001 and SGN35-008A.**

| ADC | study | $AUC_{0\text{-}inf}$ µg.day/ml | $C_{max}$ µg/ml | $T_{max}$[a] day | $t_{1/2}$ day | CL L/h | $V_{ss}$ L |
|---|---|---|---|---|---|---|---|
| | SG035-0001 | 79.4 (30%) | 32.0 (29%) | 0.089 | 4.4 (38%) | 0.073 (17%) | 8.2 (24%) |
| | SGN35-008A | 89.8 (25%) | 36.7 (34%) | 0.024 | 2.9 (66%) | 0.068 (26%) | 10.0 (34%) |
| MMAE | study | $AUC_{0\text{-}inf}$ ng.day/ml | $C_{max}$ ng/ml | $T_{max}$ day | $t_{1/2}$ day | CL L/h | $V_{ss}$ L |
| | SG035-0001 | 37.0 (47%) | 4.97 (43) | 2.1 | 3.6 (25%) | | |
| | SGN35-008A | 40.1 (53%) | 4.98 (67%) | 3.0 | 3.7 (19%) | | |

[a] Tmax shown in the table is Median

In support of the current application, PK results from the ECHELON-2 study, with brentuximab given in combination with cyclophosphamide, doxorubicin and prednisone, were submitted. This section of the assessment report summarizes PK findings from this ECHELON-2 study. ECHELON-2 was a randomized, double-blind, double-dummy, active-comparator, multicentre, phase 3 study in patients with previously untreated, CD30+ peripheral T-cell lymphoma (PTCL) designed with the primary objective of comparing the PFS obtained with A+CHP versus that obtained with CHOP for frontline treatment of PTCL.

In the ECHELON-2 study, PK and anti-therapeutic antibody (ADA) assessments were performed for all patients who received brentuximab vedotin, and exposure-effect analyses were applied to evaluate select safety and efficacy outcomes.

In Study ECHELON-2, patients were randomized 1:1 into 1 of 2 treatment arms:

A+CHP consists of:

- A: Brentuximab vedotin: 1.8 mg/kg administered by IV infusion on Day 1 of each 21-day cycle.
- C: Cyclophosphamide: 750 mg/m2 administered by IV infusion on Day 1 of each 21-day cycle.
- H: Doxorubicin: 50 mg/m2 administered by IV infusion on Day 1 of each 21-day cycle.
- P: Prednisone: 100 mg PO daily on Days 1-5 of each 21-day cycle.

CHOP consists of:

- C: Cyclophosphamide: 750 mg/m2 administered by IV infusion on Day 1 of each 21-day cycle.
- H: Doxorubicin: 50 mg/m2 administered by IV infusion on Day 1 of each 21-day cycle.
- O: Vincristine: 1.4 mg/m2 (dose capped at 2 mg) was administered by IV on Day 1 of each 21-day cycle.
- P: Prednisone: 100 mg PO daily on Days 1-5 of each 21-day cycle.

In each 21-day cycle, patients received cyclophosphamide, doxorubicin, and vincristine or placebo for vincristine in the stated order and according to institutional standards on Day 1; prednisone was administered by mouth on Days 1-5. Brentuximab vedotin IV infusion or placebo for brentuximab vedotin was administered on Day 1 of every 21-day cycle within 1 hour of completing treatment with other agents administered IV. In the absence of infusion-related reactions, brentuximab vedotin was to be administered as a 30-minute infusion.

Methods

Sparse PK and immunogenicity measurements were made in all brentuximab vedotin-treated patients (A+CHP) for the determination of serum concentrations of ADC, plasma concentrations of MMAE, ADA and neutralizing anti-therapeutic antibodies (nADA) (Table 4).

**Table 4. Study SGN35-014 (ECHELON-2): PK and immunogenicity sampling timepoints**

| Cycle | Study Day | Time | Window | Relative Time a | PK | ATA |
|---|---|---|---|---|---|---|
| 1-2 | Day 1 | Predose | Within prior 24 hr | Start of infusion | X | X |
| | Day 1 | End of infusion (30 min) | Within 30 min post end of infusion | End of infusion | X | |
| | Day 3 | 48 hr | ± 24 hr | Start of infusion | X | |
| 3+ | Day 1 | Predose | Within prior 24 hr | Start of infusion | X | X [b] |
| EOT | | | | | X | X |

Source: m5.3.5.1 CSR SGN35-014, Table 9-4.
ATA: antitherapeutic antibody (ies); EOT: end of treatment; PK: pharmacokinetic.
[a] Relative to infusion of brentuximab vedotin or placebo replacement.
[b] Cycles 3 and 4 only.

Serum concentrations of ADC were quantified using a previously validated sandwich enzyme-linked immunosorbent assay (ELISA) method, and plasma samples were analysed for MMAE using a previously validated liquid chromatography tandem mass spectrometry method.

Descriptive statistics, including number of patients, mean, standard deviation, geometric mean, percent coefficient of variation (%CV), median, minimum, and maximum were used to summarize concentrations of analyte for the patients who received brentuximab vedotin. In addition, exploratory exposure-response analyses of ADC and MMAE were performed and are described under section 2.3.4 (PK/PD modelling).

Immunogenicity assessment

Immunogenicity assessments to evaluate anti-therapeutic antibodies (ADA) and neutralising ADA were performed only for patients who received at least 1 dose of brentuximab vedotin. Blood samples were collected before administration of the study drugs at Cycle 1, Cycle 2, Cycle 3, and Cycle 4, and at end of treatment (EOT) as depicted in Table 4.

The assessment of ADA was determined using a previously validated electrochemiluminescence assay. The assessment for nADA was performed for ADA-positive samples only using a previously validated ELISA-based nADA assay.

**PK Parameters for Brentuximab Vedotin ADC and MMAE in PTCL patients from the ECHELON-2 study**

Summary statistics of ADC serum concentrations following IV administration of 1.8 mg/kg brentuximab vedotin Q3W in the A+CHP arm (as compared to those obtained in the ALCANZA (Study C25001), applying a 1.8 mg/kg brentuximab dose as single agent in patients with CTCL) are presented below.

Three out of 217 evaluable patients had measurable serum ADC concentrations in the predose sample at C1D1 and one out of 218 evaluable patients had measurable plasma MMAE concentrations in the predose sample at C1D1.

**Table 5. Studies ECHELON-2 and ALCANZA (C25001): Comparison of ADC and MMAE PK concentrations**

| | | ADC Concentration [a], ng /mL (%CV) | | MMAE Concentration [a], ng/mL (%CV) | |
|---|---|---|---|---|---|
| | | ECHELON-2 N=223 FL PTCL | ALCANZA N=66 r/r CTCL | ECHELON-2 N=223 FL PTCL | ALCANZA N=66 r/r CTCL |
| Cycle 1 | $C_{eoi}$ | 32.33 (26%) | 37.39 (23%) | 0.27 (170%) | ND |
| | $C_{48hr}$/ $C_{max}$ [b] | 8.49 (54%) | ND | 3.66 (73%) | 2.75 (58%) |
| | $C_{trough}$ | 0.43 (96%) | 0.35 (381%) | 0.09 (120%) | 0.08 (73%) |
| Cycle 2 | $C_{eoi}$ | 30.02 (29%) | ND | 0.23 (87%) | ND |
| | $C_{48hr}$/ $C_{max}$ [b] | 9.05 (43%) | ND | 2.25 (55%) | ND |
| | $C_{trough}$ | 0.71 (47%) | ND | 0.10 (84%) | ND |
| Cycle 3 | $C_{eoi}$ | ND | 34.43 (37%) | ND | ND |
| | $C_{48hr}$/ $C_{max}$ [b] | ND | ND | ND | 2.82 (41%) |
| | $C_{trough}$ | 0.83 (47%) | 0.61 (56%) | 0.10 (78%) | 0.09 (84%) |

Source: m5.3.5.1 CSR SGN35-014 Table 14.1.6.1, 14.1.6.2, m2.7.2-CTCL Table 2.b, and Table 2.d.
ADC: antibody-drug conjugate; Ceoi: concentration at the end of infusion; Cmax: maximum concentration; Ctrough: trough plasma/serum drug concentration; CTCL: cutaneous T-cell lymphoma; %CV: percent coefficient of variation; FL: frontline; MMAE: monomethyl auristatin E; ND: not determined; PK: pharmacokinetic; PTCL: peripheral T-cell lymphoma; r/r: relapsed/refractory.
[a] Geometric mean (%CV).
[b] $C_{48hr}$ for ADC, $C_{max}$ for MMAE.

The geometric mean (%CV) serum ADC trough concentrations after Cycle 3 (C4D1 predose) through Cycle 8 (C8D1 predose) were consistent over time and ranged from 0.83 µg/mL (47%) to 0.92 µg/mL (43%-47%) (data not shown in table). The geometric mean (%CV) plasma MMAE trough concentrations after Cycle 3 (C4D1 predose) up to Cycle 8 (C8D1 predose) were consistent over time and ranged from 0.08 ng/mL (46%) to 0.10 ng/mL (78-84%) (data not shown in table). Steady state therefore is assumed to be present at C4D1.

Overall, PK parameter estimates for Concentration at end of infusion ($C_{eoi}$), maximum concentration ($C_{max}$) and trough plasma drug concentration ($C_{trough}$) appeared comparable between the ECHELON-2 and ALCANZA studies for both ADC and MMAE.

Additionally, as part of the submission of the ALCANZA study (EMEA/H/C/002455/II/048), a population PK meta-analysis was conducted that integrated brentuximab vedotin monotherapy PK data from 380 patients with CD30+ haematological malignancies and included 58 patients with relapsed/refractory ALCL from Study SG035-004. The results of that analysis indicated there were no clinically meaningful differences in brentuximab vedotin PK across the tumour types evaluated (HL, sALCL, mycosis fungoides, primary cutaneous anaplastic large cell lymphoma, or non-specified haematological malignancies).

Collectively, these results support the findings that the serum and plasma PK characteristics of ADC and MMAE, respectively, following administration of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone were similar to PK characteristics of monotherapy.

### *Pharmacokinetic interaction studies*

No data was provided on the effect of brentuximab on the PK of cyclophosphamide, doxorubicin, and prednisone, which were co-administered with brentuximab in the ECHELON-2 study.

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

No new data on the mechanism of action were submitted.

### *Primary and secondary pharmacology*

No new data on primary and secondary pharmacology were submitted.

## 2.3.4. PK/PD modelling

An exploratory analysis was conducted in the ECHELON-2 study for brentuximab vedotin ADC and MMAE to examine exposure-response relationships. Only data from ECHELON-2 were used in this evaluation.

The objectives of this exposure-response analysis were:

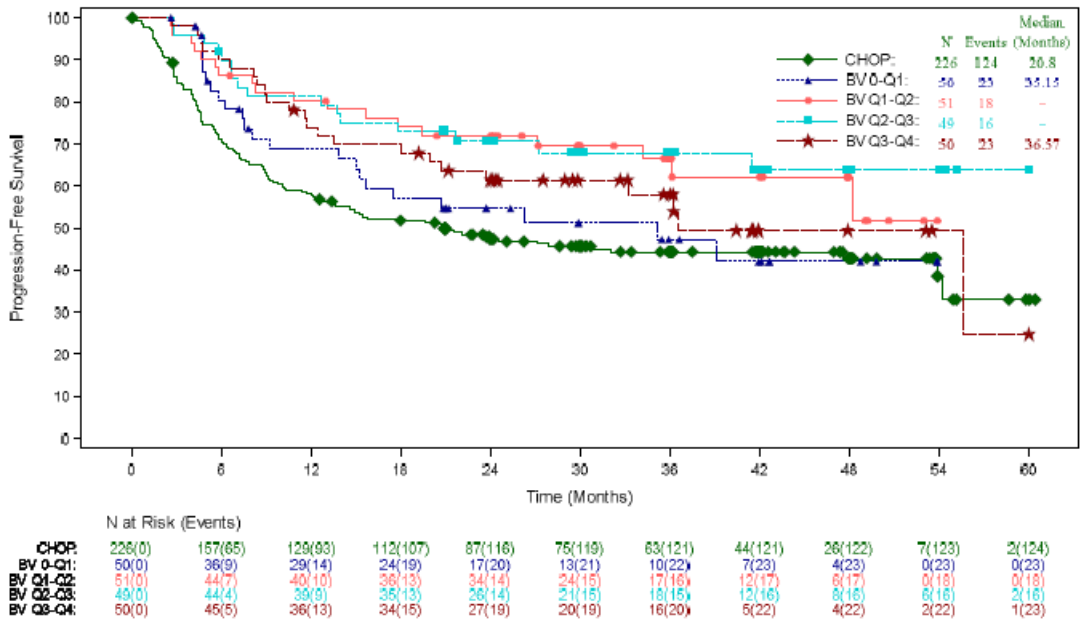
- To assess relationships between steady-state trough ADC concentrations and Progression free survival (PFS) as evaluated by an independent review facility (IRF).
- To assess relationships between steady-state trough ADC and MMAE concentrations and the following AEs:

- Grade 4 or higher neutropenia.
- Febrile neutropenia.
- Grade 2 or higher peripheral neuropathy.
- Any Grade 3 or higher TEAE.

**Exposure-Efficacy relationship**

An analysis was conducted to determine if PFS was balanced across quartiles of steady-state ADC serum trough concentrations on the A+CHP arm.

Figure 2 presents Kaplan-Meier curves for PFS per IRF versus days of treatment. ADC serum trough concentration values on C4D1 predose were grouped by quartiles and a separate curve for the CHOP arm is provided as a reference.




Source: m5.3.5.1 CSR SGN35-014, Figure 14.2.1.34.
A+CHP: brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone; ADC: antibody-drug conjugate; BV: brentuximab vedotin; C4D1: Cycle 4 Day 1; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; IRF: independent review facility; ITT: intent-to-treat; LLOQ: lower limit of quantitation; PFS: progression-free survival; Q: quartile.
Included all patients in the ITT population in the CHOP arm and patients in the ITT population with evaluable concentration values at C4D1 in the A+CHP arm. Patients in the A+CHP arm were categorized into 4 groups based on their ADC predose concentration values on C4D1, using the overall quartiles of the C4D1 predose values in the A+CHP arm. The intervals used for categorization are inclusive of all the upper bounds and exclusive of the lower bounds except for 0 - Q1 (inclusive on both sides). Patients with missing concentration values were not included.
The Q1, Q2, and Q3 values of ADC trough (C4D1) concentrations in A+CHP were 0.6095, 0.909, and 1.186, respectively.
Below the LLOQ will be imputed as 0 for quartile calculation.

**Figure 2. Study SGN35-014: Kaplan-Meier Plots for PFS per IRF by Quartiles of ADC Trough Concentration (ECHELON-2 study)**

No meaningful differences were observed between the curves for PFS per IRF by increasing quartiles of ADC trough concentrations, the quartiles do not order by quartile rank, and are separated from the PFS curve for the CHOP arm. The frequency of PFS events appears to be balanced across quartiles of ADC trough concentrations.

**Exposure-Safety relationship**

The incidence of Grade 3 or higher TEAEs, neutropenia, febrile neutropenia, and peripheral neuropathy was evaluated by quartiles of ADC serum or MMAE plasma steady-state trough concentrations for evaluable patients in the A+CHP arm. There was no apparent trend between steady-state trough (C4D1 predose) ADC concentrations and the incidence of any Grade 3 or higher TEAE, Grade 4 or higher neutropenia, febrile neutropenia, or Grade 2 or higher peripheral neuropathy (Table 6).

**Table 6. Study SGN35-014 (ECHELON-2): incidence of TEAEs of interest by quartiles of ADC trough concentration**

| | | A+CHP (N=223) | | | |
|---|---|---|---|---|---|
| | CHOP (N=226) n (%) | BV Q1 (N=50) n (%) | BV Q2 (N=51) n (%) | BV Q3 (N=49) n (%) | BV Q4 (N=50) n (%) |
| TEAE (Grade 3 or higher) | 146 (65) | 35 (70) | 29 (57) | 29 (59) | 35 (70) |
| Neutropenia (Grade 4 or higher) | 49 (22) | 11 (22) | 7 (14) | 10 (20) | 13 (26) |
| Febrile neutropenia | 33 (15) | 12 (24) | 10 (20) | 4 (8) | 9 (18) |
| Peripheral neuropathy (SMQ) (Grade 2 or higher) | 35 (15) | 10 (20) | 10 (20) | 8 (16) | 11 (22) |

Source: m5.3.5.1 CSR SGN35-014, Table 14.3.1.43.
A+CHP: brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone; ADC: antibody-drug conjugate; BV: brentuximab vedotin; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: standardised MedDRA query; Q: quartile; TEAE: treatment-emergent adverse event.

Steady-state MMAE trough concentrations did not appear to be associated with the incidence of Grade 2 or higher peripheral neuropathy, whereas there appeared to be a trend between quartiles of steady-state trough MMAE concentrations and the incidence of Grade 3 or higher TEAEs, Grade 4 or higher neutropenia, and febrile neutropenia (Table 7), with the observed incidence of these events being numerically greater in the third and fourth quartile compared to the first or second quartile of steady-state trough MMAE concentrations.

**Table 7. Study SGN35-014 (ECHELON-2): incidence of TEAEs of interest by quartiles of MMAE trough concentration**

| | | A+CHP (N=223) | | | |
|---|---|---|---|---|---|
| | CHOP (N=226) n (%) | MMAE Q1 (N=48) n (%) | MMAE Q2 (N=49) n (%) | MMAE Q3 (N=49) n (%) | MMAE Q4 (N=45) n (%) |
| TEAE (Grade 3 or higher) | 146 (65) | 26 (54) | 23 (47) | 34 (69) | 37 (82) |
| Neutropenia (Grade 4 or higher) | 49 (22) | 7 (15) | 7 (14) | 14 (29) | 10 (22) |
| Febrile neutropenia | 33 (15) | 5 (10) | 4 (8) | 13 (27) | 13 (29) |
| Peripheral neuropathy (SMQ) (Grade 2 or higher) | 35 (15) | 11 (23) | 9 (18) | 7 (14) | 11 (24) |

Source: m5.3.5.1 CSR SGN35-014, Table 14.3.1.42.
A+CHP: brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone; ADC: antibody-drug conjugate; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; MMAE: monomethyl auristatin E; Q: quartile; SMQ: standardised MedDRA query; TEAE: treatment-emergent adverse event.

## Immunogenicity Results

The electrochemiluminescent assay used to detect antitherapeutic antibodies in the ECHELON-2 study samples had a drug tolerance of up to 12.5 µg/mL brentuximab vedotin for a 100 ng/mL positive

antibody control and up to 25 µg/mL brentuximab vedotin for 250 ng/mL and 500 ng/mL positive antibody controls.

The enzyme-linked immunosorbent-based immunoassay (ELISA) method for the determination of neutralizing antibodies (nATA) had a drug tolerance of up to 5 µg/mL brentuximab vedotin for a 250 ng/mL positive antibody control. In the A+CHP arm, baseline ATA samples were available for 205 of 226 patients in the intent-to-treat (ITT) population; samples were missing for 18 patients, and 3 patients did not receive study treatment. The majority of patients were ATA-negative at baseline (81%) and most remained ATA negative throughout postbaseline visits.

| | **A+CHP (N=226) n (%)** |
|---|---|
| ATA negative at baseline | 184 (81) |
| Negative postbaseline | 139 (62) |
| Positive post baseline | 40 (18) |
| Transiently positive postbaseline | 39 (17) |
| Persistently positive postbaseline | 1 (0) |
| Missing | 5 (2) |
| ATA positive at baseline | 21 (9) |
| Negative postbaseline | 12 (5) |
| Positive postbaseline | 9 (4) |
| Transiently positive postbaseline | 8 (4) |
| Persistently positive postbaseline | 1 (0) |

Source: m5.3.5.1 CSR SGN35-014, Table 11-7.
A+CHP: brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone; ATA: antitherapeutic antibody (ies); ITT: intent-to-treat.
Transiently positive is defined as 1 or 2 postbaseline confirmed ATA positive responses. Persistently positive was defined as more than 2 postbaseline confirmed ATA positive responses. Negative was defined as ATA response negative (not confirmed positive) at all postbaseline time points.

A total of 49 of 205 patients (24%) were confirmed positive for ATA at any postbaseline visit; 40 patients who tested ATA negative at baseline and 9 patients who were confirmed ATA positive at baseline. Of the 49 ATA-positive patients, 47 patients (96%) were transiently ATA positive, and 2 patients (4%) were persistently ATA positive. The majority of ATA-positive patients first had a confirmed positive result at Cycle 2. The rate of ADA positive patients in the pivotal ECHELON-2 trial lies within the range of previous studies.

The PK of ADC did not appear to be altered in persistently ATA-positive patients.

Five patients on the A+CHP arm tested positive for nATA to brentuximab vedotin. The PK of ADC did not appear to be altered in nATA-positive patients. Four of the 5 patients first tested positive for nATA at Cycle 2; the other patient first tested positive at Cycle 3. All 5 patients had an objective response, although 2 of the 5 patients subsequently experienced disease progression.

No notable differences were observed between the PFS-independent review facility (IRF) curves or incidence of treatment-emergent adverse event (TEAE) for ATA-negative and ATA-positive patients.

## 2.3.5. Discussion on clinical pharmacology

In support of the current application, PK results from the ECHELON-2 study, with brentuximab given in combination with cyclophosphamide, doxorubicin and prednisone, were submitted.

In this respect, the PK of the brentuximab antibody drug conjugate (ADC) and its MMAE part were assessed, based on sparse sampling during the study. Overall, ADC and MMAE PK parameter estimates for the concentration at the end of infusion ($C_{eoi}$), maximum concentration ($C_{max}$) and trough plasma drug concentration ($C_{trough}$) over time appeared comparable between the ECHELON-2 and ALCANZA (the latter with brentuximab given as single agent) studies for both ADC and MMAE. Steady state is assumed to be present at C4D1.

After multiple-dose IV infusion of 1.8 mg/kg ADCETRIS every 3 weeks, the pharmacokinetics of ADC and MMAE were similar to those of monotherapy.

Based on product characteristics and *in vitro* data, brentuximab vedotin is not expected to affect the PK of cyclophosphamide, doxorubicin, and prednisone, or vice versa.

The rate of ADA positive patients in the pivotal ECHELON-2 trial lies within the range of previous studies. Therefore, maintaining the current wording on immunogenicity in the SmPC is considered acceptable.

As regards to the exposure-efficacy analysis, no meaningful differences were observed between the curves for PFS per IRF by increasing quartiles of ADC trough concentrations. As seen in the K-M graph patients in the A+CHP arm displayed consistent treatment benefit based on PFS across all quartiles of brentuximab vedotin exposure. The Kaplan-Meier plots did not rank order by quartiles of ADC trough concentration, tended to overlap and were separated from the PFS curve for the CHOP arm.

OS curves per Quartile of exposure to ADC are largely overlapping regardless of AUC. For PFS these results are not as homogenous. Nevertheless, the provided data show that reduced doses are not necessarily negatively impacting efficacy outcomes. With respect to the *exposure-safety* analysis, steady-state ADC trough concentrations did not appear to be associated with the incidence of Grade 3 or higher TEAEs, Grade 4 or higher neutropenia, febrile neutropenia or Grade 2 or higher peripheral neuropathy. Likewise, steady-state MMAE trough concentrations did not appear to be associated with the incidence of Grade 2 or higher peripheral neuropathy, whereas there appeared to be a trend between MMAE trough concentrations and the incidence of Grade 3 or higher TEAEs, Grade 4 or higher neutropenia, and febrile neutropenia. These results are also consistent with previously observed exposure-safety relationships for brentuximab vedotin monotherapy (r/r CTCL; ALCANZA) and in combination with chemotherapy (ECHELON-1). Additional exposure-safety analyses indicated that time-averaged MMAE exposure (MMAE AUC/Time) was significantly related to the incidence of Grade 4 neutropenia ($p=0.006$), febrile neutropenia ($p<0.0001$) and ≥Grade 3 TEAE($p<0.0001$). ADC AUC/Time and Cycle were statistically significant predictors of the incidence of ≥Grade 2 or higher peripheral neuropathy ($p=0.034$).

In ALCANZA, the relationship between brentuximab vedotin exposure and Grade 3 or higher TEAEs and Grade 2 or higher peripheral neuropathy was evaluated. In that study, ADC exposure was found to be a predictor of Grade 3 or higher TEAEs. In ECHELON-1, the relationship between brentuximab vedotin exposure and Grade 3 or higher TEAEs, Grade 4 or higher neutropenia, febrile neutropenia and Grade 2 or higher peripheral neuropathy was evaluated; ADC exposure was found to be a predictor of febrile neutropenia and Grade 2 or higher peripheral neuropathy. In ECHELON-1, like in ECHELON-2, MMAE exposure was found to be a predictor of Grade 3 or higher TEAEs, Grade 4 or higher neutropenia, and febrile neutropenia. MMAE Cmax levels versus change in neutrophil count did not reveal a clear correlation.

For patients experiencing treatment-related toxicities at the starting dose, protocol-specified dose reductions for brentuximab vedotin were recommended as supported by exposure-safety analyses that revealed relationships between MMAE exposure and the incidence of all evaluated AE outcomes of clinical interest (Grade 4 or higher neutropenia, febrile neutropenia, and Grade 3 or higher TEAEs).

Collectively, these results support the findings that the safety profile of brentuximab vedotin can be adequately managed by the dose modification/dose reduction criteria established in ECHELON-2.

Additional analyses indicated that the PTCL disease type had no clinically meaningful impact on the exposure-safety relationships. Differences in safety profiles observed across the PTCL subtypes, and thus the actual exposure-safety analyses for the largest PTCL disease types studied (sALCL, PTCL-NOS and AITL) were mainly attributed to differences in age among patients in the diseases studied (see also discussion on Clinical Safety).

### 2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of ADCETRIS in combination with CHP were evaluated in a single phase 3 study in 223 patients (SGN35-014/ECHELON-2). After multiple-dose IV infusion of 1.8 mg/kg ADCETRIS every 3 weeks, the pharmacokinetics of ADC and MMAE were similar to those of monotherapy. Overall, provided PK and exposure-response data support the current application for the extension of indication for Adcetris.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

The approved dose for brentuximab vedotin monotherapy is 1.8 mg/kg IV administered every 3 weeks (Q3W). This was the MTD in a phase 1, dose-escalation study (SG035-0001), and evaluated in 2 phase 2 studies (SG035-0003 and -0004) in subjects with CD30-positive hematologic malignancies.

**SGN35-011** is a phase 1 dose finding study of brentuximab vedotin (BV) administered sequentially/concurrently with multi-agent chemotherapy in treatment-naive patients with CD30+ mature T-cell and NK-cell neoplasms. This study consisted of 3 arms; in part 1 only sALCL patients were included.

- Part 1, arm 1: This arm aimed to evaluate safety and tumor activity of BV 1.8mg/kg Q3W in cycle (C)1 and C2, followed by CHOP in C3-C8, followed by BV in C9-16 for responders.
- Part 1, arm 2: This arm aimed to evaluate the MTD of BV (1.8 mg/kg Q3W, in case of ≥2 of 6 DLTs in C1 dose was to be de-escalated to 1.2mg/kg) + CHP in C1-6 followed by BV 1.8mg/kg in C7-16 for responders. DLTs were defined as any Cycle 1 toxicity requiring a dose delay of ≥7 days in CHP therapy.
- Part 2, arm 3: This arm aimed to evaluate the BV MTD in combination with CHP for up to 6 cycles followed by BV 1.8 mg/kg in C9-16 for responders.

A total of 39 patients were enrolled, 13 in part 1, arm 1; 6 in part 1, arm 2 and 20 in part 2. Thirty-two of 39 patients (82%) were diagnosed with sALCL (6 ALK-positive, 26 ALK-negative). Other diagnoses included AITL (n=2), ATLL (n=2), EATL (n=1), and PTCL-NOS (n=2).

**Safety**: One DLT of a Grade 3 rash was observed in arm 2 with 1.8 mg/kg BV+ CHP among 6 treated patients in the maximum tolerated dose (MTD) cohort. Based on this the MAH enrolled patients in Part 2 of the study at the dose of 1.8 mg/kg. Patients received 6 cycles of A+CHP, administered every 3 weeks. Refer to clinical safety for further safety outcomes.

**Efficacy:** The best ORR was seen in all patients in both treatment regimens (100% ORR). The CR rate was 77% for sequential and 92% for combination treatment. Two-year PFS rates were 54% and 56% for the sequential and combination treatment regimens, respectively. Three-year OS rates were 62% and 80% in the sequential and combination treatment groups, respectively.

The MAH considered that the MTD was not reached at 1.8 mg/kg brentuximab vedotin. Thus, the recommended dose of brentuximab vedotin was 1.8 mg/kg every 3 weeks in combination with CHP.

The doses of cyclophosphamide, doxorubicin, vincristine, and prednisone were based on approved labelling instructions and institutional standards.

## 2.4.2. Main study

## Study ECHELON-2

### *Methods*

ECHELON-2 (SGN35-014) is a randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas.

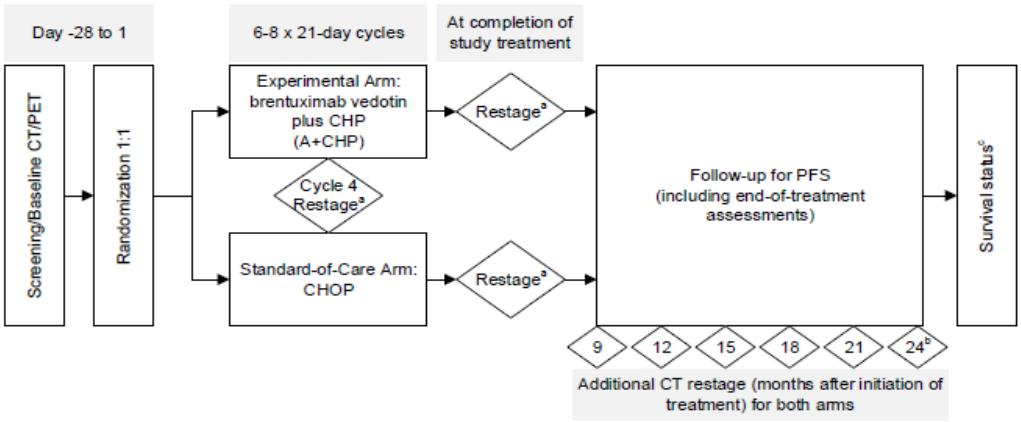



**Figure 3. Study design**

## Study participants [1]

The main inclusion criteria were:

- Patients (≥18 years ECOG PS≤2) with newly diagnosed, CD30-positive PTCL (per the Revised European-American Lymphoma WHO 2008 classification) by local assessment. Eligible histologies were:
    - ALK-positive sALCL with an IPI score ≥2
    - ALK-negative sALCL
    - PTCL-NOS

1

    - Angioimmunoblastic T-cell lymphoma (AITL)
    - Adult T-cell leukemia/lymphoma
    - Enteropathy-associated T-cell lymphoma (EATL)
    - Hepatosplenic T-cell lymphoma
- FDG-avid disease by PET and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.
- Normal liver and renal function, no neutropenia or thrombocytopenia

The main exclusion criteria were:

- History of another primary invasive cancer, haematologic malignancy, or myelodysplastic syndrome that had not been in remission for at least 3 years.
- Current diagnosis of any of the following:
    - Primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. Cutaneous ALCL with extracutaneous tumor spread beyond locoregional lymph nodes was eligible (previous single-agent treatment to address cutaneous and locoregional disease was permissible)
    - Mycosis fungoides (MF), including transformed MF
- History of progressive multifocal leukoencephalopathy (PML).
- Cerebral/meningeal disease related to the underlying malignancy.
- Prior treatment with brentuximab vedotin.
- Baseline peripheral neuropathy ≥Grade 2 (per the NCI CTCAE, version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome.
- Left ventricular ejection fraction less than 45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), or myocardial infarction within the 6 months prior to enrollment, or previous treatment with complete cumulative doses of doxorubicin or other anthracyclines.
- Any active Grade 3 infection within 2 weeks prior to the first dose of study treatment; HIV, hepatitis B or hepatitis C infection.
- Current therapy with other systemic anti-neoplastic or investigational agents.
- Females who were pregnant or breastfeeding.

The protocol stipulated that 75% ± 5% of enrolled subjects were required to have a diagnosis of sALCL to support the secondary endpoint of PFS in this population.

The 3 following criteria were used to declare CD30 positivity by local assessment: CD30 detected in 10% or greater of neoplastic cells; CD30 staining at any intensity above background and membranous, cytoplasmic, and/or Golgi pattern of expression of the CD30 antigen.

Submission of the tumour block or unstained slides from a diagnostic biopsy was also required prior to randomization for subsequent central confirmation of CD30 expression, histologic subtype, and ALK status for subjects with a diagnosis of sALCL.

Subjects were randomized at 132 study centers in North America, Europe, and other regions, including the Asia Pacific region and the Middle East.

## Treatments

The administered treatments are shown in Table 8. Brentuximab vedotin IV infusion or placebo was administered on Day 1 of every 21-day cycle within 1 hour of completing treatment with other agents administered via IV. In the absence of infusion-related reactions, brentuximab vedotin was to be administered as a 30-minute infusion. Subjects were to receive 6 to 8 cycles. Dose reduction for neuropathy required reducing brentuximab vedotin (placebo) and vincristine (placebo), see Table 9.

**Concomitant therapy included:**

- Premedication for infusion-related reaction (only in subjects with prior event in this study).
- Prophylaxis for Pneumocystis jiroveci pneumonia infection was to be considered for all subjects.
- Intrathecal prophylactic treatment for cerebral/meningeal disease was permitted at the discretion of the investigator.
- Transfusions and platelet and/or colony-stimulating factors per institutional practice were permitted.
- Chemomobilization of stem cells, consolidative SCT, and/or radiotherapy (only after completion of EOT procedures).

**Table 8. Summary of study treatments**

| | Study Treatment | |
|---|---|---|
| | A+CHP | CHOP |
| Blinded study drug A[a,b] | | |
| Brentuximab vedotin 1.8 mg/kg IV on Day 1 | X | |
| Placebo solution IV on Day 1 | | X |
| Cyclophosphamide 750 mg/m$^2$ IV on Day 1 | X | X |
| Doxorubicin 50 mg/m$^2$ IV on Day 1[c] | X | X |
| Prednisone 100 mg po daily on Days 1-5 (±1 day) | X | X |
| Blinded study drug B[b] | | |
| Vincristine 1.4 mg/m$^2$ (dose capped at 2 mg) IV on Day 1 | | X |
| Placebo saline IV on Day 1 | X | |

A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; IV=intravenously; PO=by mouth.

d Administered within 1 hour of completing treatment with other study drugs administered IV.

e Prepared by the site pharmacist; pharmacy blind was to be maintained.

f Doxorubicin could be administered over 48 hours, according to institutional standards.

**Table 9. Dose recommendations for treatment-associated neuropathy**

| Grade of Treatment-Associated Neuropathy | Recommended Dose Modification | |
|---|---|---|
| | Sensory Neuropathy | Motor Neuropathy |
| 1 | Continue study treatment at same dose level. | Continue study treatment at same dose level. |
| 2 | Continue study treatment at the same dose level. | Reduce brentuximab vedotin to 1.2 mg/kg, and reduce vincristine to 1 mg. |
| 3 | Reduce brentuximab vedotin to 1.2 mg/kg, and reduce vincristine to 1 mg. | Discontinue treatment with brentuximab vedotin and vincristine. |
| 4 | Discontinue treatment with brentuximab vedotin and vincristine. | Discontinue treatment with brentuximab vedotin and vincristine. |

## Objectives

Given the results of treatment with brentuximab vedotin in the relapsed and refractory setting, the MAH hypothesized that a treatment approach that incorporates brentuximab vedotin as part of multi-agent frontline induction therapy may yield a PFS and OS benefit. Thus, a superiority trial was conducted.

**Primary Objective**

- To compare the PFS as determined by an IRF between the 2 treatment arms

**Secondary Objectives**

- To compare the PFS per IRF between the 2 treatment arms for subjects with sALCL
- To compare the remission rates (CR and ORR) per IRF following the completion of study treatment between the 2 treatment arms
- To compare OS between the 2 treatment arms
- To evaluate the safety and tolerability of the 2 treatment arms

**Additional Objectives**

- To evaluate medical resource utilization (MRU) and calculate utility values
- To characterize the incidence of anti-therapeutic antibodies (ATA) to brentuximab vedotin

## Outcomes/endpoints

**Primary Endpoint**

- PFS per IRF

**Key Secondary Endpoints**

- PFS per IRF for subjects with sALCL
- CR rate per IRF following the completion of study treatment
- OS
- ORR per IRF following the completion of study treatment

**Additional Endpoints**

- Incidence of ATA to brentuximab vedotin
- MRU based on the number of medical care encounters
- Quality of life measured by EORTC QLQ-C30, FACT/GOG-NTX subscale, and EQ-5D-3L

Response assessment was done at baseline, C4(D15-20), last planned cycle of treatment (D15-20); end of treatment (EOT) (30-37 post last dose). On 3 monthly basis between 9-24 months after the first dose and after 24 months after the first dose every 6 months.

## Sample size

Approximately 450 patients (~225 patients per treatment arm) will be randomized in this study. The target proportion of patients with a diagnosis of sALCL per central pathology assessment will be 75% (±5%).

Approximately 238 events (progression or death due to any cause) are required for the final analysis to detect a hazard ratio of 0.6895 (23.93 months median PFS for the A+CHP arm versus 16.5 months for the CHOP arm) using the log-rank test with 80% power and an overall one-sided alpha level of 0.025.

An accrual period of 42 months (approximately 11 patients per month) is anticipated. An additional 18-month follow-up period is expected post-accrual of last patient to observe the specified number of PFS events with a 5% overall drop-out rate. Assuming a hazard ratio (HR) of 0.6895, a total of approximately 450 patients will be randomized.

The sample size was amended during the study based on analysis of blinded pooled data from this study, final PFS data from the lead-in safety study (SGN35-011), and newly available data from the International T-Cell Project (TCP), the sponsor determined that ECHELON-2's original design overestimated the event accrual rate. The protocol was amended twice (see also conduct of the study) in relation to the sample size:

- In March 2015 (amendment 3) the sample size was updated from 300 to 450.
- In May 2018 (amendment 4) it was indicated that the final primary analysis of PFS per IRF would occur after the earliest of a total of 238 events in the ITT analysis set or in August 2018 if 238 PFS events had not been accrued before that time

## Randomisation

Randomization was performed centrally using an interactive web response system (IWRS) that assigned a unique subject randomization number but did not specify the actual treatment assignment. Randomization numbers and their corresponding treatment assignments were assigned to subjects per the randomization list by sequential ascending block number, and by sequential ascending randomization numbers within the appropriate strata.

Subjects were randomized in a 1:1 manner to receive either A+CHP or CHOP. Randomization was stratified by:

- ALK-positive sALCL versus all other histologic types (per local pathology assessment)
- International Prognostic Index (IPI) (0-1, 2-3 and 4-5)

## Blinding (masking)

Brentuximab vedotin and vincristine were dispensed in a double-blinded, double-dummy manner. A pharmacy blind was enforced and investigators, subjects, the IRF, and the sponsor were blinded to treatment assignments.

Unblinding of a subject's treatment assignment prior to study closure was permitted at the time of documented disease progression or in emergency circumstances (via a formal unblinding procedure).

## Statistical methods

Analysis populations: The Intent-to-Treat (ITT) analysis set included all randomized subjects. The efficacy analysis were done in the ITT set. The Safety Analysis Set included all subjects who received any amount of brentuximab vedotin or any component of CHOP; subjects who received any dose of brentuximab vedotin were analysed in the A+CHP arm; subjects who did not receive brentuximab vedotin but received any dose of any component of CHOP were analysed in the CHOP arm.

PFS: the time from the date of randomization to the date of first documentation of progressive disease (PD), death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurred first. Kaplan-Meier methods were used to assess PFS. The stratified log-rank test without adjustments for covariates was used in the primary evaluation of PFS using the ITT analysis set and was tested at an overall one-sided, α=0.025 level. Cox regression of PFS was used to estimate the hazard ratio of the A+CHP arm to the CHOP arm. Censoring rules for the primary analysis of PFS are summarized in Table 10.

**Table 10. PFS censoring rules**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline and/or post baseline tumor assessment | Day following date of randomization | Censored |
| No documented progression | Date of last radiographic tumor assessment (or the date of randomization in the absence of a post-baseline radiographic tumor assessment) | Censored |
| PD documented between scheduled visits | Date of radiologic tumor assessment demonstrating PD | Event |
| Treatment discontinuation for undocumented progression after the last radiographic tumor assessment | Date of last radiographic tumor assessment or the date of randomization in the absence of a post-baseline radiographic tumor assessment | Censored |
| New anticancer therapy to treat residual or progressive disease initiated prior to documented progression, including palliative radiotherapy (excludes post-treatment chemotherapy given for stem cell mobilizations, excludes consolidative autologous or allogeneic SCT and excludes post-treatment consolidative radiotherapy) | Start date of new anticancer therapy | Event |
| Post-treatment consolidative radiotherapy, post-treatment chemotherapy given for stem cell mobilizations, consolidative autologous or allogeneic SCT | Date of last radiographic tumor assessment or the date of randomization in the absence of a post-baseline radiographic tumor assessment | Censored |
| Death before first PD assessment | Date of death | Event |
| Death between radiographic tumor assessment visits | Date of death | Event |
| Death or progression after more than one consecutively missed radiographic tumor assessment | Date of last radiologic tumor assessment prior to missed visits or the date of randomization in the absence of a post-baseline radiographic tumor assessment prior to missed visits | Censored |

Sensitivity analyses of PFS per IRF will be performed, including, but will not be limited to, the following:

1. A stratified log-rank analysis using the stratification factors as recorded in the CRF at baseline

2. An analysis where patients receiving SCT or consolidative radiotherapy are censored

3. An analysis where patients receiving new anticancer therapy are censored rather than considered to have had an event

4. An analysis assessing the impact of missing data/assessments where patients who missed one or more of the most recent scheduled assessments are treated as events at the time of the next scheduled assessment on the experimental arm

5. An analysis where initiation of consolidative radiotherapy and undocumented progression (e.g. progression identified by the Investigator on the basis of symptomatic deterioration) are considered events

6. An analysis where, for patients with a CR at EOT, initiation of consolidative radiotherapy or receipt of SCT are considered events

7. An analysis where patients who discontinue treatment for undocumented progression after the last radiographic tumor assessment are considered to have had an event at the time of treatment discontinuation; and where patients who die or progress after more than one consecutively missed radiographic tumor assessment are considered to have had an event on the date of death or progression

8. An analysis following EMA censoring guidelines where receipt of new anticancer therapy is not considered an event nor a reason for censoring and where patients who die or progress after more than one consecutively missed radiographic tumor assessment are considered to have had an event on the date of death or progression

Key secondary endpoints: A fixed sequence testing procedure (Westfall 2001) will be used to ensure type I error control for key secondary endpoints at an overall one-sided alpha level of 0.025.

PFS per IRF in Subjects with sALCL: endpoint was analysed in the same manner as the primary analysis of PFS per IRF. Subjects needed to have a central confirmation of the sALCL diagnosis.

Complete Remission Rate: The CR rate was defined as the proportion of subjects with CR per IRF following the completion of study treatment according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Subjects whose disease response was not assessable were scored as non-responders for calculating the CR rate. The CR rate between treatment arms was tested using the Cochran-Mantel-Haenszel (CMH) method, stratified by the randomization stratification factors. The absolute CR rate and exact two-sided 95% CI using the Clopper-Pearson method (Clopper 1934) were summarized by treatment arm.

Overall Survival: OS was defined as the time from randomization to death due to any cause (OS=date of death – date of randomization + 1). Any subject for whom death was not already known was censored for OS on the date the subject was last known to be alive (i.e., date of last contact), or data cut-off date. Subjects lacking data beyond the day of randomization were censored on the date of randomization (i.e., OS duration of 1 day).The stratified log-rank test without adjustments for covariates was used in the evaluation of OS between treatment arms. OS was analysed using Kaplan Meier methodology. The two-sided 95% CIs for the median were calculated using the complementary log-log transformation method (Collett 1994).

Objective Response Rate: The ORR was defined as the proportion of subjects with CR or PR per IRF following the completion of study treatment according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Subjects whose disease response was not assessable were scored as non-responders for calculating the ORR. The ORR between the treatment arms was tested using the CMH

method, stratified by the randomization stratification factors. The absolute ORR and exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) were summarized by treatment arm.

ATA: The ATA incidence rate is defined as the proportion of patients that develop ATA at any time during the study. ATA incidence will be summarized by treatment group.

MRU: Medical resource utilization data include medical care encounters related to study treatment or treatment for lymphoma. Medical resource utilization (MRU) data were summarized using descriptive statistics by treatment group.

QoL: Quality of life was measured using 3 different PRO instruments: the EORTC QLQC30, FACT/GOG-NTX, and EQ-5D-3L. PRO instrument total/subscale scores and change from baseline were summarized by treatment group and visit using descriptive statistics. In addition, the change from baseline was analysed using linear mixed models. Sensitivity analyses for missing data were conducted using imputation and pattern mixture models. PRO scores were also summarized by PFS status. PRO were measured at C1,D1, C2&3, D1, EOT and at long term follow up.

Multiplicity:
A fixed-sequence testing procedure was performed for the key secondary endpoints at an unadjusted alpha level until the preceding null hypothesis was not rejected. Testing was carried out in the following order: 0) PFS per IRF (primary endpoint); 1) PFS per IRF for subjects with centrally-confirmed sALCL; 2) CR per IRF; 3) OS; and 4) ORR per IRF.

One formal interim analysis for futility was planned for this study when approximately 50% of patients have completed EOT. This analysis focuses on the CR after EOT. At this analysis a cut-off date for the database was to be determined.

Missing data:
Apart from time-to-event endpoints and setting missing to failure for ORR and CR, all other endpoints excluded patients with missing data.

Pooling of strata:
In case of empty strata, pooling rules were prespecified. In general, missing strata defined by IPI & ALK positive sALCL will be pooled with the same IPI score and 'other types than ALK positive' sALCL (see the SAP).

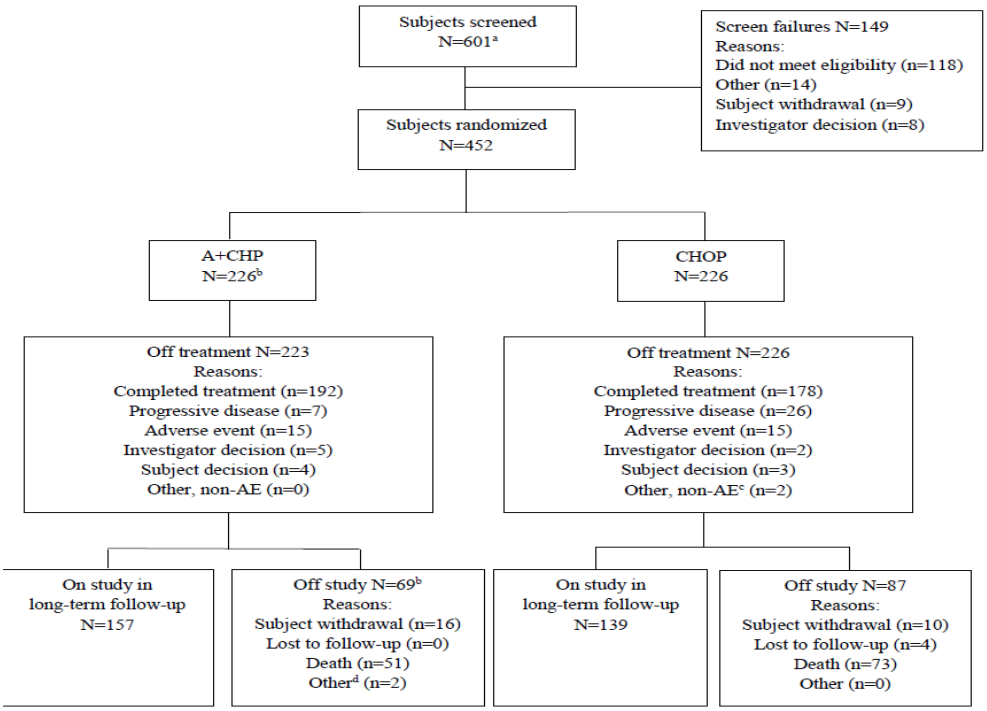
The primary analysis of PFS per IRF will occur after the earliest of

- a total of 238 events in the ITT analysis set have occurred
- August 2018 if 238 PFS events have not been accrued before that time.

## *Results*

## Participant flow

Overall, 449 subjects (99%) received treatment as randomized. Three subjects randomized to the A+CHP arm did not receive study treatment; 1 subject withdrew consent prior to treatment, 1 subject died prior to treatment, and 1 subject was found to be ineligible after randomization and was withdrawn from the study.




a Screening informed consents were obtained for 7 subjects to allow sites to perform screening activities that were not considered standard of care at their sites. The remaining 594 subjects signed the full informed consent for the study.
b Includes 3 subjects who were randomized to the A+CHP arm but did not receive study treatment.
c Other reasons were subject hospitalization until death for 1 subject, and death for the other subject.
d Other reasons for study discontinuation were change in diagnosis for 1 subject and 1 subject who was found to be ineligible after randomization and who did not receive any study treatment.

**Figure 4. Summary of subject disposition**

## Recruitment

The first subject enrolled on 24-Jan-2013 and the last subject visit for the primary analysis was on 15-Aug-2018 (date last subject assessed for the primary analysis per protocol).

## Conduct of the study

### Protocol amendments

The protocol was amended 4 times. The most important changes are summarized below:

**Amendment 1 Changes (27-Sep-2012)**

- The formal interim analysis for efficacy has been removed.
- Clarification that the IDMC will review the interim analysis for futility

**Amendment 2 Changes (31-Jan-2013)**

- Elevated ORR per IRF from Exploratory analysis to Secondary Objective/Secondary Endpoint

**Amendment 3 Changes (05 Mar 2015)**

- Sample size updated from 300 to 450, with ±238 events needed to detect a HR of 0.6895 using the log-rank test with >80% power and an overall one-sided alpha level of 0.025. The accrual period was updated from 24 months to 42 months, and follow-up time to PFS analysis updated to 18 months. The number of estimated OS events at the time of the primary analysis of PFS has been updated from 164 to 185

- PFS censoring dates have been updated from study day 1 or first dose date to the date of randomization for consistency. PFS sensitivity analysis following EMA censoring guidelines added to support submission to EMA

**Amendment 4 Changes (15 May 2018)**

- Specified that the primary efficacy analysis of PFS per IRF will use a data cut-off of August 2018 if the protocol-specified number of 238 PFS events have not been accrued before that time.
- Clarified that new anticancer therapy for progressive disease will also be considered a PFS event.

**Protocol deviations and violations**

Important protocol deviations (defined as protocol violations by Seattle Genetics) are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on subject's rights, safety, or welfare. Of the 452 subjects randomized in the study, 55 (12%) had a protocol violation. The proportion of subjects who had protocol violations was the same on each treatment arm: 27 subjects (12%) on the A+CHP arm and 28 subjects (12%) on the CHOP arm. See Table 11.

**Table 11. Protocol deviations ITT**

| | A+CHP (N=226) n (%) | CHOP (N=226) n (%) | Total (N=452) n (%) |
|---|---|---|---|
| Any important protocol deviation[a] | 27 (12) | 28 (12) | 55 (12) |
| Reason for important protocol deviation[b] | | | |
| 1.0 Inclusion criterion | 4 (2) | 4 (2) | 8 (2) |
| 2.0 Exclusion criterion | 1 (0) | 0 | 1 (0) |
| 4.0 Study drug administration | 7 (3) | 8 (4) | 15 (3) |
| 6.0 Study conduct | 10 (4) | 15 (7) | 25 (6) |
| 6.2 Informed consent | 3 (1) | 2 (1) | 5 (1) |
| 6.3 SAE reporting | 2 (1) | 0 | 2 (0) |
| 6.4 Administrative issues | 1 (0) | 0 | 1 (0) |
| 6.5 Source documents | 1 (0) | 1 (0) | 2 (0) |

Approximately half of the study conduct violations were related to stratification errors, which were reported for 6 subjects (3%) on each treatment arm. The other study conduct violations were primarily related to isolated instances where procedures/visits were not done. The majority of the drug administration violations (12 of 22) consisted of instances where subjects received the wrong dose of treatment.

Three site-level violations were reported; 2 of these (Sites 48001 and 36002) were drug accountability violations where a shipment of study drug was lost. In both cases, the staff were retrained, and the violations were not repeated. The 3rd site-level violation (Site 39002) was related to repeated failure to conduct CT scans of the neck. The site staff was retrained on appropriate scanning procedures, and potential corrective action was discussed and agreed upon with the Investigator.

A total of 8 potential unblinding incidents occurred in error for single subjects or subsets of subjects, both at the sponsor and study site level. In 3 cases, emails containing potentially unblinding information were sent from the central PK lab to sponsor staff and another 3 cases emails were sent from study site to sponsor staff. Two cases involved site staff being potentially unblinded to their subject's assignments. In each case, emails/communications that contained potentially unblinding information were quickly recalled and deleted from affected mailboxes/computers to control further dissemination of the data.

## Baseline data

## Numbers analysed

Efficacy analyses were performed using the ITT analysis set, which included all 452 randomized subjects; 226 subjects randomized to A+CHP and 226 subjects randomized to CHOP. In total 45% of the patients derived from sites in the EU, 28% from the US, 21% from Asia and 6% from other sites.

A summary of demographics and subject characteristics is shown in Table 12, Table 13 and Table 14.

**Table 12. Baseline demographic and patient characteristics (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Age (years) | | | |
| n | 226 | 226 | 452 |
| Mean (STD) | 55.3 (14.7) | 54.8 (15.5) | 55.1 (15.1) |
| Median | 58.0 | 58.0 | 58.0 |
| Min, Max | 18, 85 | 18, 83 | 18, 85 |
| Age group, n (%) | | | |
| <65 | 157 (69) | 156 (69) | 313 (69) |
| ≥65 | 69 (31) | 70 (31) | 139 (31) |
| Gender, n (%) | | | |
| Male | 133 (59) | 151 (67) | 284 (63) |
| Female | 93 (41) | 75 (33) | 168 (37) |
| Race, n (%) | | | |
| Asian | 45 (20) | 54 (24) | 99 (22) |
| Black or African American | 12 (5) | 6 (3) | 18 (4) |
| Native Hawaiian or Other Pacific Islander | 1 (0) | 0 | 1 (0) |
| White | 139 (62) | 142 (63) | 281 (62) |
| Other | 3 (1) | 2 (1) | 5 (1) |
| Unknown | 26 (12) | 22 (10) | 48 (11) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 10 (4) | 4 (2) | 14 (3) |
| Not Hispanic or Latino | 186 (82) | 193 (85) | 379 (84) |
| Unknown | 30 (13) | 29 (13) | 59 (13) |
| ECOG performance status[a], n (%) | | | |
| 0 | 84 (37) | 93 (41) | 177 (39) |
| 1 | 90 (40) | 86 (38) | 176 (39) |
| 2 | 51 (23) | 47 (21) | 98 (22) |

**Table 13. Baseline disease characteristics (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Diagnosis, per local assessment, n (%) | | | |
| sALCL | 162 (72) | 154 (68) | 316 (70) |
| ALK-positive | 49 (22) | 49 (22) | 98 (22) |
| ALK-negative | 113 (50) | 105 (46) | 218 (48) |
| PTCL-NOS | 29 (13) | 43 (19) | 72 (16) |
| AITL | 30 (13) | 24 (11) | 54 (12) |
| ATLL | 4 (2) | 3 (1) | 7 (2) |
| EATL | 1 (0) | 2 (1) | 3 (1) |
| Time from diagnosis to first dose of study treatment (months) | | | |
| n | 222 | 224 | 446 |
| Mean (STD) | 1.1 (1.5) | 1.1 (0.9) | 1.1 (1.3) |
| Median | 0.8 | 0.9 | 0.9 |
| Min, Max | 0, 19 | 0, 10 | 0, 19 |
| Disease staging at diagnosis, n (%) | | | |
| Stage I | 12 (5) | 9 (4) | 21 (5) |
| Stage II | 30 (13) | 37 (16) | 67 (15) |
| Stage III | 57 (25) | 67 (30) | 124 (27) |
| Stage IV | 127 (56) | 113 (50) | 240 (53) |
| Initial diagnosis of cutaneous ALCL (for subjects with sALCL), n (%) | 13 (6) | 4 (2) | 17 (4) |
| Time from cutaneous ALCL diagnosis to sALCL diagnosis (months) | | | |
| n | 11 | 4 | 15 |
| Mean (STD) | 16.0 (20.6) | 9.8 (12.8) | 14.4 (18.6) |
| Median | 4.8 | 4.7 | 4.8 |
| Min, Max | 1, 69 | 1, 29 | 1, 69 |
| Baseline IPI score, n (%) | | | |
| 0 | 8 (4) | 16 (7) | 24 (5) |
| 1 | 45 (20) | 32 (14) | 77 (17) |
| 2 | 74 (33) | 78 (35) | 152 (34) |
| 3 | 66 (29) | 66 (29) | 132 (29) |
| 4 | 29 (13) | 25 (11) | 54 (12) |
| 5 | 4 (2) | 9 (4) | 13 (3) |

**Table 14. Baseline disease characteristics continued (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Serum LDH per local laboratory, n (%) | | | |
| ≤1 × ULN | 113 (50) | 97 (43) | 210 (46) |
| >1 × ULN | 113 (50) | 129 (57) | 242 (54) |
| Extranodal disease involvement, n (%) | | | |
| ≤1 site | 142 (63) | 146 (65) | 288 (64) |
| >1 site | 84 (37) | 80 (35) | 164 (36) |
| HTLV-1 status, n (%) | | | |
| Positive | 5 (2) | 4 (2) | 9 (2) |
| Negative | 216 (96) | 219 (97) | 435 (96) |
| Intended number of cycles, n (%) | | | |
| 6 | 185 (82) | 182 (81) | 367 (81) |
| 8 | 41 (18) | 44 (19) | 85 (19) |
| Intention of stem cell transplant following completion of study regimen, n (%) | | | |
| Yes | 89 (39) | 81 (36) | 170 (38) |
| No | 136 (60) | 144 (64) | 280 (62) |
| Baseline bone marrow biopsy-lymphoma involvement, n (%) | | | |
| Yes | 30 (13) | 34 (15) | 64 (14) |
| No | 196 (87) | 192 (85) | 388 (86) |
| Percent CD30 positive cells, per local assessment[a] | | | |
| n | 224 | 226 | 450 |
| Mean (STD) | 76.5 (32.7) | 77.0 (30.7) | 76.8 (31.7) |
| Median | 90.5 | 90.0 | 90.0 |
| Min, Max | 10, 100 | 10, 100 | 10, 100 |
| Percent CD30 positive cells, per central review | | | |
| n | 222 | 220 | 442 |
| Mean (STD) | 81.1 (28.4) | 77.6 (30.6) | 79.4 (29.5) |
| Median | 95.0 | 90.0 | 95.0 |
| Min, Max | 0, 100 | 0, 100 | 0, 100 |

a Two patients had local CD30 percentage values reported by the site to be ≥10%, but exact percentage values were not reported.

The median CD30 expression (cells) per subtype was:

- PTCL-NOS: 25% in the A+CHP arm and 60% in the CHOP arm
- AITL: 18% in the A+CHP arm and 15% in the CHOP arm
- ATLL: 60% in the A+CHP arm and 70% in the CHOP arm
- EATL: 90% in the A+CHP arm and 55% in the CHOP arm

**Exposure**

The duration of treatment was similar between the treatment arms; the median number of cycles received was the same on both treatment arms; 6.0 (range, 1 to 8).

In total 156 (70%) of the patients in the A+CHP arm received 6 cycles of treatment and 140 (62%) patients in the CHOP arm and respectively 18% and 19% of subjects receiving 8 cycles.

The median number of weeks of treatment per subject was 18.1 (range, 3 to 34) on the A+CHP arm and 18.0 (range, 3 to 31) on the CHOP arm.

The median cumulative brentuximab vedotin dose was 762.0 mg (range 94, 1431) in A+CHP arm. The median cumulative vincristine dose was 12 mg (range 2, 16) in the control arm. The exposure of cyclophosphamide and doxorubicin was comparable between the two arms. (See also clinical safety section.)

**Subsequent therapies**

For a summary of all subsequent anti-cancer therapies, see Table 15 .Brentuximab vedotin-containing therapy was given in 23 (10%) of the A+CHP patients and in 49 (22%) of the CHOP arm. From these patients, objective responses were attained by 13/23 subjects (57%) on the A+CHP arm and 24/49 subjects (49%) on the CHOP arm.

In total 50 patients (22%) in the A+CHP arm and 39 patients in the CHOP arm (17%) received SCT, see table below.

**Table 15. Summary of Subsequent Treatment (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Subjects who received subsequent new anti-cancer therapy, n (%) | 65 (29) | 96 (42) | 161 (36) |
| Systemic therapy for residual or progressive disease | 59 (26) | 94 (42) | 153 (34) |
| Palliative radiation | 10 (4) | 8 (4) | 18 (4) |
| Systemic therapy for secondary malignancy | 7 (3) | 3 (1) | 10 (2) |
| Consolidative treatment received, n (%) | 61 (27) | 44 (19) | 105 (23) |
| Consolidative radiotherapy[a] | 14 (6) | 6 (3) | 20 (4) |
| Consolidative stem cell transplant | 50 (22) | 39 (17) | 89 (20) |
| Autologous | 49 (22) | 39 (17) | 88 (19) |
| Allogeneic | 1 (0) | 0 | 1 (0) |

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a. Consolidative radiotherapy is derived from CRF page with medical resource utilization (LRMRU), excluding patients with conditioning radiotherapy for total body from stem cell transplant page (LTFUSCT). In LRMRU, only records with hospitalization date and outpatient visit date after last treatment date and before the earliest of PD date per investigator and new anti-cancer therapy date will be include.
b. In total, there are 3 types of different anti-cancer therapies: systemic therapy for residual or progressive disease, palliative radiotherapy, systemic therapy for secondary malignancy.
Data snapshot: 20SEP2018
Source: O:\Projects\SGN-35\sg035-0014\csr_errata_1432\v02\outputs\tlfs\pgms\t-sum-atutx.sas Output: t-sum-atutx-itts.rtf (30NOV18:11:56) Data: adsl, adconmed, adeff

**Table 16. Summary of patients receiving SCT (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Patients received consolidative SCT after last treatment date, n (%) | | | |
| Yes | 50 (22) | 39 (17) | 89 (20) |
| No | 176 (78) | 187 (83) | 363 (80) |
| Proportion difference[a], (95% C.I.[b]) (CHOP - A+CHP) | | | -4.9 (-12.2, 2.5) |
| Proportion of consolidative SCT after last treatment date for baseline intended patients, n (%) | 40/89 (45) | 32/81 (40) | 72/170 (42) |
| Proportion difference, (95% C.I.[b]) (CHOP - A+CHP) | | | -5.4 (-20.3, 9.4) |

## Outcomes and estimation

**Primary Efficacy Analysis PFS per IRF**

As of the 15 August 2018 data cut-off date, 219 subjects (48%) had experienced a PFS event; 95/226 subjects (42%) on the A+CHP arm and 124/226 subjects (55%) on the CHOP arm. PFS per IRF was significantly improved on the A+CHP arm compared with the CHOP arm (stratified HR 0.71 [95% CI: 0.54, 0.93], P=0.011) (Table 17).

**Table 17. PFS per IRF summary (ITT)**

| | A+CHP (N=226) | CHOP (N=226) |
|---|---|---|
| Number of subjects with a PFS event, n (%) | 95 (42) | 124 (55) |
| Disease progression per Cheson | 71 (31) | 86 (38) |
| Death | 13 (6) | 17 (8) |
| New therapy[a] | 11 (5) | 21 (9) |
| Stratified hazard ratio (95% CI) (A+CHP to CHOP) | 0.71 (0.54, 0.93) | |
| Stratified log-rank P value[b] | 0.0110 | |
| Median PFS (months) (95% CI)[c] | 48.20 (35.15, -) | 20.80 (12.68, 47.57) |
| 25th, 75th percentile | 8.87, - | 4.70, - |
| Observed min, max | 0.03+, 60.06+ | 0.03+, 60.45+ |
| Censored, n (%) | 131 (58) | 102 (45) |
| Estimated progression-free rate (95% CI)[c] at: | | |
| 6 months | 82.1% (76.4%, 86.6%) | 70.8% (64.3%, 76.3%) |
| 12 months | 71.7% (65.1%, 77.2%) | 58.2% (51.4%, 64.3%) |
| 24 months | 61.4% (54.4%, 67.6%) | 47.4% (40.6%, 53.8%) |
| 36 months | 57.1% (49.9%, 63.7%) | 44.4% (37.6%, 50.9%) |
| Median PFS follow-up (months) (95% CI)[d] | 35.91 (32.26, 41.46) | 41.79 (36.04, 42.12) |

a New anticancer therapy to treat residual or progressive disease initiated prior to IRF-documented progression per Cheson, including palliative radiotherapy. No subjects had an event due to palliative radiotherapy.
b From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization.
c PFS rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method (Collett, 1994).
d Median PFS follow-up is calculated from the Kaplan-Meier method switching the PFS event/censored status, i.e. PFS event as censored and censored as PFS event.

Source: Table 14.2.1.1a

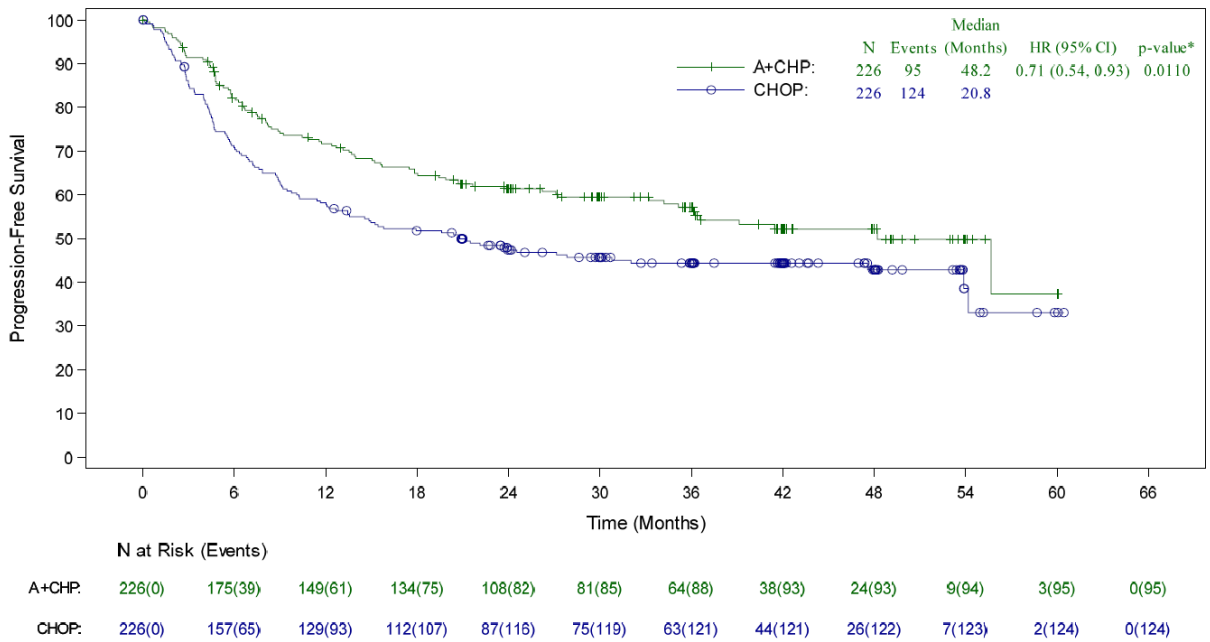
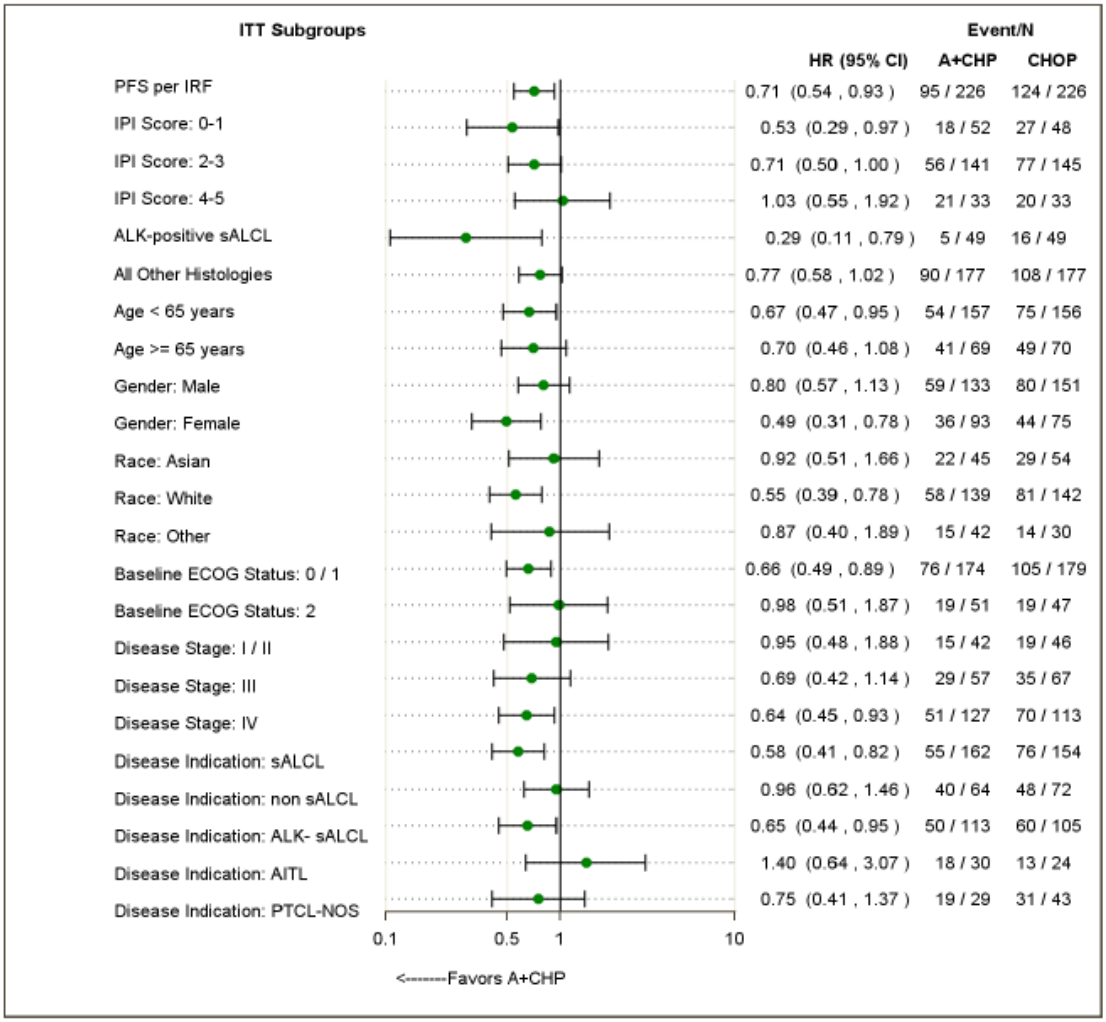



**Figure 5. Kaplan-Meier plot of PFS per IRF (ITT)**

**Table 18. Reasons for PFS censoring (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Censored, n (%) | 131 (58) | 102 (45) | 233 (52) |
| No adequate baseline tumor assessment, or no adequate post-baseline tumor assessment | 5 (2) | 2 (1) | 7 (2) |
| PFS event documented right after more than one consecutive missed visit | 3 (1) | 0 | 3 (1) |
| No documented progression, still on study | 115 (51) | 93 (41) | 208 (46) |
| Off Study | 8 (4) | 7 (3) | 15 (3) |
| Withdrawal of consent | 8 (4) | 5 (2) | 13 (3) |
| Lost to follow-up | 0 | 2 (1) | 2 (0) |
| Other | 0 | 0 | 0 |

**Table 19. PFS subgroup analyses (ITT)**

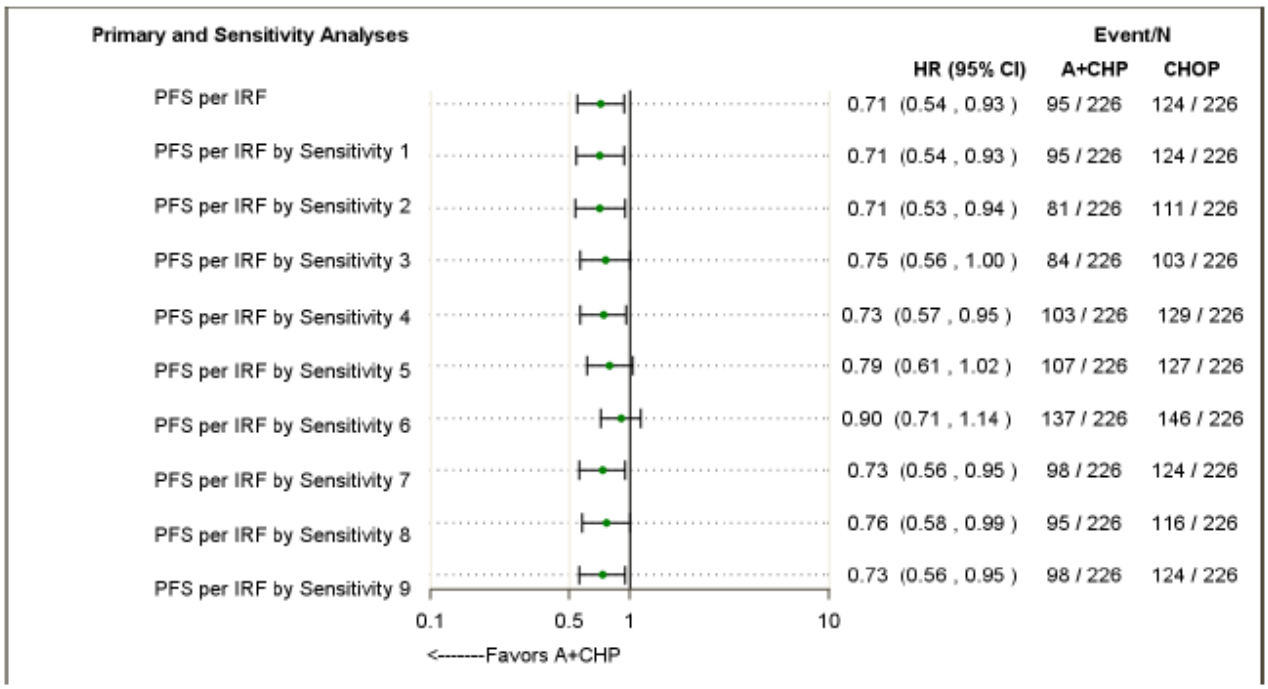



HR is calculated from the Cox regression model considering stratification factors at randomization
Source: Figure 14.2.1.23

HR is calculated from cox regression model considering stratified factors from randomization.
Stratified HR can not be calculated for race subgroup 'Other' and disease subgroup 'EATL'.
Data snapshot: 20SEP2018
Source: O:\Projects\SGN-35\sg035-0014\CSR_DBL_1374\v01\outputs\tlfs\pgms\f-forest-hr.sas Output: f-forest-pfs-irf-itts.rtf(14OCT18:18:35) Data: adsl, adtte

For the PFS sensitivity analyses see Table 20.

**Table 20. PFS- primary and sensitivity analyses (ITT)**




HR is calculated from cox regression model considering stratified factors from randomization.
Sensitivity analysis 1: A stratified log-rank analysis using the stratification factors as recorded in the CRF at baseline.
Sensitivity analysis 2: An analysis in which patients receiving SCT or consolidative radiotherapy are censored.
Sensitivity analysis 3: An analysis in which patients receiving new anticancer therapy are censored rather than considered to have had an event (ignore secondary malignancy therapy)
Sensitivity analysis 4: Patients who missed two or more of the most recent scheduled assessments are treated as events at the time of the next scheduled assessment.
Sensitivity analysis 5: An analysis in which initiation of consolidative radiotherapy and undocumented progression (e.g. progression identified by the Investigator on the basis of symptomatic deterioration) are considered events.
Sensitivity analysis 6: An analysis in which, for patients with a CR at EOT, initiation of consolidative radiotherapy or receipt of SCT are considered events.
Sensitivity analysis 7: An analysis in which patients who discontinue treatment for undocumented progression after the last radiographic tumor assessment are considered to have had an event at the time of treatment discontinuation and in which patients who die or progress after more than one consecutively missed radiographic tumor assessment are considered to have had an event on the date of death or progression.
Sensitivity analysis 8: An analysis following EMA censoring guidelines in which receipt of new anticancer therapy is not considered an event nor a reason for censoring and in which patients who die or progress after more than one consecutively missed radiographic tumor assessment are considered to have had an event on the date of death or progression.
Sensitivity analysis 9: An analysis where patients who die, progress, or receive new therapy after more than one consecutively missed adequate tumor assessment are considered to have had an event on the date of death, progression, or new therapy.
Data snapshot: 20SEP2018
Source: O:\Projects\SGN-35\sg035-0014\csr_errata_1432\v02\outputs\tlfs\pgms\f-forest-hr-sens.sas Output: f-forest-pfs-irf-sens-itts.rtf(30NOV18:11:56) Data:

**Table 21. Summary of PFS per IRF, Sensitivity analysis 8 (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 95 (42) | 116 (51) | 211 (47) |
| Disease Progression per Cheson | 76 (34) | 90 (40) | 166 (37) |
| Death | 19 (8) | 26 (12) | 45 (10) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.76 (0.58, 0.99) |
| Stratified Log-rank p-value[a] | | | 0.0443 |
| Median PFS (months) (95% C.I.)[b] | 48.20 (36.14, -) | 26.02 (15.44, 54.18) | 41.46 (27.24, 55.66) |
| 25th, 75th percentile | 10.91, - | 6.41, - | 7.85, - |
| Observed min, max | 0.03+, 60.06+ | 0.03+, 60.45+ | 0.03+, 60.45+ |
| Censored, n (%) | 131 (58) | 110 (49) | 241 (53) |
| Estimated progression-free rate (95% C.I.)[b] at: | | | |
| 6 months | 85.3% (79.9%, 89.4%) | 75.9% (69.7%, 81.1%) | 80.6% (76.6%, 84.0%) |
| 12 months | 74.0% (67.6%, 79.4%) | 62.5% (55.8%, 68.6%) | 68.3% (63.7%, 72.4%) |
| 24 months | 62.3% (55.4%, 68.5%) | 50.9% (44.0%, 57.4%) | 56.6% (51.7%, 61.1%) |
| 36 months | 57.4% (50.1%, 64.0%) | 47.2% (40.2%, 53.9%) | 52.3% (47.3%, 57.1%) |
| 48 months | 50.8% (42.5%, 58.5%) | 44.8% (37.3%, 51.9%) | 48.0% (42.5%, 53.3%) |

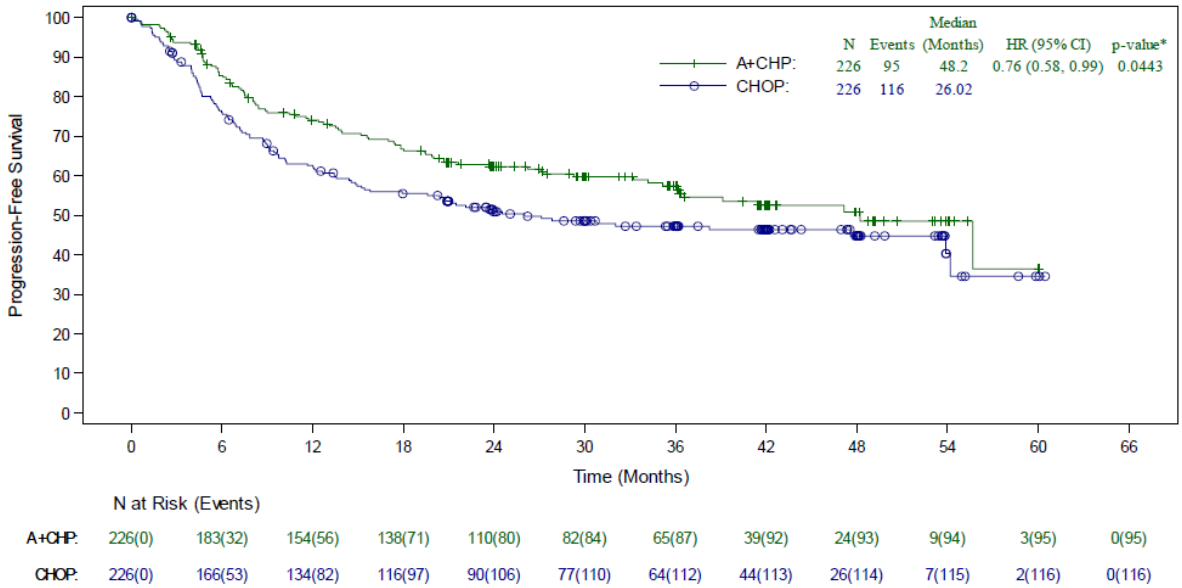



**Figure 6. Progression-Free Survival per IRF by Treatment Arm, Sensitivity analysis 8 (ITT)**

**Table 22. Summary of Censoring Reasons for PFS per IRF, Sensitivity 8 (ITT)**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Censored, n (%) | 131 (58) | 110 (49) | 241 (53) |
| No adequate baseline tumor assessment, or no adequate post-baseline tumor assessment | 5 (2) | 3 (1) | 8 (2) |
| No documented progression, still on study | 117 (52) | 100 (44) | 217 (48) |
| Off Study | 9 (4) | 7 (3) | 16 (4) |
| Withdrawal of consent | 9 (4) | 5 (2) | 14 (3) |
| Lost to follow-up | 0 | 2 (1) | 2 (0) |
| Other | 0 | 0 | 0 |

### Key secondary endpoints

According to the Applicant all alpha-protected key secondary endpoints in this study were met.

**PFS per IRF for sALCL patients**

The PFS for subjects with sALCL was significantly improved on the A+CHP arm compared with the CHOP arm (stratified HR 0.59 [95% CI: 0.42, 0.84], P=0.0031). The median PFS per IRF for subjects with sALCL was 55.66 months (95% CI: 48.20, –) on the A+CHP arm versus 54.18 months (95% CI: 13.44, –) on the CHOP arm.

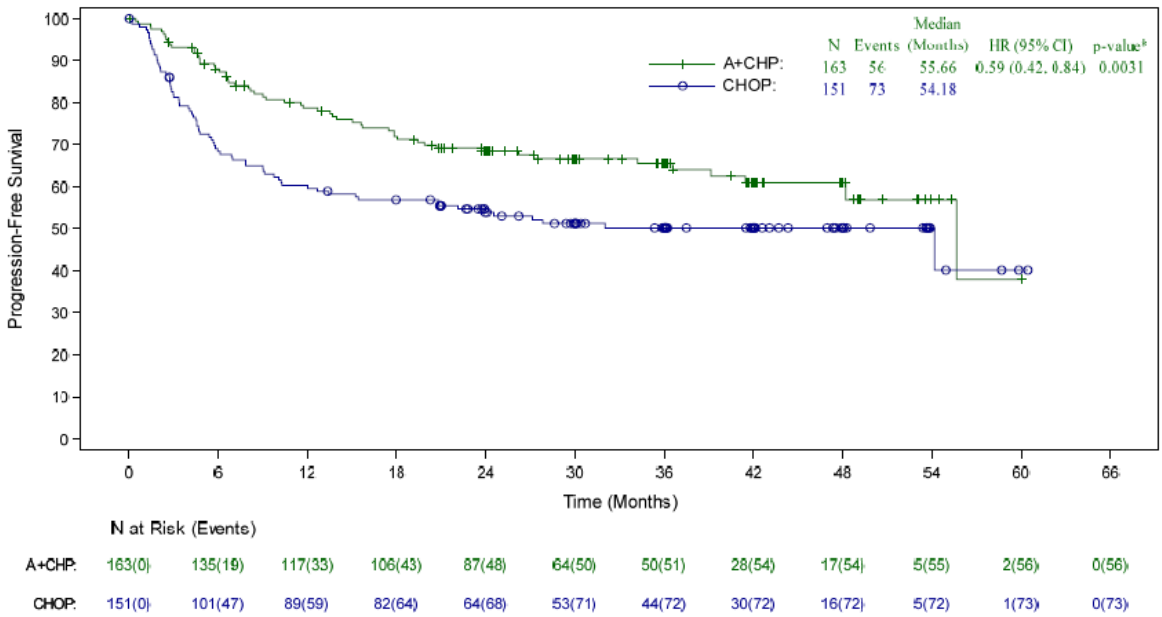



**Figure 7. PFS per IRF for subjects with sALCL (ITT)**

**Table 23. Summary of PFS per IRF for sALCL patients**

| | A+CHP (N=163) | CHOP (N=151) | Total (N=314) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 56 (34) | 73 (48) | 129 (41) |
| Disease Progression per Cheson | 40 (25) | 46 (30) | 86 (27) |
| Death | 9 (6) | 13 (9) | 22 (7) |
| New Therapy[a] | 7 (4) | 14 (9) | 21 (7) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.59 (0.42, 0.84) |
| Stratified Log-rank p-value[b] | | | 0.0031 |
| Median PFS (months) (95% C.I.)[c] | 55.66 (48.20, -) | 54.18 (13.44, -) | 54.18 (41.46, -) |
| 25th, 75th percentile | 15.61, - | 4.57, - | 7.85, - |
| Observed min, max | 0.03+, 60.06+ | 0.03+, 60.45+ | 0.03+, 60.45+ |
| Censored, n (%) | 107 (66) | 78 (52) | 185 (59) |
| Estimated progression-free rate (95% C.I.)[c] at: | | | |
| 6 months | 88.0% (81.8%, 92.2%) | 68.4% (60.3%, 75.2%) | 78.5% (73.5%, 82.7%) |
| 12 months | 78.7% (71.4%, 84.4%) | 60.3% (51.9%, 67.6%) | 69.8% (64.3%, 74.6%) |
| 24 months | 68.4% (60.4%, 75.2%) | 53.9% (45.5%, 61.5%) | 61.4% (55.6%, 66.7%) |
| 36 months | 65.5% (57.1%, 72.7%) | 50.2% (41.6%, 58.1%) | 58.1% (52.1%, 63.6%) |

**Table 24 Summary of Progression-Free Survival (PFS) per IRF - ITT Analysis Set - ALK Positive sALCL**

| | A+CHP (N=49) | CHOP (N=49) | Total (N=98) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 5 (10) | 16 (33) | 21 (21) |
| Disease Progression per Cheson | 2 (4) | 11 (22) | 13 (13) |
| Death | 1 (2) | 3 (6) | 4 (4) |
| New Therapy[a] | 2 (4) | 2 (4) | 4 (4) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.29 (0.11, 0.79) |
| Stratified Log-rank p-value[b] | | | 0.0100 |
| Median PFS (months) (95% C.I.)[c] | - (-, -) | - (-, -) | - (-, -) |
| 25th, 75th percentile | -, - | 4.57, - | -, - |
| Observed min, max | 0.03+, 60.06+ | 0.1, 59.83+ | 0.03+, 60.06+ |
| Censored, n (%) | 44 (90) | 33 (67) | 77 (79) |
| Estimated progression-free rate (95% C.I.)[c] at: | | | |
| 6 months | 93.6% (81.3%, 97.9%) | 73.5% (58.7%, 83.6%) | 83.3% (74.2%, 89.4%) |
| 12 months | 89.0% (75.5%, 95.3%) | 69.4% (54.4%, 80.3%) | 78.9% (69.3%, 85.9%) |
| 24 months | 89.0% (75.5%, 95.3%) | 69.4% (54.4%, 80.3%) | 78.9% (69.3%, 85.9%) |
| 36 months | 89.0% (75.5%, 95.3%) | 66.9% (51.7%, 78.3%) | 77.6% (67.7%, 84.8%) |
| 48 months | 89.0% (75.5%, 95.3%) | 66.9% (51.7%, 78.3%) | 77.6% (67.7%, 84.8%) |
| Median PFS follow-up (months) (95% C.I.)[d] | 35.61 (29.50, 41.89) | 37.49 (30.39, 42.09) | 36.14 (32.26, 41.89) |

**Table 25 – Summary of Progression-Free Survival (PFS) per IRF - ITT Analysis Set - ALK Negative sALCL**

| | A+CHP (N=113) | CHOP (N=105) | Total (N=218) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 50 (44) | 60 (57) | 110 (50) |
| Disease Progression per Cheson | 38 (34) | 38 (36) | 76 (35) |
| Death | 7 (6) | 10 (10) | 17 (8) |
| New Therapy[a] | 5 (4) | 12 (11) | 17 (8) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.65 (0.44, 0.95) |
| Stratified Log-rank p-value[b] | | | 0.0235 |
| Median PFS (months) (95% C.I.)[c] | 48.20 (23.72, -) | 15.44 (9.03, -) | 27.83 (18.04, 55.66) |
| 25th, 75th percentile | 11.73, 55.66 | 4.67, - | 6.54, 55.66 |
| Observed min, max | 0.03+, 60.02+ | 0.03+, 60.45+ | 0.03+, 60.45+ |
| Censored, n (%) | 63 (56) | 45 (43) | 108 (50) |
| Estimated progression-free rate (95% C.I.)[c] at: | | | |
| 6 months | 85.5% (77.4%, 90.9%) | 65.9% (55.9%, 74.2%) | 76.1% (69.7%, 81.2%) |
| 12 months | 74.2% (64.8%, 81.4%) | 55.1% (44.9%, 64.1%) | 65.0% (58.1%, 71.0%) |
| 24 months | 59.4% (49.4%, 68.1%) | 44.8% (34.9%, 54.2%) | 52.4% (45.4%, 59.0%) |
| 36 months | 55.2% (44.8%, 64.4%) | 40.5% (30.5%, 50.3%) | 48.2% (40.9%, 55.0%) |
| 48 months | 50.4% (38.9%, 60.8%) | 40.5% (30.5%, 50.3%) | 46.0% (38.5%, 53.2%) |
| Median PFS follow-up (months) (95% C.I.)[d] | 35.88 (29.83, 36.14) | 36.04 (29.93, 43.07) | 35.88 (30.00, 41.59) |

**CR Rate**

At the end of treatment, the CR rate by IRF assessment was 68% [61.2, 73.7] for subjects on the A+CHP arm compared with 56% [ CI: 49.0,62.3] for subjects on the CHOP arm (p=0.0066). The rate difference was 11.9[3.1, 20.8], p-value 0.0066. The median duration of CR was similar on both treatment arms (52.70 months [range, 0.03+ to 57.46+] for A+CHP versus 49.94 months [range, 0.03+ to 57.43+] for CHOP). Concordance rates between IRF and investigator were (~82%) for the CR rate.

**Overall survival**

The median OS observation time is 42.12 months. In total 124 (27%) OS events were observed. In the A+CHP arm 51 (23%) events and 73 (32%) in the CHOP arm. The median OS had not been reached in either treatment arm. The stratified HR was 0.66 (95% CI: 0.46, 0.95), p=0.0244.

A total of 72 subjects (16%) received brentuximab vedotin-containing subsequent therapy: 23 subjects (10%) on the A+CHP arm and 49 subjects (22%) on the CHOP arm. Objective responses were attained by 13/23 subjects (57%) on the A+CHP arm and 24/49 subjects (49%) on the CHOP arm.

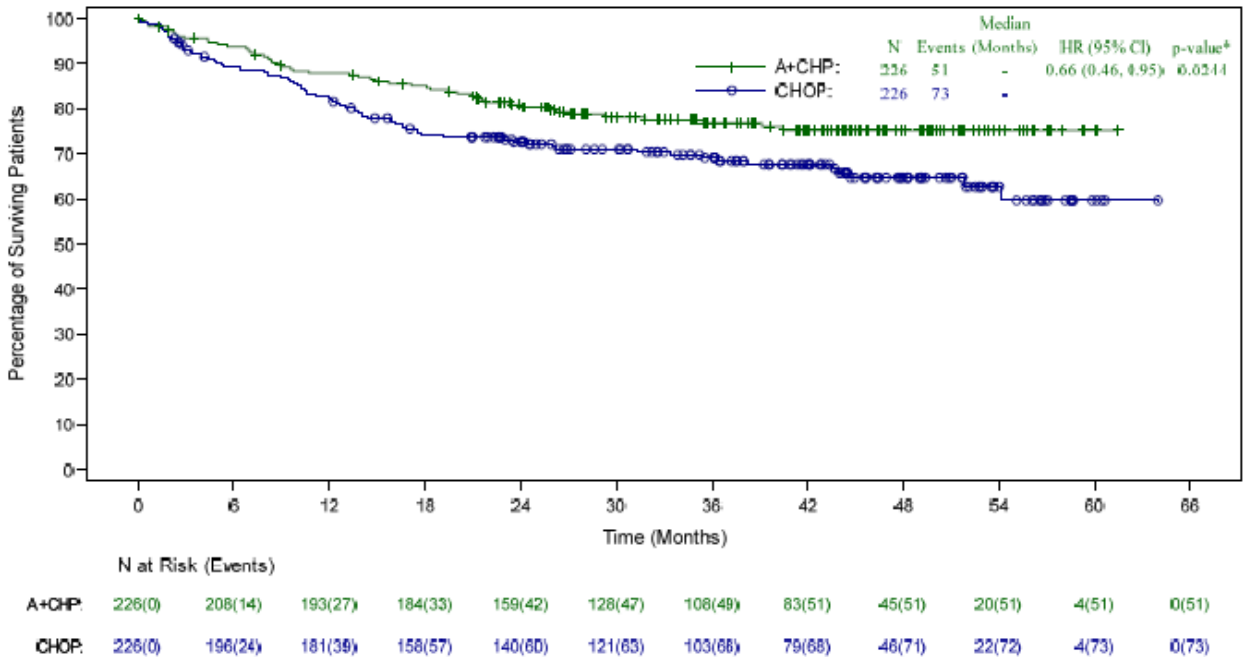



**Figure 8. Kaplan Meier curve Overall survival (ITT)**

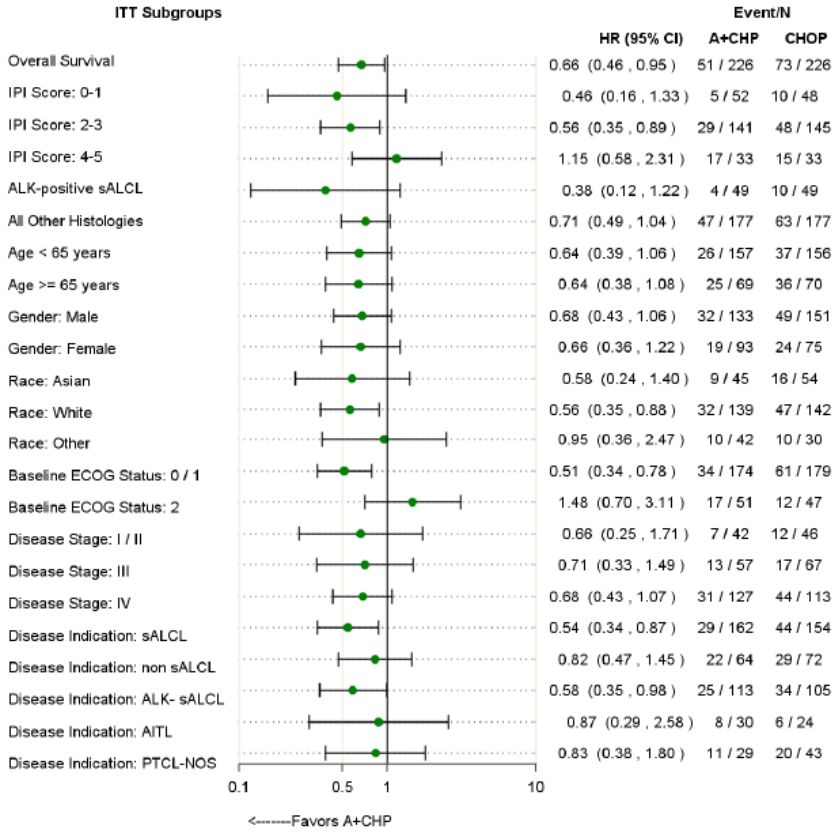
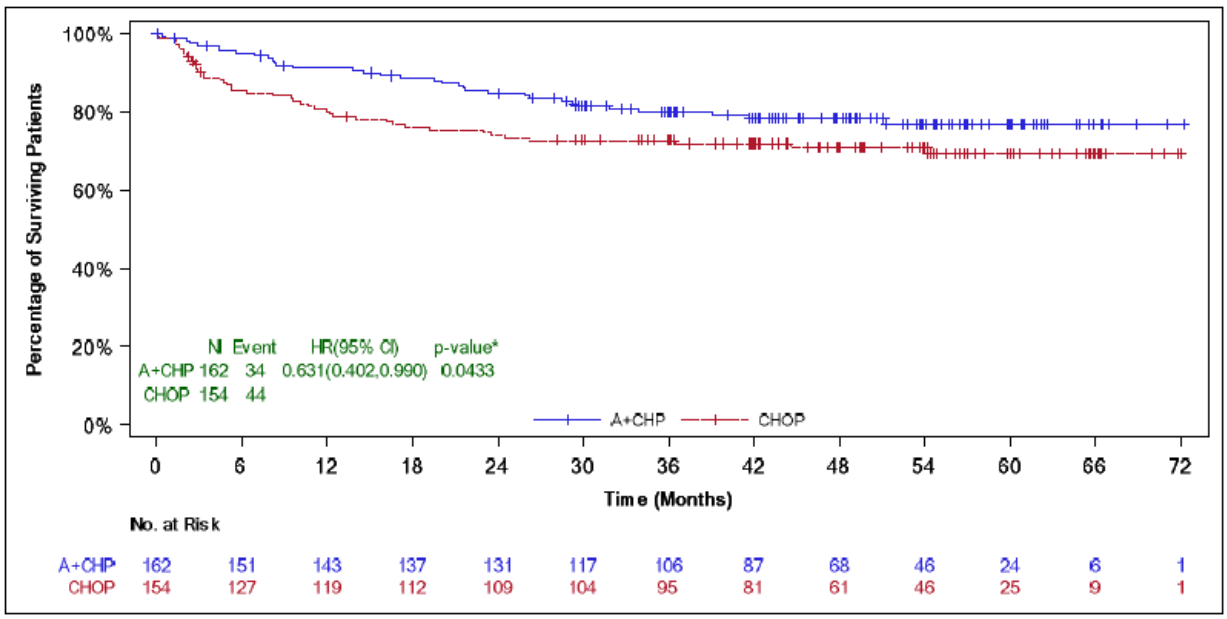



**Figure 9. Subgroup analyses for OS (ITT)**




Source: (Table 96.1.2.1.3) /bdm/tbos/SGN-035/35-14/CSR/Adhoc/EMA_RSI_2019/Figures/F96.1.2.1.3-KM_OS_subgrp, run 07 October 2019, 10:42. Data snapshot: 25SEP2019.
* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization.

**Figure 10. ECHELON-2: Updated Overall Survival (ITT Population – sALCL Subset**

**ORR Rate**

The ORR at EOT by IRF assessment was 83% [77.7, 87.8] for subjects on the A+CHP arm compared with 72% [ 65.8, 77.9] for subjects on the CHOP arm (p=0.0032) (Table 26). The rate difference was 11.1 [3.4, 18.7], p-value=0.0032. The median duration of objective response was similar on both treatment arms (52.70 months [range, 0.03 to 57.46+] for A+CHP versus 51.35 months [range, 0.03+ to 57.86+] for CHOP). Concordance rates between IRF and investigator for ORR were (~92%).

**Table 26. Response rates by IRF (ITT)**

| | A+CHP (N=226) | CHOP (N=226) |
|---|---|---|
| Response at EOT[a,b], n (%) | | |
| Complete remission (CR) | 153 (68) | 126 (56) |
| Partial remission (PR) | 35 (15) | 37 (16) |
| Stable disease (SD) | 5 (2) | 11 (5) |
| Progressive disease (PD) | 15 (7) | 31 (14) |
| Not evaluable (NE)[d] | 18 (8) | 21 (9) |
| ORR (CR+PR), n (%) | 188 (83) | 163 (72) |
| 95% CI[c] for ORR | (77.7, 87.8) | (65.8, 77.9) |
| Response rate difference (95% CI) | 11.1 (3.4, 18.7) | |
| Stratified CMH P-value for ORR | 0.0032 | |
| CR rate, n (%) | 153 (68) | 126 (56) |
| 95% CI[c] for CR rate | (61.2, 73.7) | (49.0, 62.3) |
| Response rate difference (95% CI) | 11.9 (3.1, 20.8) | |
| Stratified CMH P-value for CR rate | 0.0066 | |

**Additional endpoints**

**Incidence of ATA to Brentuximab Vedotin and effect on PFS**

On the A+CHP arm, baseline ATA samples were available for 205 of 226 subjects in the ITT analysis set; samples were missing for 18 subjects, and 3 subjects did not receive study treatment. The majority of subjects were ATA-negative at baseline (81%) and most remained ATA-negative throughout post-baseline visits.

A total of 49/205 subjects (24%) tested positive for ATA at any post-baseline visit; 40 subjects who were ATA-negative at baseline and 9 who were ATA-positive at baseline. Of the 49 ATA-positive subjects, 47 (96%) were transiently ATA-positive, and 2 (4%) were persistently ATA-positive. The majority of ATA-positive subjects first showed a positive result at Cycle 2. No notable differences were observed between the PFS curves or PFS outcomes for ATA-negative and transiently ATA-positive subjects. The 2 subjects who were persistently ATA-positive did not have PFS events and were censored between 36 and 54 months (data shown in CSR).

Five subjects on the A+CHP arm tested positive for neutralizing antibodies (nATA) to brentuximab vedotin. Four of the 5 nATA-positive subjects first tested positive for nATA at Cycle 2; the other subject first tested positive at Cycle 3. All 5 subjects had an objective response, although 2 of the 5 subjects subsequently progressed.

**Medical Resource Utilization**

The number of subjects with medical encounters was 142 (63%) in the A+CHP arm and 144 in the CHOP arm (64%). The median days hospitalized per subject was 28.0 and 29.0 days respectively. In the A+CHP arm the most frequent reason for hospitalization was related to an AE that started during

the treatment period and is ongoing (37% of the subjects; 23% in the control arm) and chemotherapy in the control arm (38%; 28% in the experimental arm).

**Quality of Life**

- EORTC QLQ c-30: The mean total scores are shown in Figure 11. While the scores were numerically lower in the A+CHP arm compared to CHOP arm, there was no statistically significant difference between the two treatment arms in total score. Some statistically significant differences between the 2 arms in change from baseline scores in favour of CHOP were observed across some cycles role functioning (Cycles 2 through 6), social functioning (Cycles 2, 3, and 6), diarrhoea (Cycles 2 and 7), nausea & vomiting (Cycles 2 and 7), pain (Cycles 2, 3, and 4). However, Only Diarrhoea at Cycle 7, which favoured CHOP, was considered clinically meaningful based on the MID of 10 (Osoba 1998).
- Neurotoxicity scores for the FACT/GOG-NTX subscale were not meaningfully different between the treatment arms, except for at EOT, where it favoured CHOP (Figure 11).

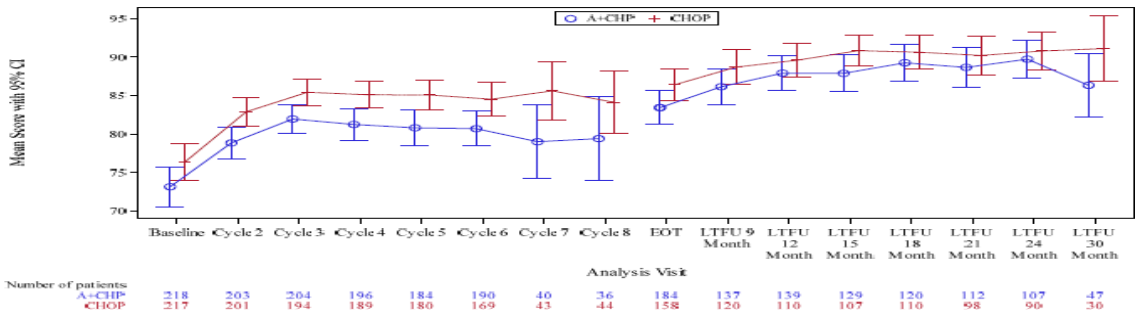



**Figure 11. Mean score over time: QLQC-30 total score (ITT Population)**

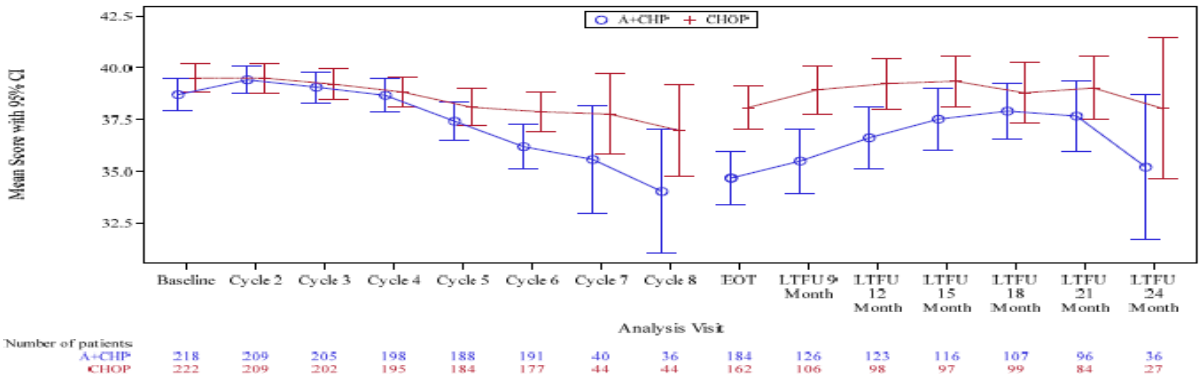



**Figure 12. Mean score over time: FACT/GOG-NTX**

- EQ-5D-3L:The mean baseline score was lower in the A+CHP arm but did not significantly differ between the A+CHP arm compared to the CHOP arm through EOT, and LTFU (see Figure 13).

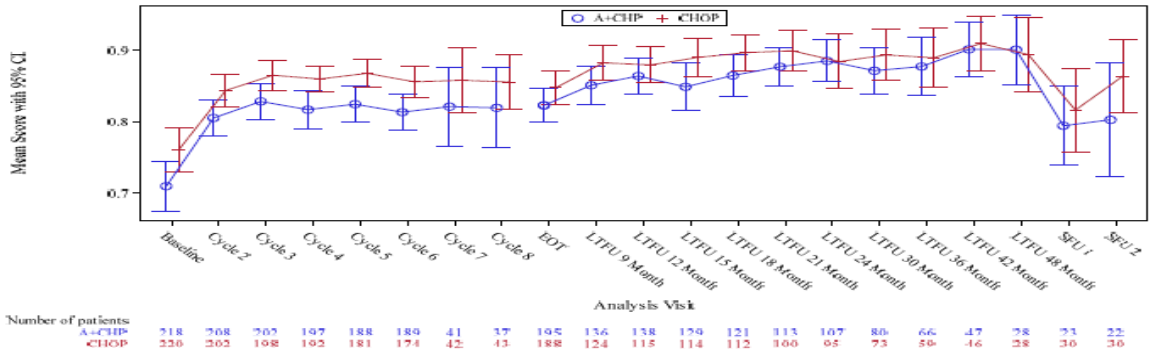



**Figure 13. Mean score over time: EQ5D US TTO (ITT Population)**

## Ancillary analyses

The PFS sensitivity analysis 8 for sALCL patients is shown in Table 27 and Figure 14.

**Table 27. Summary of PFS per IRF, Sensitivity analysis 8 ITT, sALCL patients**

| | A+CHP (N=162) | CHOP (N=154) | Total (N=316) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 55 (34) | 69 (45) | 124 (39) |
| Disease Progression per Cheson | 43 (27) | 51 (33) | 94 (30) |
| Death | 12 (7) | 18 (12) | 30 (9) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.62 (0.43, 0.89) |
| Stratified Log-rank p-value[a] | | | 0.0083 |
| Median PFS (months) (95% C.I.)[b] | 55.66 (48.20, -) | 54.18 (20.80, -) | 54.18 (48.20, -) |
| 25th, 75th percentile | 17.84, - | 5.75, - | 9.66, - |
| Observed min, max | 0.03+, 60.06+ | 0.03+, 60.45+ | 0.03+, 60.45+ |
| Censored, n (%) | 107 (66) | 85 (55) | 192 (61) |
| Estimated progression-free rate (95% C.I.)[b] at: | | | |
| 6 months | 91.1% (85.4%, 94.6%) | 73.2% (65.4%, 79.6%) | 82.4% (77.6%, 86.2%) |
| 12 months | 81.2% (74.1%, 86.5%) | 63.6% (55.3%, 70.8%) | 72.6% (67.2%, 77.3%) |
| 24 months | 68.8% (60.7%, 75.6%) | 56.4% (47.9%, 64.0%) | 62.8% (57.0%, 68.0%) |
| 36 months | 64.9% (56.4%, 72.2%) | 52.6% (43.9%, 60.5%) | 58.9% (52.9%, 64.5%) |
| 48 months | 61.8% (52.5%, 69.8%) | 52.6% (43.9%, 60.5%) | 57.5% (51.2%, 63.2%) |

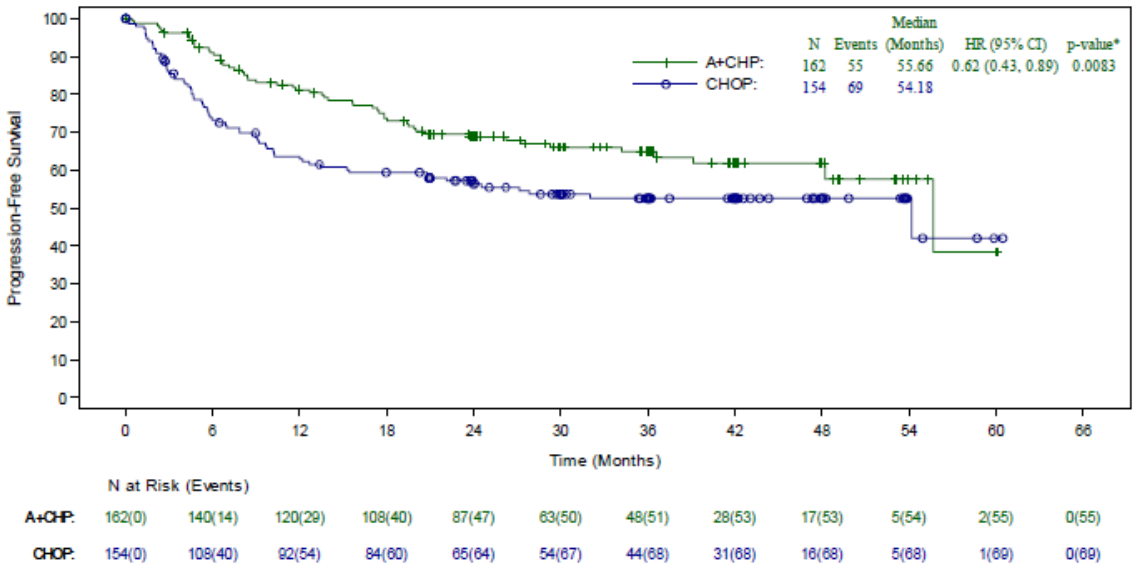



**Figure 14. PFS per IRF by Treatment Arm, Sensitivity 8**

**Subsequent Anti-tumour Therapies**

At the time of the primary analysis, a lower proportion of subjects on the A+CHP arm had received subsequent antitumor therapies compared with subjects on the CHOP arm (29% versus 42%). A total of 72 subjects (16%) received brentuximab vedotin-containing subsequent therapy:

23 subjects (10%) on the A+CHP arm and 49 subjects (22%) on the CHOP arm. Objective responses were attained by 13/23 subjects (57%) on the A+CHP arm and 24/49 subjects (49%) on the CHOP arm.

The time to subsequent therapy favoured A+CHP over CHOP (HR 0.57 [0.41, 0.78]); the median time was not reached in either arms.

**Table 28 Summary of Subsequent Treatment - ITT Analysis Set**

| | A+CHP (N=226) | CHOP (N=226) | Total (N=452) |
|---|---|---|---|
| Subjects who received subsequent new anti-cancer therapy, n (%) | 65 (29) | 96 (42) | 161 (36) |
| Systemic therapy for residual or progressive disease | 59 (25) | 94 (40) | 153 (32) |
| Palliative radiation | 10 (4) | 8 (3) | 18 (4) |
| Systemic therapy for secondary malignancy | 7 (3) | 3 (1) | 10 (2) |
| Consolidative treatment received, n (%) | 61 (27) | 44 (19) | 105 (23) |
| Consolidative radiotherapy[a] | 14 (6) | 6 (3) | 20 (4) |
| Consolidative stem cell transplant | 50 (22) | 39 (17) | 89 (20) |
| Autologous | 49 (22) | 39 (17) | 88 (19) |
| Allogeneic | 1 (0) | 0 | 1 (0) |
| Number of different type[b] of anti-cancer therapies per patient | | | |
| n | 65 | 96 | 161 |
| Mean (STD) | 1.2 (0.4) | 1.1 (0.3) | 1.1 (0.3) |
| Median | 1.0 | 1.0 | 1.0 |
| Min, Max | 1, 2 | 1, 2 | 1, 2 |
| Anti-Cancer treatments ever received, regimen name, n (%) | | | |
| Brentuximab vedotin-containing | 23 (10) | 49 (22) | 72 (16) |

**Receipt of Subsequent Stem Cell Transplantation**

Multiple analyses by treatment arm and receipt or non-receipt of subsequent stem cell transplantation (SCT) were conducted for the ITT population (data on file). These included analyses of PFS per IRF, OS, best overall response, and response at the end of treatment. Safety summaries were also produced by SCT status, and time to SCT was analysed by treatment arm among the subset of ITT patients receiving subsequent SCT.

A total of 50 subjects (22%) on the A+CHP arm versus 39 subjects (17%) on the CHOP arm received consolidative SCT following completion of study treatment. Consolidative radiotherapy was received by 14 subjects (6%) on the A+CHP arm versus 6 subjects (3%) on the CHOP arm

**Impact of Subsequent Therapies on OS**

Of 219 patients who experienced a PFS event, 189 patients experienced a PFS event other than death; 82 patients (36%) in the A+CHP arm and 107 patients (47%) in the CHOP arm.

**Table 29– ECHELON-2: Use of Subsequent Therapies Following a PFS Event Other Than Death (ITT Population)**

| | A+CHP (N=226) | CHOP (N=226) |
|---|---|---|
| Number of patients with a PFS event other than death, n (%) | 82 (36) | 107 (47) |
| Disease progression per Cheson | 71 (31) | 86 (38) |
| New therapy (a) | 11 (5) | 21 (9) |
| Patients who received new subsequent systemic anticancer therapy for residual or progressive disease, n (%) | 57 (25) | 94 (42) |
| Patients receiving subsequent anticancer treatment containing brentuximab vedotin, n (%) | 21 (9) | 48 (21) |

Source: Output: t-sum-subtx-pfs-no-dth-itt.rtf (01MAR19:10:09) Data: adtte, adconmed (data on file).
(a) New anticancer therapy to treat residual or progressive disease initiated prior to IRF-documented progression per Cheson, including palliative radiotherapy. No patients had an event due to palliative radiotherapy.

A total of 57 of the 226 A+CHP arm patients (25% of A+CHP patients) received subsequent systemic anticancer therapy to treat residual or progressive disease compared with 94 of 226 CHOP patients (42% of CHOP patients), and brentuximab vedotin was the most frequently used subsequent anticancer therapy in both arms (21 of 57 A+CHP patients compared with 48 of 94 CHOP patients). Despite the use of brentuximab vedotin as subsequent therapy in the control arm, a statistically significant OS advantage was still observed in the A+CHP treatment arm.

**Exploratory Analyses of CD30 Expression and Efficacy**

No difference in PFS was seen in a pre-specified analysis of CD30 expression levels above and below the median. The variability of CD30 expression levels across different histological subtypes confounded the analysis and limited the interpretation of the results.

Exploratory analyses were conducted to examine the relationship between CD30 expression and overall response and duration of response in non-sALCL patients. In both AITL and PTCL-NOS subtypes, CRs at the end of treatment were observed across the range of CD30 expression values, including those at the bottom of the range (10%) included in the trial for patients treated with A+CHP. In addition, durable CRs were observed in AITL and PTCL-NOS patients treated with A+CHP, even for patients with low CD30 expression. Similar results were observed with CHOP.

**Analysis according to disease stage**

**Table 30**–Summary of Progression-Free Survival (PFS) per IRF ITT Analysis Set - Disease Stage I and II

| | A+CHP (N=42) | CHOP (N=46) | Total (N=88) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 15 (36) | 19 (41) | 34 (39) |
| Disease Progression per Cheson | 12 (29) | 10 (22) | 22 (25) |
| Death | 2 (5) | 3 (7) | 5 (6) |
| New Therapy[a] | 1 (2) | 6 (13) | 7 (8) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.95 (0.48, 1.88) |
| Stratified Log-rank p-value[b] | | | 0.8755 |
| Median PFS (months) (95% C.I.)[c] | 55.66 (23.72, 55.66) | - (15.80, -) | 55.66 (27.10, -) |
| 25th, 75th percentile | 10.45, 55.66 | 9.20, - | 10.45, - |
| Observed min, max | 0.03+, 55.66 | 0.66, 60.45+ | 0.03+, 60.45+ |

**Table 31**–Summary of Progression-Free Survival (PFS) per IRF ITT Analysis Set - Disease Stage III

| | A+CHP (N=57) | CHOP (N=67) | Total (N=124) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 29 (51) | 35 (52) | 64 (52) |
| Disease Progression per Cheson | 25 (44) | 25 (37) | 50 (40) |
| Death | 0 | 4 (6) | 4 (3) |
| New Therapy[a] | 4 (7) | 6 (9) | 10 (8) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.69 (0.42, 1.14) |
| Stratified Log-rank p-value[b] | | | 0.1416 |
| Median PFS (months) (95% C.I.)[c] | 36.14 (15.05, -) | 23.72 (12.68, -) | 32.03 (15.05, -) |
| 25th, 75th percentile | 8.08, - | 5.82, - | 6.28, - |
| Observed min, max | 1.64, 60.02+ | 0.03+, 59.83+ | 0.03+, 60.02+ |

**Table 32**–Summary of Progression-Free Survival (PFS) per IRF ITT Analysis Set - Disease Stage IV

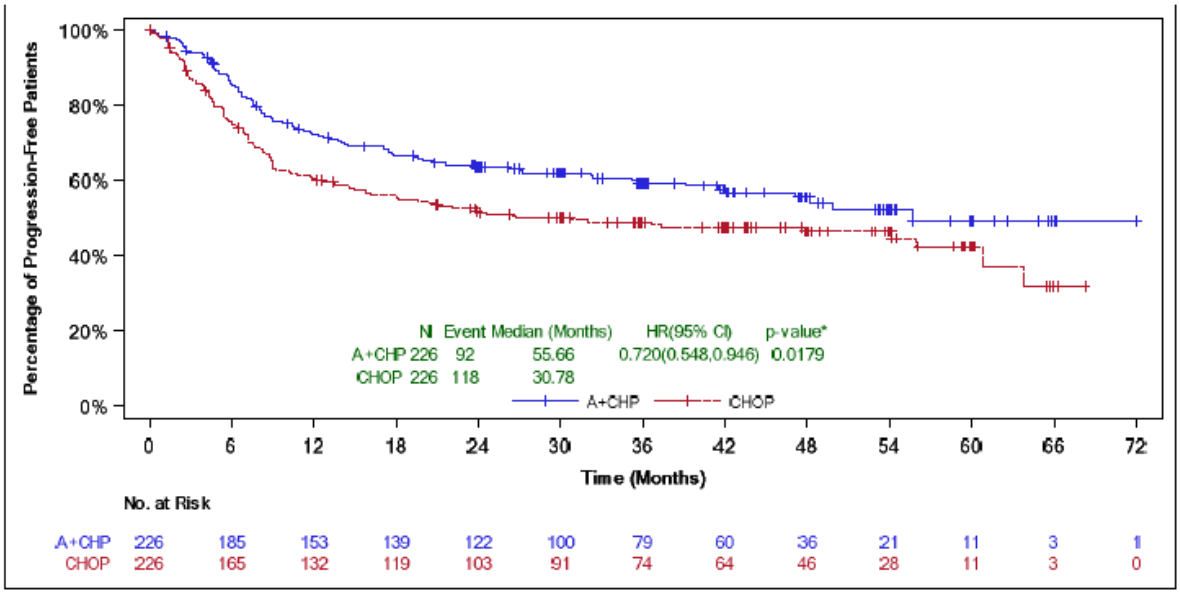
| | A+CHP (N=127) | CHOP (N=113) | Total (N=240) |
|---|---|---|---|
| Number of patients with a PFS event, n (%) | 51 (40) | 70 (62) | 121 (50) |
| Disease Progression per Cheson | 34 (27) | 51 (45) | 85 (35) |
| Death | 11 (9) | 10 (9) | 21 (9) |
| New Therapy[a] | 6 (5) | 9 (8) | 15 (6) |
| Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP) | | | 0.64 (0.45, 0.93) |
| Stratified Log-rank p-value[b] | | | 0.0173 |
| Median PFS (months) (95% C.I.)[c] | 48.20 (34.20, -) | 10.25 (7.20, 27.83) | 30.78 (17.48, 53.88) |
| 25th, 75th percentile | 8.25, - | 4.34, 54.18 | 5.62, - |
| Observed min, max | 0.03+, 60.06+ | 0.2, 60.06+ | 0.03+, 60.06+ |

**Treatment assignments unblinding prior to the primary analysis** occurred for 128 subjects overall; 55 subjects on the A+CHP arm and 73 subjects on the CHOP arm. Ten instances of unblinding were for emergency circumstances (4 subjects on the A+CHP arm and 6 subjects on the CHOP arm) and 118 instances of unblinding were for individual subjects who had progressed (51 subjects on the A+CHP arm and 67 subjects on the CHOP arm). The MAH declares that in all cases the sponsor remained blinded.

**Analyses per investigator:** PFS per investigator (HR 0.70 [0.53, 0.92], p=0.0096) was similar to PFS per IRF. Of the 452 cases assessed for PFS events, 438 (97%) were concordant between the investigator and IRF. A similar level of concordance was observed in both treatment arms (96% for A+CHP; 98% for CHOP).

The response rate difference for the CR rate per investigator (CR rate difference was 12.4 [3.7, 21.2), p=0.0043) was slightly higher than the IRF analysis. The response rate difference for ORR rate per investigator was comparable to the IRF analysis (ORR difference per investigator was 11.1 [3.9, 18.2], p value-0.0018).

**Updated PFS outcomes**




Source: (Table 96.1.2.1.2) /bdm/tbos/SGN-035/35-14/CSR/Adhoc/EMA_RSI_2019/Figures/F96.1.2.1.2-KM_PFS_INV_sen8_subgrp, run 07 October 2019, 10:43. Data snapshot: 25SEP2019.
* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization

**Figure 15 ECHELON-2: Updated PFS per Investigator, EMA censoring rules (i.e. sensitivity analysis 8) (ITT Population).**

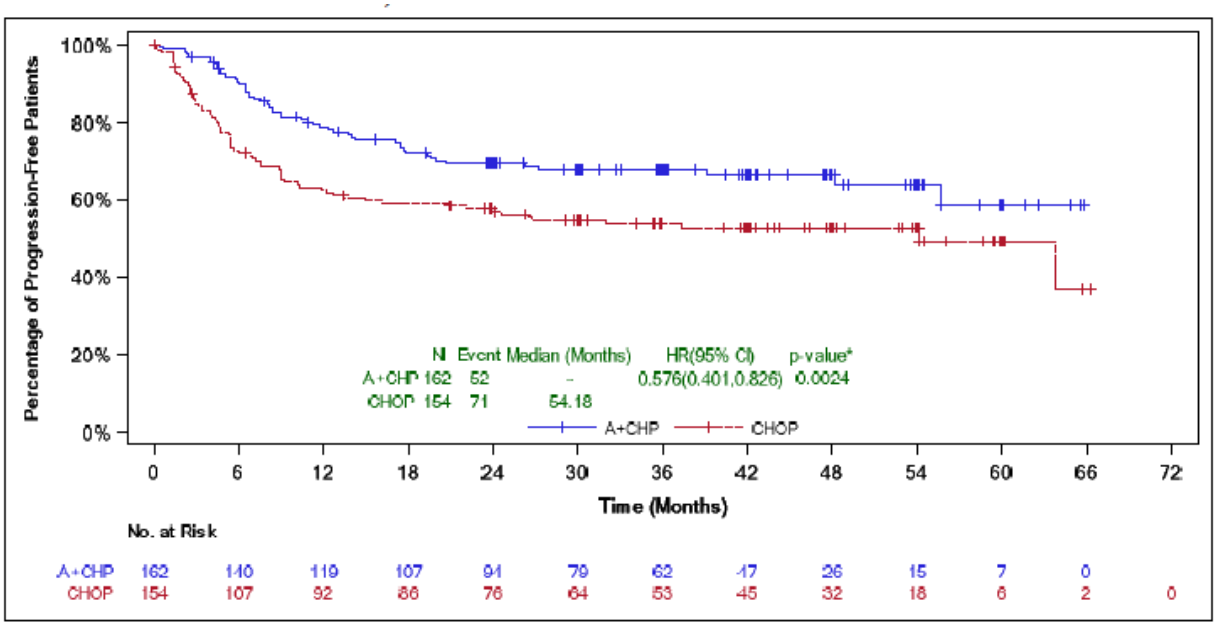



**Figure 16. Updated PFS per Investigator, EMA censoring rules (i.e. sensitivity analysis 8) (ITT Population – sALCL Subset)**

***Bayesian Hierarchical Model analyses***

The shrinkage estimates of the PFS HRs with the corresponding 95% credible intervals by disease subtype.

**Table 33 Summary of Bayesian Hierarchical Model Analysis of PFS per IRF by Disease Subtype in SGN35-014 (ECHELON-2)**

| Disease Subtype | Events/N | Naïve Subtype Results | | Bayesian Shrinkage Estimates | |
|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% Credible Interval |
| ALK+ sALCL | 21/98 | 0.29 | (0.11, 0.79) | 0.55 | (0.21, 0.88) |
| ALK- sALCL | 110/218 | 0.65 | (0.44, 0.95) | 0.68 | (0.49, 0.92) |
| PTCL-NOS | 50/72 | 0.75 | (0.41, 1.37) | 0.71 | (0.50, 1.08) |
| AITL | 31/54 | 1.40 | (0.64, 3.07) | 0.87 | (0.57, 1.92) |
| ATLL | 4/7 | 0.76 | (0.10, 5.51) | 0.70 | (0.33, 1.49) |

AITL; angioimmunoblastic T-cell lymphoma; ALK-: anaplastic lymphoma kinase–negative; ALK+: anaplastic lymphoma kinase–positive; ATLL: adult T-cell leukemia/lymphoma; HR: hazard ratio; PFS: progression-free survival; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; sALCL: systemic anaplastic large-cell lymphoma.

Out of 300,000 iterations, the BHM identifies 2.3 clusters on average (median=2). The most extreme lying populations (ALK+sALCL: HR=0.29, AITL: HR=1.40) were assigned to clusters as follows:

**Table 34 Summary of Clusters Containing AITL or ALK+ sALCL**

| | AITL | ALK+ sALCL |
|---|---|---|
| Cluster includes no other disease subtypes | 29.2% (a) | 30.0% (b) |
| Cluster includes ALK-sALCL (c) | 45.7% | 50.9% |
| Cluster includes non-ALK- sALCL subtype (d) | 25.1% | 19.2% |
| Total | 100% | 100% |

(a) Cluster only includes AITL.
(b) Cluster only includes ALK+ sALCL.
(c) Cluster includes AITL and ALK-sALCL, or ALK+ sALCL and ALK-sALCL respectively.
(d) Among the cluster including AITL or ALK+ sALCL with non-ALK-sALCL subtypes, AITL and ALK+ sALCL are clustered together without any other subtypes in 1.5% of iterations.
AITL=angioimmunoblastic T-cell lymphoma, ALK=anaplastic lymphoma kinase, sALCL=systemic anaplastic large-cell lymphoma.

**Table 35 Summary of Bayesian Hierarchical Model Analysis of PFS per IRF by Disease Subtype, Excluding ALK+ sALCL**

| Disease Subtype | Events/N | Naïve Subtype Results | | Bayesian Shrinkage Estimates | |
|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% Credible Interval |
| ALK- sALCL | 110/218 | 0.65 | (0.44, 0.95) | 0.71 | (0.52, 0.95) |
| PTCL-NOS | 50/72 | 0.75 | (0.41, 1.37) | 0.75 | (0.54, 1.12) |
| AITL | 31/54 | 1.40 | (0.64, 3.07) | 0.89 | (0.59, 1.90) |
| ATLL | 4/7 | 0.76 | (0.10, 5.51) | 0.70 | (0.44, 1.58) |

AITL=angioimmunoblastic T-cell lymphoma, ALK-=anaplastic lymphoma kinase–negative, ATLL=adult T-cell leukemia/lymphoma, HR=hazard ratio, PFS=progression-free survival, PTCL-NOS=peripheral T-cell lymphoma, not otherwise specified, sALCL=systemic anaplastic large-cell lymphoma.

## *Summary of main study*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 36 Summary of Efficacy for trial ECHELON-2**

| | | | |
|---|---|---|---|
| **Title:** ECHELON-2 | | | |
| Study identifier | SGN35-014 | | |
| Design | a randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | From 24-Jan-2013 till 15-Aug 2018<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | A+CHP | | brentuximab vedotin and cyclophosphamide, doxorubicin and prednisone for 6-8 cycles (n=226) |
| | CHOP | | cyclophosphamide, doxorubicin vincristine and prednisone for 6-8 cycles (n=226) |
| Endpoints and definitions | Primary endpoint | PFS | Time from the date of randomization to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurred first. By IRF. |
| | Secondary endpoint | PFS in Subjects with sALCL | PFS in Subjects with sALCL, analysed in same manner as primary endpoint |
| | Secondary endpoint | CR rate | The complete remission rate was defined as the proportion of subjects with CR per IRF following the completion of study treatment according to the Revised Response Criteria for Malignant Lymphoma at end of treatment |
| | Secondary endpoint | OS | Overall survival was defined as the time from randomization to death due to any cause (OS=date of death – date of randomization + 1) |
| | Secondary endpoint | ORR rate | The objective response rate was defined as the proportion of subjects with CR or PR per IRF following the completion of study treatment according to the Revised Response Criteria for Malignant Lymphoma at end of treatment |
| | | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Intent to treat | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | **A+CHP** | **CHOP** |
| | Number of subjects | 226 | 226 |
| | PFS events (%)<br><br>Median PFS months (95%CI) | 95 (42%)<br><br>48.20 (35.2, NE) | 124 (55%)<br><br>20.80 (12.7, 47.6) |
| | | | |
| | | | |
| | | | |
| | CR rate (95%CI) | 68% (61.2, 73.7) | 56% (49.0, 62.3) |
| | | | |
| | OS events (%)<br><br>Median OS (95%CI) | 51 (23%)<br><br>NE (NE) | 73 (32%)<br><br>NE (54.2, NE) |
| | | | |
| | ORR rate (95%CI) | 83% (77.7, 87.8) | 72% (65.8, 77.9) |
| | | | |
| Effect estimate per comparison | Primary endpoint PFS | Comparison groups | A+CHP vs CHOP |
| | | HR | 0.71 |
| | | 95%CI | 0.54, 0.93 |
| | | P-value | 0.0110 |
| | Secondary endpoint CR rate | Comparison groups | A+CHP vs CHOP |
| | | Rate difference | 11.9 |
| | | 95%CI | 3.1, 20.8 |
| | | P-value | 0.0066 |
| | Secondary endpoint OS | Comparison groups | A+CHP vs CHOP |
| | | HR | 0.66 |
| | | 95%CI | 0.46, 0.95 |
| | | P-value | 0.0244 |
| | Secondary endpoint ORR | Comparison groups | A+CHP vs CHOP |
| | | Rate difference | 11.1 |
| | | 95%CI | 3.4, 18.7 |
| | | P-value | 0.0032 |
| | | | |
| Analysis description | Primary Analysis | | |
| Analysis population and time point description | sALCL Population | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | **A+CHP** | **CHOP** |
| | Number of subjects | 162[a] | 154[a] |
| | PFS events (%)<br><br>Median PFS, months (95%CI) | 56 (34%)<br><br>55.7 (48.20, NE) | 73 (48%)<br><br>54.2 (13.44, NE) |
| | CR rate (95%CI) | 71% (63.3, 77.8) | 53% (45.0, 61.3) |
| | OS Events (%)<br><br>Median OS (95%CI) | 29 (18%)<br><br>NE (NE) | 44 (29%)<br><br>NE (NE) |
| | ORR rate (95%CI) | 88% (81.6, 92.3) | 71% (62.9, 77.8) |
| Effect estimate per comparison | Secondary endpoint PFS in sALCL | Comparison groups | A+CHP vs CHOP |
| | | HR | 0.59 |
| | | 95%CI | 0.42, 0.84 |
| | | P-value | 0.0031 |
| | CR rate in sALCL | Comparison groups | A+CHP vs CHOP |
| | | Response rate difference | 17.7 |
| | | 95%CI | 7.2, 28.3 |
| | | P-value | 0.0004 |
| | OS in sALCL | Comparison groups | A+CHP vs CHOP |
| | | HR | 0.54 |
| | | 95%CI | 0.34, 0.87 |
| | | P-value | 0.0096 |
| | ORR in sALCL | Comparison groups | A+CHP vs CHOP |
| | | Response rate difference | 16.9 |
| | | 95%CI | 8.1, 25.7 |
| | | P-value | <0.0001 |
| Notes | [a]For the sALCL population: PFS per IRF is calculated using patients with centrally- confirmed sALCL, with n=163 patients in A+CHP arm and n=151 in CHOP arm. OS, CR and ORR are calculated using patients with locally-diagnosed sALCL. | | |

## *Analysis performed across trials (pooled analyses and meta-analysis)*

Results from literature, Phase 1 and Phase 2 studies of brentuximab vedotin in PTCL (Pro, Horwitz, Fanale), and the ECHELON-2 study are presented. Taken together, the supportive evidence from case reports and case series in PTCL histological subtypes not included in ECHELON-2 allows for extrapolation of efficacy and safety to between 81-98% of PTCL histologies.

**Table 37 Summary of Efficacy and Safety Data with Brentuximab Vedotin by PTCL Subtype**

| PTCL[a] Subtype | Incidence (%) | | Line | Drug(s) | Efficacy | Consistent With Known Safety Profile? | Data Sources |
|---|---|---|---|---|---|---|---|
| | Int'l[b] | EU[c] | | | | | |
| PTCL-NOS | 25.9 | 44.8 | 1st line | BV+CHP | SGN35-011<br>(N=2), ORR=100%, CR=100% | ✓ | (Fanale, Horwitz et al. 2014), (Fanale, Horwitz et al. 2018) |
| | | | R/R | SA BV | SGN35-012<br>(N=21), ORR=33%, CR=14% | ✓ | (Horwitz, Advani et al. 2014) |
| | | | 1st line | BV+CHP | ECHELON-2<br>(N=29), ORR=79%, CR=66%<br>PFS HR 0.75 (95% CI 0.41, 1.37) vs CHOP | ✓ | ECHELON-2 |
| AITL | 18.5 | 15.7 | R/R | SA BV | SG035-0001<br>(N=1); ORR=0% | ✓ | (Younes, Bartlett et al. 2010) |
| | | | 1st line | BV+CHP | SGN35-011<br>(N=2), ORR=100%, CR=100% | ✓ | (Fanale, Horwitz et al. 2014), (Fanale, Horwitz et al. 2018) |
| | | | 1st line | BV+CHP | ECHELON-2<br>(N=29), ORR= 77%, CR=60%<br>PFS HR 1.40 (95% CI 0.64, 3.07) vs CHOP | ✓ | ECHELON-2 |
| ALK+ ALCL | 6.6 | 8.8 | R/R | SA BV | SG035-0004<br>(N=16) – ORR=81%, CR=69% | ✓ | (Pro, Advani et al. 2012) |
| | | | 1st line | BV+CHP | SGN35-011<br>(N=3) – ORR=100%, CR=100% | ✓ | (Fanale, Horwitz et al. 2014), (Fanale, Horwitz et al. 2018) |
| | | | 1st line | BV+CHP | ECHELON-2<br>(N=49) – ORR=94%, CR=80%<br>PFS HR 0.29 (95% CI 0.11, 0.79) vs CHOP | ✓ | ECHELON-2 |
| ALK- ALCL | 5.5 | 12.3 | R/R | SA BV | SG035-0004<br>(N=42) – ORR=88%, CR=55% | ✓ | (Pro, Advani et al. 2012) |
| | | | 1st line | BV+CHP | SGN35-011<br>(N=16) – ORR=100%, CR=88% | ✓ | (Fanale, Horwitz et al. 2014), (Fanale, Horwitz et al. 2018) |
| | | | 1st line | BV+CHP | ECHELON-2<br>(N=113) – ORR=85%, CR=67%<br>PFS HR 0.65 95% CI (0.44, 0.95) vs CHOP | ✓ | ECHELON-2 |
| ***BIA ALCL*** | -- | -- | 1st line | BV+ surgical excision | 1 patient, CR after 6 cycles, DOR= 3 years | ✓ | (Alderuccio, Desai et al. 2018) |
| | | | 1st line | SA BV | 1 patient, CR after 18 cycles, DOR= 20 months | ✓ | (Stack and Levy 2019) |
| EATL | 4.7 | 1.4 | 1st line | BV+CHP | Stage IV w/ IPI=2; CR @ EOT; PFS 7 months | ✓ | (Fanale, Horwitz et al. 2014) |
| | | | 1st line | BV+CHP | 1 patient in ECHELON-2, IPI 2-3 at baseline, received 1 dose of A+CHP developed septic shock, leukopenia and thrombocytopenia; drug was permanently discontinued. Patient died 3 months later. | ✓ | ECHELON-2 |
| ENK TCL | 10.4 | 5.9 | R/R | SA BV | BV as salvage with metabolic CR after 3 cycles | ✓ | (Park, Kim et al. 2017) |
| | | | R/R | SA BV | 2 patient case series, both PD with BV | ✓ | (Brammer, Chihara et al. 2018) |
| | | | R/R | SA BV | BV as salvage with metabolic CR after 3 cycles | ✓ | (Poon and Kwong 2016) |

| PTCL[a] Subtype | Incidence (%) | | Line | Drug(s) | Efficacy | Consistent With Known Safety Profile? | Data Sources |
|---|---|---|---|---|---|---|---|
| | Int'l[b] | EU[c] | | | | | |
| | | | R/R | SA BV | BV as salvage with CR after 4 cycles | ✓ | (Kim, Moon et al. 2015) |
| ATLL | 9.6 | 3.9 | 1st line | SA BV | Pt 1: CR @ EOT, PFS 7.1 months;<br>Pt 2: CR @ EOT, PFS 22.8 months | ✓ | (Fanale, Horwitz et al. 2014) |
| | | | R/R | SA BV | 1 patient report, CR after 6 cycles | ✓ | (Sanchez, Bhattacharya et al. 2016) |
| | | | 1st line | BV+CHP | N=4; CR=50% | ✓ | ECHELON-2 |
| T-PLL | -- | 3.6 | R/R | SA BV | PR after 3 cycles of BV, DOR 4 months | ✓ | (Senchak and Pickens 2016) |
| | | | R/R | BV+chemo | Pt 1: PR with BV + alemtuzumab, followed by BV + pralatrexate; DOR 6.7 months to death | ✓ | (Hasanali, Saroya et al. 2015) |
| | | | | | Pt 2: BV + alemtuzumab resulted in PR in skin with 5 month DOR | ✓ | (Hasanali, Saroya et al. 2015) |
| T-LGLL | -- | 2.1 | R/R | SA BV | CR after 3 cycles, DOR >1 year | ✓ | (Lewis, Miranda et al. 2018) |
| Total | 81% | 98% | | | | | |

**Table 38 Other PTCL Histological Subtypes**

| PTCL Subtype (a) | Incidence | Considerations |
|---|---|---|
| **Systemic EBV+ T-cell lymphoma of childhood** | NR | Childhood diseases are outside scope of current application for adult patients with CD30+ PTCL. |
| ***Follicular T-cell lymphoma*** | NR | Provisional entity only recently described by WHO. |
| ***Nodal PTCL with $T_{FH}$ phenotype*** | NR | Provisional entity only recently described by WHO. |
| **Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)** | NR | Formerly EATL Type 2 |
| ***Indolent T-cell lymphoproliferative disorder (LPD) of the GI tract*** | NR | Provisional entity only recently described by WHO. |
| Aggressive NK-cell leukemia (b) | 0.87% | |
| *Chronic LPD of Natural Killer cells* | NR | Provisional entity only recently described by WHO. |
| **Hydroa vacciniforme-like LPD** (b) | 0% | |

*(a) Provisional entity (italics);* **Changes from 2008 classification (bold);** ***provisional entity and change from 2008 classification (bold, italics).***
(b) Incidence Rate and Prevalence Estimates of Peripheral T-Cell Lymphoma in Europe in 2017 based on country-specific studies that report age and gender specific results when available. When unavailable, based on extrapolated results from studies based in comparable populations (Zhang and Dalal 2019). Incidence and prevalence of T-cell lymphoma in the EMA member states: methodology for estimation in rare malignancies of CTCL and PTCL (PRO66). ISPOR Europe 2019, Copenhagen, Denmark. November 2019.
NR=not reported.

## *Clinical studies in special populations*

**Elderly**

In the ECHELON-2 trial patients up to 85 years were included. Approximately 45% of the patients were ≥60 years (103 patients in the A+CHP arm and 100 patients in the CHOP arm). 69 (30.5%) and 70 patients (31.0%) were aged ≥65 years, respectively. Results for PFS per IRF according to age groups were consistent with those of the ITT population (age group <65 years: HR 0.67; age group ≥65 years 0.70).

**Paediatric patients**

Eligibility was restricted to patients Age ≥18 years.

**Pregnancy and lactation**

No data is available in pregnant or lactating woman.

### *Supportive study(ies)*

The Applicant submitted supportive study **SGN35-012**, a phase 2 single arm trial study of brentuximab vedotin 1.8mg/kg in relapsed or refractory non-Hodgkin lymphoma (NHL). The main study population of this study consisted of r/r DLBCL patients with the aim of studying brentuximab vedotin monotherapy and combination therapy with rituximab, but also patients with relapsed or refractory PTCL were studied in Part A of the study. This part was designed to evaluate the antitumor activity of brentuximab vedotin as a single agent in patients with relapsed or refractory NHL.

In total 13 patients with AITL and 22 patients with PTCL-NOS were included. Most patients had advanced disease, refractory to frontline therapy. Retrospective, it was shown that 6 of the CD30+ patients (17%) had CD30-negative disease (n=2 AITL and n=4 PTCL-NOS).

The ORR was 41% [24.6, 59.3] for total CD30+ T-cell lymphomas treated with brentuximab vedotin monotherapy, including 54% [25.1, 80.8] for CD30+ AITL patients and 33% [14.6, 57] for patients with PTCL-NOS.

The CR rate was 24% [10.7, 41.2] for total CD30+ T-cell lymphomas including 38% [13.9, 68.4] for CD30+ AITL patients and 14% [3, 36.3] for patients with PTCL-NOS. The estimated median duration of objective response by Kaplan-Meier analysis was 7.6 months [1.4, NE].

The estimated median PFS was 2.5 months [1.4, 6.1], 6.7 months for AITL patients, and 1.6 months for patients with PTCL-NOS. The median OS was 18.1 months [6.8, 33.6], 20.1 months for AITL, and 17 months for PTCL-NOS.

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

The pivotal study ECHELON-2 (SGN35-014) was a randomized, double-blind controlled study of brentuximab vedotin and CHP (A+CHP) versus CHOP for treatment-naïve CD30 positive PTCL patients. This design was acceptable.

The PTCL types that were allowed in the study were sALCL (ALK+ IPI score ≥2 and all ALK-), PTCL-NOS, AITL, ATTL, EATL and HSTCL. It should be noted that the WHO 2016 classifies these as separate entities due to differences in disease biology and therapeutic strategies. The above PTCL types represent a large part of the target population. The remaining types are very rare in the EU, except for patients with ALK+ IPI score<2 and NKTCL, the 6$^{th}$ most common subtype in the EU. Some subgroups of PTCL (nodal, extranodal and leukemic) were excluded from the pivotal study. In addition, all disease stages were eligible, although for Stage 1 patients shortened chemotherapy schedule followed by curatively intended radiotherapy is recommended (ESMO guideline). For enrolment, the trial required CD30 expression ≥10% per immunohistochemistry (see section 5.1 of the SmPC).

Importantly, the protocol required 75± 5% of the study participants to have a sALCL diagnosis, as the ECHELON-2 study serves to fulfil the category 3 commitment as agreed upon at time of the MAA (MEA-015). As sALCL constitutes 15% of the PTCLs, sALCL is overrepresented in the study population. This

could be of concern in relation to the broad applied indication of CD30+ PTCL population. Moreover, sALCL differs from other subtypes in terms of biology, prognosis (ALK+ has a better prognosis, but also ALK- ALCL than other PTCL types) and CD30 expression (ALCL per definition expresses CD30 cell ≥75%, in other subtypes the frequency and intensity of CD30 expression varies). Based on this information, it is not evident that results in sALCL PTCL can be extrapolated to other CD30+ PTCL types. As per the CHMP advice informative numbers of patients with different subtypes needed to be included as PTCL is a heterogeneous disease (EMA/288880/2012).

The dosing regimen of brentuximab vedotin (in combination with CHP) is the same as the monotherapy dose (1.8mg/kg q3w). This dose and regimen was investigated in the Phase 1 study SGN35-011. The study included an option for a reduced dosing of 1.2 mg/kg in case the initial dose of 1.8 mg/kg would lead to unacceptable toxicity. As only 1 DLT was observed in 6 treated patients at that dose the MTD was determined to be 1.8 mg/kg for the combination therapy. The choice of replacing vincristin with brentuximab vedotin was considered reasonable by CHMP (EMA SA 2012) given the related mechanism of action for vincristine and the cytostatic component of brentuximab vedotin (MMAE). Patients were to receive 6-8 cycles of brentuximab vedotin 1.8 mg/kg and CHP and vincristine placebo in the experimental arm and 6-8 cycles of CHOP and brentuximab vedotin placebo in the control arm.

CHOP is considered an acceptable control treatment for most patients. However, in ESMO clinical guidance, CHOEP is an option for fit patients ≤60 years of age with nodal PTCL (PTCL-NOS, AITL, ALCL) as population-based studies indicate an EFS benefit of CHOEP over CHOP, but no OS benefit has been shown. The CHMP had suggested to allow addition of etoposide in the control arm for younger patients with ALK+ ALCL on physician's discretion (EMA/288880/2012) however the actual contribution of etoposide to CHOP is not fully determined in terms of OS. It is stated in section 5.1 of the SmPC that only patients with CD30+ PTCLs for whom a CHOP-based regimen is recommended were eligible for enrolment.

The primary endpoint in SGN35-014 was PFS per IRF, defined as the time from the date of randomization to the date of first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first. Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilising peripheral blood stem cells, or consolidative autologous or allogeneic stem cell transplant were not considered as disease progression or as having started new anticancer therapy. Key secondary endpoints included PFS per IRF for patients with centrally-confirmed sALCL, CR rate per IRF following the completion of study treatment, OS and ORR per IRF following the completion of study treatment which were tested by a fixed sequence testing procedure following the statistical significance of PFS per IRF.

The primary and key secondary endpoints are considered appropriate to evaluate the benefit of A+CHP in PTCL patients and were agreed in the context of CHMP scientific advice.

The primary PFS analysis patients were censored for post-treatment chemotherapy for stem cell mobilization and consolidative radiotherapy, and new anti-cancer therapy was considered an event. The first is not representative of clinical practice which considers SCT a treatment goal to postpone progression and the latter is not in accordance with EMA guidance. Therefore, PFS sensitivity analysis in accordance with EMA guidance was considered important.

Efficacy analysis was on a true ITT set. The assessment schedule for PFS is considered sufficiently granular given the median PFS in the control arm. Analyses methods for CR and ORR considered missing data as failures and are acceptable. Key secondary endpoints were tested in a fixed sequence testing procedure, which is acceptable to control type I error. One interim analysis was planned which is considered acceptable as it was only for futility and executed by an independent DMC. The protocol

allowed for unblinding at request at time of documented progression to determine subsequent treatment. This was considered acceptable in the scientific advice (EMA/559606/2012). Of note, according to the SAP all endpoints except time to event endpoints (and apparently ORR and CR) had patients deleted from the analysis if data were missing.

Changes in the protocol affecting the primary outcome (PFS) included the following:

- The sample size was amended during the study based on analysis of blinded pooled data from this study, final PFS data from the lead-in safety study (SGN35-011), and newly available data from the International T-Cell Project (TCP), the sponsor determined that original design of ECHELON-2 overestimated the event accrual rate. As this was not driven by seeing (unblinded) outcomes and effectively only changed the timing but not the number of analyses, this is considered acceptable.
- The timing of the final analysis was changed from reaching 238 events to either reaching that or reaching August 2018, whichever occurred first. The data cut-off was in August 2018 with 219 events (48%). This is considered acceptable as the targeted number of events is almost reached.
- New anti-cancer therapy was labelled as event for the primary PFS analysis.
- A sensitivity analysis using the EMA censoring rules for PFS was added.
- The PFS interim analysis for efficacy was removed, which strengthens the design.

Protocol violations were evenly distributed among the two arms, did not have a high frequency and are not expected to have impacted outcomes, except for that there were 8 potential unblinding incidents. It is unlikely that these reported events have impacted study results to a large extent.

## Efficacy data and additional analyses

The ITT analysis set consisted of 452 subjects, 226 in the A+CHP arm and 226 in the CHOP arm. The baseline demographic characteristics are representative for the EU target PTCL population. Regarding disease characteristics, as per protocol most patients had sALCL (70%; ALK- 48%, ALK+22%). Other subtypes studied were PTCL-NOS (16%), AITL 12%, ATLL (n=7; 2%) and EATL (n=3;1%) and no HSTCL patients were included. Since ATLL and HSTCL are very rare and EATL patients have a poor performance status, low recruitment for these subtypes may be expected. The enrolled population mainly reflects the nodal entities of PTCL whereas extranodal (EATL, N=3) and leukemic (ATLL, N=7) subtypes are rarely reflected.

The primary endpoint and alpha-protected, key secondary endpoints, which were evaluated hierarchically, were met. The median PFS per IRF for the ITT population was 48.2 months on the ADCETRIS + CHP arm versus 20.8 months on the CHOP arm. The stratified hazard ratio was 0.71 (95% CI: 0.54; 0.93, p=0.011), indicating a 29% reduction in the risk of PFS events for ADCETRIS + CHP versus CHOP. For overall survival, the stratified hazard ratio was 0.66 (95% CI: 0.46; 0.95, p=0.024), a 34% reduction in the risk of OS events for ADCETRIS + CHP versus CHOP.

PFS per IRF for patients with centrally-confirmed sALCL was a pre-specified key secondary endpoint. The median PFS per IRF was 55.7 months on the ADCETRIS + CHP arm versus 54.2 months on the CHOP arm. The stratified hazard ratio was 0.59 (95% CI: 0.42; 0.84), compatible with a statistically significant 41% reduction in the risk of PFS events for ADCETRIS + CHP versus CHOP (p-value=0.003).

Subgroup analyses were performed for patients with locally-diagnosed sALCL. For overall survival, the stratified hazard ratio was 0.54 (95% CI: 0.34; 0.87), a 46% reduction in the risk of OS events for

ADCETRIS + CHP versus CHOP. At the end of treatment, the CR rate by IRF assessment was 71.0% for patients on the A+CHP arm compared with 53.2% for patients on the CHOP arm with a difference of 17.7% (95% CI: 7.2%; 28.3%). At the end of treatment, the ORR rate by IRF assessment was 87.7% for patients on the A+CHP arm compared with 70.8% for patients on the CHOP arm with a difference of 16.9% (95% CI: 8.1%; 25.7%). In the subgroup of patients with ALK+ sALCL and ALK- sALCL the stratified hazard ratio for PFS per IRF was 0.29 (95% CI: 0.11; 0.79) and 0.65 (95% CI: 0.44; 0.95), respectively.

Superiority in primary definition of PFS of A+CHP over the CHOP arm has been shown in the overall study population (HR 0.71 [0.54, 0.93], p=0.011), best represented by differences in PFS event rates at 1 year (71.7% versus 58.2%) and 2 years (61.4% versus 47.4%,) due to plateau formation in the KM curves. The difference in PFS rate ≥1 year, when the curves are flattening, is indicative of longer term benefit. The observed effect size is deemed clinically relevant. Possible informative drop-out (subject withdrawal + lost to follow-up + other) was balanced between arms and small (A+CHP vs CHOP: 16+0+2 vs 10+4+0, i.e. 8.0 vs 6.2%), the same holds for possibly informative censoring, which are not likely to impact the efficacy conclusions.

As stated above, PFS sensitivity analysis 8 (i.e., according to EMA censoring rules) is the preferred analysis. The PFS HR is 0.76 [0.58,0.99], p=0.0443 in this analysis. The PFS rates at 1 year of 74.0% versus 62.5% in the A+CHP vs CHOP arm and at 2 year respectively 62.3% versus 50.9%, are supportive of the primary analysis. Informative censoring also does not appear to have impacted the outcomes of this sensitivity analyses.

PFS is supported by differences in CR rate (68% versus 56%, p=0.0066) and ORR rate (83% versus 72%, p=0.0032) favoring A+CHP over CHOP (ITT population). Median duration of response (respectively 52.7 versus 51.4 months) was similar between the two arms. It is encouraging that response rate outcomes are driven by the difference in CRs. The OS is immature with a total 124 (27%) OS events observed (median OS not reached) and influenced by subsequent therapies, but in support of PFS (OS HR 0.66 [0.46, 0.95], p=0.0244). Thus, the clinically relevant PFS differences at 1 or 2 year with flattening of the KM curve after 1 year, is supported by a trend in OS in favour of A+CHP over CHOP. Notably, an OS benefit has not previously been shown for first line PTCL patients compared to CHOP. The MAH committed to providing the final OS analysis.

In the ECHELON-2 study approximately 70% of the studied patients were diagnosed with sALCL, as such the number of subjects representing other PTCL subgroups are small, making the interpretation of the efficacy of A+CHP over CHOP difficult for non-sALCL subjects, especially in light of the only limited benefit of the A+CHP regimen over CHOP in some cases (HR 0.96). Additional ad-hoc analyses conducted by the applicant, included PFS, CR rate for non sALCL histologies (PTCL-NOS, AITL, ATLL, EATL combined and individually). These were not powered for statistical analysis and the small sample size limits the ability to draw definitive conclusions.

In order to extrapolate the hazard ratio for PFS for the subtypes, a semiparametric Bayesian hierarchical model (BHM) was implemented. Extrapolation of outcomes from sALCL patients to non-sALCL patients was proposed based on CD30 expression. The BHM was based on biological and prognostic similarities between ECHELON-2 patients and rare subgroups, including five subtypes in the model (ALK+ sALCL, ALK- sALCL, PTCL-NOS, AITL, and ATLL). EATL subgroup was excluded due to the small sample size enrolled in ECHELON-2 (N=3). Hazard Ratio estimates from BHM were smaller than 1 across different disease subtypes, supporting the conclusion that the superior effect of A+CHP compared to CHOP is consistent across histologic subtypes. Robustness of the results were demonstrated by sensitivity analyses using four different prior distributions (from informative to non-informative priors) and additionally by excluding the ALK+sALCL from the BHM, giving consistent results.

Additionally, to evaluate the impact of ALK+ sALCL on the shrinkage estimates of the subtype specific PFS HRs, a further sensitivity analysis was performed by excluding ALK+ sALCL from the BHM. The results are very similar to the model results that include ALK+ sALCL. Therefore, it can be concluded that the amount of borrowing from ALK+ sALCL is relatively limited.

It has however not been shown that CD30 expression alone is a requirement for a response from A+CHP compared to CHOP in non-sALCL patients, nor that that brentuximab vedotin induces a significant bystander effect at low CD30 expression. Furthermore, it is questionable whether the BHM estimated effects are the true underlying effects of the populations included in the study, as the model assumes that the modelled effects in smaller populations (i.e. non-sALCL PTCL types) are similar to those in large populations (i.e. sALCL). This assumption is not considered appropriate as updated KM curves for PFS and OS per subtype indicate heterogeneity in prognosis (plateau vs non-plateau) and treatment effect (non-crossing versus early crossing) across the CD30+ PTCL types. Also, to accurately predict outcomes for CD30 PTCL populations not included in the pivotal study the model requires the assumption that the range of effects in the included populations is representative for other, not-included populations. As PTCLs have different disease biology, clinical features, and prognosis, this assumption was not supported.

A threshold of CD30 expression in 10% or greater of neoplastic cells has been used as the definition of CD30 positivity (inclusion criterion). The 10% threshold was selected to exceed the local assays' error margin in order to give a reliable result of CD30 expression. Additional analysis on PFS, ORR, and duration of response showed that CD30 expression is not predictive of response to A+CHP.

There are also several other subgroups where the HR of the PFS approaches 1 (patients with stage I/II disease, ECOG2, IPI 4-5 and Asian patients), most likely this is due to the small number of subjects in these subgroups.

There was no clinically meaningful difference in QoL in the A+CHP arm compared to CHOP arm, except for diarrhoea in cycle 7 which reached a moderate MID difference, which is not considered sufficiently consistent for concerns on diminished QoL in A+CHP patients compared to CHOP. Exploratory analyses indicate no notable difference in medical resource utilization.

Brentuximab vedotin-containing subsequent therapy was given in 23 (10%) of the A+CHP patients and in 49 (22%) of the CHOP arm. Responses were attained by 13/23 subjects (57%) on the A+CHP arm and 24/49 subjects (49%) on the CHOP arm. Of note, this is a non-randomized comparison. There is no apparent difference in patients who receive SCT (22% in the A+CHP and 17% in the CHOP arm).

No notable differences were observed between ATA-negative, transiently ATA-positive subjects (n=47) and persistently ATA-positive (=2) patients. Five patients were nATA-positive, all had an objective response, though 2 of the 5 subjects subsequently progressed; however due to the small number of nATA positive patients no definite conclusions on the effects of nATAs can be made.

The MAH performed a phase 1 study (SGN35-011) of brentuximab vedotin in CD30+ in T-cell and NK-cell neoplasms. In this study the 1.8mg/kg was tested with CHP. DLTs defined as a delay of ≥7 days in CHP therapy in Cycle 1, did not meet the prespecified level which would allow de-escalation of the BV dose. The definition of a DLT is not supported, but as no major safety issues have arisen, the dose selection is considered acceptable. Efficacy outcomes of those who received A+CHP in this study appear supportive for the outcomes of the pivotal study.

A phase 2 study (SGN35-012), a single arm phase 2 single arm trial of brentuximab vedotin 1.8mg/kg as a monotherapy in relapsed or refractory NHL was submitted. Disease activity as measured by overall response rates was observed in patients with relapsed refractory AITL (ORR= 54%, n=13) and

PTCL-NOS (ORR= 33%, n=22). As this was a non-comparative study, it is unclear whether the observed effects were beneficial. Also, discrepancies arise as to why efficacy results for the subgroups of AITL and PTCL-NOS in 2nd line and with brentuximab vedotin monotherapy are reverse to those in the frontline treatment with A+CHP – therefore the use of these results as supportive data was not considered.

## Additional expert consultation

The CHMP consulted the SAG Oncology on the following questions:

1. Are the results obtained in the overall study population relevant also for the under-represented non-sALCL PTCL subtypes?

A special emphasis was given to the fact that peripheral T cell lymphomas (PTCLs) should be referred to as PTCL disease entities and not subtypes; although historically they have been considered as a heterogenous group but one disease entity, PTCLs are markedly heterogeneous at the clinical, pathological, histogenetic, and molecular levels and can have variable prognoses. In the 2016 revision of the WHO classification of lymphoid neoplasms[2], mature T and NK cell lymphomas and lymphoproliferative disorders comprise 27 distinct entities in addition to PTCL not otherwise specified (PTCL-NOS).

Further, the experts questioned the significance of CD30 expression in CD30+ PTCL entities, that is, whether CD30 positivity simply signifies the presence of CD30 in the malignant T-cell or in bystander B-cells (such as in AITL) and by that whether CD30 expression plays a direct role in the proliferation of a malignant phenotype or whether it reflects expression in the milieu setting that enhances tumour growth and survival. As all these mechanisms maybe present, the relative contribution of each would have an impact on the efficiency of targeting CD30 by BV.

The experts also debated on the correlation of CD-30 expression with A-CHP activity and the MAH's argument that levels just above the arbitrary threshold level of the assay (10%) are associated with a CR on A+CHP therapy. It is possible that achieving CR in patients with low CD-30 expression may very well be attributed to the backbone treatment (CHP); and consequently, extrapolation of the results from highly CD-30+ sALCL to such populations would be problematic.

Therefore, overall, even if we consider the ECHELON-2 trial as a type of basket protocol of different PTCL entities, CD-30 may not be an adequate biomarker to identify responders and allow extrapolating considerations in under-represented populations in the study.

Looking at the data the K-M curves of the non-ALCL entities PTCL NOS and AITL can be seen as superimposable for the first year but later on as there are very few patients any conclusions are difficult to make. The positive efficacy results in the ITT population are therefore driven by the predominant sALCL population. While considering the subgroups presented in the forest plot of PFS and OS the results and CI are indeed towards the right direction, however, the point estimates are quite different. However, AITL did not seem to follow this pattern for PFS (ITT population). It also has to be considered that the disease distribution at the time of design and outset of the trial was likely different than what would be selected after applying 2016 criteria that distinguish ALK-negative ALCL

[2] The 2016 revision of the World Health Organization classification of lymphoid neoplasms; *Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. Blood. 2016 May 19; 127(20):2375-90.*

from PTCL NOS and from AITL. There have been significant progress and changes in the allocation of lymphomas to these three entities over the recent years.

A Bayesian Hierarchical Model (BHM) designed by the applicant company to improve the reliability of estimates of effect size through borrowing information among the disease entities while still allowing for heterogeneity of PFS effect, showed apparent improved estimates of PFS hazard ratios for PTCL entities with small sample sizes. The SAG experts commented in relation to the borrowing of information element -based on CD-30 expression- and considered it would be useful to reflect on such modelling and under which conditions it could be acceptable to interpret the data. In particular, it was considered that the rationale to allow such borrowing has to be obtained externally, since the outcome-adaptive approach does not seem to have enough information to determine whether borrowing is appropriate and is therefore of limited use (Freidlin B, Korn EL. 2013). Furthermore, depending on the admissibility of borrowing, the trial as a whole (where all the data are pooled, i.e., extreme borrowing) has to be called into question.

2. Can the overall results be extrapolated to PTCL subtypes that were not studied?

Based on the above considerations the experts would not consider extrapolation to PTCL entities not studied in ECHELON-2. Most of PTCL entities not included in the study would not be eligible for treatment with a CHOP-based regimen under current recommendations, thus there would be no rationale for the A-CHP combination in these entities, e.g. HSTL, EATL, MEITL, ENKTL.

### 2.4.4. Conclusions on the clinical efficacy

The results from the pivotal ECHELON-2 study show in the study population of mainly sALCL patients a clinically relevant PFS advantage of A+CHP combination over CHOP supported by secondary efficacy parameters, among which a trend to OS benefit. Considering the above discussion, the indication for the combination of Adcetris with cyclophosphamide, doxorubicin and prednisone (CHP) is restricted to adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

The submission of the ECHELON-2 study also fulfills the post authorisation meausure MEA-015. It was agreed with the CHMP that this randomized, controlled trial would examine patients with newly diagnosed mature T-cell lymphoma (MTCL, also known as PTCL), including 75% (±5%) of patients with sALCL, (N=300), in order to provide safety data in the sALCL population. The ECHELON-2 study included 70% of patients with sALCL and submission of the ECHELON-2 study with this application serves to fulfill MEA-015 and its required enrollment of 75% (±5%) of patients with sALCL. The MAH will provide final OS analysis from ECHELON-2 when available (Q1 2021) in the context of follow-on MEA 015.1.

## *2.5. Clinical safety*

### Introduction

The safety profile of brentuximab vedotin administered as monotherapy was based on a single arm phase II studies in 160 patients diagnosed with relapsed or refractory HL or sALCL, a placebo controlled Phase III trial (AETHERA) in 165 HL patients at increased risk for relapse after ASCT, and a phase 3, open-label, randomised, multicentre study in 128 patients with histologically confirmed CD30+ CTCL (Study C25001). The safety and tolerability of brentuximab plus chemotherapy for the frontline treatment of advanced HL was analysed in the ECHELON-1 study. The combination of

brentuximab with AVD (doxorubicin [A], vinblastine [V] and dacarbazine [D]) was in line with brentuximab vedotin as monotherapy and the known safety profile of the chemotherapy backbone. This summary of clinical safety (SCS) presents the clinical safety findings from Study SGN35-014 (ECHELON-2).

## Patient exposure

The ECHELON-2 safety population included all patients who received any amount of brentuximab vedotin or any component of CHOP. Treatment arm was determined according to the actual treatment received, regardless of the randomization treatment assignment. Subjects who received any dose of brentuximab vedotin were grouped into the experimental arm. Patients who did not receive brentuximab vedotin but received any dose of any component of CHOP were grouped into the standard-of-care treatment arm. All safety endpoints were summarized using the safety population, which consisted of 223 patients in the A+CHP arm and 226 patients in the CHOP arm.

A median of 6 cycles (range, 1-8 cycles) of study treatment was reported for patients across the 2 treatment arms over a median of 18.1 weeks (range, 3-34 weeks) for the A+CHP arm and a median of 18.0 weeks (range, 3-31 weeks) for the CHOP arm. Administration of 6 cycles of the study treatment was planned for 82% of patients in the A+CHP arm and 81% of patients in the CHOP arm; 70% of patients in the A+CHP arm and 62% of patients in the CHOP arm received 6 cycles of study treatment.

### Dose Modifications

Permitted dose modifications included dose delays, dose reductions, dose eliminations (ie, temporary stoppages allowed for cyclophosphamide and doxorubicin only), and dose discontinuations (ie, stoppages of 1 component in the multi-agent regimen for the remainder of the study). For blinded study treatment, the permitted dose reductions defined in the protocol were 1.2 mg/kg for brentuximab vedotin and 1 mg for vincristine. Unplanned dose adjustments were considered either infusion interruptions, infusions stopped early, or dose errors.

**Table 39 Study SGN35-014: Dose Modification by Patient (Safety Population)**

| | A+CHP N=223 | | |
|---|---|---|---|
| | Brentuximab Vedotin (mg/kg) | Cyclophosphamide | Doxorubicin (mg/m$^2$) |
| **All Cycles, n (%)** | | | |
| Dose delayed due to AE | | | |
| Yes | 59 (26) | 58 (26) | 57 (26) |
| No | 164 (74) | 165 (74) | 166 (74) |
| Dose reduced due to AE | | | |
| Yes | 21 (9) | 18 (8) | 17 (8) |
| No | 202 (91) | 205 (92) | 206 (92) |
| | **CHOP N=226** | | |
| | Vincristine (mg/m$^2$) | Cyclophosphamide (mg/m$^2$) | Doxorubicin (mg/m$^2$) |
| **All Cycles, n (%)** | | | |
| Dose delayed due to AE | | | |
| Yes | 28 (12) | 27 (12) | 28 (12) |
| No | 198 (88) | 199 (88) | 198 (88) |
| Dose reduced due to AE | | | |
| Yes | 24 (11) | 11 (5) | 11 (5) |
| No | 202 (89) | 215 (95) | 215 (95) |

**Exposure-Response Analysis Results and Relationship to Safety**

The incidence of Grade 3 or higher TEAEs, Grade 4 or higher neutropenia, febrile neutropenia, and Grade 2 or higher PN was evaluated by quartiles of ADC serum or MMAE plasma trough concentrations for evaluable subjects in the A+CHP arm.

**Table 40 Study SGN35-014: Incidence of TEAEs of Interest by Quartiles of ADC Trough Concentration**

| | | A+CHP (N=223) | | | |
|---|---|---|---|---|---|
| | CHOP (N=226) n (%) | BV Q1 (N=50) n (%) | BV Q2 (N=51) n (%) | BV Q3 (N=49) n (%) | BV Q4 (N=50) n (%) |
| TEAE (Grade 3 or higher) | 146 (65) | 35 (70) | 29 (57) | 29 (59) | 35 (70) |
| Neutropenia (Grade 4 or higher) | 49 (22) | 11 (22) | 7 (14) | 10 (20) | 13 (26) |
| Febrile neutropenia | 33 (15) | 12 (24) | 10 (20) | 4 (8) | 9 (18) |
| Peripheral neuropathy (SMQ) (Grade 2 or higher) | 35 (15) | 10 (20) | 10 (20) | 8 (16) | 11 (22) |

**Table 41 Study SGN35-014: Incidence of TEAEs of Interest by Quartiles of MMAE Trough Concentration**

| | | A+CHP (N=223) | | | |
|---|---|---|---|---|---|
| | CHOP (N=226) n (%) | MMAE Q1 (N=48) n (%) | MMAE Q2 (N=49) n (%) | MMAE Q3 (N=49) n (%) | MMAE Q4 (N=45) n (%) |
| TEAE (Grade 3 or higher) | 146 (65) | 26 (54) | 23 (47) | 34 (69) | 37 (82) |
| Neutropenia (Grade 4 or higher) | 49 (22) | 7 (15) | 7 (14) | 14 (29) | 10 (22) |
| Febrile neutropenia | 33 (15) | 5 (10) | 4 (8) | 13 (27) | 13 (29) |
| Peripheral neuropathy (SMQ) (Grade 2 or higher) | 35 (15) | 11 (23) | 9 (18) | 7 (14) | 11 (24) |

**Demographics**

The ECHELON-2 ITT population consisted of 226 patients each in the A+CHP and CHOP arms. A total of 133 men (59%) and 93 women (41%) were randomized to the A+CHP arm and 151 men (67%) and 75 women (33%) were randomized to the CHOP arm. The median age of randomized patients was 58 years (range, 18-85 years for the A+CHP arm and 18-83 years for the CHOP arm); 31% of patients randomized to each treatment arm were aged 65 years or older. An ECOG performance status of 1 was reported for 90 patients (40%) in the A+CHP arm and 86 patients (38%) in the CHOP arm and an ECOG performance status of 2 was reported for 51 patients (23%) in the A+CHP arm and 47 patients (21%) in the CHOP arm (see Clinical efficacy section).

**Baseline Disease Characteristics**

The ECHELON-2 ITT population consisted of 226 patients each in the A+CHP and CHOP arms. Most of the randomized patients had advanced stage and intermediate-risk disease as is typical of this patient population at the time of clinical presentation. Baseline disease characteristics are presented in the efficacy section.

**Concomitant Medications**

At least 1 concomitant medication was reported for almost all patients in the safety population. The most frequently reported concomitant medications (≥25% of patients) for the A+CHP arm were ondansetron hydrochloride (48% of patients), allopurinol (42%), paracetamol and filgrastim (39% each), pegfilgrastim (34%), Bactrim (sulfamethoxazole/trimethoprim) (28%), and omeprazole (26%).

The most frequently reported concomitant for the CHOP arm were paracetamol (41% of patients), ondansetron hydrochloride (40%), filgrastim (39%), allopurinol (38%), Bactrim (sulfamethoxazole/trimethoprim) (32%), and pegfilgrastim (26%).

At least 1 G-CSF concomitant medication was reported for 171 patients (77%) in the A+CHP arm and 162 patients (72%) in the CHOP arm. Filgrastim and lenograstim were the most commonly reported across treatment arms.

## Adverse events

Safety summaries included AEs reported during the safety evaluation period, defined as the period during or after the first dose of the drug regimen up to 30 days after the last dose of any component of the drug regimen. The frequency and severity of peripheral neuropathy (PN) reported in the study were evaluated by a comprehensive review of the PN Standardised MedDRA Query (SMQ) broad (MedDRA Version 21.0). Patients with ongoing PN after the safety evaluation period were followed until of PN resolution or study closure.

In response to a slightly higher than expected infection rate in the safety population, observed after review of the results from the interim futility analysis, the IDMC recommended that the sponsor remind investigators of the use of prophylactic growth factor support in accordance with current American Society of Clinical Oncology (ASCO) [11] or European Society for Medical Oncology (ESMO) guidelines. Safety analyses included an assessment of the impact of granulocyte colony stimulating factor (G-CSF) primary prophylaxis on neutropenia and associated complications, including febrile neutropenia and infections.

TEAEs of any grade, treatment-related (brentuximab vedotin or vincristine) TEAEs, Grade 3 or higher TEAEs, serious adverse events (SAEs), and AEs that resulted in study treatment discontinuation were reported for a similar proportion of patients across treatment arms. SAEs considered related to brentuximab vedotin were reported for a higher proportion of patients in the A+CHP arm than the SAEs considered related to vincristine for patients in the CHOP arm. A higher proportion of SAEs with the outcome of death were reported for the CHOP arm than the A+CHP arm.

At least 1 treatment-related SAE attributed to brentuximab vedotin was reported for 58 patients (26%) in the A+CHP arm and at least 1 treatment-related SAE attributed to vincristine was reported for 45 patients (20%) in the CHOP arm. At least 1 Grade 5 TEAE was reported for 8 patients (4%) in the A+CHP arm and 16 patients (7%) in the CHOP arm.

**Table 42 Study SGN35-014: Overview of AE Profile (Safety Population)**

| | A+CHP (N=223) | CHOP (N=226) |
|---|---|---|
| Subjects with at least 1 TEAE, n (%) [a] | 221 (99) | 221 (98) |
| Subjects with blinded study treatment-related TEAE [b] | 201 (90) | 193 (85) |
| Subjects with CHP treatment-related TEAE [b] | 198 (89) | 205 (91) |
| Maximum severity of TEAE [a] | | |
| Grade 1 | 15 (7) | 23 (10) |
| Grade 2 | 59 (26) | 52 (23) |
| Grade 3 | 77 (35) | 67 (30) |
| Grade 4 | 62 (28) | 63 (28) |
| Grade 5 | 8 (4) | 16 (7) |
| <Grade 3 | 74 (33) | 75 (33) |
| ≥Grade 3 | 147 (66) | 146 (65) |
| Subjects with any SAE | 87 (39) | 87 (38) |
| Subjects with any blinded study treatment-related SAE [b] | 58 (26) | 45 (20) |
| Subjects with any CHP treatment-related SAE [b] | 62 (28) | 53 (23) |
| Subjects who discontinued study treatment due to AE | 14 (6) | 15 (7) |
| Subjects who discontinued treatment due to blinded study treatment-related AE [b] | 10 (4) | 10 (4) |
| Subjects who discontinued treatment due to CHP-related AE | 8 (4) | 7 (3) |

**Treatment-Emergent Adverse Events**

Treatment-emergent adverse events that occurred in ≥10% of subjects in the A+CHP treatment arm are summarized in Table 43.

**Table 43 TEAEs reported for ≥10% of subjects in the A+CHP arm by preferred term (safety analysis set)**

| Preferred Term | A+CHP (N=223) n (%) | CHOP (N=226) n (%) |
|---|---|---|
| Subjects with at least 1 TEAE | 221 (99) | 221 (98) |
| Nausea | 103 (46) | 87 (38) |
| Peripheral sensory neuropathy | 100 (45) | 92 (41) |
| Diarrhoea | 85 (38) | 46 (20) |
| Neutropenia | 85 (38) | 85 (38) |
| Constipation | 64 (29) | 67 (30) |
| Alopecia | 58 (26) | 56 (25) |
| Pyrexia | 58 (26) | 42 (19) |
| Vomiting | 57 (26) | 39 (17) |
| Fatigue | 54 (24) | 46 (20) |
| Anaemia | 46 (21) | 36 (16) |
| Febrile neutropenia | 41 (18) | 33 (15) |
| Decreased appetite | 39 (17) | 27 (12) |
| Dyspnoea | 32 (14) | 24 (11) |
| Headache | 31 (14) | 31 (14) |
| Dizziness | 28 (13) | 20 (9) |
| Cough | 27 (12) | 22 (10) |
| Hypokalaemia | 27 (12) | 18 (8) |
| Stomatitis | 27 (12) | 27 (12) |
| Asthenia | 26 (12) | 16 (7) |
| Weight decreased | 26 (12) | 17 (8) |
| Insomnia | 25 (11) | 31 (14) |
| Myalgia | 24 (11) | 19 (8) |
| Oedema peripheral | 24 (11) | 18 (8) |
| Rash | 22 (10) | 15 (7) |

**Treatment-Related Adverse Events**

Brentuximab vedotin-related AEs reported for at least 10% of subjects on the A+CHP arm included peripheral sensory neuropathy (44%), neutropenia (34%), and nausea (32%). Vincristine-related AEs reported for at least 10% of subjects on the CHOP arm also included peripheral sensory neuropathy (38%), neutropenia (30%), and nausea (27%).

**Table 44 Brentuximab vedotin or vincristine-related AEs reported for ≥10% of subjects in the A+CHP arm (safety analysis set)**

| Preferred Term | A+CHP (N=223) n (%) | CHOP (N=226) n (%) |
|---|---|---|
| Any event | 201 (90) | 193 (85) |
| Peripheral sensory neuropathy | 98 (44) | 87 (38) |
| Neutropenia | 75 (34) | 68 (30) |
| Nausea | 71 (32) | 61 (27) |
| Constipation | 47 (21) | 50 (22) |
| Alopecia | 38 (17) | 30 (13) |
| Diarrhea | 36 (16) | 16 (7) |
| Fatigue | 36 (16) | 36 (16) |
| Febrile neutropenia | 35 (16) | 28 (12) |
| Vomiting | 32 (14) | 25 (11) |
| Anemia | 30 (13) | 23 (10) |
| Decreased appetite | 26 (12) | 16 (7) |
| Pyrexia | 22 (10) | 14 (6) |

This table only includes adverse events that occurred within safety analysis period, as defined as Day 1 up to 30 days after the last dose of any component of the regimen. Events related to blinded study treatment could also be related to other components of the regimen
Source: Table 14.3.1.27

**Grade 3 or Higher Adverse Events**

A total of 147 subjects (66%) on the A+CHP arm versus 146 subjects (65%) on the CHOP arm experienced at least 1 ≥ Grade 3 AE. The Grade 3 or higher TEAEs reported for at least 5% of patients in the A+CHP arm were neutropenia (35% of patients), febrile neutropenia (18%), anaemia (13%), leukopenia (7%), diarrhoea and thrombocytopenia (6% each), and pneumonia (5%). The Grade 3 or higher TEAEs reported for at least 5% of patients in the CHOP arm were neutropenia (34%), febrile neutropenia (15%), anaemia (10%), leukopenia (6%) (Table 45).

**Table 45 Grade 3 or higher AEs occurring in ≥2% of subjects in the A+CHP arm (safety analysis set)**

| Preferred Term | A+CHP (N=223) n (%) | CHOP (N=226) n (%) |
|---|---|---|
| Any event | 147 (66) | 146 (65) |
| Neutropenia | 77 (35) | 76 (34) |
| Febrile neutropenia | 41 (18) | 33 (15) |
| Anemia | 30 (13) | 23 (10) |
| Leukopenia | 16 (7) | 14 (6) |
| Diarrhea | 13 (6) | 2 (1) |
| Thrombocytopenia | 13 (6) | 9 (4) |
| Pneumonia | 12 (5) | 5 (2) |
| Hypokalemia | 8 (4) | 3 (1) |
| Peripheral sensory neuropathy | 8 (4) | 6 (3) |
| Sepsis | 6 (3) | 4 (2) |
| Nausea | 5 (2) | 4 (2) |
| Dyspnea | 4 (2) | 4 (2) |
| Hyperglycemia | 4 (2) | 1 (0) |
| Pulmonary embolism | 4 (2) | 7 (3) |
| Pyrexia | 4 (2) | 0 |
| Urinary tract infection | 4 (2) | 1 (0) |

Table only includes adverse events that occurred within the safety analysis period, defined as Day 1 up to 30 days after the last dose of any component of the regimen. Treatment-emergent adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of brentuximab vedotin or any component of multiagent chemotherapy (CHOP or CHP).
Source: Table 14.3.1.29

Of the 147 subjects who had Grade 3 or higher AEs on the A+CHP arm, 62 (42%) had Grade 4 events and 8 cases (5 %) had Grade 5 (fatal) events. On the CHOP arm, of the 146 subjects who had Grade 3 or higher AEs, 63 (43%) had Grade 4 events and 16 cases (11%) had Grade 5 (fatal) events. On both the A+CHP arm and the CHOP arm, the most common Grade 4 event was neutropenia, which occurred in 46 subjects (21%) on the A+CHP arm versus 47 subjects (21%) on the CHOP arm.

On the A+CHP arm, brentuximab vedotin-related ≥ Grade 3 AEs reported for ≥10% of subjects were neutropenia (30%) and febrile neutropenia (16%). On the CHOP arm, vincristine-related ≥ Grade 3 AEs reported for ≥10% of subjects were also neutropenia (27%) and febrile neutropenia (12%).

**Adverse Events by Histologic Subtype**

Summaries of TEAEs by disease subtype were presented for subjects with sALCL, subjects with PTCL-NOS, subjects with AITL, subjects with EATL and subjects with ATLL. The safety profile was generally similar across all histologic subtypes evaluated; most common TEAEs occurred at a similar incidence across subtypes.

**Adverse Events by Cycles of Treatment**

A summary of TEAEs by preferred term and number of cycles of study treatment received (≤6 versus >6 cycles) is presented in the CSR. The overall incidence and profile of TEAEs for both the A+CHP and CHOP treatment arms was generally similar regardless of the number of treatment cycles received.

## Deaths

As of the August 15, 2018 data cut-off date, 123 deaths had been reported; 50 on the A+CHP arm and 73 on the CHOP arm. Of the 50 deaths on the A+CHP arm, 36 were disease related, 10 were not

disease related, and disease relationship was unknown for 4 subjects. Of the 73 deaths on the CHOP arm, 58 were disease related, 7 were not disease related, and disease relationship was unknown for 8 subjects. One additional subject on the A+CHP arm died after randomization, but before receiving study treatment; this subject is included in the OS analysis.

A total of 21 subjects (5%) died within 30 days of the last dose of any component of the treatment regimen; 8 subjects (4%) on the A+CHP arm and 13 subjects (6%) on the CHOP arm. In addition, 3 subjects on the CHOP arm died due to Grade 5 AEs that had a start date within 30 days of the last dose of CHOP, but died outside of the safety analysis period. Approximately half of the deaths within 30 days of the last dose of any component of the treatment regimen were disease related (11/21; 52%).

In both treatment arms, the majority of deaths reported ≥30 days of the last dose of any component of the treatment regimen were disease-related (32/42 subjects [76%] on the A+CHP arm and 51/60 subjects [85%] on the CHOP arm). All AEs resulting in death are summarized below. Death narratives have been presented.

**Table 46 Adverse events resulting in death (safety analysis set)**

| Preferred Term | A+CHP (N=223) n (%) | CHOP (N=226) n (%) |
|---|---|---|
| Any event | 8 (4) | 16 (7) |
| Acute kidney injury | 1 (0) | 0 |
| Cardiac arrest | 1 (0) | 1 (0) |
| Peripheral T-cell lymphoma unspecified | 1 (0) | 0 |
| Pneumonia | 1 (0) | 0 |
| Pneumonia aspiration | 1 (0) | 0 |
| Pulmonary cavitation | 1 (0) | 0 |
| Sepsis | 1 (0) | 2 (1) |
| Ventricular fibrillation | 1 (0) | 0 |
| Anaplastic large cell lymphoma T- and null-cell types | 0 | 8 (4) |
| Arrhythmia | 0 | 1 (0) |
| Death | 0 | 1 (0) |
| Febrile neutropenia | 0 | 1 (0) |
| Hydrocephalus | 0 | 1 (0) |
| Multiple organ dysfunction syndrome | 0 | 2 (1) |
| Septic shock | 0 | 1 (0) |

## Serious adverse events

SAEs were reported for 87 subjects (39%) on the A+CHP arm and 87 subjects (38%) on the CHOP arm. The most frequently reported SAEs on the A+CHP arm were febrile neutropenia in 31 subjects (14%), pneumonia in 11 subjects (5%), pyrexia in 9 subjects (4%), and neutropenia in 8 subjects (4%). All other SAEs were reported for ≤2% of subjects on the A+CHP arm.

Brentuximab vedotin-related SAEs were reported for 58/223 subjects (26%) on the A+CHP arm; vincristine-related SAEs were reported for 45/226 subjects (20%) on the CHOP arm. Brentuximab vedotin-related SAEs that occurred in ≥2% of subjects on the A+CHP arm were febrile neutropenia (11%), pneumonia (4%), and neutropenia and sepsis (2% each); all other brentuximab vedotin-related SAEs occurred in <2% of subjects. Vincristine-related SAEs that occurred in ≥2% of subjects

on the CHOP arm were febrile neutropenia (10%) and neutropenia (2%); all other vincristine-related SAEs occurred in <2% of subjects.

**Table 47 Serious adverse events occurring in ≥2 subjects in the A+CHP arm (safety analysis set)**

| Preferred Term | A+CHP (N=223) n (%) | CHOP (N=226) n (%) |
|---|---|---|
| Any event | 87 (39) | 87 (38) |
| Febrile neutropenia | 31 (14) | 26 (12) |
| Pneumonia | 11 (5) | 3 (1) |
| Pyrexia | 9 (4) | 7 (3) |
| Neutropenia | 8 (4) | 6 (3) |
| Pneumonitis | 5 (2) | 0 |
| Sepsis | 5 (2) | 4 (2) |
| Diarrhea | 4 (2) | 3 (1) |
| Acute kidney injury | 3 (1) | 0 |
| Deep vein thrombosis | 3 (1) | 2 (1) |
| Respiratory failure | 3 (1) | 2 (1) |
| Tumour lysis syndrome | 3 (1) | 0 |
| Cellulitis | 2 (1) | 0 |
| Clostridium difficile colitis | 2 (1) | 0 |
| Dehydration | 2 (1) | 3 (1) |
| Device related infection | 2 (1) | 0 |
| Influenza | 2 (1) | 0 |
| Neutropenic infection | 2 (1) | 1 (0) |
| Peripheral sensory neuropathy | 2 (1) | 0 |
| Pneumocystis jirovecii pneumonia | 2 (1) | 0 |
| Pulmonary embolism | 2 (1) | 5 (2) |
| Urinary tract infection | 2 (1) | 0 |

**Adverse Events Resulting in Treatment Discontinuation**

A total of 29 subjects (6%) experienced an AE that resulted in discontinuation of all components of study treatment; 14 subjects (6%) on the A+CHP arm and 15 subjects (7%) on the CHOP. One additional subject on the A+CHP arm (Subject 81005-0208) discontinued treatment due to an AE of Grade 3 dyspnoea that occurred outside of the safety analysis period. Two subjects on each arm (1%) discontinued treatment due to peripheral sensory neuropathy. All other AEs leading to treatment discontinuation were reported for a single subject.

Subjects who discontinued brentuximab vedotin or vincristine due to an AE were allowed to continue to receive the other components of CHP. Four subjects (2%) in the A+CHP arm discontinued brentuximab vedotin treatment, and 5 subjects (2%) in the CHOP arm discontinued vincristine treatment.

**Adverse Events Leading to Dose Delays**

Doses of brentuximab vedotin were delayed because of AEs in 59/223 subjects (26%) on the A+CHP arm; doses of vincristine were delayed because of AEs in 28/226 subjects (12%) on the CHOP arm. The most common reasons for dose delays on the A+CHP arm were neutropenia (5%), pneumonia (3%), and pyrexia (2%). All other AEs resulting in dose delays on the A+CHP arm occurred in 3 or fewer subjects. The most common reasons for dose delays on the CHOP arm were neutropenia (4%), and leukopenia and pyrexia (2% each). All other AEs resulting in dose delays on the CHOP arm occurred in 1 subject.

**Adverse Events Leading to Dose Reduction**

Doses of brentuximab vedotin were reduced because of AEs in 21/223 subjects (9%) on the A+CHP arm; doses of vincristine were reduced because of AEs for 24/226 subjects (11%) on the CHOP arm. The most common reasons for dose reductions on the A+CHP arm were peripheral sensory neuropathy (5%) and peripheral motor neuropathy (2%). All other AEs resulting in dose reductions on the A+CHP arm occurred in ≤1 subject. The most common reasons for dose reductions on the CHOP arm were peripheral motor neuropathy (4%), peripheral sensory neuropathy (2%), and febrile neutropenia (1%). All other AEs resulting in dose reductions on the CHOP arm occurred in ≤1 subject.

**Peripheral Neuropathy**

Per MedDRA SMQ analysis, a total of 49 subjects (11%) enrolled had pre-existing PN. The proportion of subjects with pre-existing PN was the same in both treatment arms (11%). Treatment-emergent PN was reported for 117 subjects (52%) on the A+CHP arm and 124 subjects (55%) on the CHOP arm. The majority of treatment-emergent PN events on both treatment arms were Grade 1. Thirty-three subjects (15%) on the A+CHP arm versus 26 subjects (12%) on the CHOP arm had PN events of Grade 2 in worst severity. Worst severity Grade 3 PN was reported for 8 subjects (4%) on the A+CHP arm and 10 subjects (4%) on the CHOP arm. Grade 4 PN was reported for a single subject on the A+CHP arm.

**Table 48 Overall summary of peripheral neuropathy (SMQ) adverse events (safety analysis set)**

| | A+CHP (N=223) | CHOP (N=226) |
|---|---|---|
| Subjects with preexisting PN, n (%) | 24 (11) | 25 (11) |
| Subjects with treatment-emergent PN | 117 (52) | 124 (55) |
| Grade 2 | 33 (15) | 26 (12) |
| Grade 3 | 8 (4) | 10 (4) |
| Grade 4 | 1 (0) | 0 |
| Subjects with treatment-emergent PN severity worsening from preexisting to postbaseline | 7 (3) | 3 (1) |
| Subjects with treatment-emergent PN severity worsening from preexisting then returning to baseline severity or better | 4 (2) | 1 (0) |
| Subjects with treatment-related PN | 112 (50) | 111 (49) |
| Grade 2 | 29 (13) | 21 (9) |
| Grade 3 | 7 (3) | 8 (4) |
| Grade 4 | 1 (0) | 0 |
| Subjects with dose modification due to PN [a] | 16 (7) | 16 (7) |
| Subjects with dose modification and study treatment discontinuation due to PN | 0 | 0 |
| Subjects with dose modification and brentuximab vedotin or vincristine discontinuation due to PN [b] | 0 | 1 (0) |
| Completed treatment | 16 (7) | 14 (6) |

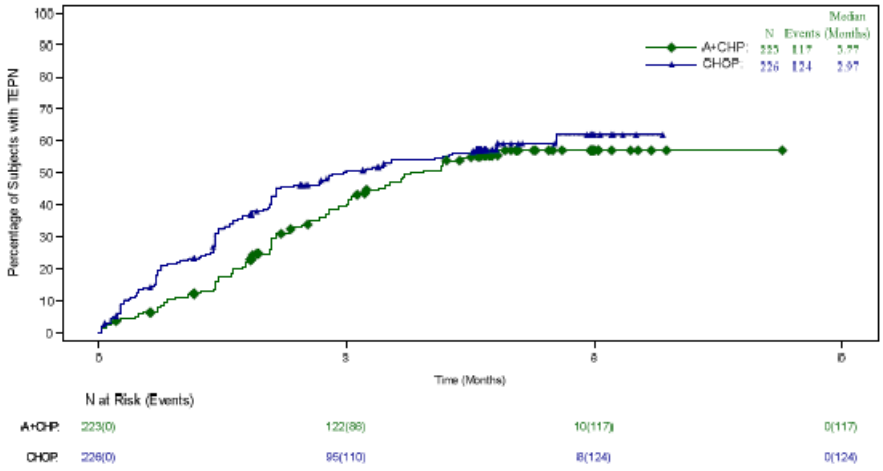
Source: SGN35-014 Table 14.3.1.66.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; AE: adverse event; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; MedDRA: Medical Dictionary for Regulatory Activities; PN: peripheral neuropathy; SMQ: Standardised MedDRA Query.
MedDRA Version 21.0 was applied.
[a] Dose reduction or dose delay attributed to PN.
[b] Only includes subjects with a PN event that resulted in both dose modification and treatment discontinuation.

*Treatment Discontinuation and Dose Modifications for Peripheral Neuropathy*

Peripheral sensory neuropathy resulted in study treatment discontinuation for 3 patients each across treatment arms. PMN resulted in study treatment discontinuation for 2 patients in the CHOP arm. Peripheral sensory neuropathy resulted in a dose reduction for 11 patients (5%) in the A+CHP arm and 4 patients (2%) in the CHOP arm, and PMN for 4 patients (2%) in the A+CHP arm and 8 patients (4%) in the CHOP arm. Peripheral sensorimotor neuropathy also resulted in a dose reduction for 1 patient in the A+CHP arm. Muscular weakness, autonomic neuropathy, and paraesthesia resulted in a dose reduction for 1 patient each in the CHOP arm.

*Onset of Treatment-Emergent Peripheral Neuropathy*

Among patients with at least 1 treatment emergent PN (SMQ) event of any grade, first onset was reported at a median of 9.1 weeks (range, 0-21 weeks) for the A+CHP arm and at a median of 6.1 weeks (range, 0-24 weeks) for the CHOP arm. The median time to onset corresponded to approximately Cycle 3 for the A+CHP arm and approximately Cycle 2 for the CHOP arm. First onset of the highest (worst) grade PN event was reported at a median of 10.0 weeks (range, 0-40 weeks) for the A+CHP arm and at a median of 6.5 weeks (range, 0-30 weeks) for the CHOP arm.




Source: SGN35-014 Figure 14.3.1.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; K-M: Kaplan-Meier; MedDRA: Medical Dictionary for Regulatory Activities; PN: peripheral neuropathy; SMQ: Standardised MedDRA Query; TEPN: treatment-emergent peripheral neuropathy.

**Figure 17 K-M Plot of Time to Onset of Treatment-Emergent PN (SMQ) Events (Safety Population)**

*Resolution or Improvement of Peripheral Neuropathy*

Among patients with at least 1 treatment-emergent PN (SMQ) event, resolution was reported for 58 patients (50%) in the A+CHP arm and 79 patients (64%) in the CHOP arm, and improvement for 14 patients in the A+CHP arm and 15 patients in the CHOP arm (12% each) at last follow-up. Resolution of PN events was reported at a median of 17.0 weeks (range, 0-195 weeks) and improvement at a median of 8.1 weeks (range, 3-84 weeks) for the A+CHP arm and at a median of 11.4 weeks (range, 0-220 weeks) and 7.6 weeks (range, 2-101 weeks) for the CHOP arm, respectively. At the time of last follow-up, PN was reported to be ongoing for 61 patients (52%) in the A+CHP arm and 45 patients (36%) in the CHOP arm, and the majority of ongoing PN events were Grade 1. Grade 3 PN was reported for 2 patients in the A+CHP arm and 1 patient in the CHOP arm. Updated results for the resolution of PN events show a resolution in PN events of 54%. The median time to resolution of PN events was 19 weeks.

**Febrile Neutropenia**

A total of 41 subjects (18%) on the A+CHP arm versus 33 subjects (15%) on the CHOP arm experienced treatment-emergent febrile neutropenia. On both treatment arms, the majority of subjects who had febrile neutropenia had Grade 3 events (36/41 [88%] for A+CHP versus 26/33 [79%] for CHOP); Grade 4 events were reported for 5/41 subjects (12%) on the A+CHP arm versus 6/33 subjects (18%) on the CHOP arm. One Grade 5 event was reported on the CHOP arm.

For the 41 subjects on the A+CHP arm who had at least 1 event of febrile neutropenia, the median time to onset of the first event was 1.9 weeks (range, 1 to 23), which was similar to the median time to onset for the 33 subjects on the CHOP arm who had at least 1 febrile neutropenia event (median of

1.6 weeks [range, 1 to 23]). With the exception of the single fatal event of febrile neutropenia reported for a subject on the CHOP arm, all events of febrile neutropenia resolved. The median time to resolution was similar for both treatment arms (0.9 weeks [range, 0 to 2] for the A+CHP arm versus 0.9 weeks [range, 0 to 3] for the CHOP arm).

**Table 49 Summary of febrile neutropenia adverse events (safety analysis set)**

| | A+CHP (N=223) n (%) | CHOP (N=226) n (%) |
|---|---|---|
| Subjects with treatment-emergent febrile neutropenia | 41 (18) | 33 (15) |
| Worst severity Grade 3 | 36 (16) | 26 (12) |
| Worst severity Grade 4 | 5 (2) | 6 (3) |
| Worst severity Grade 5 | 0 | 1 (0) |
| Subjects with treatment-related febrile neutropenia | 39 (17) | 33 (15) |
| Worst severity Grade 3 | 35 (16) | 26 (12) |
| Worst severity Grade 4 | 4 (2) | 6 (3) |
| Worst severity Grade 5 | 0 | 1 (0) |
| Dose modifications[a] due to febrile neutropenia | 6 (3) | 4 (2) |
| Discontinued treatment due to febrile neutropenia | 0 | 0 |
| Completed treatment | 5 (2) | 3 (1) |
| Number of cycles completed for subjects who completed less than the intended number of cycles[b] | 1 (0) | 1 (0) |
| n | 1 | 1 |
| Mean (SD) | 5.0 (-) | 5.0 (-) |
| Median | 5.0 | 5.0 |
| Min, max | 5, 5 | 5, 5 |

Table only includes adverse events that occurred within the safety analysis period, defined as Day 1 up to 30 days after the last dose of any component of the regimen. One subject died before their FN resolved. TEAEs are presented and defined as newly occurring (not present at baseline) or worsening after first dose of brentuximab vedotin or any component of multiagent chemotherapy (CHOP or CHP).

a Dose reduction or dose delay attributed to an adverse event of peripheral neuropathy

b Intended number of cycles is either 6 or 8

Source: Table 14.3.1.70

*Impact of Primary Prophylaxis with G-CSF on Febrile Neutropenia*

The use of G-CSF according to institutional guidelines was allowed per protocol for the management of subjects who developed neutropenia. After enrollment of approximately 65% of study participants, the IDMC recommended that Seattle Genetics remind investigators to use prophylactic growth factor support per ASCO guidelines. G-CSF primary prophylaxis was defined as administration of pegfilgrastim or filgrastim on Day 1 or 8 of Cycle 1 for an indication of "prophylaxis" on the case report form (CRF).

G-CSF primary prophylaxis was administered to 75 subjects (34%) on the A+CHP treatment arm and 61 subjects (27%) on the CHOP arm. Febrile neutropenia at any time during treatment was reported for 16% of A+CHP subjects who received G-CSF primary prophylaxis compared with 20% of subjects who did not receive G-CSF primary prophylaxis. Similar results were reported for the CHOP arm (11% versus 16%). Grade 3 or higher neutropenia was reported for 13% of A+CHP subjects who received G-CSF primary prophylaxis versus 45% of subjects who did not receive G-CSF primary prophylaxis. Similar results were reported for the CHOP arm (13% versus 42%).

**Table 50 Study SGN35-014: AEs of Interest by G-CSF Primary Prophylaxis (Safety Population)**

| | A+CHP (N=223) | | CHOP (N=226) | |
|---|---|---|---|---|
| | No G-CSF prophylaxis (N=148) | G-CSF primary prophylaxis (N=75) | No G-CSF prophylaxis (N=165) | G-CSF primary prophylaxis (N=61) |
| Incidence of febrile neutropenia in Cycle 1, n (%) | 17 (11) | 9 (12) | 18 (11) | 4 (7) |
| Incidence of febrile neutropenia on study, n (%) | 29 (20) | 12 (16) | 26 (16) | 7 (11) |
| Incidence of neutropenia, n (%) * | 73 (49) | 12 (16) | 76 (46) | 10 (16) |
| Incidence of Grade 3 or higher neutropenia, n (%) * | 67 (45) | 10 (13) | 69 (42) | 8 (13) |
| Incidence of Grade 4 or higher neutropenia, n (%) * | 39 (26) | 7 (9) | 43 (26) | 6 (10) |
| Incidence of Grade 3 or higher TEAEs, n (%) | 107 (72) | 40 (53) | 114 (69) | 32 (52) |
| Incidence of infections and infestations (SOC), n (%) | 79 (53) | 37 (49) | 74 (45) | 28 (46) |
| Incidence of Grade 3 or higher infections and infestations (SOC), n (%) | 30 (20) | 12 (16) | 23 (14) | 8 (13) |
| Incidence of any SAEs on study, n (%) | 55 (37) | 31 (41) | 58 (35) | 27 (44) |
| Incidence of SAEs of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, or infections and infestations (SOC), n (%) | 41 (28) | 23 (31) | 37 (22) | 15 (25) |
| Incidence of any Grade 5 AEs, n (%) | 4 (3) | 4 (5) | 12 (7) | 4 (7) |

Source: SGN35-014 Table 14.3.1.77.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; AE: adverse event; C2D1: Cycle 2 Day 1; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF: granulocyte colony stimulating factor; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
Patient Incidence: A patient was counted once in each row if they met any of the criteria for that row. Percentages are based on the number of patients in the column.
Events in Cycle 1 were those with start date from first dose date and before C2D1 dose date or Day 22 for those without C2D1 dose administration).
* Neutropenia included PTs of 'neutropenia' and 'neutrophil count decreased'.

**Neutropenia, Other Hematologic Abnormalities**

**Table 51– Study SGN35-014: Treatment-Emergent Neutropenia, Anaemia, Thrombocytopenia (Safety Population)**

| | A+CHP (N=223) | CHOP (N=226) |
|---|---|---|
| Neutropenia, anaemia, thrombocytopenia of any grade, n (%) | 195 (87) | 193 (85) |
| Neutropenia | 132 (59) | 131 (58) |
| Anaemia | 147 (66) | 133 (59) |
| Thrombocytopenia | 38 (17) | 29 (13) |

Source: SGN35-014 Table 14.3.1.44.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term.
PTs of neutropenia and neutrophil count decreased were counted as neutropenia.
PTs of thrombocytopenia and platelet count decreased were counted as thrombocytopenia.
PTs of anaemia and lab toxicity of anemia were counted as anaemia.
This table only includes AEs that occurred within safety evaluation period, as defined as Day 1 up to 30 days after the last dose of any component of the treatment regimen. All CTCAE grades were included.

At least 1 dose modification for neutropenia was reported for 16 patients (7%) in the A+CHP arm and 11 patients (5%) in the CHOP arm. A dose delay was the most commonly reported dose modification for neutropenia across treatment arms and was reported for 12 patients (5%) in the A+CHP arm and 9 patients (4%) in the CHOP arm. Neutropenia resulted in dose delay and dose reduction but was not reported as a cause of study treatment discontinuation.

The number of patients with neutropenia, anaemia and thrombocytopenia per grade was overall comparable between the treatment arms.

**Immunogenicity: Antidrug Antibody Status**

Immunogenicity-evaluable patients were defined as the patients who had a baseline and at least 1 post-baseline assessment for ADA (Safety population Immunogenicity-evaluable patients).

Samples for ADA assessment were available for 205 patients of the 226 patients randomized to the A+CHP arm; samples were missing for 18 subjects and 3 subjects from the ITT population did not receive the study treatment. A total of 205 patients in the A+CHP arm had a baseline and at least 1 post-baseline assessment for ADA (Immunogenicity-evaluable patients). At baseline, 184 patients (81%) were ADA negative and 21 patients (9%) were confirmed ADA positive.

**Table 52 Study SGN35-014: ADA (Safety Population; Immunogenicity Evaluable Patients)**

| | A+CHP (N=226) |
|---|---|
| ADA negative at baseline | 184 (81) |
| Negative postbaseline | 139 (62) |
| Positive postbaseline | 40 (18) |
| Transiently positive postbaseline | 39 (17) |
| Persistently positive postbaseline | 1 (0) |
| Missing | 5 (2) |
| ADA positive at baseline | 21 (9) |
| Negative postbaseline | 12 (5) |
| Positive postbaseline | 9 (4) |
| Transiently positive postbaseline | 8 (4) |
| Persistently positive postbaseline | 1 (0) |

Source: SGN35-014 Table 14.2.6.1.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; ADA: antidrug antibody.

No notable differences were observed with respect to AE reporting between transiently ATA-positive and ATA-negative subjects. The low number of persistently-ATA positive subjects (n=1) precludes interpretation of the data.

**Infusion-Related Reactions**

Routine premedication for IRRs was not to be administered before the first dose of brentuximab vedotin or vincristine. Patients who experienced an IRR were to be premedicated before subsequent infusions. Overall, 10 subjects (4%) on the A+CHP arm and 13 subjects (6%) on the CHOP arm experienced IRRs. On both arms, the majority of IRRs were < Grade 3 in severity (80% and 100% for A+CHP versus CHOP, respectively). Brentuximab vedotin IRRs were reported for 5 subjects (2%) on the A+CHP arm. Three subjects had IRRs at Cycle 1, 1 subject had an IRR at Cycle 2, and 1 subject had an IRR at Cycle 6. None of the 5 subjects who experienced a brentuximab vedotin IRR tested positive for ATA at baseline. A total of 3 subjects (1%) experienced IRRs to vincristine. IRRs to cyclophosphamide or doxorubicin were reported for 13 subjects (3%) and 14 subjects (3%), respectively.

**Other adverse events of interest**

Summaries for AEs of infections, hepatotoxicity and secondary malignancies are summarized below.

**Table 53. Summary of TEAEs of infections (Safety population)**

| | A+CHP N=223 n (%) | | | | | | CHOP N=226 n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary System Organ Class Preferred Term | All | Drug Related | Grade ≥3 | Serious Adverse Event | Rslt. in Study Drug Disc. | Fatal | All | Drug Related | Grade ≥3 | Serious Adverse Event | Rslt. in Study Drug Disc. | Fatal |
| Subjects with at Least One Treatment-Emergent Infections[a] | 116 (52) | 41 (18) | 42 (19) | 37 (17) | 2 (<1) | 2 (<1) | 102 (45) | 51 (23) | 31 (14) | 24 (11) | 4 (2) | 3 (1) |

**Table 54. Summary of TEAEs of hepatotoxicity (Safety population)**

| SMQ Name<br>Primary System Organ Class<br>Preferred Term | A+CHP N=223 n (%) | | | | | | CHOP N=226 n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | Drug Related | Grade ≥3 | Serious Adverse Event | Rslt. in Study Drug Disc. | Fatal | All | Drug Related | Grade ≥3 | Serious Adverse Event | Rslt. in Study Drug Disc. | Fatal |
| Subjects with at Least One Treatment-Emergent Hepatoxicitiy (a) | 20 (9) | 8 (4) | 2 (<1) | 1 (<1) | 0 | 0 | 4 (2) | 2 (<1) | 1 (<1) | 0 | 0 | 0 |

The majority of hepatoxicity events were liver enzyme elevations not resulting in study drug discontinuation.

Summaries of second and secondary malignancies are presented below in (A+CHP-treated patients) and (CHOP-treated patients). In these tables, events not representing potential PTCL worsening or recurrence are shown in **bold** font.

**Table 55. TEAEs of secondary malignancies in ECHELON-2 (Safety population, A+CHP patients)**

| Number of cycles received | Reported term for AE | Causality |
|---|---|---|
| 6 | **Neoplasm malignant** | unrelated |
| 2 | PTCL unspecified | unrelated |
| 6 | Mycosis fungoides | unrelated |
| 6 | **Myelodysplastic syndrome** | related |
| 6 | **Mycosis fungoides** | unrelated |
| 6 | **Papillary thyroid cancer** | unrelated |
| 6 | Tumour haemorrhage | unrelated |
| 6 | Metastases to CNS | unrelated |
| | Metastases to CNS | unrelated |
| | Metastases to CNS | unrelated |
| 6 | PTCL unspecified | unrelated |

**Table 56. TEAEs of secondary malignancies (Safety population, CHOP patients)**

| Number of cycles received | Reported term for AE | Causality |
|---|---|---|
| 4 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 6 | Metastases to bone | unrelated |
| 8 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 2 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 3 | Anaplastic large cell lymphoma T- and null cell types | unrelated |

| | | |
|---|---|---|
| 4 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 3 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 3 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 1 | Anaplastic large cell lymphoma T- and null cell types | unrelated |
| 6 | Non-Hodgkin's Lymphoma | unrelated |
| 6 | **T-cell type acute leukaemia** | unrelated |
| 6 | **Mycosis fungoides** | unrelated |

## Laboratory findings

Abnormal clinical laboratory values that were considered a clinically significant change from baseline or resulted in premature discontinuation of drug regimen, a dose modification, or other therapeutic intervention were reported as TEAEs.

At least 1 post-baseline Grade 3 haematology value was reported for 63 patients (28%) in the A+CHP arm and 69 patients (31%) in the CHOP arm, and at least 1 Grade 4 haematology value for 5 patients (2%) in the A+CHP arm and 9 patients (4%) in the CHOP arm.

Grade 4 low absolute neutrophil count and low neutrophils were reported for 3 patients each and Grade 4 low lymphocytes was reported for 2 patients (1% each) in the A+CHP arm; and Grade 4 low absolute neutrophil count and low neutrophils were reported for 4 patients each and Grade 4 low lymphocytes was reported for 5 patients (2% each) in the CHOP arm.

The Grade 3 haematology values reported for the A+CHP arm were low lymphocytes for 50 patients (22%), low absolute neutrophil count and low neutrophils for 14 patients each (6%), low leukocytes for 12 patients (5%), low haemoglobin for 9 patients (4%), and high haemoglobin and low platelets for 1 patient each. Grade 3 haematology values reported for the CHOP arm were low lymphocytes for 56 patients (25%), low leukocytes for 21 patients (9%), low absolute neutrophil count and low neutrophils for 15 patients each (7%), low haemoglobin for 13 patients (6%), and high lymphocytes and low platelets for 1 patient each.

At least 1 post-baseline Grade 3 serum chemistry value was reported for 19 patients (9%) in the A+CHP arm and 21 patients (9%) in the CHOP arm, and at least 1 Grade 4 serum chemistry value for 6 patients (3%) in the A+CHP arm and 2 patients (1%) in the CHOP arm. Grade 4 high glucose was reported for 1 patient in the A+CHP arm, and Grade 4 high urate was reported for 5 patients (2%) in the A+CHP arm and 2 patients (1%) in the CHOP arm.

Grade 3 serum chemistry abnormalities reported for the A+CHP arm included high glucose for 7 patients (3%), low sodium and low phosphate for 4 patients each (2%), low potassium and high ALT for 3 patients each (1%), low albumin for 2 patients (1%), and high ALP, high sodium and low calcium for 1 patient each. Grade 3 serum chemistry abnormalities reported for the CHOP arm included high glucose and low sodium for 6 patients each (3%), low albumin, low phosphate for 3 patients each (1%), high potassium and low potassium for 2 patients each (1%), and high ALT, low calcium for 1 patient each.

*Vital Signs and Physical Findings*

Clinically significant findings pertaining to physical examinations and vital signs data were reported as TEAEs. An improved ECOG performance status of -1 was reported for 37 patients (17%) in the A+CHP arm and 32 patients (14%) in the CHOP arm; an improved ECOG performance status of -2 was reported for 3% of patients in each treatment arm.

## Supportive studies

Safety results are presented for the 2 supportive studies of brentuximab vedotin in combination with CHP and as monotherapy in adult patients with CD30+ PTCL.

***Study SGN35-011:***

A phase 1, open-label, 3-arm, dose finding study evaluating the safety and activity of sequential and combination frontline treatment approaches of brentuximab vedotin with either CHP or CHOP in patients with previously untreated CD30+ mature T- and NK-cell neoplasms. (See also Dose response study).

A total of 26 treatment-naïve patients with CD30+ PTCL were enrolled in the combination treatment portion of the study. Six patients were enrolled in the maximum tolerated dose (MTD) cohort and the MTD was not exceeded at the dose of A+CHP 1.8 mg/kg. Patients received 6 cycles of A+CHP, administered every 3 weeks. Responders could then receive an additional 8 to 10 cycles of brentuximab vedotin up to a maximum of 16 cycles.

TEAEs of any grade reported for the combination treatment arm included peripheral sensory neuropathy (69% of patients) nausea (65%), fatigue and diarrhoea (58% each), alopecia (54%), dyspnoea (46%), constipation (38%), peripheral oedema (35%), and anaemia, chills, febrile neutropenia, upper respiratory tract infection, and myalgia (31% each). Dyspnoea of any grade was reported for 12 patients and considered related to brentuximab vedotin for 4 patients. At least 1 Grade 3 or higher TEAE was reported for 19 patients (73%) and included febrile neutropenia (31% of patients), neutropenia (23%), anaemia (15%), and pulmonary embolism (12%).

No treatment-related mortality was observed. SAEs were reported for 50% of patients. SAEs reported for more than 1 patient were febrile neutropenia, reported for 8 patients (31%) and pyrexia and cardiac failure, reported for 2 patients each (8%). An AE resulted in dose reduction for 9 patients (35%), mostly during the maintenance treatment period, and peripheral sensory neuropathy was reported as the cause of dose reduction for 7 patients (27%). No IRRs to brentuximab vedotin were reported. Treatment-emergent PN was reported for 19 patients (73%) and included a Grade 3 PN event for 2 patients. Patients with PN were managed with dose delays and dose reductions. During PTFU, PN was reported as either resolved or improved for 18 of the 19 patients in which it was reported and resolution of all PN events was reported for 9 patients.

***Study SGN35-012***

Study SGN35-012 was a phase 2, open-label, single arm study of brentuximab vedotin (1.8 mg/kg) in relapsed refractory non- Hodgkin lymphoma. The primary endpoint was ORR with key secondary endpoints including safety, correlation of CD30 expression with RR, response duration and PFS.

Enrolled patients received brentuximab vedotin 1.8 mg/kg every 3 weeks until disease progression or unacceptable toxicity. A planned subset analysis included 35 patients with relapsed or refractory PTCL, including 22 patients with PTCL-NOS and 13 patients with AITL. The median age of enrolled patients

was 64 years (range, 33-83 years). Most patients had Stage III or Stage IV disease at the time of study entry and had received a median of 2 prior anticancer therapies (range, 1-9). Disease was refractory to the most recent therapy for 63% of patients.

All 35 patients with relapsed or refractory PTCL received at least 1 dose of brentuximab vedotin. Patients received a median of 3 cycles (range, 1-21 cycles) over a median of 9 weeks (range, 2-78 weeks) with a longer treatment period reported for patients who responded to the study drug. A median of 8.5 cycles (range, 4-21 cycles) was reported for responding patients over a median treatment period of 26 weeks (range, 12-78 weeks). At least 1 TEAE of any grade was reported for 32 patients (91%). The most commonly reported TEAEs of any grade were peripheral sensory neuropathy (37% of patients), fatigue (34%), pyrexia (23%), decreased appetite (20%), and diarrhoea, nausea (17% each). Grade 3 or higher TEAEs reported for these 35 patients included neutropenia (14% of patients), peripheral sensory neuropathy and hyperkalaemia (9% each), and acute renal failure, anaemia, dehydration, disease progression, pneumonia, thrombocytopenia, tumour lysis syndrome, urinary tract infection (6% each). At least 1 Grade 4 TEAE was reported for 3 patients. The Grade 4 TEAEs reported were pneumonia, sepsis, hyperkalaemia, lipase increased, confusional state, and pulmonary oedema. A treatment-related SAE was reported for 4 patients, which included Grade 5 acute respiratory distress syndrome (ARDS), and Grade 3 pyrexia, rash and pneumonia. An AE resulted in study drug discontinuation for 20% of patients. The AEs that resulted in study drug discontinuation included peripheral sensory neuropathy (6% of patients), and ARDS, encephalopathy, Pneumocystis jirovecii pneumonia, pyrexia, and sepsis (3% each). The death of 3 patients was reported within 30 days of the last dose of brentuximab vedotin. ARDS was reported as the cause of death for 1 patient with refractory AITL as a complication of disease progression and infection. The death of the other 2 patients was related to disease progression. The death of 1 patient was reported 33 days after the last dose of brentuximab vedotin, which was attributed to complications including sepsis. The safety results were consistent with the known safety profile of single-agent brentuximab vedotin and no new safety signals were identified in patients treated up to 21 cycles.

## Safety in special populations

### Safety in PTCL types

Of the Safety population, 63 A+CHP-treated patients (28%) and 72 CHOP-treated patients (32%) had PTCL histological subtypes other than sALCL. Patients with PTCL-NOS represented 29 A+CHP-treated patients (13%) and 43 CHOP-treated patients (19%); patients with AITL represented 29 A+CHP-treated patients (13%) and 24 CHOP-treated patients (11%); patients with ATLL and EATL represented 2% or less of the treated patient population in both treatment arms, respectively.

*Demography and Disease Characteristics*

**Table 57 ECHELON-2: Summary of Demographics and Baseline Subject Characteristics (ITT Population)**

| | Non-ALCL | | sALCL | |
|---|---|---|---|---|
| | A+CHP (N=64) | CHOP (N=72) | A+CHP (N=162) | CHOP (N=154) |
| Age (years) | | | | |
| n | 64 | 72 | 162 | 154 |
| Mean (STD) | 62.5 (10.01) | 61.9 (11.95) | 52.5 (15.29) | 51.5 (15.91) |
| Median | 64.0 | 63.5 | 55.0 | 54.0 |
| Min, Max | 35, 81 | 38, 82 | 18, 85 | 18, 83 |
| Age group, n (%) | | | | |
| <65 | 33 (52) | 38 (53) | 124 (77) | 118 (77) |
| ≥65 | 31 (48) | 34 (47) | 38 (23) | 36 (23) |
| Gender, n (%) | | | | |
| Male | 38 (59) | 41 (57) | 95 (59) | 110 (71) |
| Female | 26 (41) | 31 (43) | 67 (41) | 44 (29) |

*Safety Profile*

The overall safety profile of A+CHP and CHOP by patients' disease subtype (sALCL versus non-sALCL) was analysed in a non-randomized comparison. Serious treatment-emergent adverse events were in A+CHP arm: 35 [56%] non-ALCL patients vs 51 [32%] ALCL patients and CHOP arm: 30 [42%] non-sALCL patients vs 55 [36%] ALCL patients.

The difference is driven by a higher incidence of febrile neutropenia and infections. The incidence of febrile neutropenia in the A+CHP arm was 17 (27%) non-ALCL patients vs 14 (9%) ALCL patients and in the CHOP arm was 14 (19%) non-ALCL patients vs 12 (8%) ALCL patients. The incidence of serious infections in the A+CHP arm was 18 (29%) non-ALCL patients vs 19 (12%) ALCL patients and in CHOP arm was 10 (14%) non-sALCL patients vs 14 (9%) ALCL patients.

*G-CSF Primary Prophylaxis*

In ECHELON-2, G-CSF primary prophylaxis was recommended after approximately 60% of patients were enrolled; therefore only 1/3 of patients in both arms received G-CSF primary prophylaxis support.

In a non-randomized comparison the impact of G-CSG PP on febrile neutropenia was most pronounced in non-sALCL patients in the A+CHP arm. A reduction in the incidence of neutropenia with G-CSF prophylaxis is seen and G-CSF has limited effect on grade≥ 3 AEs infections and infestations, SAEs, and -SAEs febrile neutropenia, neutropenia, (neutropenic) sepsis, pyrexia or infections and infestations (SOC)- in non-sALCL patients. No impact of G-CSF PP was observed in non-sALCL patients in CHOP arm. With G-CSF PP, the incidence of febrile neutropenia in non-sALCL patients is the same in both arms (25%) and <15% in sALCL patients in both arms.

*Non-hematologic Toxicity*

Additionally, the safety profile for non-haematological toxicity was comparable between disease subtypes and treatment arms. No difference in PN incidence was observed between arms or disease subtypes. Peripheral sensory neuropathy was experienced by 48% of sALCL patients and 37% non-sALCL patients in the A+CHP arm; in the CHOP arm, 42% of sALCL patients and 38% of non-sALCL patients experienced peripheral sensory neuropathy, with 2 patients in each treatment arm discontinuing treatment due to peripheral neuropathy.

**Table 58 ECHELON-2: Treatment-Emergent Adverse Event Summary by Disease Subtype (Safety Population)**

| Primary System Organ Class<br>Preferred Term | PTCL subtype | A+CHP sALCL=160 nonALCL=63 | | | | | | CHOP sALCL=154 nonALCL=72 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TEAE | Related | Gr≥3 | Serious | D/C | Fatal | TEAE | Related | Gr≥3 | Serious | D/C | Fatal |
| **Any event** | *sALCL* | 159 (99) | 143 (89) | 94 (59) | 51 (32) | 6 (4) | 4 (3) | 150 (97) | 129 (84) | 98 (64) | 55 (36) | 14 (9) | 15 (10) |
| | *nonALCL* | 62 (98) | 58 (92) | 53 (84) | 35 (56) | 8 (13) | 4 (6) | 71 (99) | 64 (89) | 48 (67) | 30 (42) | 1 (1) | 1 (1) |
| | | | | | | | | | | | | | |
| Blood and lymphatic system disorders | *sALCL* | 86 (54) | 70 (44) | 75 (47) | 20 (13) | 0 | 0 | 81 (53) | 64 (42) | 71 (46) | 20 (13) | 1 (<1) | 1 (<1) |
| | *nonALCL* | 46 (73) | 38 (60) | 42 (67) | 20 (32) | 0 | 0 | 42 (58) | 33 (46) | 40 (56) | 15 (21) | 0 | 0 |
| Neutropenia | *sALCL* | 59 (37) | 50 (31) | 54 (34) | 5 (3) | 0 | 0 | 59 (38) | 50 (32) | 53 (34) | 6 (4) | 0 | 0 |
| | *nonALCL* | 26 (41) | 24 (38) | 23 (37) | 3 (5) | 0 | 0 | 26 (36) | 18 (25) | 23 (32) | 0 | 0 | 0 |
| Febrile neutropenia | *sALCL* | 20 (13) | 17 (11) | 20 (13) | 14 (9) | 0 | 0 | 16 (10) | 13 (8) | 16 (10) | 12 (8) | 1 (<1) | 1 (<1) |
| | *nonALCL* | 21 (33) | 18 (29) | 21 (33) | 17 (27) | 0 | 0 | 17 (24) | 15 (21) | 17 (24) | 14 (19) | 0 | 0 |
| Infections and infestations | *sALCL* | 73 (46) | 19 (12) | 23 (14) | 19 (12) | 0 | 0 | 63 (41) | 27 (18) | 17 (11) | 14 (9) | 4 (3) | 3 (2) |
| | *nonALCL* | 43 (68) | 22 (35) | 19 (30) | 18 (29) | 2 (3) | 2 (3) | 39 (54) | 24 (33) | 14 (19) | 10 (14) | 0 | 0 |
| Pneumonia | *sALCL* | 9 (6) | 4 (3) | 6 (4) | 5 (3) | 0 | 0 | 3 (2) | 2 (1) | 2 (1) | 1 (<1) | 1 (<1) | 0 |
| | *nonALCL* | 7 (11) | 4 (6) | 6 (10) | 6 (10) | 1 (2) | 1 (2) | 3 (4) | 3 (4) | 3 (4) | 2 (3) | 0 | 0 |
| Sepsis | *sALCL* | 3 (2) | 1 (<1) | 3 (2) | 2 (1) | 0 | 0 | 3 (2) | 2 (1) | 3 (2) | 3 (2) | 2 (1) | 2 (1) |
| | *nonALCL* | 3 (5) | 3 (5) | 3 (5) | 3 (5) | 1 (2) | 1 (2) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| Gastrointestinal disorders | *sALCL* | 121 (76) | 82 (51) | 12 (8) | 6 (4) | 0 | 0 | 106 (69) | 77 (50) | 17 (11) | 11 (7) | 0 | 0 |
| | *nonALCL* | 54 (86) | 40 (63) | 17 (27) | 7 (11) | 1 (2) | 0 | 50 (69) | 37 (51) | 6 (8) | 7 (10) | 0 | 0 |
| Diarrhoea | *sALCL* | 55 (34) | 23 (14) | 6 (4) | 1 (<1) | 0 | 0 | 34 (22) | 13 (8) | 1 (<1) | 1 (<1) | 0 | 0 |
| | *nonALCL* | 30 (48) | 13 (21) | 7 (11) | 3 (5) | 0 | 0 | 12 (17) | 3 (4) | 1 (1) | 1 (1) | 0 | 0 |
| Nausea | *sALCL* | 74 (46) | 48 (30) | 2 (1) | 0 | 0 | 0 | 64 (42) | 42 (27) | 3 (2) | 3 (2) | 0 | 0 |
| | *nonALCL* | 29 (46) | 22 (35) | 3 (5) | 1 (2) | 0 | 0 | 23 (32) | 18 (25) | 1 (1) | 1 (1) | 0 | 0 |

| Primary System Organ Class<br>Preferred Term | PTCL subtype | A+CHP sALCL=160 nonALCL=63 | | | | | | CHOP sALCL=154 nonALCL=72 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TEAE | Related | Gr≥3 | Serious | D/C | Fatal | TEAE | Related | Gr≥3 | Serious | D/C | Fatal |
| Vomiting | *sALCL* | 45 (28) | 28 (18) | 1 (<1) | 0 | 0 | 0 | 30 (19) | 17 (11) | 3 (2) | 2 (1) | 0 | 0 |
| | *nonALCL* | 12 (19) | 4 (6) | 1 (2) | 1 (2) | 0 | 0 | 9 (13) | 8 (11) | 1 (1) | 1 (1) | 0 | 0 |
| Skin and subcutaneous tissue disorders | *sALCL* | 72 (45) | 32 (20) | 4 (3) | 1 (<1) | 0 | 0 | 73 (47) | 34 (22) | 4 (3) | 1 (<1) | 1 (<1) | 0 |
| | *nonALCL* | 39 (62) | 21 (33) | 3 (5) | 1 (2) | 1 (2) | 0 | 28 (39) | 13 (18) | 2 (3) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | *sALCL* | 58 (36) | 16 (10) | 10 (6) | 8 (5) | 2 (1) | 1 (<1) | 55 (36) | 13 (8) | 8 (5) | 4 (3) | 1 (<1) | 0 |
| | *nonALCL* | 28 (44) | 6 (10) | 6 (10) | 7 (11) | 2 (3) | 1 (2) | 32 (44) | 6 (8) | 5 (7) | 3 (4) | 0 | 0 |
| Nervous system disorders | *sALCL* | 104 (65) | 87 (54) | 8 (5) | 4 (3) | 1 (<1) | 0 | 99 (64) | 76 (49) | 16 (10) | 6 (4) | 3 (2) | 1 (<1) |
| | *nonALCL* | 40 (63) | 33 (52) | 5 (8) | 2 (3) | 1 (2) | 0 | 46 (64) | 39 (54) | 4 (6) | 0 | 0 | 0 |
| Peripheral sensory neuropathy | *sALCL* | 77 (48) | 73 (46) | 5 (3) | 2 (1) | 1 (<1) | 0 | 65 (42) | 58 (38) | 4 (3) | 0 | 2 (1) | 0 |
| | *nonALCL* | 23 (37) | 22 (35) | 3 (5) | 0 | 1 (2) | 0 | 27 (38) | 27 (38) | 2 (3) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | *sALCL* | 46 (29) | 18 (11) | 15 (9) | 5 (3) | 1 (<1) | 0 | 36 (23) | 11 (7) | 12 (8) | 3 (2) | 0 | 0 |
| | *nonALCL* | 27 (43) | 16 (25) | 5 (8) | 2 (3) | 0 | 0 | 22 (31) | 9 (13) | 2 (3) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | *sALCL* | 60 (38) | 14 (9) | 2 (1) | 1 (<1) | 0 | 0 | 44 (29) | 6 (4) | 2 (1) | 2 (1) | 0 | 0 |
| | *nonALCL* | 23 (37) | 5 (8) | 2 (3) | 0 | 0 | 0 | 31 (43) | 6 (8) | 2 (3) | 0 | 0 | 0 |
| Vascular disorders | *sALCL* | 22 (14) | 4 (3) | 4 (3) | 2 (1) | 0 | 0 | 31 (20) | 13 (8) | 8 (5) | 3 (2) | 0 | 0 |
| | *nonALCL* | 14 (22) | 3 (5) | 2 (3) | 3 (5) | 0 | 0 | 18 (25) | 8 (11) | 3 (4) | 1 (1) | 0 | 0 |
| Investigations | *sALCL* | 35 (22) | 14 (9) | 4 (3) | 0 | 0 | 0 | 14 (9) | 6 (4) | 2 (1) | 1 (<1) | 0 | 0 |
| | *nonALCL* | 17 (27) | 4 (6) | 2 (3) | 0 | 0 | 0 | 12 (17) | 5 (7) | 1 (1) | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | *sALCL* | 2 (1) | 0 | 2 (1) | 2 (1) | 0 | 0 | 17 (11) | 0 | 16 (10) | 13 (8) | 2 (1) | 8 (5) |
| | *nonALCL* | 2 (3) | 0 | 1 (2) | 2 (3) | 1 (2) | 1 (2) | 3 (4) | 0 | 3 (4) | 2 (3) | 0 | 0 |

| Primary System Organ Class<br>Preferred Term | PTCL subtype | A+CHP sALCL=160 nonALCL=63 | | | | | | CHOP sALCL=154 nonALCL=72 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TEAE | Related | Gr≥3 | Serious | D/C | Fatal | TEAE | Related | Gr≥3 | Serious | D/C | Fatal |
| Cardiac disorders | *sALCL* | 15 (9) | 2 (1) | 3 (2) | 5 (3) | 2 (1) | 2 (1) | 11 (7) | 2 (1) | 5 (3) | 4 (3) | 2 (1) | 2 (1) |
| | *nonALCL* | 8 (13) | 2 (3) | 1 (2) | 0 | 0 | 0 | 6 (8) | 1 (1) | 2 (3) | 2 (3) | 0 | 0 |
| Renal and urinary disorders | *sALCL* | 17 (11) | 3 (2) | 2 (1) | 4 (3) | 0 | 1 (<1) | 12 (8) | 2 (1) | 0 | 1 (<1) | 0 | 0 |
| | *nonALCL* | 11 (17) | 4 (6) | 2 (3) | 2 (3) | 0 | 0 | 11 (15) | 3 (4) | 1 (1) | 1 (1) | 0 | 0 |
| Hepatobiliary disorders | *sALCL* | 2 (1) | 1 (<1) | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| | *nonALCL* | 3 (5) | 2 (3) | 1 (2) | 1 (2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 59. ECHELON-2: Impact of G-CSF Primary Prophylaxis Use on Adverse Events of Interest by Disease Subtype**

| | | A+CHP | | | | CHOP | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No GCSF PP | GCSF PP | Difference (%) | Total | No GCSF PP | GCSF PP | Difference (%) | Total |
| Ns (%) | *sALCL* | 109 (68) | 51 (32) | | 160 (100) | 117 (76) | 37 (24) | | 154 (100) |
| | *nonALCL* | 39 (62) | 24 (38) | | 63 (100) | 48 (67) | 24 (33) | | 72 (100) |
| Incidence of febrile neutropenia on study | *sALCL* | 14 (13) | 6 (12) | 1 | 20 (13) | 15 (13) | 1 (3) | 10 | 16 (10) |
| | *nonALCL* | 15 (38) | 6 (25) | 13 | 21 (33) | 11 (23) | 6 (25) | -2 | 17 (24) |
| Incidence of neutropenia | *sALCL* | 51 (47) | 8 (16) | 31 | 59 (37) | 53 (45) | 7 (19) | 26 | 60 (39) |
| | *nonALCL* | 22 (56) | 4 (17) | 39 | 26 (41) | 23 (48) | 3 (13) | 35 | 26 (36) |
| Incidence of grade 3 or higher neutropenia | *sALCL* | 48 (44) | 6 (12) | 32 | 54 (34) | 49 (42) | 5 (14) | 28 | 54 (35) |
| | *nonALCL* | 19 (49) | 4 (17) | 32 | 23 (37) | 20 (42) | 3 (13) | 29 | 23 (32) |
| Incidence of grade 4 or higher neutropenia | *sALCL* | 27 (25) | 4 (8) | 17 | 31 (19) | 31 (26) | 4 (11) | 15 | 35 (23) |
| | *nonALCL* | 12 (31) | 3 (13) | 18 | 15 (24) | 12 (25) | 2 (8) | 17 | 14 (19) |
| Incidence of grade 3 or higher TEAEs | *sALCL* | 73 (67) | 21 (41) | 26 | 94 (59) | 79 (68) | 19 (51) | 17 | 98 (64) |
| | *nonALCL* | 34 (87) | 19 (79) | 8 | 53 (84) | 35 (73) | 13 (54) | 19 | 48 (67) |
| Incidence of infections and infestations (SOC) | *sALCL* | 51 (47) | 22 (43) | 4 | 73 (46) | 47 (40) | 16 (43) | -3 | 63 (41) |
| | *nonALCL* | 28 (72) | 15 (63) | 9 | 43 (68) | 27 (56) | 12 (50) | -6 | 39 (54) |
| Incidence of grade 3 or higher infections and infestations (SOC) | *sALCL* | 18 (17) | 5 (10) | 7 | 23 (14) | 14 (12) | 3 (8) | 4 | 17 (11) |
| | *nonALCL* | 12 (31) | 7 (29) | 2 | 19 (30) | 9 (19) | 5 (21) | -2 | 14 (19) |
| Incidence of any serious adverse events on study | *sALCL* | 35 (32) | 16 (31) | 1 | 51 (32) | 40 (34) | 15 (41) | -7 | 55 (36) |
| | *nonALCL* | 20 (51) | 15 (63) | -12 | 35 (56) | 18 (38) | 12 (50) | -12 | 30 (42) |
| Incidence of serious adverse events of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, or infections and infestations (SOC) | *sALCL* | 24 (22) | 12 (24) | -2 | 36 (23) | 24 (21) | 5 (14) | -7 | 29 (19) |
| | *nonALCL* | 17 (44) | 11 (46) | -2 | 28 (44) | 13 (27) | 10 (42) | -15 | 23 (32) |
| Incidence of any grade 5 adverse events | *sALCL* | 1 (<1) | 3 (6) | -5 | 4 (3) | 11 (9) | 4 (11) | -2 | 15 (10) |
| | *nonALCL* | 3 (8) | 1 (4) | -4 | 4 (6) | 1 (2) | 0 | -2 | 1 (1) |

**Age**

A total of 139 patients in the ECHELON-2 ITT population, 69 patients in the A+CHP arm and 70 patients in the CHOP arm were aged 65 years or older. Within this age group, a median age of 70.0 years (range, 65-85 years) was reported for the A+CHP arm and 71.0 years (range, 65-83 years) for the CHOP arm. Within this age group, an ECOG performance status of 1 was reported for 25 patients (36%) in the A+CHP arm and 29 patients (41%) in the CHOP arm and an ECOG performance status of 2 for 15 patients (22%) in the A+CHP arm and 13 patients (19%) in the CHOP arm. Subgroup analyses were performed by age group (≥65 years versus <65 years) to compare the incidence of TEAEs of any grade, the incidence of febrile neutropenia, and the impact of G-CSF primary prophylaxis on febrile neutropenia.

**Table 60 Study SGN35-014: Overview of AEs by Age Group (Safety Population; ⩾65 Years Versus <65 Years)**

| | Age ≥65 years | | Age <65 years | |
|---|---|---|---|---|
| | A+CHP (N=69) | CHOP (N=70) | A+CHP (N=154) | CHOP (N=156) |
| Subjects with any TEAE, n (%) | 69 (100) | 68 (97) | 152 (99) | 153 (98) |
| Subjects with blinded study treatment-related event, n (%) [a] | 65 (94) | 63 (90) | 136 (88) | 130 (83) |
| Subjects with CHP treatment-related event, n (%) | 63 (91) | 65 (93) | 135 (88) | 140 (90) |
| Max severity of TEAE, n (%) | | | | |
| Grade 1 | 3 (4) | 6 (9) | 12 (8) | 17 (11) |
| Grade 2 | 15 (22) | 11 (16) | 44 (29) | 41 (26) |
| Grade 3 | 20 (29) | 22 (31) | 57 (37) | 45 (29) |
| Grade 4 | 26 (38) | 24 (34) | 36 (23) | 39 (25) |
| Grade 5 | 5 (7) | 5 (7) | 3 (2) | 11 (7) |
| Max severity of TEAE, n (%) | | | | |
| <Grade 3 | 18 (26) | 17 (24) | 56 (36) | 58 (37) |
| ≥Grade 3 | 51 (74) | 51 (73) | 96 (62) | 95 (61) |
| Subjects with any SAE, n (%) | 34 (49) | 39 (56) | 53 (34) | 48 (31) |
| Subjects with any blinded study treatment-related SAE, n (%) | 23 (33) | 20 (29) | 35 (23) | 25 (16) |
| Subjects with any CHP treatment-related SAE, n (%) | 26 (38) | 25 (36) | 36 (23) | 28 (18) |
| Subjects who discontinued treatment due to AE, n (%) | 8 (12) | 5 (7) | 6 (4) | 10 (6) |
| Subjects who discontinued treatment due to blinded treatment-related AE, n (%) | 5 (7) | 4 (6) | 5 (3) | 6 (4) |
| Subjects who discontinued treatment due to CHP treatment-related AE, n (%) | 4 (6) | 3 (4) | 4 (3) | 4 (3) |

**Febrile Neutropenia by Age Group: ECHELON-2**

**Table 61 Study SGN35-014: Febrile Neutropenia by Age Group (Safety Population; ⩾65 Years Versus <65 Years)**

| | Age ≥65 years | | Age <65 years | |
|---|---|---|---|---|
| | A+CHP (N=69) | CHOP (N=70) | A+CHP (N=154) | CHOP (N=156) |
| Subjects with treatment-emergent febrile neutropenia, n (%) | 20 (29) | 17 (24) | 21 (14) | 16 (10) |
| Grade 3 | 17 (25) | 14 (20) | 19 (12) | 12 (8) |
| Grade 4 | 3 (4) | 3 (4) | 2 (1) | 3 (2) |
| Grade 5 | 0 | 0 | 0 | 1 (1) |
| Subjects with any treatment-related febrile neutropenia, n (%) | 18 (26) | 17 (24) | 21 (14) | 16 (10) |
| Grade 3 | 16 (23) | 14 (20) | 19 (12) | 12 (8) |
| Grade 4 | 2 (3) | 3 (4) | 2 (1) | 3 (2) |
| Grade 5 | 0 | 0 | 0 | 1 (1) |
| Subjects with any dose modification due to febrile neutropenia, n (%) [a] | 3 (4) | 1 (1) | 3 (2) | 3 (2) |
| Discontinued treatment due to febrile neutropenia, n (%) [b] | 0 | 0 | 0 | 0 |
| Completed treatment | 2 (3) | 1 (1) | 3 (2) | 2 (1) |
| Number of completed cycles for subjects who completed less than the intended number of cycles [c] | 1 (1) | 0 | 0 | 1 (1) |
| n | 1 | 0 | 0 | 1 |
| Mean (SD) | 5.0 (-) | - (-) | - (-) | 5.0 (-) |
| Median | 5.0 | - | - | 5.0 |
| Min, max | 5, 5 | -, - | -, - | 5, 5 |

Source: SGN35-014 Table 14.3.1.71.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; max: maximum; Min: minimum.
[a] Dose reduction or dose delay attributed to febrile neutropenia.
[b] Only includes subjects with febrile neutropenia that resulted in both dose modification and treatment discontinuation.
[c] Intended number of cycles was either 6 or 8 cycles.

| Subset of Patients With Treatment-emergent Febrile Neutropenia | Age ≥65 years | | Age <65 years | |
|---|---|---|---|---|
| | A+CHP (N=69) | CHOP (N=70) | A+CHP (N=154) | CHOP (N=156) |
| Time to first onset of Grade 3 febrile neutropenia among those with at least 1 Grade 3 event, weeks [a] | | | | |
| n | 18 | 15 | 19 | 13 |
| Mean (SD) | 5.1 (5.1) | 3.9 (5.3) | 5.0 (7.1) | 8.0 (8.0) |
| Median | 2.0 | 1.6 | 1.7 | 4.4 |
| Min, max | 1, 15 | 1, 17 | 1, 23 | 1, 23 |
| Time to first onset of Grade 4 febrile neutropenia among those with at least 1 Grade 4 event, weeks | | | | |
| n | 3 | 3 | 2 | 3 |
| Mean (SD) | 2.4 (2.0) | 2.3 (1.5) | 3.3 (1.6) | 1.3 (0.1) |
| Median | 1.3 | 1.6 | 3.3 | 1.3 |
| Min, max | 1, 5 | 1, 4 | 2, 4 | 1, 1 |
| Time to first onset of worst grade febrile neutropenia among those with at least 1 event, weeks | | | | |
| n | 20 | 17 | 21 | 16 |
| Mean (SD) | 4.9 (4.9) | 3.8 (5.0) | 4.8 (6.8) | 6.9 (7.6) |
| Median | 2.0 | 1.6 | 1.9 | 2.9 |
| Min, max | 1, 15 | 1, 17 | 1, 23 | 1, 23 |

Source: SGN35-014 Table 14.3.1.74.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; max: maximum; Min: minimum.
Table only includes AEs reported during safety evaluation period, defined as Day 1 up to 30 days after the last dose of any component of the regimen.
[a] Does not include events with first occurrence of Grade 3 febrile neutropenia subsequent to Grade 4 febrile neutropenia.

| Subset of patients with treatment-emergent Febrile Neutropenia | Age ≥65 years | | Age <65 years | |
|---|---|---|---|---|
| | A+CHP (N=20) | CHOP (N=17) | A+CHP (N=21) | CHOP (N=16) |
| Subjects with resolution of all febrile neutropenia events, n (%) [a] | 20 (100) | 17 (100) | 21 (100) | 15 (94) |
| Subjects with improvement of febrile neutropenia events, n (%) [b] | 0 | 0 | 0 | 1 (6) |
| Time to resolution of febrile neutropenia events, weeks [c] | | | | |
| Number of events | 41 | 25 | 34 | 21 |
| Mean (SD) | 1.0 (0.4) | 0.9 (0.5) | 1.0 (0.6) | 1.0 (0.7) |
| Median | 0.9 | 0.9 | 0.8 | 0.9 |
| Min, max | 0, 2 | 0, 2 | 0, 2 | 0, 3 |

Source: SGN35-014 Table 14.3.1.76.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; max: maximum; Min: minimum.
Table only includes AEs reported during safety evaluation period, defined as Day 1 up to 30 days after the last dose of any component of the regimen.
[a] Resolution was defined as event status of resolved/recovered or resolved/recovered with sequelae; or return to baseline or lower severity as of the latest assessment for preexisting events.
[b] Resolution implies improvement. In addition, for events that were not resolved, improvement was defined as decrease by at least 1 grade from the worst grade with no higher grade thereafter. Patients with improvement in any event at last follow up were those with at least 1 improved event and date of improvement was before last follow-up date. Subjects with all events resolved were excluded.
[c] For resolution, summary of time from first onset to resolution for individual events.

*Impact of Primary Prophylaxis on Febrile Neutropenia by Age Group: ECHELON-2*

The results of the assessment performed to compare the impact of G-CSF primary prophylaxis on the safety profile of patients 65 years of age or older suggest that G-CSF primary prophylaxis was generally associated with an improved safety profile regardless of age (Table 44). The trend was observed across treatment arms.

Among the 33 patients in the A+CHP arm and the 28 patients in the CHOP arm 65 years of age or older who received G-CSF primary prophylaxis, a trend of improved safety outcomes was observed compared with the outcomes for patients in the same age group who did not receive G-CSF primary prophylaxis. Neutropenia of any grade, Grade 3 or higher neutropenia, febrile neutropenia during the study, and Grade 3 or higher TEAEs were reported for a smaller proportion of patients in both treatment arms who received G-CSF primary prophylaxis than those who did not receive G-CSF primary prophylaxis.

**Table 62 Study SGN35-014: AEs of Interest by G-CSF Primary Prophylaxis (Safety Population; ⩾65 Years Versus <65 Years)**

| | A+CHP (N=223) | | CHOP (N=226) | |
|---|---|---|---|---|
| | No Primary G-CSF Prophylaxis N=148 | Primary G-CSF Prophylaxis N=75 | No Primary G-CSF Prophylaxis N=165 | Primary G-CSF Prophylaxis N=61 |
| Age, ≥65 years | 36 (24) | 33 (44) | 42 (25) | 28 (46) |
| Febrile neutropenia in Cycle 1 | 7 (19) | 5 (15) | 9 (21) | 4 (14) |
| Febrile neutropenia on study | 13 (36) | 7 (21) | 12 (29) | 5 (18) |
| Neutropenia of any grade [a] | 14 (39) | 8 (24) | 21 (50) | 5 (18) |
| Grade 3 or higher neutropenia [a] | 14 (39) | 7 (21) | 18 (43) | 4 (14) |
| Grade 4 or higher neutropenia [a] | 13 (36) | 7 (21) | 12 (29) | 4 (14) |
| Grade 3 or higher TEAEs | 31 (86) | 20 (61) | 34 (81) | 17 (61) |
| Infections and infestations (SOC) | 19 (53) | 15 (45) | 22 (52) | 14 (50) |
| Grade 3 or higher infections and infestations (SOC) | 8 (22) | 5 (15) | 11 (26) | 6 (21) |
| Any SAEs on study | 17 (47) | 17 (52) | 20 (48) | 17 (61) |
| SAEs of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, or SOC infections and infestations | 13 (36) | 11 (33) | 15 (36) | 11 (39) |
| Any Grade 5 AE | 2 (6) | 3 (9) | 3 (7) | 2 (7) |
| | | | | |
| Age, <65 years | 112 (76) | 42 (56) | 123 (75) | 33 (54) |
| Febrile neutropenia in Cycle 1 | 10 (9) | 4 (10) | 9 (7) | 0 |
| Febrile neutropenia on study | 16 (14) | 5 (12) | 14 (11) | 2 (6) |
| Neutropenia of any grade [a] | 59 (53) | 4 (10) | 55 (45) | 5 (15) |
| Grade 3 or higher neutropenia [a] | 53 (47) | 3 (7) | 51 (41) | 4 (12) |
| Grade 4 or higher neutropenia [a] | 26 (23) | 0 | 31 (25) | 2 (6) |
| Grade 3 or higher TEAEs | 76 (68) | 20 (48) | 80 (65) | 15 (45) |
| | No Primary G-CSF Prophylaxis N=148 | Primary G-CSF Prophylaxis N=75 | No Primary G-CSF Prophylaxis N=165 | Primary G-CSF Prophylaxis N=61 |
| Infections and infestations (SOC) | 60 (54) | 22 (52) | 52 (42) | 14 (42) |
| Grade 3 or higher infections and infestations (SOC) | 22 (20) | 7 (17) | 12 (10) | 2 (6) |
| Any SAEs on study | 38 (34) | 14 (33) | 38 (31) | 10 (30) |
| SAEs of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, or SOC infections and infestations | 28 (25) | 12 (29) | 22 (18) | 4 (12) |
| Any Grade 5 AE | 2 (2) | 1 (2) | 9 (7) | 2 (6) |

Source: SGN35-014 Table 14.3.1.77.
A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; AE: adverse event; C2D1: Cycle 2 Day 1; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF: granulocyte colony stimulating factor; SAE: serious adverse event; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
A patient was counted once in each row if they met any of the criteria for that row. Percentages are based on the number of subjects in the column.
Primary prophylaxis with G-CSF was defined as use of G-CSF by Day 8 of treatment, where Day 1 is treatment start date Events in Cycle 1 were those with start date from first dose date and before Cycle 2 Day 1 dose date (or Day 22 for those without C2D1 dose.
[a] Neutropenia includes Preferred Terms of 'Neutropenia' and 'Neutrophil count decreased'.

### Hepatic and renal insufficiency

Patients with hepatic or severe renal impairment were excluded from the study.

### Pregnancy and lactation

The current guidelines for use of each of the anticancer therapies used in ECHELON-2 during pregnancy and lactation are provided in the respective labels.

As a requirement for enrollment in ECHELON-2, women of childbearing potential must have had a negative serum or urine β-hCG (beta human chorionic gonadotrophin) pregnancy test result within 7 days of the first dose of study treatment, and must have agreed to use an effective contraception method during the treatment period of the study and for at least 6 months after the last dose of the drug regimen. Women of non-childbearing potential were those who had been postmenopausal for longer than 1 year or who had a bilateral tubal ligation or hysterectomy.

Men who had partners of childbearing potential must have agreed to use an effective contraceptive method during the treatment period of the study and for 6 months after the last dose of the drug regimen.

## Post marketing experience

Brentuximab vedotin was first approved in the US on 19 August 2011, its International Birth Date (IBD) in the US and has since been granted marketing authorization in 72 countries /regions. As of 18 February 2019, the estimated cumulative exposure to brentuximab vedotin commercial product was approximately 24,196 patients in the US and Canada, and approximately 34,005 patients in the rest of world (Latin America, Japan, North Asia). The cumulative exposure globally to commercial brentuximab vedotin since its initial launch is estimated to be 58,201 patients. A summary is presented of ADRs by SOC received through spontaneous reporting sources as of 18 February 2019, including reports from regulatory authorities and literature articles from both healthcare professionals and non-healthcare professionals.

**Table 63 ADRs From Postmarketing Sources By SOC As Of 18 February 2019**

| | Spontaneous Including Regulatory Authorities (Worldwide) and Literature Sources | | | Noninterventional Postmarketing Study and Reports From Other Solicited Sources [a] |
|---|---|---|---|---|
| MedDRA System Organ Class | Serious | Nonserious | Total | Serious |
| Infections and infestations | 377 | 185 | 562 | 181 |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 434 | 142 | 576 | 185 |
| Blood and lymphatic system disorders | 260 | 271 | 531 | 232 |
| Immune system disorders | 153 | 72 | 225 | 17 |
| Endocrine disorders | 1 | 1 | 2 | 1 |
| Metabolism and nutrition disorders | 78 | 82 | 160 | 38 |
| Psychiatric disorders | 29 | 37 | 66 | 9 |
| Nervous system disorders | 318 | 789 | 1107 | 133 |
| Eye disorders | 18 | 21 | 39 | 3 |
| Ear and labyrinth disorders | 5 | 13 | 18 | 2 |
| Cardiac disorders | 94 | 18 | 112 | 21 |
| Vascular disorders | 63 | 41 | 104 | 12 |
| Respiratory, thoracic and mediastinal disorders | 278 | 134 | 412 | 80 |
| Gastrointestinal disorders | 224 | 397 | 621 | 107 |
| Hepatobiliary disorders | 87 | 50 | 137 | 22 |
| Skin and subcutaneous tissue disorders | 182 | 598 | 780 | 35 |
| Musculoskeletal and connective tissue disorders | 54 | 179 | 233 | 10 |
| Renal and urinary disorders | 45 | 36 | 81 | 20 |
| Pregnancy, puerperium and perinatal conditions | 1 | 11 | 12 | 0 |
| Reproductive system and breast disorders | 3 | 13 | 16 | 2 |
| Congenital, familial and genetic disorders | 2 | 2 | 4 | 3 |
| **MedDRA System Organ Class** | **Serious** | **Nonserious** | **Total** | **Serious** |
| General disorders and administration site conditions | 488 | 1218 | 1706 | 231 |
| Investigations | 183 | 314 | 497 | 90 |
| Injury, poisoning and procedural complications | 69 | 1142 | 1211 | 22 |
| Surgical and medical procedures | 10 | 6 | 16 | 14 |

Source: PBRER Brentuximab Vedotin 18 February 2019 Appendix 3.
ADR: adverse drug reaction; MedDRA: Medical Dictionary for Regulatory Activities; PBRER: Periodic Benefit Risk Evaluation Report; SOC: System Organ Class.
Table shows spontaneous individual case safety reports, including reports from healthcare professionals, consumers, scientific literature, competent authorities, and solicited noninterventional individual case safety reports, including those from noninterventional studies.
[a] Does not include interventional clinical studies or investigator-initiated studies.

## 2.5.1. Discussion on clinical safety

### Patient population and exposure

Safety was presented from ECHELON-2 a randomized, double-blinded, double-dummy, active-comparator, multicenter study in patients with previously untreated PTCL who received A+CHP or CHOP. The ECHELON-2 safety population included all patients who received any amount of brentuximab vedotin or any component of CHOP. Treatment arm was determined according to the actual treatment received, regardless of the randomization treatment assignment. The safety population consisted of 223 patients in the A+CHP arm and 226 patients in the CHOP arm.

Patients in both treatment arms could receive 6 or 8 cycles of study treatment. A median of 6 cycles (range 1 to 8 cycles) was reported for both treatment arms, administered over a similar median duration of approximately 18 weeks (range 3.0 to 34 weeks*).* In total, 70% of patients in the A+CHP arm and 62% of patients in the CHOP arm received 6 cycles, 18% resp. 19% received 8 cycles of study treatment (see Study design under Clinical Efficacy section).

The PTCL subtypes that were allowed in the study were sALCL (ALK+ IPI score ≥2 and all ALK-), PTCL-NOS, AITL, ATTL, EATL and HSTCL. Most of the randomized patients had advanced stage and intermediate-risk disease as is typical of this patient population at the time of clinical presentation. The median age of randomized patients was 58 years (range, 18-85 years for the A+CHP arm and 18-83 years for the CHOP arm); 31% of patients were aged 65 years or older. Most patients had an ECOG 0 or 1, an ECOG performance status of 2 was reported for 51 patients (23%) in the A+CHP arm and 47 patients (21%) in the CHOP arm.

*Adverse events, serious adverse events and deaths*

In the ECHELON-2 trial almost all patients experienced 1 TEAE of any grade in both treatment arms (99% A+CHP vs 98% CHOP). The most common reported TEAE in both regimens were nausea, peripheral sensory neuropath, diarrhoea, neutropenia, constipation, alopecia, pyrexia, and vomiting occurring in more than 25% of the subjects. It is noted that the occurrence of TEAE GI adverse events (nausea, vomiting, diarrhoea) is higher in the A+CHP arm compared to CHOP, which is partly reflected in the higher use of anti-emetics as co-medication (e.g. ondansetron hydrochloride use 48% A+CHP vs 40% in CHOP). Diarrhoea was more commonly reported as treatment-emergent in A+CHP subjects (38% versus 20%) and assessed as treatment related in 16% (brentuximab vedotin) or 7% (vincristine related). The incidence of grade 3 or higher treatment emergent diarrhoea was higher in the A+CHP arm (6%) then CHP arm (1%). The Grade 3 diarrhoea events lasted a median of 4.5 days (range, 2 to 18 days), this however apparently did not lead to dose delay, dose reduction or discontinuation of the study drugs. GI events are considered manageable with existing standards of care. At least 1 TEAEs Grade 3 or higher occurred in a similar frequency in both treatment arms (66 vs 65%) and at least 1 drug-related SAE was reported for 39% (A+CHP) and 38% (CHOP) of the subjects. There are slightly more subjects with any ≥Grade 3 brentuximab vedotin or vincristine-related event (116 (52%) vs 104 (46%)) as well as SAEs related to brentuximab vedotin or vincristine (58 (26%) vs 45 (20%)). In the A+CHP arm, brentuximab vedotin-related ≥ Grade 3 AEs reported for ≥10% of subjects were neutropenia (30%) and febrile neutropenia (16%). On the CHOP arm, vincristine-related ≥ Grade 3 AEs reported for ≥10% of subjects were also neutropenia (27%) and febrile neutropenia (12%). Febrile neutropenia (14% of patients in the A+CHP arm and 12% of patients in the CHOP arm) was the most commonly reported SAE across treatment arms.

As of the August 15, 2018 cut-off date, a total of 123 deaths were reported, 50 on the A+CHP arm and 73 on the CHOP arm. Of the 50 deaths on the A+CHP arm, 36 were disease related, 10 were not disease related, and disease relationship was unknown for 4 subjects. Of the 73 deaths on the CHOP arm, 58 were disease related, 7 were not disease related, and disease relationship was unknown for 8 subjects. Eight subjects (4%) on the A+CHP arm and 13 subjects (6%) on the CHOP arm died within 30 days of the last dose of any component of the treatment regimen. Approximately half of the deaths within 30 days of the last dose of any component of the treatment regimen were disease related (11/21; 52%). Grade 5 TEAE occurred in 4% (8 cases) in A+CHP subjects and 7 % (16 cases) in the CHOP treated subjects. In A+CHP subjects adverse events leading to death were acute kidney injury, cardiac arrest, peripheral T cell lymphoma unspecified, pneumonia, pneumonia aspiration, pulmonary cavitation, sepsis and ventricular fibrillation (1 case each). In the CHOP arm anaplastic large T cell lymphoma was the most common AE leading to death (8 cases), followed by sepsis and multiple organ dysfunction.

Dose delay was the most frequently reported dose modification due to AEs for patients across treatment arms. Doses of brentuximab vedotin were delayed in 59/223 subjects (26%) on the A+CHP arm with the most common reasons neutropenia (5%), pneumonia (3%), and pyrexia (2%). Doses of vincristine were delayed because of AEs in 28/226 subjects (12%) on the CHOP arm due to neutropenia (4%), and leukopenia and pyrexia (1% each). An AE resulted in dose reduction of brentuximab vedotin in 21/223 subjects (9%) and a reduction of vincristine occurred in 24/226 subjects (11%). The most common reasons for dose reductions on the A+CHP arm were peripheral sensory neuropathy (5%) and peripheral motor neuropathy (2%). An AE resulted in premature study drug discontinuation for 14% A+CHP patients (6%) and 15 CHOP patients (7%), two subjects on each arm discontinued treatment due to peripheral sensory neuropathy.

The safety results of 2 supportive studies of brentuximab vedotin in combination with CHP and as monotherapy in adult patients with CD30+ PTCL showed a similar safety profile consistent with that for ECHELON-2 for adult patients with CD30+ PTCL treated with A+CHP in the frontline setting and brentuximab vedotin as monotherapy in the relapsed or refractory setting.

Adverse of special interest included peripheral neuropathy, febrile neutropenia, neutropenia and other haematological abnormalities (anaemia, thrombocytopenia) hepatotoxicity, infections and secondary malignancies.

*Peripheral Neuropathy*

In the clinical trial of Adcetris as combination therapy with CHP, treatment emergent neuropathy occurred in 52% of the population; peripheral motor neuropathy occurred in 9% of patients. Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 177 weeks. At the time of last evaluation, 64% who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 19.0 weeks (ranged from 0 weeks to 205 weeks).

A similar frequency and severity of treatment-related PN events were reported across treatment arms (50% of patients in the A+CHP arm and 49% of patients in the CHOP arm). Most of the PN events across treatment arms were Grade 1. Peripheral neuropathy led to treatment discontinuation in 1%, dose reductions in 7% and dose delays in <1% of patients. For patients who experienced peripheral neuropathy the median time of onset was 9.1 weeks. Patients who discontinued due to peripheral neuropathy received a median of 5 doses of A+CHP before discontinuation of one or more agents. Among patients with at least 1 treatment-emergent PN (SMQ) event, resolution was reported for 63 patients (54%) in the A+CHP arm and 80 patients (65%) in the CHOP arm. Improvements were reported for 12 (10%) patients in the A+CHP arm and 15 (12%) patients in the CHOP arm. At the time of last follow-up, PN was ongoing for 56 patients (48%) in the A+CHP arm and 44 patients (35%) in the CHOP arm, and the majority of ongoing PN events were Grade 1. The incidence of PN in ECHELON-2 was lower than the monotherapy trials AETHERA and ALCANZA (each 67%) and it is noted that the cases of PN less commonly lead to dose modifications. The median onset of PN was earlier for the CHOP patients (9.1 weeks vs. 6.1 weeks). In conclusion, the rate and severity as well as the resolution rate is in line with that expected of brentuximab vedotin therapy and similar to CHOP treatment.

*Neutropenia*

Treatment-emergent febrile neutropenia was reported in both arms (18% A+CHP and 15% CHOP). In both treatment arms, the majority of subjects who had febrile neutropenia had Grade 3 events (36/41 [88%] for A+CHP versus 26/33 [79%] for CHOP; the median time to onset was in the first cycle of treatment (1.9 resp. 1.6 weeks). Anaemia and thrombocytopenia in the A+CHP arm were observed

slightly more frequent, though comparable to the CHOP arm. Febrile neutropenia resulted in dose modifications for a small proportion (2% to 3%) of patients.

*G-CSF prophylaxis*

G-CSF primary prophylaxis was allowed per protocol and administered to 75 subjects (34%) on the A+CHP treatment arm and 61 subjects (27%) on the CHOP arm. In a non-randomized comparison between subjects with and without primary G-CSF prophylaxis, the prophylaxis severely reduced neutropenia rates, however appeared to have a limited effect on the reduction of febrile neutropenia, (Gr ≥3) infections and SAEs. Refer to section safety in PTCL types for more details. The SmPC recommends the administration of G-CSF primary prophylaxis for all patients being treated with A+CHP, beginning at Cycle 1.

*Immunogenicity*

49 of 205 ATA-evaluable subjects (24%) in the A+CHP arm were ATA positive, among which 5 (5/49, 10%) positive for nATA. Only 2 cases were persistently positive for ATA post baseline. No notable differences were observed with respect to AE reporting between transiently ATA-positive and ATA-negative subjects.

Infusion related reactions (IRRs) occurred in 10 subjects (4%) on the A+CHP arm and 13 subjects (6%) on the CHOP arm with the majority of IRRs were < Grade 3 in severity. None of the 5 subjects who experienced a brentuximab vedotin IRR tested positive for ATA at baseline. The safety information included in the SmPC section 4.4 is considered sufficient.

*Other events of special interest*

The incidence for hepatotoxicity (9%) was comparable to the observed incidences for brentuximab vedotin monotherapy (CTCL 11%, HL at risk of relapse 7%) and in combination with AVD (untreated HL 19%). The same applies for infections (52%, compared to monotherapy (60 % HL at risk of relapse; CTCL 44%) and in combination with AVD (previously untreated HL 55%)). The reporting rates of malignancies (4%) was comparable in other studies with monotherapy (HL at risk for relapse 2%, CTCL 6%) and in combination with AVD (previously untreated HL 1.5%)). In these reports, the progression of underlying lymphoma might be included. The actual incidence of secondary malignancy is not yet known- see SmPC sections 4.4 and 4.8.

*Special populations*

A total of 139 patients in the ECHELON-2 ITT population, 69 patients (31%) in the A+CHP arm and 70 patients (31%) in the CHOP arm were aged 65 years or older. Subgroup analyses were performed by age group (≥65 years versus <65 years) to compare the incidence of TEAEs of any grade, the incidence of febrile neutropenia, and the impact of G-CSF primary prophylaxis on febrile neutropenia. As expected, a higher incidence of TEAEs for patients aged 65 years and older was observed. The overall incidence and profile of TEAEs for both the A+CHP and CHOP treatment arms was generally similar regardless of age; however, in both treatment arms, the incidence of ≥ Grade 3 TEAEs and SAEs was higher in subjects ≥65 years. The incidence of Grade 3 neutropenia, febrile neutropenia, and Grade 3 or higher infections and infestations was lower in subjects aged <65 years. In both treatment arms, the median time to onset and the median time to resolution was similar, regardless of age. Among the 33 patients in the A+CHP arm and the 28 patients in the CHOP arm ≥65 years who received G-CSF primary prophylaxis, a trend of improved safety outcomes was observed, comparable with the outcomes for patients in the same age group who did not receive G-CSF primary prophylaxis. The AE profile in elderly is in line with the previous studies of brentuximab vedotin and adequately covered in the SmPC.

*Safety in PTCL types*

In non-sALCL patients (thus including PTCL-NOS and AITL) the safety profile of A+CHP can be considered more severe compared to CHOP, as illustrated by more≥ grade 3 TEAE, more SAEs and a higher percentage of discontinuations due to AEs. This difference appears mostly due to AEs in blood and lymphatic disorders, GI disorders, infections and infestations and metabolism/nutrition disorders. Moreover, the safety of A+CHP in non-sALCL patients can be considered more severe compared to the ITT. Notably, non-sALCL patients were older than sALCL patients (non-sALCL patients 48% ≥65 s vs sALCL 23% ≥65 years). The uncertainty whether the safety profile (AEs in blood and lymphatic disorders, GI disorders, infections and infestations and metabolism/nutrition disorders) of A+CHP is more pronounced over CHOP in non-sALCL PTCL and can all be mitigated by G-CSF prophylaxis in clinical practice was discussed with experts (see Additional expert consultation below).

*Safety in supportive studies*

The safety profile for A+CHP in the Phase 1 study SGN35-011 was overall comparable to that in ECHELON-2 except for a higher rate of patients discontinuing treatment due to an AE (23% vs 4%). The AEs leading to discontinuations were similar to those in the ECHELON-2 trial.

The different study design and treatment used in the supportive study SGN35-012 does not allow for a conclusion of the safety profile of A+CHP. However, the safety data for the 35 patients with PTCL appears to be in line with the established safety profile of brentuximab vedotin monotherapy.

## Additional expert consultations

The SAG- O was consulted on the following question on Clinical Safety:

- Please discuss whether a differential safety profile depending on PTCL subtypes is plausible.

The SAG experts agreed that differences in safety across PTCL entities would not be expected.

It should be noted that non-sALCL patients were older than sALCL patients (non-sALCL patients 48% ≥65 s vs sALCL 23% ≥65 years); a plausible correlation could be to older age of patients and not to histology and nevertheless the numbers in terms of AEs are too small to draw any conclusions. It was also considered that haematological toxicity can easily be managed by adding G-CSF, as primary prophylaxis.

## 2.5.2. Conclusions on clinical safety

The safety profile for patients with the combination of Adcetris with CHP arm was generally consistent with the known AE profile for patients treated with brentuximab vedotin in combination with chemotherapy. No new safety signals were identified.

## 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## 2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 15.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 15.2 with the following content:

## Safety concerns

| Summary of Safety Concerns | |
|---|---|
| Important identified risks | • Peripheral Neuropathy (sensory and motor)<br>• Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia)<br>• Infections (including bacteraemia, sepsis, septic shock and opportunistic infections)<br>• Infusion-related reactions<br>• Hyperglycaemia<br>• Anti-drug antibodies |
| Important potential risks | • Severe hepatotoxicity<br>• Pulmonary toxicity<br>• Thymus depletion (paediatric) |
| Missing information | • Long term safety |

## Pharmacovigilance plan

**Table Part III.1: Ongoing and planned additional pharmacovigilance activities**

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| C25006: Ph 4, open-label, single-arm study of brentuximab vedotin in patients with r/r sALCL<br>(SOB 010)<br>Status: Ongoing | Single-agent efficacy (ORR, duration of tumor control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT; OS), safety and tolerability, PK, immunogenicity | ADAs | Primary CSR | 31 March 2021 |
| MA25101 (PASS): Observational cohort study of the safety of brentuximab vedotin in the treatment of r/r | Safety; identification of potential risk factors for peripheral neuropathy | Peripheral neuropathy (sensory & motor); Myelosuppression (including neutropenia, febrile neutropenia, | Interim CSR<br><br>Second Interim analysis | 30 April 2016 (completed)<br>Within the annual renewal 21 April 2017 (completed) |

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| CD30+ HL and r/r sALCL<br>(SOB 008 & SOB 009)<br>Ongoing | | thrombocytopenia and anaemia); Infections (including bacteriemia, sepsis, septic shock, and opportunistic infections); IRRs; hyperglycemia; Severe hepatotoxicity, Pulmonary toxicity (devoid of concomitant bleomycin); longer-term safety | Final CSR | 31 December 2020 |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| C25004: An Open-Label Study of brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients with Advanced Stage Newly Diagnosed Hodgkin lymphoma [PIP study 3]<br>Ongoing | Safety; determination of MTD or highest HPD in combination<br>Evaluation of PK, immunogenicity, activity of combination therapy, and mobilization of peripheral blood stem cells for ASCT | Safety in pediatrics; thymus depletion (pediatric) | FPI;<br>LPLV | By 30 November 2017 (fulfilled)<br>By 31 December 2020 |

Abbreviations: A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone, ADME=absorption, distribution, metabolism, excretion, ASCT=autologous stem cell transplant, ADA=anti-drug antibody, CR=complete response, CSR=clinical study report, DBL=database lock [date], FPFV=First patient first visit; FPI=First patient in; HL=Hodgkin lymphoma, HPD=highest planned dose, IRR=infusion-related reaction, LPLV= Last Patient Last Visit, last patient out, LTFU=long-term follow-up, MTD=maximum tolerated dose, OS=overall survival, PASS=post-authorization safety study, PBO=placebo, Ph=phase, PFS=progression-free survival, PIP=pediatric investigational plan, PK=pharmacokinetic(s), Q=quarter, r/r=relapsed [or] refractory, RP2D=recommended phase 2 dose, sALCL=anaplastic large cell lymphoma (systemic), SCT=stem cell transplant.

## *Risk minimisation measures*

| Safety concern | Risk minimization measures |
|---|---|
| Peripheral Neuropathy (Sensory and Motor) | **Routine risk minimization measures:**<br>SmPC Section 4.8<br>SmPC sections 4.2 and 4.4 where there are recommendations regarding monitoring patients for symptoms of neuropathy, such<br>as hypoesthesia, hyperesthesia, paraesthesia, discomfort, burning sensation, neuropathic pain or weakness) and the possibility of delaying or reducing the dose in<br>patients who experience new or worsening neuropathy.<br>Package Leaflet section 2 and section 4<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Myelosuppression (including | **Routine risk minimization measures:** |

| Safety concern | Risk minimization measures |
|---|---|
| Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia) | SmPC Section 4.8<br>SmPC Sections 4.2 and 4.4 where there are recommendations for patients to have a full blood count prior to administration of each dose of brentuximab vedotin and for close monitoring of patients who develop neutropenia. If patients develop febrile neutropenia, they should be managed according to best medical practice. Dose delays should be considered in patients who develop neutropenia and growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia in monotherapy with brentuximab vedotin.<br>In combination therapy for the frontline treatment of HL, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose<br>Package Leaflet section 2 and section 4<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Infections (including bacteriemia, sepsis, septic shock and opportunistic infections) | **Routine risk minimization measures:**<br>SmPC Section 4.8<br>SmPC Section 4.4 where there is a recommendation for patients to be carefully monitored during treatment for the emergence of possible serious infections and opportunistic infections.<br>Package Leaflet section 2 and section 4<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Infusion-Related Reactions (IRRs) | **Routine risk minimization measures:**<br>SmPC Section 4.8<br>SmPC Section 4.2 and Section 4.4 where there is information about the possibility of patients developing immediate and delayed infusion-related reactions (IRRs) including anaphylactic reactions and a recommendation that administration of brentuximab vedotin should either be interrupted or immediately and permanently discontinued and appropriate medical therapy administered, if an IRR or anaphylactic reaction occurs. The SmPC also recommend restarting the infusion at a slower rate after symptom resolution and pre-medicating patients who have experienced a prior IRR with pre-medications such as paracetamol, an antihistamine, and a corticosteroid.<br>Package Leaflet section 2 and section 4<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Hyperglycemia | **Routine risk minimization measures:**<br>SmPC Section 4.8<br>SmPC Section 4.4 where there is a recommendation that any patient who experiences hyperglycemia should have their serum glucose closely monitored and antidiabetic treatment should be administered as appropriate.<br>Package Leaflet section 2 and section 4<br>Legal status |

| Safety concern | Risk minimization measures |
|---|---|
| | **Additional risk minimization measures:**<br>None |
| Anti-drug Antibodies (ADAs) | **Routine risk minimization measures**:<br>SmPC Section 4.8<br>SmPC Section 4.4, where there is a statement that a higher incidence of infusion-related reactions (IRRs) has been observed in patients with persistently positive Anti-Drug Antibodies (ADAs) relative to patients with transiently positive ADA and never positive ADA. It is recommended that the infusion should be interrupted if patients develop IRRs.<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Severe hepatotoxicity | **Routine risk minimization measures:**<br>SmPC Section 4.2<br>SmPC Section 4.8<br>SmPC Section 4.4 where there is a recommendation that patients receiving brentuximab vedotin therapy should have a liver function test before initiating treatment and routinely monitored during treatment with brentuximab vedotin. Patients who experience hepatotoxicity may require a dose delay, change in dose, or discontinuation of brentuximab vedotin.<br>Package Leaflet section 2 and section 4<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Pulmonary toxicity | **Routine risk minimization measures:**<br>SmPC Section 4.8<br>SmPC Sections 4.3 and 4.4 prohibits the combined use of brentuximab vedotin and bleomycin as it causes pulmonary toxicity. The SmPC also contain a recommendation that if new or worsening pulmonary symptoms are observed, a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Brentuximab vedotin therapy should be stopped during evaluation and until symptomatic improvement.<br>Package Leaflet section 2 and section 4<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Thymus Depletion (Pediatric) | **Routine risk minimization measures:**<br>SmPC Section 4.2<br>SmPC Section 5.3<br>Legal status<br>**Additional risk minimization measures:**<br>None |
| Long term safety | **Routine risk minimization measures:**<br>SmPC Section 4.2<br>SmPC Section 5.1<br>Legal status |

| Safety concern | Risk minimization measures |
|---|---|
| | **Additional risk minimization measures:**<br>None |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- In accordance with articles 59(3) and 61(1) of Directive 2001/83/EC, the MAH included the results of user testing of the Patient Information Leaflet (PIL) during review the marketing authorisation application for ADCETRIS in 2012. An assessment of all changes made to the Patient Information Leaflet, since the original application, was submitted during review of the most recently approved new indication for Adcetris (Procedure EMEA/H/C/002455/II/55).
- This variation application seeks approval for the use of ADCETRIS in combination with chemotherapy for patients with previously untreated CD30+ PTCL. The safety profile in this population is similar to that already approved, and the changes to the PIL are minor. Furthermore, there have been no changes to the layout of the PIL.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Peripheral T cell lymphomas (PTCLs) are a group of heterogeneous malignant lymphoproliferative disorders that originate from post-thymic T cells or mature natural killer (NK) cells. Systemic anaplastic large cell lymphoma (sALCL) may be ALK- 9.4%, or ALK+ 6.4) and has a high expression of CD30 (the target of Adcetris) at ≥75% of the tumour cells.

The acclaimed indication is: ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

### 3.1.2. Available therapies and unmet medical need

The treatment of newly diagnosed PTCL patients depends on subtype, age, IPI and comorbidities. Most PTCL patients are treated in a trial. Outside trials, the recommended first line therapy for patients with PTCL-NOS, AITL and ALCL is CHOP.

There is an unmet need across PTCL entities due to the low long-term survival rates and the toxicity of the treatment regimens.

### 3.1.3. Main clinical studies

The pivotal study in this application is ECHELON-2 (SGN35-014), a randomized (1:1), double-blind controlled study of 6-8 cycles brentuximab vedotin 1.8 mg/kg and CHP (A+CHP) versus 6-8 cycles of CHOP for treatment-naïve CD30 positive PTCL patients. sALCL (ALK+ IPI score ≥2 and all ALK-), PTCL-NOS, AITL, ATTL, EATL and HSTCL were allowed in the study. The protocol stipulated that 75± 5% of the enrolled subjects needed to have a diagnosis of sALCL. The ECHELON-2 study serves to fulfil a commitment for additional pharmacovigilance activity as agreed upon at time of the MAA (Category 3, MEA-015).

The ITT analysis set consisted of 452 subjects, 226 in the A+CHP arm and 226 in the CHOP arm. Most patients had sALCL (70%; ALK- in 48% and ALK+ in 22%). The other PTCLs studied were PTCL-NOS (16%), AITL 12%, ATLL (n=7; 2%) and EATL (n=3;1%). No HSTCL patients were included.

As supportive studies, a dose escalation study (SGN35-011) to evaluate toxicity of A+CHP (n=26) and sequential to CHOP (n=13) was submitted. A phase 2 study (SGN35-012) of brentuximab vedotin monotherapy in patients with relapsed/refractory NHL (AITL (n=13) and PTCL-NOS (n=22)) was also submitted.

## *3.2. Favourable effects*

The primary endpoint PFS per IRF showed a statistically significant advantage of A+CHP over CHOP in the overall study population (HR 0.71 [0.54, 0.93], p=0.011). The PFS rates at 12 months is 71.7% versus 58.2% and at 24 months respectively 61.4% versus 47.4%. In a PFS sensitivity analysis performed, the PFS HR was 0.76 [0.58,0.99], p=0.0443 with PFS rates at 2 year of 62.3% in the A+CHP and 50.9% in the CHOP arm. Thus, the sensitivity analyses support the primary endpoint.

Key secondary endpoints were tested in a fixed sequence testing procedure and all were statistically significant (PFS per IRF in sALCL, CR in total sample, OS in total sample, ORR in total sample). The PFS HR in sALCL patients was 0.59 [0.42, 0.84], p=0.0031. The 2-year PFS rates were 68.4% and 53.9% and the median PFS was 55.7 in the A+CHP arm versus 54.2 months in the CHOP arm.

PFS is supported by differences in CR rate (68% versus 56%, p=0.0066) and ORR rate (83% versus 72%, p=0.0032) favoring A+CHP over CHOP. ORR rate is driven by the difference in CRs. The median duration response was respectively 52.7 versus 51.4 months. The OS HR was 0.66 [0.46, 0.95], p=0.0244 with 27% of the OS events. The median OS was not reached in both arms.

Efficacy outcomes of the dose finding study SGN35-011 appear supportive for the efficacy observed in the pivotal study. In the phase 2 study (SGN35-012) in relapsed refractory AITL and PTCL-NOS patients anti-disease activity of brentuximab vedotin was observed.

Fewer patients received subsequent new anticancer treatment in the A+CHP arm compared to the CHOP arm: 65/226 (29%) vs 96/226 (42%) and the estimated subsequent therapy free rate was higher in the A+CHP arm compared to the CHOP arm.

PFS benefit of A+CHP over CHOP is observed in ALK+ (HR: 0.29, nominal p value: 0.01) and ALK- sALCL patients (HR: 0.65, nominal p value p = 0.02).

PFS in sALCL patients is supported by a more favourable CR rate (71% vs 53.2%) and more favourable point estimate for OS (HR 0.54 [0.34-0.87]) in a subgroup analysis.

The study population does not represent the complete CD30+ PTCL target population. It is estimated that sALCL constitutes approximately 15% of the PTCLs, but due to the protocol requirement for 75± 5% sALCL patients in the study, sALCL is overrepresented in the ITT. Notably, the study was not

powered/did not include sufficient numbers of patients to conclude on the benefit of A+CHP in the various studied non-sALCL PTCL entities. As a consequence, the indication was limited to focus of sALCL patients.

## *3.3. Uncertainties and limitations about favourable effects*

There are no uncertainties on the favourable effects of Adcetris in the treatment of patients with previously untreated CD30+ sALCL.

## *3.4. Unfavourable effects*

The AE profile for patients in the A+CHP arm was generally consistent with the known AE profile for patients treated with brentuximab vedotin in combination with chemotherapy. No new safety signals were identified. In the ECHELON-2 trial almost all patients experienced 1 TEAE of any grade in both treatment arms (99% A+CHP vs 98% CHOP). The most common reported TEAE in both regimens were nausea, peripheral sensory neuropath, diarrhoea, neutropenia, constipation, alopecia, pyrexia, and vomiting, occurring in more than 25% of the subjects.

At least 1 TEAEs ≥Grade 3 occurred in a similar frequency in both treatment arms (66 vs 65%) and at least 1 drug-related SAE was reported for 39% (A+CHP) and 38% (CHOP) of the subjects. On both study arms, treatment-related (either brentuximab or vincristine) ≥ Grade 3 AEs reported for ≥10% of subjects was neutropenia and febrile neutropenia.

Doses of brentuximab vedotin were delayed due to an AE in 59/223 subjects (26%) and doses of vincristine were delayed because of AEs in 28/226 subjects (12%). AEs resulting in a dose reduction of brentuximab vedotin in 21/223 subjects (9%) and a reduction of vincristine occurred in 24/226 subjects (11%). AEs resulted in premature study drug discontinuation for 14 A+CHP patients (6%) and 15 CHOP patients (7%).

A similar frequency and severity of treatment-related peripheral neuropathy (PN) events were reported across treatment arms (50% of patients in the A+CHP arm and 49% in the CHOP arm). Most of PN events across treatment arms were Grade 1. PN (sensory and motor) resulted in a dose modification in 7% (16 cases) across treatment arms, mainly dose reduction. Two subjects on each arm discontinued treatment due to peripheral sensory neuropathy.

Treatment-emergent febrile neutropenia was reported in both arms (18% A+CHP and 15% CHOP). On both treatment arms, the majority of subjects who had febrile neutropenia had Grade 3 events (36/41 [88%] for A+CHP versus 26/33 [79%] for febrile neutropenia resulted in dose modifications for a small proportion (2% to 3%) of patients. G-CSF primary prophylaxis was administered to 75 subjects (34%) on the A+CHP treatment arm and 61 subjects (27%) on the CHOP arm.

In both treatment arms, the incidence of ≥ Grade 3 TEAEs and SAEs; Grade 3 neutropenia, febrile neutropenia and ≥Grade 3 infections was higher in subjects ≥65 years. The AE profile in elderly is in line with the previous studies of brentuximab vedotin and adequately described in the SmPC.

The type of AEs of the subgroups of sALCL and non-sALCL are in alignment with that of the overall safety population.

## 3.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties regarding the unfavourable effects.

## 3.6. Effects Table

**Effects Table for brentuximab vedotin and CHP (A+CHP) versus CHOP for treatment-naïve patients with CD30-positive mature T-cell lymphomas (data cut-off: 15-Aug-2018)**

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PFS | Progression free survival-median | Months | 48.2 [35.2,-] | 20.8 [12.7, 47.6] | PFS HR 0.71 [0.54, 0.93], p=0.011 -supported by CR rate and ORR.<br>- OS is immature but in support of PFS (HR 0.66).<br>- In PFS analysis according to EMA guidance the PFS HR is 0.76 [0.58,0.99], p=0.0443<br>- Results of ITT population mainly driven by sALCL (70%) and PTCL-NOS (16%) subgroups- PFS driven by effect in sALCL patients: PFS HR 0.59 (see below)<br>- PFS outcomes in non-sALCL patients are inconclusive (HR 0.96 [0.62, 1.46])<br>Lack of efficacy data for PTCL - subtypes not studied in ECHELON-2<br>- PFS event rates at 1 and 2 years are most representative for clinical benefit due to plateau formation in the KM curves. | |
| | - At 1 year | % | 71.7 [65.1,77.2] | 58.2 [51.4, 64.3] | | |
| | - At 2 years | % | 61.4 [54.4, 67.6] | 47.4 [40.6, 53.8] | | |
| CR rate | Complete response at end of treatment | % | 68% [61.2, 73.7] | 56% [49.0, 62.3] | CR rate difference p=0.0066<br>ORR results are driven by CR rate and in line. | |
| PFS in sALCL patients | Progression free survival in sALCL patients-median | Months | 55.7 | 54.2 | PFS in sALCL patients HR 0.59 [0.42, 0.84], p=0.0031.<br>- The PFS in sALCL patients is supported by CR rate and OS HR 0.54 [0.34-0.87] in sALCL patients | |
| | -at 2 years | | 68.4% | 53.9% | | |
| **Unfavourable Effects** | | | | | | |
| At least 1 TEAE of any grade | Incidence as percentage of patients from the safety population | % | 99 | 98 | The most common reported TEAE in both regimens were nausea, peripheral sensory neuropath, diarrhoea, neutropenia, constipation, alopecia, pyrexia, and vomiting occurring in more than 25% of the subjects.<br>Safety data mainly from sALCL (70%) and PTCL-NOS (16%) population<br><br>Dataset for subgroups of AITL, ATLL and EATL limited | |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| | | | | | Lack of safety data for other PTCL subtypes not studies in ECHELON-2 | |
| At least 1 TEAE grade 3 or higher | Incidence as percentage of patients from the safety population | % | 66 | 65 | Brentuximab vedotin-related ⩾ 10% of subjects were neutropenia (30%) and febrile neutropenia (16%). Vincristine-related ⩾10% of subjects were also neutropenia (27%) and febrile neutropenia (12%). | |
| at least 1 drug-related SAE | Incidence as percentage of patients from the safety population | % | 39 | 38 | Febrile neutropenia (14% of patients in the A+CHP arm and 12% of patients in the CHOP arm) was the most commonly reported SAE across treatment arms. | |
| On study death | Number of deaths that occurred within 30 days of the last dose of frontline therapy | N | 50 | 73 | Deaths were considered disease related for 36 patients (16%) in the A+CHP arm and for 58 patients (26%) in the CHOP arm. | |
| AE resulting in premature study drug discontinuation | Incidence as percentage of patients from the safety population | % | 6 | 7 | Similar discontinuation rate reflects manageable safety profile for A+CHP | |

Abbreviations: PFS=progression free survival, HR= hazard ratio, OS= overall survival, CR= complete response PTCL= peripheral T-cell lymphoma's, sALCL= anaplastic large cell lymphoma, primary systemic type

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The pivotal study demonstrated a clinically relevant effect in PFS of A+CHP over CHOP in the overall study population (PFS HR 0.71 [0.54, 0.93], p=0.011), best represented by PFS event rates at 1 year (71.7% versus 58.2%) and 2 years (61.4% versus 47.4%), reflected by plateau formation in the KM curves. The sensitivity analyses showed the PFS effect to be robust and PFS results are supported by the key secondary endpoints CR rate and OS benefit with a HR of 0.66. These results were considered as driven by the predominant sALCL disease group. The PFS in sALCL patients (70% of the ITT) was a key secondary endpoint and the first to be tested in a hierarchical testing procedure. This analysis confirmed the PFS benefit of A+CHP over CHOP in sALCL patients (HR 0.59 [0.42, 0.84], p=0.0031). These outcomes are supported by CR and OS data in sALCL patients.

On safety, in the overall study population A+CHP showed an incidence, type, and severity of AEs comparable to CHOP and the toxicity of A+CHP is considered generally manageable.

### 3.7.2. Balance of benefits and risks

The HR for PFS benefit of A+CHP over CHOP in sALCL patients was 0.59 [0.42, 0.84], p=0.0031 which is a clinically relevant outcome and is supported by CR and OS data in sALCL patients.

The safety profile is in line with the well-known profile of Adcetris in combination with chemotherapy and is considered generally manageable.

An update on Overall Survival will be provided in the context of the follow up of MEA015; a final study report is expected by Q1 2021.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## *3.8. Conclusions*

The overall B/R of Adcetris is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II and IIIB |

Extension of indication to include in combination with cyclophosphamide, doxorubicin, and prednisone treatment of adults with previously untreated sALCL for Adcetris; as a consequence, section(s) 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are being updated to reflect the indication. The Package Leaflet (PL) is updated in accordance. Version 15.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annexes I, II, IIIB and to the Risk Management Plan are recommended.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion 'Adcetris-H-C-2455-II-0070'

**References**


1. The 2016 revision of the World Health Organization classification of lymphoid neoplasms; Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. Blood. 2016 May 19; 127(20):2375-90.

2. Freidlin B, Korn EL. Borrowing information across subgroups in phase II trials: is it useful? Clinical cancer research: an official journal of the American Association for Cancer Research. 2013;19(6):1326-34.